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Osteoporotic fracture fixation – a biomechanical perspective

Guest Editors: Peter Augat, Jörg Goldhahn

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Osteoporotic fracture fixation – a biomechanical perspective

Guest Editors:

Peter Augat
Jörg Goldhahn

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Osteoporotic Fracture Fixation – A Biomechanical Perspective

Guest Editors: Peter Augat, Jörg Goldhahn

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Editorial

Osteoporotic fracture fixation – a biomechanical perspective

Bone tissue changes with age and most of these changes become accentuated with osteoporosis. If the age associated alterations in bone tissue exceed a significant threshold, it may qualify for being osteoporotic. Thus the effects of age and osteoporosis on bone become indistinguishable, both leading to a steadily increasing number of fragility fractures. The burden of illness for these fragility fractures is immense, frequently leading to hospitalization, long term nursing home care, musculoskeletal disabilities and death [1–3]. Orthopaedic surgeons are typically the first who are confronted with patients after a fragility fracture. Although the treatment of patients with fragility fractures requires a holistic approach, the major problem of their management continues to be how to achieve optimum fracture fixation allowing early mobilization and promoting a successful bone repair response [4,5].

Fragility fractures are more challenging to treat compared to fractures in otherwise healthy bone. Although most orthopaedic surgeons would agree with this statement, there is little evidence to scientifically support it. More importantly there is only limited consensus on possible explanations why fractures in osteoporotic patients constitute a challenge and how this should be addressed. Strategies to improve outcome of patients after fragility fractures currently address biological and biomechanical perspectives. However, the available evidence how fragility fractures are effectively treated is sparse and relies mostly on basic and pre-clinical research. Transfer of this evidence into clinical decision making is difficult for the individual being either a scientist or a clinician, rarely both. Thus, finding a consensus for the adequate treatment for fragility fractures remains a challenge.

The Orthopaedic Trauma Care (OTC) Foundation is a global network of scientists and surgeons, dedicated to the advancement of osteosynthesis and trauma care. Their members have identified fragility fractures as one of the current burning issue in trauma care which requires mutual discussions among scientists and clinicians alike. They have decided to discuss the two most important perspectives on the treatment of fragility fractures – biological and biomechanical – in two expert workshops. While the results of the first workshop "Osteoporotic fractures – the biological perspective" have been published [6], the current volume is based on a workshop held in Boston, MA in November 2014 entitled "Osteoporotic fractures – the biomechanical perspective."

The current volume will not only summarize the available evidence from basic research for the treatment of fragility fractures but will also put this information into a clinical perspective. All the manuscripts included are authored by scientists and surgeons and focus on finding a consensus to the benefit of the patient with a fragility fracture. The first series of manuscripts addresses the biomechanical properties of aged and osteoporotic bone. They describe the local and global changes that occur in bone with aging and osteoporosis and also explain the clinically relevant differences in mechanical properties between trabecular and cortical bone tissue. Although a large armamentarium of radiological equipment is available for the quantification of bone mineral it often remains vague how this will affect fixation stability during surgery. Thus, it will be addressed what determines the fixation stability in fragile bone and how this can be practically evaluated. The last topic in this first series illustrates the biomechanical considerations of fracture fixation in fragile bone and how failure of fracture fixation can be explained and also hopefully avoided.

The second series of manuscripts describes why healing of osteoporotic fractures appears to be different from healing in normal bone and how this can be employed to develop improved strategies for the management of osteoporotic fractures. Among these strategies for the management of fragility fractures, the use of bone augmentation became very popular and will be discussed in a separate manuscript. With increased activity levels of elderly individuals, fractures of osteoporotic bone also occur after traumatic events with significant mechanical impact [7]. These fractures sometime lead to bone defects which require bone void fillers. As it is currently unclear which are the most successful materials for this purpose a manuscript on the development of these materials has also been included.

The last series of manuscripts reviews methods for the fixation of fractures around prostheses. Patients with periprosthetic fractures often have advanced age and present with many comorbidities – a situation which requires immediate mobilization. Approaches to provide sufficient stabilization vary greatly and will be reviewed in two manuscripts.

Conflict of interest

Peter Augat serves as a member of the research committee of the OTC Foundation. Jörg Goldhahn is employee of Novartis AG.

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Failure of fracture fixation in osteoporotic bone

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ABSTRACT

This manuscript will provide an overview of how the age and osteoporosis related changes in mechanical properties of bone affect the stability of osteosynthesis constructs, both from a mechanical as well as from a clinical perspective. The manuscript will also address some of the principles of fracture fixation for osteoporotic fractures and discuss applications of osteoporotic fracture fixation at sites typically affected by fragility fractures, namely the distal radius, the proximal humerus, the femur and the spine. The primary aim of operative treatment in elderly individuals is the avoidance of immobilization of the patient. In selected cases conservative treatment might be required. Generally, choice of treatment should be individualized and based on the evaluation of patient-specific, fracture-specific and surgeon-specific aspects. The orthopaedic surgeon plays an essential role in enabling functional recovery by providing good surgery but a multidisciplinary approach is essential in order to support the patient to regain his/her quality of life after fragility fracture. Overall, the therapy of fractures in osteoporotic bone in the elderly requires a multidisciplinary therapeutic acute care concept including treatment of co-morbidities and correct choice of timing, and technique of the operative intervention.

Introduction

In an aging population the number of fractures seen in orthopedic institutions steadily increases. The treatment and care of these elderly patients constitutes a challenge for the individual orthopedic surgeon, the hospital staff and the health care systems worldwide. Many of these challenges are related to the age of the patient and the frequency of comorbidities. Therefore, the successful treatment of the fracture with fast recovery of the mobility is essential for the patient's survival and wellbeing. A reasonable return to function and a successful healing in the elderly requires a mechanical stable internal fixation and rapid rehabilitation. Elderly individuals will not be able to adhere to partial weight-bearing protocols and thus require osteosynthesis which tolerates full weight-bearing. Thus the need for stable internal fixation in osteoporotic bone is paramount. The hardware for fracture fixation is typically designed to maintain its stability during full weight bearing. However, the bone in elderly individuals often lacks mechanical strength for stable anchorage of plates, screws or nails. Age related degradation of bone and the additional bone weakening through age related diseases such as osteoporosis reduce the ability of bone to withstand increased loading. Often the bone around screws and nails fails prematurely and leads to subsidence, cut through or cut out of metal hardware and ultimately to failure of fracture fixation [1]. This manuscript will provide an overview of how the age and osteoporosis related changes in mechanical properties of bone affect the stability of osteosynthesis constructs, both from a mechanical as well as from a clinical perspective. Principles of fracture fixation for osteoporotic fractures will also be discussed. However, it should be recognized that fragility fractures require a multidisciplinary management of the acute fracture episode and ongoing activities to prevent secondary fractures [2]. The orthopaedic surgeon plays an essential role in enabling functional recovery by providing good surgery but a multidisciplinary approach is essential for the fracture patient to regain his quality of life.

Mechanical properties of bone in osteoporosis

The ability of bone to resist fracture and withstand loads depends on the amount of bone (bone mass), its distribution in space and the intrinsic material properties of the bone tissue [3]. Using engineering principles these factors can be used to predict failure load of a given bone with fairly high accuracy [4,5]. However, the failure load for a bone with certain strength will strongly depend on the loading mode. A proximal femur will fracture at considerably lower loads if the loading mode is a sideways fall on the greater trochanter as compared to loading applied to the femoral head in a stance configuration [5].

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In order to determine the risk of a fracture to occur the concept of factor of risk was introduced. The factor of risk can be computed as the ratio of applied load and load at which the bone structure would fail [6].

In osteoporosis bone mass is reduced and the microarchitecture of bone is deteriorated leading to enhanced bone fragility and increased fracture risk [7]. The reduction in bone mass mainly results from increased bone resorption and inadequate bone formation leading to a negative remodeling balance [8]. Although less well understood, also the intrinsic material properties of bone tissue are affected by aging and osteoporosis [9]. Intrinsic changes that have been previously described include compositional factors such as mineralization distribution, content of collagen and cross linking profiles of inter- and intrafibrillar collagen connections [10].

Aging and osteoporosis affect elastic properties as well as strength properties of bone. Elastic properties describe the deformation which occurs under loading (stiffness) before failure, while strength describes the stress (force per unit area) at which failure occurs. For cortical bone, stiffness decreases by 1–2% per decade and strength decreases by 2–5% per decade [11]. Most importantly the energy required to fracture a bone may decrease by up to 10% per decade beyond the age of 35 years [6,12]. For trabecular bone the mechanical competence is mainly determined by the apparent density and the orientation of the trabecular network, explaining up to 90% of its variance [13,14]. As the relationship of density with mechanical properties is non-linear, the decreasing apparent density of trabecular bone with aging is associated with accentuated deterioration of the mechanical properties. At age of 80 years the strength of the bone from the proximal femur is reduced by more than 50% from its strength at young age [15]. Even more pronounced is the loss of mechanical strength at the spine were the strength reduction during lifetime has been reported to amount to up to 70% [16]. As the load to fracture for a whole bone depends on both cortical and trabecular bone material properties the overall strength of bone is dramatically reduced with aging. The proximal femur loses about 50% of its strength and 70% of its energy to failure between the age of 35 years and 75 years [17]. Even more dramatic is the loss of strength at the spine where a loss of 80% of compressive strength have been reported in men and women [18]. These dramatic age related changes in the material properties indicate that the factor of risk for fracture is increased and traumatic events which are benign at young age will become enormously hazardous in the elderly.

Considering the concept of factor of risk for a fracture not only the strength of the bone but also the applied load has to be taken into account. With aging muscle performance and coordination deteriorate and lead to an increased risk of falling and also to a decreased ability to support falls. The potential energy which is generated during a fall from standing height largely exceeds the energy required to fracture the proximal femur. Thus without any energy absorption by soft tissue dampening, muscle contraction or compensatory movement, the load acting on the proximal femur during falling would inevitably lead to hip fracture [19].

Failure of fracture fixation

Failure of internal fixation in osteoporotic bone typically results from bone failure rather than implant breakage [20]. The deterioration of cortical and trabecular bone with aging and osteoporosis goes along with a considerable reduction of fixation strength of osteosynthesis materials [21]. This reduction in fixation strength has been demonstrated for most types of osteosynthesis materials including screws, plates, nails and fixators (Table 1). It appears that at locations which are prone to osteoporotic fractures also the effect of bone density on fixation stability is most pronounced. In cortical bone; in which the extent of deterioration of bone mechanical properties with age is less pronounced, the thickness of the cortical bone has shown to have a dramatic effect on the fixation stability of osteosynthesis implants [22,23]. Compared to thick cortices the holding force decreases by 1000 N (or 50%) per 1 mm loss of cortical thickness. This might generate differences in holding power of bone screws of up to 2000 N within an individual bone and highlights the importance of placing bone screws in the bone with thick cortices wherever possible.

The role of locked plating

It is generally assumed that locking plate constructs have mechanical advantages compared to conventional plate constructs and that these advantages are of particular benefit in osteoporotic bone [20,34]. Biomechanical studies so far have demonstrated that in osteoporotic bone locking plates create increased fatigue strength and increased ultimate failure loads compared to conventional plates [35,36]. Furthermore; it appears that the fixation stability of locked plates is less susceptible to reduction in bone mineral density compared to conventional plating constructs (Table 1). The major reason for failure in conventional plating of osteoporotic bone is break out of the screws and/or fracture of the bone through one of the screw holes. Thus the stress within the bone at the site of the screws appears

Table 1.
Loss of mechanical properties for osteosynthesis constructs related to age and osteoporosis

Type of implant	Location	Loading mode	Mechanical property	Loss in mechanical property (%)*	References
Pedicel screw	Vertebrae cervical	Axial screw pull out	Failure force	37	[24]
		Screw tightening	Failure torque	35	
Vertebral body replacement	Vertebrae lumbar	Axial compression	Force	55–75	[25]
Cage & Fixator	Vertebrae lumbar	Flexion/Extension	Stiffness (1/ROM**)	60–80	[26]
Pedicle Screw	Sacrum (S1)	Cantilever bending	Failure force	64	[27]
Conventional plate	Tibia proximal	Tibial plateau compression	Failure force	40	[28]
Conventional plate	Tibia distal	External rotation	Failure torque	70	[29]
Locking plate				14	
Locking screws	Tibia shaft	Axial pull out	Failure force	15	[22]
		Cantilever bending	Failure force	18	
Cancellous screws	Humerus head	Axial pull out	Failure force	18	[30]
Conventional plate	Humerus proximal	Cyclic fatigue	Cycles to failure	70	[31]
Locking plate				59	
Hip screw	Femural head	Cyclic fatigue	Stiffness (1/subsidence)	55	[32]
Proximal femoral nail	Femur proximal	Cyclic fatigue	Cycles to failure	48	[33]

*Loss in mechanical property was calculated as percentage reduction observed for the low density (osteoporosis) group or population with respect to the high density (normal bone) group or population.
**ROM: Range of motion.

to be of importance for fixation failure. The major difference between locking and conventional constructs is the load transfer between fracture fragments. Conventional plates rely on frictional load transfer between the plate and the bone. Thus loads are transferred from the bone to the plate across the fracture area and back to the bone again. If the applied load to the fractured bone exceeds the frictional force, the construct becomes unstable mainly because the bone screws begin to toggle due to shear [34]. Friction in conventional plating is produced by compressing the plate on to the bone by tightening the compression screws. This compression induces a considerable amount of preload in the bone tissue around the screws which further increases the risk of screw break out.

In locked plating the plate is not compressed on to the bone surface and load transfer from the bone to the plate is always achieved through the head of the locking screw. The load transfer from the bone to the screw is distributed along the length of the screw wherever the screw is in contact with bone. Furthermore, the locking mechanism of the screw within the plate prevents individual screws from toggling in the bone and cutting through the bone by cyclic fatigue. As there is no compressional force during plate application in locked plating; the bone around the screws experiences very little preload in the absence of physiological loading.

In a recent computational study the stresses within the bone around the screws have been computed for conventional plates and for locking plates [37,38]. It has been shown that in osteoporotic bone locking plates indeed demonstrate clinical benefit by producing considerably lower tensile strains in the bone around the bone screws. This provides a mechanical explanation for the improved performance of locking plates in poorer bone quality and explains previously reported higher incidence of screw loosening using the conventional plates [39]. In good quality bone however, locking screws caused similar strains to conventional screws and did not show much mechanical advantages, suggesting that simple fractures in healthy bone should be treated with reduction and absolute stability using conventional plate constructs [37]. Finally, compared to conventional plates locking screw constructs are less likely to fail by screw breakage or screw loosening. Locking screws typically possess a thicker core diameter and thus provide increased bending stiffness and strength. If correctly locked into the plate screws rather break off at the screw plate interface but do not become loose from the plate [40].

Treatment of fragility fractures

The treatment of osteoporotic fractures is determined by three main factors: The soft tissues, the fracture configuration, and the patients' status. In elderly patients, each of these three factors may present particular problems [41] as thin soft tissues and skin due to atrophy or malnutrition, ischaemic changes and poor healing, oedema, ulcers and chronic skin lesions. Fracture configuration is often comminuted, and even patient factors are often complex in the elderly, because the majority of patients have also medical comorbidities which require careful treatment.

The aim of surgical acute care after fragility fracture in the elderly is a fracture management with stable fracture fixation facilitating early full weight bearing. Compared with younger patients, elderly patients do not tolerate pain, blood loss, immobilization, surgical mistakes, and operative revisions. Mental condition and functional requirements of the elderly patient strongly influence the decision for operative treatment of the fragility fracture. It is important to notice, that the overall complication rate and mechanical implant failure following surgical treatment of fragility fractures are significantly higher compared with non-fragility fractures [42]. As demonstrated earlier in this manuscript osteoporotic/aged bone is the main cause of failure of fracture fixation rather than implant failure itself. Complication rates after surgical therapy of osteoporosis-related fractures are twice as high as after treatment of healthy bone. The implant related failure rate in osteoporosis-related fractures is estimated to be about 10–25% [1]. Surgical treatment of these fragility fractures is associated with a higher rate of complications as mal- or nonunion [43]. Surgical success is based on the correct indication as well as on the correct surgical technique ("surgeon factor"), biological factors (e.g. perfusion of fracture fragments) and on biomechanical factors (e.g. bone quality, fracture configuration, anatomical reduction). Also patients' collaboration during the postoperative care ("patient factor") is a mandatory prerequisite for sustainable success of the therapy.

It is common consent from epidemiological studies that persistent, non-treated osteoporosis significantly increases the risk for another fracture [44] and aggravates fracture fixation in various implants e.g. single screws, screw-plate constructs, intramedullary nails or dynamic hip screws at different bone locations as proximal humerus, proximal femur or vertebra under different loading modes as quasi-static or limited cyclic [21].

Principles of fracture fixation in osteoporotic bone

Techniques of open reduction and internal fixation (ORIF) have commonly been developed for normal healthy bone. In osteoporotic bone it is paramount to consequently apply these techniques. Sometimes it might be necessary to modify traditional techniques in order to avoid fixation failure and achieve satisfactory healing results [1]. Fracture treatment by ORIF aims at (1) primary stability of the fracture in order to initiate fracture healing under some sort of functional movement, (2) secondary stability in order to enable bony consolidation, (3) correct alignment and adequate fracture reduction in order to avoid malalignment and inadequate loading of joints, and finally (4) a mechanical environment which promotes bone formation and prevents delayed union or non-union.

Primary stability

Several biomechanical principles can be employed to achieve sufficient primary stability in osteoporotic bone. As we have seen earlier a critical point in fracture fixation of osteoporotic bone is the interface between implant and bone. Thus, internal fixation devices that allow load sharing with host bone should be chosen to minimize stress at the bone–implant interface. This can be achieved by employing fixation devices which have a maximum of contact area between implant and bone. Examples are long plates and nails with many locking options or plates with a larger surface area providing more possibilities for screw placement. Plates with a larger contact area effectively reduce the local compressional strain on the bone. Similarly, more thinner screws generate smaller local strain in cortical as well as trabecular bone compared to fewer thicker screws [45]. Thinner screws have the additional advantage of providing more flexibility and thus the ability to distribute the load within a larger volume of bone. The advantages of locked plates over conventional plates in providing better stability have been discussed earlier in this manuscript.

Secondary stability

Secondary stability can only be achieved if sufficient primary stability is provided. In addition bone fatigue by brittle failure, creep or trabecular crushing has to be prevented. The limiting factor for secondary stability is the limited fatigue strength of osteoporotic bone. As bone fatigues at locations of high strain the primary principle of secondary stability is the prevention of excessive strain and strain concentrations. Thus, as mentioned before, implants which distribute the strain over a larger area by large surfaces or by more screws or bolts may prevent bone from early fatigue. Also loading which would generate excessive strains locally must be avoided. Thus, implants with additional features such as anti-rotation or anti gliding mechanisms can potentially prevent excessive shear or tensile loads [46]. Examples

are additional anti rotation screws in dynamic his screw systems, struts on screws which prevent screw rotation [47] or supporting plates for femoral neck pins (Figure 3) [48]. Finally, in certain situations the augmentation of screws with bone cement is very effective in distributing the load from the metallic implant to the bone ([49,50]).

Correct alignment and accurate fracture reposition

Correct load transfer through the fracture and the adjacent joints is an essential prerequisite for uneventful fracture healing and complete restoration of physiological function after fracture. The first and most important step in fracture fixation is thus the correct alignment of the load axes followed by reposition of the fracture fragments. Particularly with pre-contoured anatomical locked plates which do not have angle variability of the locking screws, correct alignment may sometimes be difficult to achieve. In these situations the correct placement of the first screws in the joint block is paramount. In the shaft area, temporary conventional screws may assist fragment alignment by pulling the fragments towards the plate. Depending on the fixation principle, the conventional screw should be removed or replaced by a locking screw in order to avoid a stress rising effect at the plate. Compression techniques available in extra-medullary and intramedullary implants allow effective fracture reposition but may be technically demanding [51–53]. The compression provides increased primary and secondary stability by load sharing between implant and bone [54]. Finally, bone transplants (autologous spongiosa) or bone cements support restoration of joint surfaces and enable their correct alignment [55].

Adequate mechanical environment

In fractures involving the shaft, the principle of elastic fixation which stimulates periosteal callus formation by interfragmentary movement (secondary healing response) should be employed [56]. Locking plate constructs with a long span length and a large distance between the two screws above and below the fracture are a viable option in the meta- and diaphyseal area. Typically titanium plates are preferable to steel plates because they provide more elastic deformation. In the central diaphysis a long intramedullary nail with intramedullary reaming and a maximum of locking distally and proximally should be the primary choice. Only C-type fractures involving the joints require a maximum of stability achieved by stable locking plate constructs often in combination with compression screws. For stable plate constructs which heal by a primary healing response it is essential to avoid fracture gaps and achieve accurate fracture reduction and alignment [56].

In the clinical setting, common fragility fractures having increased risk for complications include fractures of the proximal humerus, distal radius, proximal femur, and spine [57–62].

Fragility fractures of the proximal humerus

Fractures of the proximal humerus are a typical injury of the elderly patient over 65 years of age, and the majority of these fractures are related to osteoporosis [63] and to an increased risk of falls. Multiple studies revealed that osteoporosis, displaced varus fracture, insufficient restoration of medial calcar support, humeral head ischemia and insufficient fracture reduction are independent risk factors for reduction loss after surgery of proximal humerus fractures [64,65]. Therefore, fractures of the proximal humerus remain a problem difficult to treat. They are often associated with damage to the rotator cuff leading to decreased shoulder function. Preoperative assessment of local bone quality may be critical in facilitating decision making regarding surgical and non-surgical treatment [66]. In many comminuted three- or four-part fractures there is insufficient bone quality to achieve a good purchase with internal devices. Therefore, intramedullary devices have been developed that are located more medially, have a shorter lever arm than plates, preserve the blood supply of the periosteum and soft tissues, and are inserted with a minimally-invasive technique [41]. Their central location provides a uniform load distribution. However, in unstable or comminuted lateral metaphyseal fractures, and particularly if the starting point extends into the greater tuberosity, failure of fixation or fracture displacement may occur [67]. Also in head-split fractures intramedullary nailing is not indicated. Due to these concerns and also technical challenges with proximal humeral nails, anatomically pre-contoured locking compression plates have been developed, offering the advantage of divergent locking head-screws which enter the humeral head at various angles in order to maximize purchase and create an angle stable device [68–70]. Additional holes in the plate allow tension-band fixation of the rotator cuff while the anatomical design of the implant allows easier application of the plate and minimizes subacromial impingement [71]. Screw pull-out is significantly linked with decreased bone mineral density and with the minimal contact interface between implant and low density bone [72,73].

The large amount of technical proposals for the treatment of osteoporotic proximal humeral fractures demonstrates the difficulty associated with these fractures. Technical solutions to improve fracture fixation in the humerus include fixed and variable angled locking plates, the use of blades [74], the augmentation with bone cement (Figure 1) [50], augmentation with intramedullary fibular grafts [75], or iliac crest bone grafts [76]. Beside the mandatory preoperative planning including three-dimensional computer tomography scans [77] other new tools to determine local bone quality within the humeral head in real time have been developed [77]. Outcome of hemiarthroplasty is closely related to anatomical tuberosity healing and restoration of rotator cuff function, and reverse shoulder arthroplasty may provide satisfactory shoulder function in geriatric patients, rotator cuff dysfunction or failure of first-line treatment [64].

Fragility fractures of the distal radius

The osteoporotic distal radius is deficient in both cortical and trabecular bone, but early changes in cortical bone are strongest predictors for fragility fractures [78]. Therefore, osteoporotic fractures of the distal radius remain a complex entity to be surgically treated. With patients living longer and being more active, these fractures

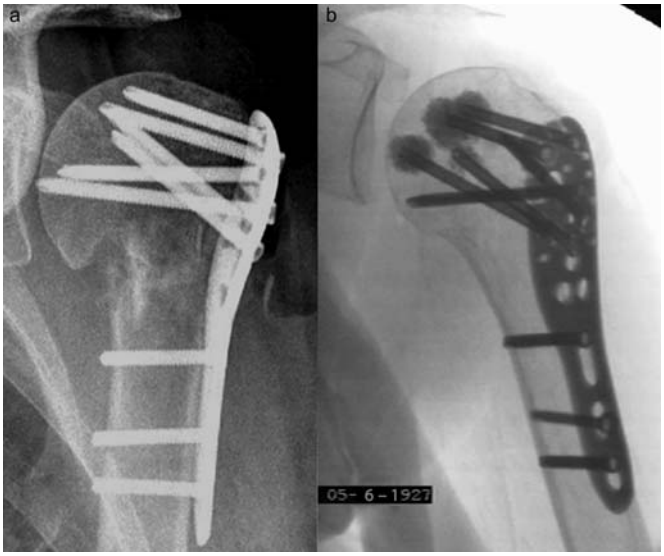

Fig. 1. Left: Failure of fracture fixation in an osteoporotic proximal humerus fracture. Inadequate reduction and insufficient calcar support resulting in articular screw perforation. Right: Locking plate fixation of an osteoporotic proximal humerus fracture reinforced by cement augmentation of the screw tips.

become increasingly prevalent. Despite various randomized trials, the most adequate fixation technique of fragility fractures has not yet been identified [79]. Available fixation techniques include Kirschner wire fixation, intrafocal pinning using the Kapandji technique, external fixation with bridging fixators, and internal fixation using dorsal or volar plates [80]. Bone grafts and calcium phosphate cements have been utilized singularly or in combination with other fixation techniques in order to augment them. When operative treatment is indicated, the volar locking plate osteosynthesis has become the treatment of choice [81]. Anatomically pre-contoured volar locking plates are most commonly used. If correctly applied they allow for early motion and have an acceptable complication profile [40,78,82]. The development of locking compression plates offered the possibility of volar plate fixation for those fractures with dorsal angulation and comminution. The volar approach minimizes soft-tissue problems while the angle stable screws maintain radial length without the need for a buttress [41]. In order to improve the development of volar locking compression plate osteosynthesis recent cadaveric studies demonstrated that cement augmentation improves biomechanical performance of volar plating of the distal radius [83] in order to avoid implant failure due to secondary loss of reduction and articular screw perforation (Figure 2).

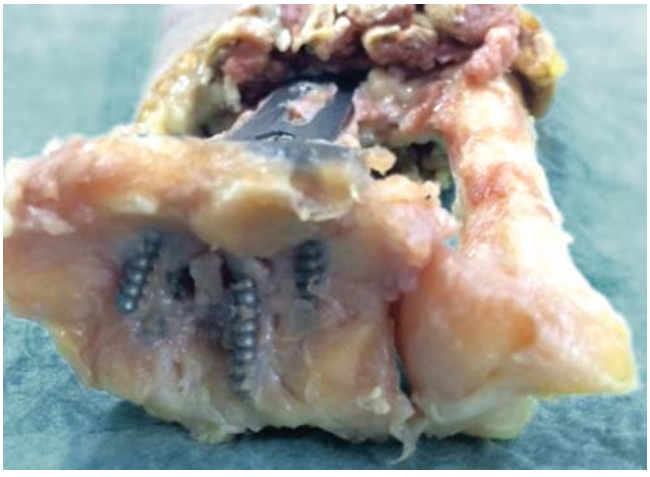

Fig. 2. Post mortem verified implant failure of an angle stable volar plate fixation in an osteoporotic distal radius AO/OTA type C fracture. Collapse of the fracture and articular perforation of the screws.

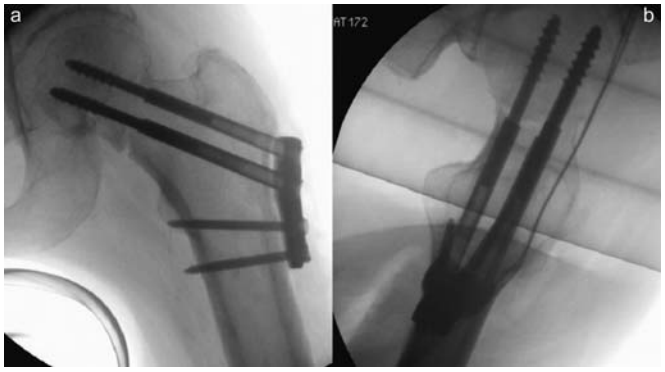

Fig. 3. Fixation of a Pauwels type III fracture of the femoral neck with a pin and plate construct (Targon, Aesculap). The plate provides angle stable support for the pins, an increased area of load support, while the screws can still slide and compact the fracture. (a: anterior-posterior and b: axial view).

Fragility fractures of the femur

Fractures around the hip have a high morbidity and mortality in the elderly population with up to 30% of patients dying within one year after surgery [84]. Proximal femoral fractures in the elderly are still increasing and are frequently associated with osteoporosis [85]. Intracapsular, undisplaced or impacted fractures are normally managed by internal fixation using modern angle stable multiple screw fixation systems (Figure 3) [48] or a dynamic hip screw (DHS). Although a major technical problem is secondary fracture impaction, the DHS allows this to occur along the axis of its screw. Accurate placement of the screw in the femoral head is best measured by the tip-apex distance and affects the performance of the device.

Particularly in osteoporotic bone the management of displaced extracapsular fractures is more controversial. The basic surgeons' choice is between prosthetic replacement, or open reduction and internal fixation. In general, age is not important but biological age with pre-injury mobility, residential status and cognitive function affect prognosis and are key factors for decision making. AO type 31 A1 and A2 fractures can be fixed by extramedullary as well as intramedullary osteosynthesis with no generalizable advantage for one or the other technique [86]. Unstable trochanteric and subtrochanteric fractures – especially AO/OTA type 31 A3 fractures – require open reduction and internal fixation. Although convincing clinical evidence still needs to be provided, it appears that cephalomedullary nails are preferable over extramedullary devices for these unstable fracture types [53,87]. Nevertheless, cephalomedullary nailing systems combine the biomechanical advantages of a sliding hip screw with those of intramedullary nailing. The sliding hip screw provides a controlled impaction of the fracture, leading to increased fracture stability, less collapse and decreased bone healing time. The intramedullary nail is located closer to the central weight bearing axis of the femur and thus reduces bending stresses by up to 30% due to shorter lever arm [88]. Mechanical implant breakage is a rare but relevant complication of cephalomedullary nailing systems especially in subtrochanteric or malreduced fractures with varus axis deviation of the proximal fragment, and is often a consequence of nonunion due to the effect of adverse shear forces [89,90].

Finally, in osteoporotic fractures of the distal femur, good radiological and functional results have been reported for the application of the anatomical angle stable plate osteosynthesis [91] but also with other angle stable fixation techniques [92].

Fragility fractures in the spine

Vertebral fractures in the elderly population constitute two different entities: traumatic fractures in osteoporotic bone and fragility fractures without adequate trauma. Vertebral fragility fractures are associated with relevant deterioration of vertebral biomechanical properties leading to the occurrence of subtle and often non-symptomatic wedge fracture. Indications for surgical intervention in osteoporotic patients are similar to non-osteoporotic patients and include radiculopathy, myelopathy, back pain, progressive spinal deformity with or without fracture, neurogenic claudication, and failure of conservative management [93]. Several surgical techniques have been developed to treat osteoporosis-related deformities, including posterior instrumentation with fusion [94]. Augmentation methods to improve pedicle screw fixation have evolved [95], including instrumentation at multiple levels, bioactive cement augmentation, and fenestrated or expandable pedicle screws, but their impact on clinical outcomes remains unknown.

Early mobilization is the key for improved outcome of patients with thoracolumbar fragility fractures. Surgical stabilization, including the use of bone cement, may be helpful in achieving this goal, although there is ongoing debate on the efficacy of this approach [96]. Options

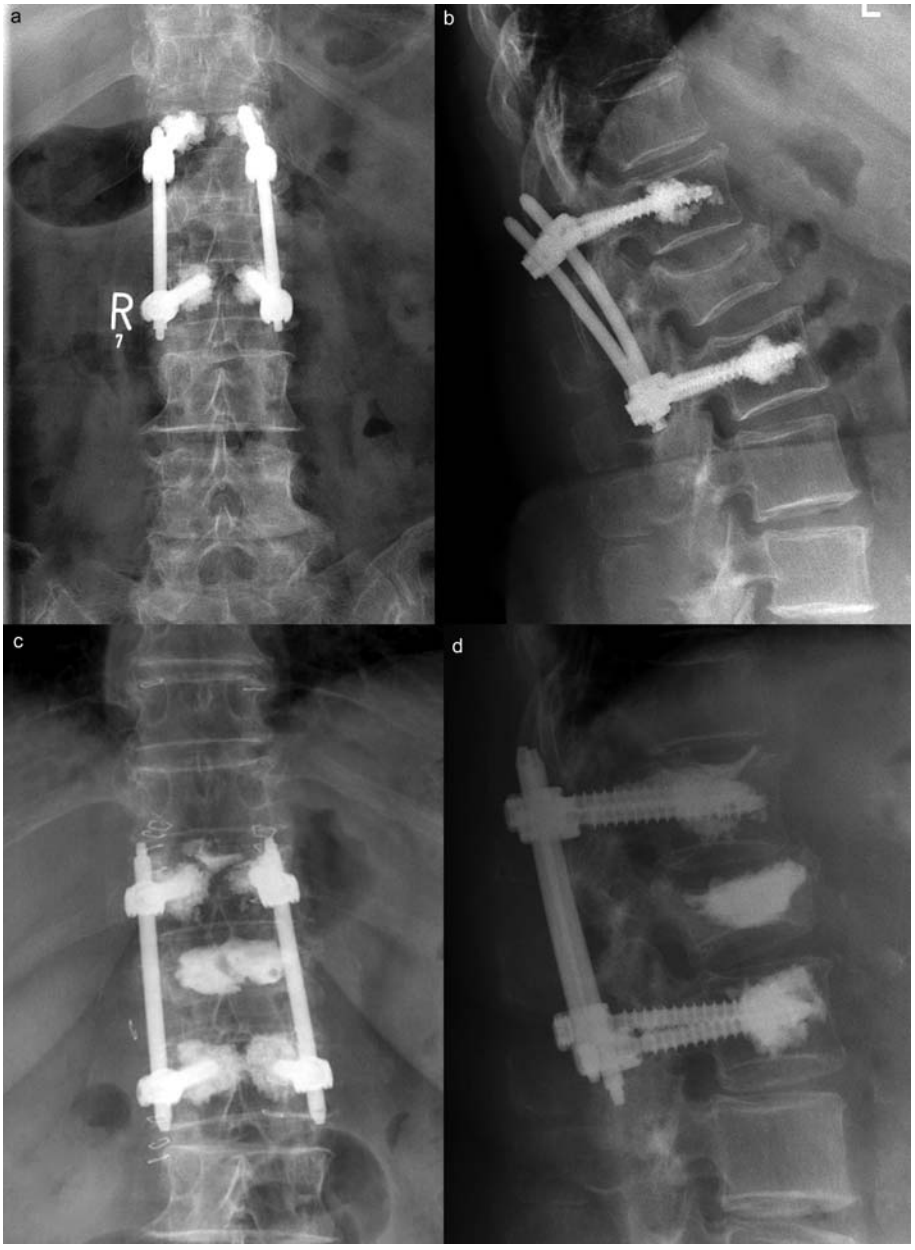

Fig. 4. Failure of fracture fixation of an osteoporotic AO/OTA type A3 of the first lumbar vertebrae (L1) in an 80-year-old female. Loss of reduction due to screw "cut-out." Fracture fixation by dorsal internal fixation combined with augmentation of the pedicle screws. (a,b) Revised situation after dorsal percutaneous cement augmentation (kyphoplasty) of the fractured vertebrae and dorsal reinstrumentation.

for cement augmentation include kyphoplasty and vertebroplasty. In many cases a permanent stabilization of the malalignment is not possible with cement augmentation alone, but requires additional dorsal instrumentation. The literature supports the use of vertebroplasty in conjunction with pedicle screw-based instrumentation (Figure 4) for treating more severe spinal deformities [97]. Anterior approaches may provide another way of treatment, but only few studies have been conducted on these implants in osteoporotic bone [97].

In odontoid fractures there is still an ongoing discussion whether they should be managed operatively or conservatively. In the management of geriatric odontoid fractures, nonsurgical support with a collar may be considered for the low-demand patient, whereas surgical fixation is favored for high-demand patients [96].

In conclusion, the therapy of fractures in osteoporotic bone primarily requires a multidisciplinary therapeutic acute care concept for the elderly including treatment of co-morbidities and correct choice, timing, and technique of the operative intervention. The primary aim of operative treatment in elderly individuals is the avoidance of immobilization of the patient. In individual cases conservative treatment might be required. Secondary therapeutic interventions involve early patient-related physical rehabilitation focused on fall prevention and osteoporosis treatment. Integration of patient' surrounding environment into this therapeutic concept is a mandatory precondition for successful therapy of fragility fractures. Generally, choice of treatment should be individualized and based on the evaluation of patient-specific, fracture-specific and surgeon-specific aspects.

Conflict of interest

The authors declare no conflict of interests.

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Bone mechanical properties and changes with osteoporosis

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ABSTRACT

This review will define the role of collagen and within-bone heterogeneity and elaborate the importance of trabecular and cortical architecture with regard to their effect on the mechanical strength of bone. For each of these factors, the changes seen with osteoporosis and ageing will be described and how they can compromise strength and eventually lead to bone fragility.

Introduction

Osteoporotic fractures occur spontaneously or as a result of minimal trauma from day-to-day activities [1]. In 90% of all hip fractures, the leading mechanism of trauma is a simple fall, [2–5] indicating bone fragility in these patients. Early detection of an impaired quality of bone is crucial in the prevention of osteoporotic fractures. Previous studies suggest broad under-diagnosis of osteoporosis [6], and the opportunity to start bone modulating therapies before the occurrence of an osteoporotic fracture is missed in up to 84% of osteoporotic fracture cases [7].

The assessment of bone mineral density (BMD) as a surrogate marker of bone strength using non-invasive methods like dual-energy X-ray absorptiometry is widely regarded as the gold-standard for diagnostic screening and as a guide prior to therapeutic decisions [8]. However, BMD accounts for only 60% of the variation in bone fragility [9], because it is unable to depict differences in bone material composition and structural design. Both characteristics influence bone strength to a large extent [10].

The unique mechanical properties of bone reflect the need to provide at the same time strength and lightweight design, stiffness and elasticity, the ability to resist deformation and to absorb energy [11]. This is possible because of the complex arrangements in compositional and micro-architectural characteristics of bone as well as continuous adjustments over time in response to dynamic extrinsic and intrinsic factors. Ageing and other factors like estrogen deficiency can affect these components and eventually result in decreased bone strength and fracture toughness [12]. Osteoporotic fractures, therefore, are the macroscopic result of a sequence of multiple nano- and micro-structural events.

This review will define the roles of (1) trabecular and cortical bone architecture, (2) structural and compositional heterogeneity in trabecular bone, and (3) alterations in collagen in determining mechanical integrity of bone. For each of these factors, the changes seen with osteoporosis and ageing will be described and how they can compromise strength and toughness, eventually lead to bone fragility.

Differences between trabecular and cortical bone

Macroscopically, the two most apparent structural features of bone are those of trabecular and cortical bone. Cortical bone forms a solid osseous shell around the bone and consists of dense and parallel, concentric, lamellar units – the osteons. Each is surrounded by a layer of cement-like substance, forming the so called cement line. The osteons are nurtured and interconnected by a system of Haversian and Volkmann's canals as well as canaliculi [11]. On its outer surface, cortical bone is covered by an envelope of connective tissue, the periosteum; and on its inner surface it is covered by the endosteum.

In contrast, trabecular bone shows a characteristic network of lamellar bone plates and rods that presents with less density, less homogeneity, and a lesser degree of parallel orientation. The trabecular

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bone is supplied by diffusion from the surrounding bone marrow; there are no vessels within trabeculae. Trabecular bone is always surrounded by a cortical bone but the thickness and strength of the cortical shell depends on location. Long bones, for example, show a higher cortex-to-trabecular bone volume ratio than vertebrae and the diaphyseal areas of long bones show a higher cortex-to-trabecular bone ratio than the metaphyseal areas [10].

Cortical bone is stiffer and able to resist higher ultimate stresses than trabecular bone, but it is also more brittle [10,13,14]. Trabecular bone *in vitro* can withstand strains up to 30%, cortical bone fails with strains of only 2%. While the biomechanical behaviour of cortical bone is rather uniform, trabecular bone shows a wide variability in strength and stiffness. This variability to the largest part depends on the trabecular bone's apparent density. Due to its heterogeneity, the apparent density and thus the trabecular bone modulus can vary 100-fold from one location to another within the same metaphysis [14].

Besides apparent density, stiffness and strength of cortical and trabecular bone depend on the loading direction, indicating its anisotropic microstructure [10,15,16]. In general, bone can resist to higher compression loads than tension loads and to higher tension loads than shear loads [15,16]. In line with this, the trabecular connectivity inside a bone – as a measure of anisotropy – contributes more to the bone's biomechanical strength than the trabecular thickness or the bone mineral density [17].

The mechanical response to loading, differs widely between cortical and trabecular bone. Cortical bone, for instance, shows small load carrying capacity when loaded beyond its range of elastic deformation (post-yield) both with tensile and compression loads [10,14]. In contrast, the load carrying capacity of trabecular bone is insignificant after tensile fracture, but even larger than for cortical bone after compressive fracture [14,18].

Each bone's location in the body and the forces acting on it determine its characteristic microstructure and composition. For example, vertebral bodies must resist high and repetitive axial compression loads but experience much less shear or tension loads. If the trabecular bone is removed from a vertebral body, this leads to increased cortical shell stresses and a disproportionate decrease in the vertebral bone's ability to withstand compression forces [19].

The femoral neck or the proximal humerus, on the other hand, is mainly subjected to shear forces and bending moments, the latter of which create a combination of compression, tension, and shear. Both show a distinct cortical structure. There is only little change in the biomechanical strength if the trabecular components are removed from a proximal femur [20], but any reduction in cortical thickness or change in cortical shape can increase the risk for sustaining a hip fracture [21] or a proximal humerus fracture [22].

In vivo, bone experiences different loads from different directions and in different intensity and frequency over time. Bone has two main structural responses to changing loading patterns: altering structural density and increasing the degree of structural orientation along the acting force vectors, i.e. anisotropy [10,14].

These adaptive responses would not be possible without the existence of continuous bone remodelling. In bone remodelling, bone tissue is removed by osteoclastic resorption and new bone is formed by osteoblasts. In the early life span after skeletal maturity the amounts of bone removed and replaced with each cycle of bone remodelling are usually equal to each other, leaving the total volume of bone unchanged. With ageing and in the setting of osteoporosis, the balance of bone resorption and formation becomes negative. The bone loss in aged and osteoporotic bone is a consequence of imbalanced and excessive bone remodelling [11].

As bone remodelling occurs on osseous surfaces, osteoporotic bone loss is a function of surface available for bone remodelling [23]. In individuals less than 65 years of age, the largest surface available for bone remodelling is the trabecular bone. In this population, trabecular bone – due to its lesser density when compared to cortical bone – provides only about 20% of the skeletal bone mass but it is responsible for most of the turnover [10,13]. Thus, the bone loss in early osteoporosis is mainly a trabecular bone loss. With increasing age, the cortical bone becomes more and more porous and, therefore, its endocortical surface increases (Figure 1). As a consequence, the largest loss of absolute bone mass due to osteoporosis occurs in cortical bone by intracortical rather than endocortical or trabecular remodelling [23].

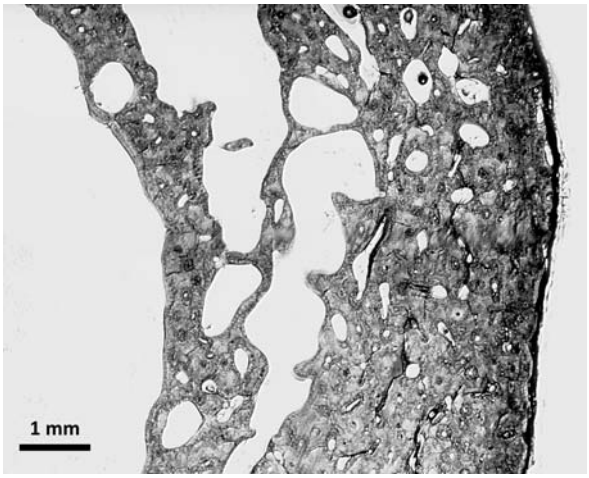

Fig. 1. Cortical bone trabecularization Trabecularization of cortical bone at the endocortical aspect of the cortex. Light microscopy of a quadrant of a female (age 91 years) femoral cortex at midshaft level.

The transition from early trabecular to later cortical bone loss is consistent with the epidemiological data on osteoporotic fractures. Vertebral compression fractures, being "trabecular fractures", are more common in individuals aged less than 65 years [24]. With increasing cortical bone loss after the age of 65 years, hip fractures, being rather "cortical fractures", become more frequent (Figure 2).

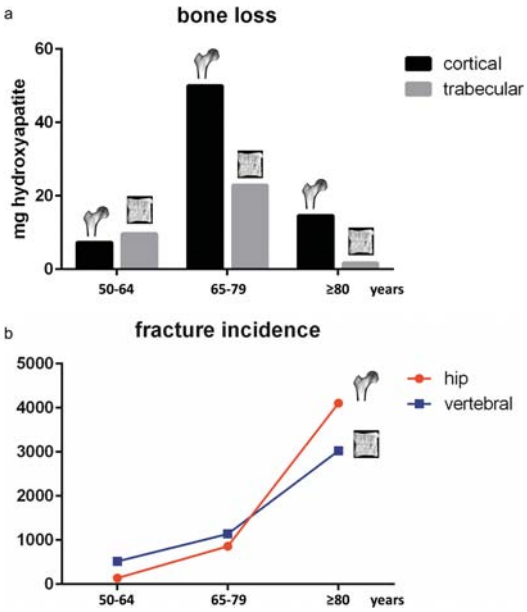

Fig. 2. Association between bone loss and fracture incidence (a) Cortical and trabecular bone loss in different age groups as shown by Zebaze et al. [20]. Early bone loss occurs in the trabecular bone, but with increasing age the bone loss becomes mainly cortical. (b) Incidence of osteoporotic hip and vertebral compression fractures in different age groups in Switzerland as shown by Svedbom et al. [21]. Vertebral compression fractures are more common in individuals aged less than 65 years. With increasing cortical bone loss after the age of 65 years, hip fractures become the most frequent entity.

The knowledge about these differences between trabecular and cortical bone and the changes of their relation due to ageing has multiple potential implications for the understanding and treatment of osteoporotic fractures. It might be advantageous to apply anti-resorptive or anabolic medication regimens that aim for modification of trabecular bone remodelling in younger patients and for modification of cortical bone remodelling in the elderly. When a fracture has occurred, different surgical approaches might be favourable that either address the "trabecular" or "cortical" character of the bone that is fractured. Bone cement, for instance, which is strong in compression and weak in shear and tension forces, is an excellent adjunct tool in the treatment of osteoporotic vertebral or even metaphyseal "trabecular fractures" [25,26]. In proximal humeral or femoral "cortical fractures," in contrast, a focus on cortical alignment is of more importance and the use of additional support by cortical grafts might be beneficial [27,28].

Changes in trabecular bone with osteoporosis and aging

Structural heterogeneity

Even a cursory examination of anatomic sites with high risk of osteoporotic fracture reveals that bone density and microstructure are not uniform throughout the trabecular compartment. This regional heterogeneity in density and microstructure is common knowledge for the proximal femur: Ward's triangle is the region of low density between the femoral neck and greater trochanter, and the primary compressive group is the region of high density and strong microstructural alignment in the femoral head and neck (Figure 3).

Density and microstructure are also not uniform throughout the vertebral centrum. Volume fraction and bone mineral density are highest in the regions of the centrum closest to the endplates and in the posterio-lateral regions [29–34]. Trabecular separation (Tb.Sp.*) and degree of anisotropy are highest in the middle and anterior regions of the centrum [33–36]. The relatively low density and high degree of anisotropy in the anterior region has been suggested as a primary cause of the high proportion of anterior wedge fractures among vertebral fractures [37,38]. In addition, the spatial variations in density and architecture throughout the vertebra change with age [30,35] and with degeneration of the intervertebral disc [38,39]. Within the population, bone loss occurs with age at a higher rate on average in the regions near the endplates than in the central regions — resulting in a more uniform density distribution — but the data also show that in many elderly individuals, the density distribution remains highly non-uniform [35,37].

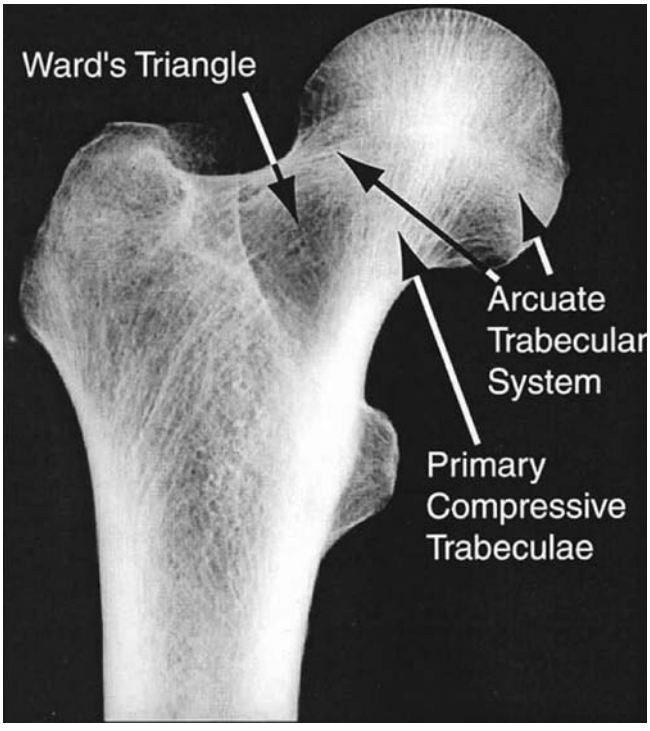

Fig. 3. Radiographic frontal view of the proximal femur. Courtesy of Dennis Carter.

The heterogeneity in density and architecture throughout bones such as the femur and vertebra have been proposed [40–43] as a major reason why the average BMD of the bone explains only ~60% of the variation in whole-bone strength. Biomechanical studies support the hypothesis that heterogeneity is important for mechanical strength. An early study using finite element modeling of the femur found that increases in bone density in a fairly small region (~5 cm^3) at the femoral neck could produce a relatively greater increase in bone strength as compared to a uniform increase throughout the entire bone [44]. Studies in the vertebra have found that the compressive failure properties of the vertebra in both static and fatigue loading conditions were predicted better by measures of density from one or several sub-regions of the centrum as compared to average density of the entire centrum [40,41].

However, the literature on the mechanisms by which regional variations in density and microstructure affect bone strength is mixed. Studies of excised specimens of trabecular bone have found that failure in compression initiates in regions of low local volume fraction [45] and that larger intra-specimen variations in trabecular thickness and tissue properties are associated with lower apparent elastic moduli [46,47]. Supporting these findings, Snyder and colleagues have reported that estimating the weakest cross-section of the vertebral body provides good predictions of vertebral strength [48,49] and fracture risk [50]. A study on a small sample of human vertebrae also reported that increased heterogeneity in volume fraction in the centrum was associated with decreased compressive strength [51]. In contrast, more recent studies have found that, increased intravertebral heterogeneity in density is associated with *increased* vertebral strength [52].

Ideally, the measures of heterogeneity that will emerge are those that have biomechanical underpinnings. For example, increased intravertebral heterogeneity may confer higher vertebral strength if this heterogeneity arises from the existence of regions of high density that are strategically placed in a centrum that is otherwise of low average density. In other words, larger structural heterogeneity could be advantageous if the particular spatial distribution of bone density matches the way that load is distributed throughout the vertebral body. Prior measurements have shown that in erect spinal postures, less than half of the total load applied to the vertebral body is distributed over the anterior half, and that this fraction decreases with age [53]. Vertebral bodies with higher density posteriorly than anteriorly would be expected to exhibit higher strength under this type of load distribution, as has been shown [52]. In addition, a prevailing hypothesis has emerged that degeneration of the intervertebral disc results in transfer of more of the applied load to the outer regions of the vertebral body, thus causing resorption in the central and mid-transverse regions [54]. Vertebrae that have undergone this adaptation may thus be less likely to fracture [53].

Even considering regional variations in density and microstructure within small but critical areas of the vertebral body may provide further insight into the mechanisms of fracture. For example, collapse of the superior endplate has long been associated with vertebral fracture, and this collapse initiates in and propagates to regions overlying trabecular bone of low density and mechanically inferior microstructure [55] (Figure 4).

In summary, large amounts of heterogeneity in density and microstructure exist throughout the trabecular compartment of the bones with high prevalence of osteoporotic fracture. Substantial

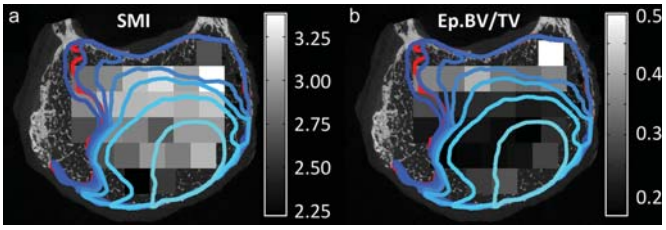

Fig. 4. Bone heterogeneity and vertebral endplate collapse Regions of endplate collapse (outlined in blue and red) and distribution of structure model index (SMI) in the trabecular bone directly underlying the endplate (grayscale): The lightest blue outline corresponds to the loading increment at which endplate collapse clearly initiated. The boundaries at subsequent loading increments are represented with progressively darker shades of blue. The red outline corresponds to the region of endplate collapse that remained after loading was complete and all load was removed. Modified from Jackman et al. [52].

evidence exists that this heterogeneity has important biomechanical consequences, but further work is required to establish mechanisms and clinical implementation of these insights.

Tissue heterogeneity

Changes in tissue composition and mechanical properties at the material/tissue level (lamellae, individual trabeculae) likely contribute to fracture risk, but up until recently these changes have been less well understood. A number of studies have sought to address this, using a combination of mechanical testing (nano-indentation, micro-mechanical testing) [56–60] and compositional analyses at the tissue level [57–59,61–64], and their findings regarding changes in tissue properties and composition during osteoporosis are conflicting. It has been reported for example that trabecular bone tissue from the proximal femur of ovariectomized sheep (12 months post-surgery) had a lower tissue modulus, as measured by nano-indentation, compared to age matched controls [56,57]. These changes were associated with a decrease in mineral content in the osteoporotic trabecular bone tissue [57,62]. Interestingly, the differences were not maintained 31 months post-surgery [57]. In contrast, micro-tensile testing showed that the stiffness and strength of ovariectomized rat trabeculae was increased by 40–90% by 54 weeks post-ovariectomy [58,59]. These increases were associated with a significant increase (11%) in the mineral content of these trabeculae, although overall bone mineral density and mass were reduced [58,59]. It has also been reported that increased calcium content and stiffness occur within individual trabeculae from human osteoporotic bone [64,65].

Variations in experimental methods, animal model or the anatomical location from which bone was chosen for analysis might explain the discrepancies between previous studies. For example decreased trabecular stiffness was reported based on nanoindentation of trabeculae from the anteromedial region of the proximal femur of the ovariectomized sheep [56,57], whereas increased trabecular stiffness was based on micro-tensile testing of trabeculae from a region below the growth plate of the tibia of ovariectomized rat bones [58,59]. Nanoindentation characterises the mechanical properties (elastic modulus, hardness) of nanometer areas of bone tissue (typically within individual lamellae), whereas micro-tensile testing assesses the mechanical behaviour of entire trabeculae. Therefore, to understand these discrepancies further a recent study sought to distinguish (1) the spatial distribution of mineral within different lamellae across individual trabeculae and (2) the variation in trabecular mineralisation in different anatomical regions of the proximal femur following the onset of estrogen deficiency [66]. Mineral content (wt% Ca) was determined using a quantitative backscattered scanning electron microscopy approach, for individual trabeculae harvested from the proximal femur of ovariectomized sheep (12 months post-OVX) and age-matched controls. It was found that the difference in mineralization between the superficial and deep lamellae of trabeculae was more pronounced in ovariectomized sheep (Figure 5), representing an increase in mineral heterogeneity of approximately 13%, compared to trabeculae from aged matched controls [66]. Moreover

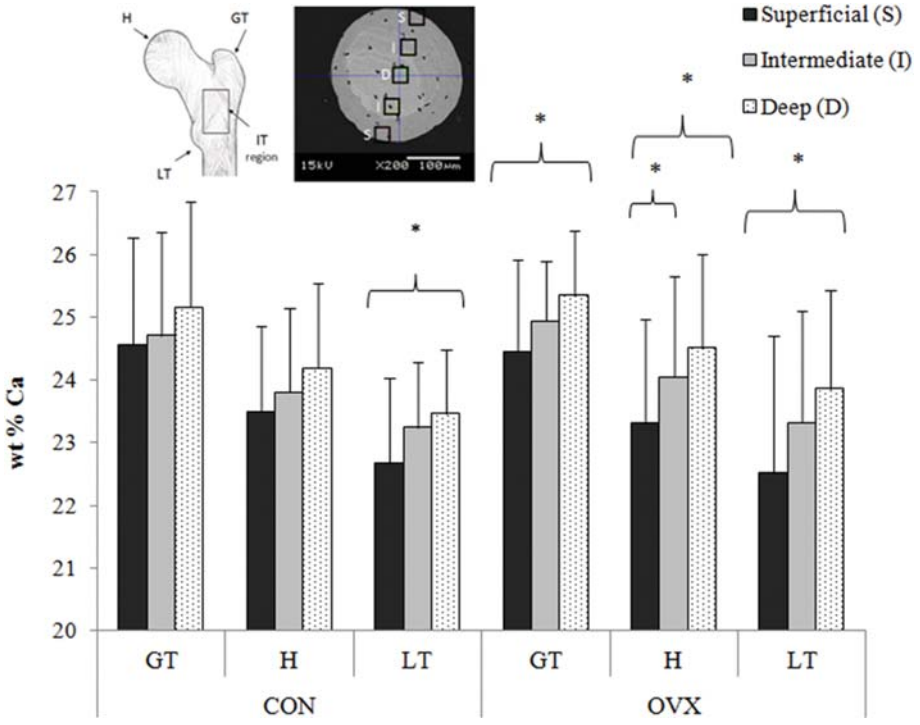

Fig. 5. Trabecular mineralization in estrogen deficiency Spatial distribution of calcium (wt% Ca) between superficial, intermediate, and deep lamellae in the greater trochanter (GT), head (H) and lesser trochanter (LT) regions of the proximal femur from 12 month ovariectomized sheep (OVX) and aged matched controls (CON). * indicates statistical significance between trabecular regions indicated by brackets ($p \leq 0.02$). Figure adapted and data from [64].

the distribution of bone mineral was shown to be dependent on anatomical location within the proximal femur, with a higher variability of mineralization between the greater and lesser trochanter regions of ovariectomized sheep (Figure 5), which coincides with the intertrochanteric fracture line [66]. These findings were undetectable by focusing solely on bone mineral density and are corroborated by studies of human osteoporotic trabeculae [64,67].

Rapid increases in bone resorption by osteoclasts occur at the onset of osteoporosis but abate over time. As such the disparity between different studies might also relate to the extent of disease progression, the timing of which likely varies between animal models and human bone. A recent study sought to understand how trabecular tissue mineralization is altered over prolonged estrogen depletion and compared this to normal age-related changes in trabecular bone tissue composition [68]. Bone mineral density distribution parameters were compared in trabeculae from the proximal femora of ovariectomized sheep that underwent estrogen deficiency for 12 or 31 months and age-matched controls. It was reported that normal ageing increases mean mineralization and mineral heterogeneity at a trabecular level and that these differences arise due to an increase in the mineralisation of the deep lamellae of the trabeculae with ageing (Figure 6). However, prolonged estrogen deficiency (31 months) leads to significantly decreased mean mineralization compared to trabeculae from both aged matched controls and a shorter duration of estrogen deficiency (12 months) (compare with Figure 5). Increased rates of bone turnover during estrogen deficiency could explain this lower mean mineralization. However, reductions in mineralization were non-uniform within the proximal femur [68]. The underlying mechanisms by which trabecular mineral heterogeneity is altered during osteoporosis might be due to hypermineralized osteocyte lacunae in osteoporotic trabecular bone and an increased bone turnover [69]. Additionally, this variability might be related to local variations in the mechanical environment, which might lead to alterations in tissue mineral content at those regions regulated by mechanosensitive bone cells [69]. Together these recent studies [66,68] reveal the importance of duration and anatomical location in assessing the effects of estrogen deficiency on trabecular bone mineralization and may explain discrepancies regarding the effect of estrogen deficiency between previous studies.

In summary, it is becoming increasingly clear that, even though overall trabecular bone mass and strength are reduced during osteoporosis, the scarce trabecular tissue that remains is more heterogeneous, with regions of trabecular tissue that are more mineralized, stiffer and stronger. It would also appear that these changes are a transient and site-specific characteristic of osteoporosis, whereby the trabecular tissue properties are altered varyingly as the disease progresses.

Changes in cortical bone with aging and osteoporosis

The biomechanical competence of a bone is determined by the amount and quality of bone material and even more importantly by the arrangement of the material in space. Geometrical measures including bone size, cross-sectional area or area moment of inertia explain up to 80% of the biomechanical competence of whole bones. For the distal radius, the best predictors of fracture load were measures of cortical bone mass, cortical area and cortical width [70]. For the proximal femur cortical area, size of the femoral neck and area moment of inertia were the strongest predictors of fracture load [70]. The combination of individual parameters in multiple regression models has provided further evidence that geometrical measurements considerably improve the prediction of bone strength beyond measurement of

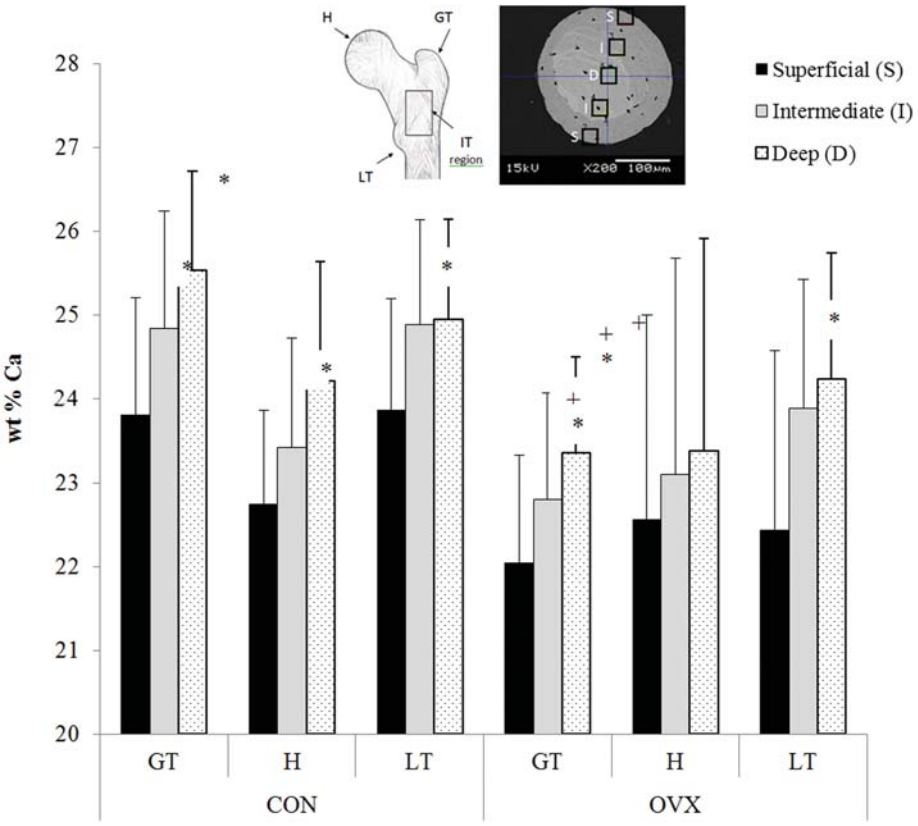

Fig. 6. Trabecular mineralization in prolonged estrogen deficiency Spatial distribution of calcium (wt% Ca) between superficial, intermediate, and deep lamellae in the greater trochanter (GT), head (H) and lesser trochanter (LT) regions of the proximal femur from 31 month ovariectomized sheep (OVX) and aged matched controls (CON). * indicates significantly different to deep lamellae within the same femoral region of the indicated group. + indicates significant difference to the same ROI of the CON group. Data from [65].

bone mineral density [71]. Consequently it has been found that fracture risk in patients is associated with certain geometrical features such as local thinning of cortical bone [72].

Furthermore, the mechanical competence of cortical bone strongly depends on its porosity. Cortical bone tissue is composed of osteons and interstitial bone. The longitudinally oriented Haversian canals and the perpendicular Volkmann canals perforate the cortical bone matrix. Towards the endocortical bone surface Haversian canals can unite and also connect with the intramedullary cavity. The Haversian canals and the resorption cavities produce a porous bone tissue with pore diameters ranging from a few up to several hundred micrometers. The number and size of the pores determine intracortical porosity and bone mineral density (Figure 7). With increasing pore size the mechanical properties of cortical bone considerably degrade. Thus porosity accounts for about 70% of elastic modulus and 55% of yield stress of cortical bone [73]. Accordingly, fracture toughness also decreases significantly with increasing porosity possibly by reducing the available area for the propagation of microcracks [74].

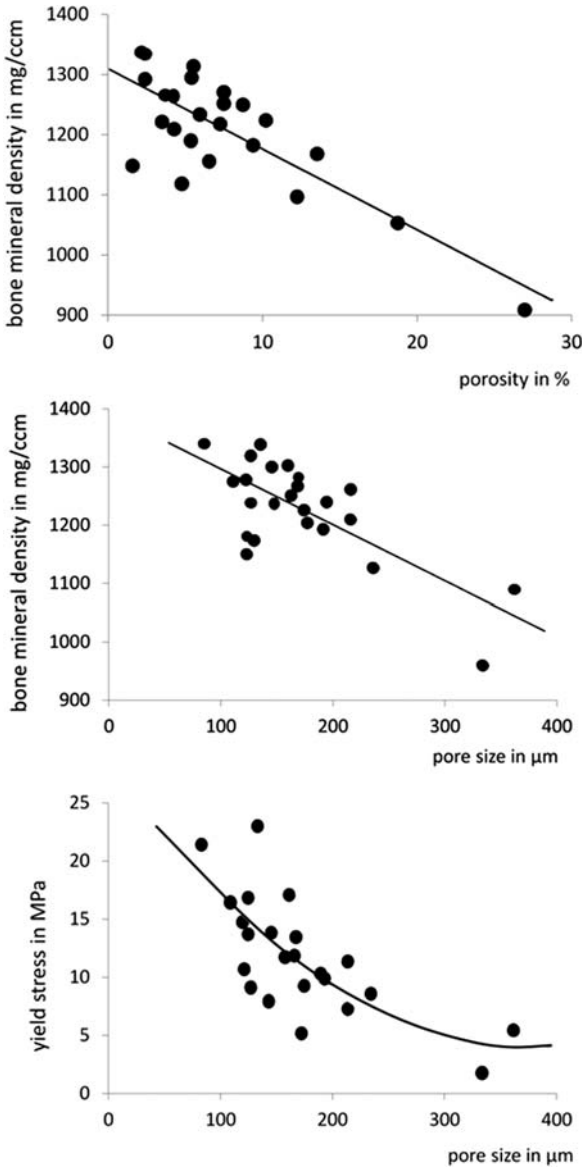

Fig. 7. Cortical bone porosity and mechanical strength Relationships among bone mineral density, and pore size in cortical bone and mechanical strength assessed by yield stress. Data from [4,6]

Age-related degradation of mechanical competence of bone appears to be more pronounced for mechanical properties associated with failure than for those associated with stiffness. Energy absorption, fracture toughness and ultimate tensile strain show age-related decrease of about 5–10% per decade, while elastic moduli in tension or compression degrade by only about 2% per decade [12]. It appears, therefore, that the relationship between failure properties and stiffness properties changes with increasing tissue maturity. This makes the accurate prediction of fracture risk even more difficult. Fracture risk prediction largely relies on non-invasive image assessment and the measurement of mineral density. However, while bone mineral density is closely related to stiffness properties of bones its association with failure strength or toughness is less pronounced.

Changes in bone's mechanical competence are explained by functional adaptation of bone structure and age-related deterioration of intrinsic mechanical properties both being directly related to bone remodeling. When bone remodeling is suppressed, the ratio of highly mineralized to new, less mineralized bone tissue is increased resulting in an increase in the homogeneity of cortical bone tissue. A more homogenous tissue allows cracks to grow more easily and thus reduces the toughness of the composite material. Furthermore, remodeling reduces the regional variability of collagen fiber orientation, leading to changes in mechanical properties. It has been shown that the collagen network itself experiences up to 50% loss in its capability to absorb energy during ageing probably because of an increase in the percentage of denatured collagen [75]. With increasing age, the degree of mineralization increases, which is reflected in an increase in mineral content of cortical bone tissue. As micro-damage in cortical bone accumulates with increasing age, there is a concomitant progressive increase in micro-crack density [76]. After the age of 50, micro-cracks accumulate in cortical bone and this occurs much more quickly in women than in men.

But not only cortical bone material changes with age, bone geometry also adapts to a modified mechanical environment. In essence, both the outer and inner diameter of the cortex increases while the thickness of the cortex is reduced [77]. In addition, the porosity of the cortex increases with age and results in a dramatic increase of the intracortical bone surface. The increase in porosity results from coalescence of Haversian channels within the cortex and from fragmentation of the endocortical bone surface. The remaining cortical remnants have similarity to trabecular bone and can be described by trabecularization of the endocortical bone (Figure 1). The porosity in cortical bone increases from about 4% in young healthy bone to around 12% at age 60 years [14] and up to almost 50% in very elderly individuals [23]. The increasing surface area of the cortical bone provides more surface to receive signals for remodeling to be initiated and thus further accelerates cortical bone loss with age. In fact, most of the trabecular appearing bone is likely to be trabecularized cortical bone fragments [78]. While at early ages bone loss dominates at trabecular sites, with increasing age bone is primarily lost in the cortex of peripheral bones. Fifty percent of the bone loss occurs at the endocortical aspect of cortical bone, thinning the cortex and leaving trabecular like cortical fragments [23].

The adaptive changes of cortical bone tissue with age are largely site-dependent. In the femoral neck bone loss is lowest in inferior regions that bear the largest loads during normal gait, whereas regions at the superior aspect which are less loaded undergo thinning of the cortex by endocortical absorption. These regions with reduced thickness however, experience highest stresses during falling and are more likely to fracture at advanced age. In the femoral shaft, a similar mechanism has been reported long ago [79]. In the distal forearm, the age-related adaptation is reflected in endosteal absorption together with periosteal apposition, increasing the area moment of inertia and thus preserving bone rigidity and strength [80] to some extent. Although this adaptive response has been observed in both women and men, it appears to be more effective in men.

Although the crucial role of cortical bone for the mechanical competence of bone and the risk of fracture has been recognized it has not really been transferred to clinical practice for fracture risk assessment or for monitoring of osteoporosis treatment. Future clinical imaging techniques will have to consider measures cortical bone geometrical features and also its local porosity.

The role of collagen

The matrix of bone is composed of both inorganic (i.e. mineral) and organic (i.e. water, collagen, and non-collagenous proteins) components. The role of mineral composition in skeletal fragility has been studied in depth, and it is generally understood that in normal bone, the mineral content provides strength and stiffness [81]. There is less known about the effect of collagen and non-collagenous proteins, but there is increasing evidence suggesting that changes in protein content and structure play important roles in age- and disease-related changes in bone. In particular, the organic matrix is considered to be responsible for bone's ductility and its ability to absorb energy prior to fracturing [82].

Ninety percent of bone's organic matrix is composed of type I collagen, a structural protein comprised of three polypeptide chains with a defined amino acid sequence, glycine-X-hydroxyproline or glycine-proline-X (X is an amino acid such as lysine). This particular sequence of amino acids allows the polypeptide chains to twist into a triple helical structure with the small glycine in the middle, and amino acids that remain exposed on the surface of the triple helix are involved in the formation of collagen crosslinks [83]. Collagen undergoes numerous post-translational modifications with aging and disease, including both enzymatic and non-enzymatic crosslinking. In general, enzymatic crosslinking is considered to be a normal process for healthy collagen and has a beneficial effect on its mechanical properties, while non-enzymatic crosslinking results in a brittle collagen network that leads to deteriorated bone mechanical properties if its accumulation exceeds normal repair [84].

Enzymatic crosslinking requires the enzyme lysyl oxidase to aid the formation of intra- or inter-fibrillar crosslinks such as pyridinoline and deoxypyridinoline [85]. The lysine-based crosslinks form in the overlap regions of fibrils in a head-to-tail fashion (Figure 8) [86]. In the maturation process, bivalent crosslinks slowly transform into a more stable, trivalent, non-reducible conformation. Mature crosslinks accumulate, inhibit collagen fibril remodeling, increase the stiffness of the fibril, and provide increased strength to the tissue [86,87]. Pyridinoline and deoxypyridinoline serve as markers of bone resorption and are indicators of collagen maturity [88]. Enzymatic crosslinks are most reliably quantified and characterized with mass spectrometry [89] or HPLC (high performance liquid chromatography) [90], but some studies indicate that FTIR (Fourier transform infrared) spectroscopy can illustrate collagen crosslink characteristics [91]. Using these methods, enzymatic crosslinks have been shown to be reduced in osteoporotic patients with hip fractures compared to healthy controls [92,93].

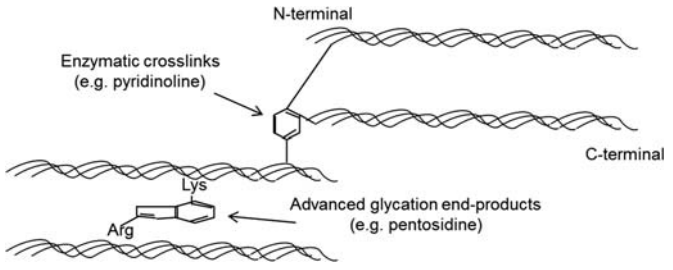

Fig. 8. Collagen cross-links A schematic illustration of enzymatic crosslinks (e.g. pyridinoline [PYD], deoxypyridinoline [DPD]) and non-enzymatic crosslinks (e.g. pentosidine [PEN]) at the molecular level.

The second pathway for collagen crosslinking does not involve any enzymes, and is termed non-enzymatic glycation. Unlike the enzymatic crosslinks, which link the ends of the collagen molecules, non-enzymatic crosslinks are found at any position along the collagen. Non-enzymatic glycation involves a reaction between an aldehyde group of a sugar (e.g. glucose) and the ε-amino group of hydroxylysine or lysine. This reaction results in the formation of glucosyl-lysine, which undergoes further reactions to form an Amadori product or Schiff base adduct. Both of these intermediate products undergo additional reactions to create crosslinks that form within and across collagen fibers and are known as advanced glycation end-products (AGEs) [86], which have been shown to accumulate in numerous tissues including skin, cartilage, tendons, and bone [94]. AGEs accumulate with age and disease [85]. Specifically, osteoporotic bone has significantly more AGEs than normal healthy bone [92,93]. The increased AGE levels can result in brittleness of tissues undergoing non-enzymatic glycation [95].

There are two methods used for quantifying AGEs in bone, and these techniques incorporate measurement of the autofluorescence emitted by most AGEs. One technique quantifies pentosidine, a single AGE crosslink and the only non-enzymatic crosslink that has been successfully isolated and quantified in bone, using HPLC [96]. As pentosidine composes less than 1% of total fluorescent AGEs in bone and is weakly correlated to the amount of total fluorescent AGEs in human bone [83,97], it is valuable to measure total fluorescent AGEs in addition to pentosidine content. The second technique quantifies the bulk fluorescence of AGEs from enzyme-digested or acid-hydrolyzed bone samples relative to a quinine sulfate standard [98], and the amount of fluorescence is normalized to collagen content. Wavelengths used in this fluorometric assay capture the excitation and emission wavelengths of several major AGE crosslinks including pentosidine, carboxymethyllysine, vesperlysines, crossline, and carboxyethyllysine [83], and thus, the relative contributions of each of these crosslinks to the total fluorescence cannot be determined from this assay.

Increased non-enzymatic glycation has been shown to reduce mechanical strength and/or toughness of bone [99,100]. Glycation levels have also been shown to be greater in cadaver specimens from hip fracture patients compared to controls, and the glycation content was correlated with several biomechanical properties in cancellous bone, but *not* in cortical bone [92,93]. Although it is generally understood that AGEs accumulate in bone, stiffen the collagen matrix, and in turn, deteriorate bone's mechanical properties, the contradictions in current literature arise for a number of reasons: (1) few *in vitro* glycation studies have been conducted, and most *in vitro* studies have been primarily conducted in cancellous bone, (2) studies conducted on *in vivo* glycation levels report pentosidine content only while a few studies report total AGEs, making the studies difficult to compare, (3) range of values for glycation levels reported vary greatly depending on the bone, location, and age range of specimens used, and (4) various mechanical testing techniques, animal models, or disease states have been used in these studies. Thus, the exact contribution of AGEs to age-related skeletal fragility remains undefined.

There is increasing evidence that AGEs directly affect cellular function through the receptor for AGE (RAGE), a surface receptor on many cell types [101]. RAGE activation is associated with inflammation, cellular dysfunction, and localized tissue destruction. In bone, activation of the RAGE receptor inhibits osteoblast proliferation and differentiation [102], reduces matrix production [103], reduces bone formation [104] and increases osteoblast apoptosis [105]. This indicates that crosslinking properties of the matrix not only alter the tissue properties, but directly control cellular function and may play an important role in the decreased bone formation found in osteoporosis [106].

In addition to enzymatic and non-enzymatic modifications of collagen, non-collagenous proteins (e.g. osteopontin, osteocalcin),

which compose 10% of bone's organic matrix, also may affect bone mechanical properties. Osteocalcin stimulates mineral maturation, inhibits bone formation, recruits osteoclast precursors to bone resorption sites, and helps with their differentiation into mature osteoclasts [107]. Osteopontin plays a role in mineralization and assists the bone resorption process by anchoring osteoclasts to the mineral matrix of the bone surface [88]. More importantly, these proteins have been recently considered to act as the glue that holds mineralized collagen fibers together. When a force is applied, these components stretch, help dissipate energy by breaking sacrificial bonds between adjacent collagen fibrils, and prevent harmful crack formation and propagation [108]. Thus, alterations to the matrix composition of both collagenous *and* non-collagenous proteins may alter bone biomechanical properties. Increased serum osteocalcin and osteopontin has been reported in postmenopausal women with osteoporosis compared to healthy controls [109,110].

In summary, there is increasing evidence of the role of bone's organic matrix on age- and disease-related changes in bone's mechanical properties. Enzymatic crosslinking of collagen is generally considered to have a positive effect on bone's mechanical properties, while non-enzymatic crosslinking can lead to deteriorated bone mechanical properties with aging and disease. Non-collagenous proteins play a role in the prevention of harmful microdamage formation. Though osteoporosis is generally defined as a loss of bone mass, there are considerable matrix changes, particularly in collagen crosslinks, which cause a loss of bone quality.

Conclusions

The bone's inorganic and organic composition, its trabecular and cortical nano-, micro-, and macroscopic architecture, and the heterogeneity of these structural features all have impact on age- and disease-related changes in bone's mechanical properties. Though osteoporosis is generally defined as a loss of bone mass, there are considerable changes of the structure and matrix itself, which can cause a loss of bone quality.

It is known, that cortical bone plays a major role in determining the mechanical competence of bone and the risk of fracture; the age-related alterations of its geometrical features and its local porosity, though, have long been poorly understood and underestimated. The number of trabeculae in trabecular bone, trabecular thickness and the degree of connectivity all influence the mechanical strength of a bone. In osteoporosis a decrease of all these characteristics is seen. Especially in bones with increased risk for osteoporotic fractures, however, the remaining trabecular tissue is largely heterogeneous, with regions of different mineralization, stiffness and strength.

Both, the trabecular and the cortical component undergo different changes at different times. Bone remodelling occurs on osseous surfaces and, thus, osteoporotic bone loss is a function of surface available for bone remodelling. The bone loss in early osteoporosis is mainly trabecular and with increasing age the bone loss becomes primarily endo- and intracortical.

The knowledge about this evolution in matrix and structure in osteoporotic bone and about the differences between trabecular and cortical bone could help with predicting, avoiding and treating osteoporotic fractures. Future clinical imaging techniques will have to consider structural measures of cortical and trabecular bone rather than focusing on bone mineral density alone. In prophylactic treatment regimens, the aimed for therapeutic region (i.e. trabecular versus cortical) and mechanisms of action within the cascade of bone remodelling might have to be chosen according to the patient's age and the individual advancement of bone changes. Eventually, when a fracture has occurred, the non-operative or surgical treatment has to be guided by both: the personality of a patient and the personality of their bone.

Conflict of interest

The authors report no conflict of interest related to the content of the manuscript.

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Fracture healing in osteoporotic bone

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KEYWORDS

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ABSTRACT

As the world population rises, osteoporotic fracture is an emerging global threat to the well-being of elderly patients. The process of fracture healing by intramembranous ossification or/and endochondral ossification involve many well-orchestrated events including the signaling, recruitment and differentiation of mesenchymal stem cells (MSCs) during the early phase; formation of a hard callus and extracellular matrix, angiogenesis and revascularization during the mid-phase; and finally callus remodeling at the late phase of fracture healing.

Through clinical and animal research, many of these factors are shown to be impaired in osteoporotic bone. Animal studies related to post-menopausal estrogen deficient osteoporosis (type I) have shown healing to be prolonged with decreased levels of MSCs and decreased levels of angiogenesis. Moreover, the expression of estrogen receptor (ER) was shown to be delayed in ovariectomy-induced osteoporotic fracture. This might be related to the observed difference in mechanical sensitivity between normal and osteoporotic bones, which requires further experiments to elucidate.

In mice fracture models related to senile osteoporosis (type II), it was observed that chondrocyte and osteoblast differentiation were impaired; and that transplantation of juvenile bone marrow would result in enhanced callus formation. Other factors related to angiogenesis and vasculogenesis have also been noted to be impaired in aged models, affecting the degradation of cartilaginous matrixes and vascular invasion; the result is changes in matrix composition and growth factors concentrations that ultimately impairs healing during age-related osteoporosis.

Most osteoporotic related fractures occur at metaphyseal sites clinically, and reports have indicated that differences exist between diaphyseal and metaphyseal fractures. An animal model that satisfies three main criteria (metaphyseal region, plate fixation, osteoporosis) is suggested for future research for more comprehensive understanding of the impairment in osteoporotic fractures. Therefore, a metaphyseal fracture or osteotomy that achieves complete discontinuity fixed with metal implants is suggested on ovariectomized aged rodent models.

Introduction

Bone tissues demonstrate a remarkable ability to regenerate following fracture injury, recovering from structural failure and lost physiological function [1]. The cascade of events following traumatic bone injury is well-documented in both stabilized and non-stabilized fractures. The former primarily heal via intramembranous ossification in which bone regenerates directly from mesenchymal cells, while the latter primarily heal via endochondral ossification in which bone regenerates through a cartilage intermediate [1–5]. Both events begin with the formation of a hematoma between the damaged bone ends and surrounding soft tissues. Inflammatory cells are recruited by local chemokines to debride the wound, which allows for the migration of mesenchymal stem cells. In stabilized fractures, these cells differentiate directly into osteoblasts and form trabecular bone [5]. In non-stabilized fractures, these cells alter their fate and differentiate into granulation and cartilage tissues [1]. A predominantly cartilaginous soft fracture callus develops and stabilizes the injury site. Then, a hard fracture callus develops through vascularization and mineralization of the extracellular matrix, which yield trabecular bone. Once trabecular bone is generated in both ossification processes, a series of bone depositions and resorptions by osteoblasts and osteoclasts, respectively, reform lamellar bone.

Despite the fine degree of orchestration during fracture healing, the process may be impaired. Currently, 10–15% of the approximately 15 million fractures that occur annually result in poor or unresolved

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healing [6]. As the aging population is expected to double by 2050 [7] and the occurrence of osteoporotic fractures rise in the near future, impairment in osteoporotic fracture healing is becoming an emerging public health concern. Moreover, it has previously been reported that the risk of non-union increases with age [8,9]; and that osteoporotic fracture is associated high morbidity, mortality rate [10,11] and increased healthcare costs.

As the pathophysiology of both post-menopausal estrogen deficiency (type I) and senile (type II) account for the major causes of osteoporosis and subsequently osteoporotic fractures, this paper is intended to review our current understanding on fracture healing in osteoporotic bone in both types and to discuss a number of key determining factors that are impaired during osteoporotic fracture healing. These factors include the recruitment, proliferation and differentiation of progenitor cells; the revascularization of callus; and also the role of mechanical sensitivity in the healing osteoporotic bone. These factors are of high potential as therapeutic targets in future research. Some experiences in animal studies on diaphyseal osteoporotic fracture are summarized in this paper; nonetheless, a general direction of future development in metaphyseal osteoporotic fracture model is suggested in order to improve our research work in terms of clinical relevance and translational applicability.

Mechanical sensitivity in estrogen deficiency-induced osteoporotic fracture (type I) and the role of estrogen receptors

A number of reports revealed the differences of mechano-biology between osteoporotic and normal bones [12] and osteoporotic fracture healing was impaired in both early [13] and late phases with decrease in callus cross-sectional area, bone mineral density (BMD) and mechanical properties [14]. The mechanism of impaired osteoporotic fracture healing is multi-factorial and some reports indicated that low sensitivity of osteoblasts to mechanical signals [15,16], reduced angiogenesis [17,18], and decreased mesenchymal stem cells [19] might be the causes. To enhance fracture healing, mechanical stimulation by means of weight bearing is the current commonest clinical approach. However, previous finding showed that osteoblasts from osteoporotic donors were less responsive to 1% cyclic strain stretching in terms of proliferation and TGFβ release, as compared with younger normal donors [15]. Therefore, this is generally believed that osteoporotic bone is less responsive to mechanical stimulation; however, there were some opposite reports, e.g. Leppänen et al showed that osteoporosis was not attributable to impaired mechano-responsiveness of aging skeleton [20]; also, male adult rats with lower estrogen level demonstrated better mechanical responses than females [21]. Hence, mechanical sensitivity of osteoporotic bone remains obscure.

To compare the responses of normal and osteoporotic fractured bones to mechanical signals, fracture healing of nine-month-old normal (Sham) and ovariectomy (OVX)-induced osteoporotic SD rats in response to cyclic vibration (35 Hz, 0.3 g where *g*=gravitational acceleration; 20 min/day and 5 days/week) were assessed using radiography, microCT, histomorphometry and four-point bending mechanical test at 2, 4, and 8 weeks post-treatment. Results showed that fracture healing in OVX animals responded to cyclic vibration very well, as reflected in all the assessment outcomes, particularly in the early phases of healing [22]. Callus formation, mineralization and remodeling were enhanced by 25–30%, while energy to failure was increased by 70% as compared to corresponding OVX control. The outcomes were comparable to those of age-matched normal fracture healing in Sham group. These findings also revealed that both intramembranous and endochondral ossification were enhanced well in osteoporotic fracture healing augmented by cyclic vibration. In the meantime, these osteogenesis findings were further substantiated by the angiogenesis data performed in another study using the same experimental design and cyclic vibration treatment [17]. Significantly increased blood flow velocity (+10–19%) and vascular volume (+25–57%) than corresponding OVX control were demonstrated at the fracture sites of OVX-induced osteoporotic rats at week 2 and 4 post-treatment, whereas its non-OVX counterpart showed +2.2–13.2% increase of vascular volume (Sham treatment vs. Sham control) at week 2–4 only. Also, similar findings were found when the mechanical loading was changed to low intensity pulsed ultrasound (1.0 kHz, 30.0 mW/cm^2 spatial-averaged temporal-averaged intensity; 20 min/day and 5 days/week) with the same study design [23], which again showed comparable responses (similar increase of energy-to-failure of OVX treatment over OVX control vs. Sham treatment over Sham control at week 8) to acoustic loading between osteoporotic fractured bone and age-matched normal one. Rubinacci et al. also verified that OVX non-fractured rats treated with vibration treatment (30 Hz, 3 g) showed significant increase in cortical and medullary areas, periosteal and endosteal perimeters but not in Sham animals, illustrating that OVX might sensitize cortical bone to mechanical stimulation [24]. All these evidences confirm that osteoporotic bones respond effectively to mechanical loading (regardless of physical or acoustic form), which was not worse than normal ones.

As the immediate effects of estrogen depletion is sensed and relayed by estrogen receptors (ERs), as well as ERs was known to function as mechanical signal transduction through its ligand-independent function [25], this is not surprising to postulate the quantity of ERs may play a role in determining bone formation during fracture healing. Furthermore, ERs have been reported to localize in fracture callus [26] that indicates the potential roles of ERs in fracture healing. When comparing the gene expression of ERs at fracture callus between 9-month-old Sham and OVX closed fractured rats, it was found that ERs expressions were significantly higher in Sham group at week 2 but later significantly lower at week 8 than OVX group, while the OVX group demonstrated an opposite trend [27]. Meanwhile, moderate correlations were found between ER-α and BMP-2 ($r = 0.545$, $p = 0.003$), between ER-α:ER-β ratio and BMP-2 ($r = 0.601$, $p = 0.001$), between BMP-2 and callus width/callus area ($r = 0.709$, $p = 0.000$/$r = 0.588$, $p = 0.001$). These gene expression data were also validated by immunohistochemistry at protein level. These findings depict that impaired healing of OVX-induced osteoporotic fracture may be associated with delayed expression of ERs.

As delayed expression of ERs may be the cause of impaired osteoporotic fracture healing, this is interesting to look into the changes of ERs expression in osteoporotic fracture healing augmented by mechanical stimulation. In the study, the fractured rats were randomly assigned to 4 groups – Sham control (SHAM), OVX-induced osteoporotic control (OVX), OVX vibration treated at 35 Hz, 0.3 g for 20 min/day and 5 days/week (OVX-VT) and OVX vibration supplemented by daily 1.5 mg/kg/day ICI182,780 (Fulvestrant, a complete ER antagonist) (OVX-VT-ICI). The results demonstrated that ER-α expression level was higher in SHAM and OVX-VT groups at week 2 and gradually decreased at week 4 and week 8, while that of OVX group showed lower expression at week 2 and later surged at week 8 [28]. Also, ER-α gene expression levels were similar between SHAM and OVX-VT groups with no significant difference between two groups. This indicated that cyclic vibration could induce the increase of ER-α level in osteoporotic fractured bone close to SHAM normal level. Interestingly, in OVX-VT-ICI group, the ER-α expression was suppressed to a significantly lower level. Similarly, the osteogenesis gene expressions (Col-1 and BMP-2) and callus morphometry parameters (callus width, callus area) echoed the ER-α data with the highest levels in SHAM and OVX-VT groups from week 2–4, while the group of OVX-VT-ICI was the lowest. This further substantiates the fractured bone's ability to transmit mechanical strain to stimulate callus formation. Both gene expression data and fracture outcomes suggested that the presence of ER-α was essential for mechanical transduction and responsible for the enhancement effects induced by cyclic loading. The induced increase of ER-α level at fracture callus may be sourced

from enhanced angiogenesis by mechanical stimulation [17], which enhanced the transportation of some mesenchymal stem cells carrying ER-α to the site [29]. Hence, estrogen deficiency-induced osteoporotic fractured bone is effective to respond to mechanical stimulation, where mechanical loading can increase the expression of ER-α at fracture callus for mechanical signal transduction and hence fracture enhancement.

The effect of aging on osteoporotic fracture healing (type II)

Our current understanding of the effects of aging on fracture repair comes from work in animal models. Although the sequence of fracture healing has been aptly described, less is known about the age-related changes to each step. Previous animal studies have described dysregulation of key processes, such as mesenchymal cell differentiation, inflammatory cell activity, and local revascularization [30–35]. While these findings are derived from rodent models, the same interconnected components are required for robust bone regeneration in human patients. Therefore, to answer the question of how aging affects the success of fracture repair, one must examine changes in cell behavior, vascular response, and extracellular matrix activity.

Unsurprisingly, bone synthesis depends on cell differentiation and growth. Mesenchymal stem cells are specifically responsible for bone regeneration. Derived from a variety of local and systemic sources, notably the periosteum and endosteum, these progenitor cells may differentiate into osteoblasts, chondroblasts, and stromal cells [36]. Previous murine studies have demonstrated age-related delays in chondrocyte and osteoblast differentiation in non-stabilized fractures [31]. During the early phases of repair, juvenile mice are able to initiate more robust periosteal reactions and more rapid cell proliferation than middle-aged and elderly mice, generating greater numbers of ColII-expressing chondrocytes and osteocalcin-expressing osteoblasts. During later phases of repair, juvenile fracture calluses contain more trabecular bone formation and display swifter bone remodeling. Although middle-aged and elderly animals eventually healed, their protracted responses suggest overall deficits in aged mesenchymal stem cell activities. Interestingly, bone marrow transplantation experiments have shown that rejuvenation of inflammatory cell lineages independent of skeletogenic cell lineages enhances fracture repair in aged animals [35]. When aged animals received juvenile bone marrow, more robust callus formation and more rapid callus remodeling were observed, indicating that independent functionality of both mesenchymal stem cells and inflammatory cells is necessary for successful healing. So, while the interactions among different cell populations during bone regeneration have been explored [4,37,38], the age-related breakdown of these relationships remains unidentified and warrants further research.

Given the burst of cellular activity following fracture, reestablishment of the local vascular supply is paramount to successful bone regeneration. Since surrounding blood vessels are concurrently damaged during skeletal injuries, a harsh ischemic microenvironment develops at the fracture site [32]. To further complicate healing in aged models, angiogenesis and vasculogenesis are impaired due to substantially suppressed expression of anabolic factors such as Hypoxia Inducible Factor-1-alpha (HIF-1α) and Vascular Endothelial Growth Factor (VEGF) [39]. Moreover, matrix metalloproteinase (MMP) activity diminishes with age, which leads to poor degradation of cartilaginous matrixes and prevents adequate vascular invasion during endochondral ossification [40–44]. The combination of decreased oxygen tension, hindered revascularization, and minimal nutrient exchange results in cell death as well as delayed osteoblast and chondroblast cell activity [45–47]. Previous animal studies suggest manipulation of the VEGF pathway to restore angiogenesis in impaired healing models, such as induced ischemic fractures [48–51]. While these treatments undoubtedly rescue otherwise delayed bone regeneration, a recent human study suggests VEGF deficiency may not be responsible for the avascularity seen in aged fracture calluses. The report describes similar expression of VEGF and Platelet-Derived Growth Factor (PDGF) in middle-aged and elderly patients at a given time point, indicating dysfunction outside of angiogenesis may be responsible for poor unions in aged populations [52]. The seemingly different conclusions that exist within current research provoke thought and indicate that more investigations must be conducted to properly assess fracture repair in elderly populations.

In addition to coordinated cellular and vascular proliferation, fracture repair depends on the establishment of an interim extracellular matrix template. The matrix at the site of injury provides a stable scaffold for cellular migration and growth factor adhesion. During the initial phase of fracture repair, a fibrin-rich matrix coalesces with platelets to form a hematoma that sequesters pro-inflammatory cytokines and other potent bioactive factors required for cell proliferation, cell differentiation, and osteoinduction [44,53–56]. Without the hematoma and its constituents, the cascade of healing responses fails to occur and terminates in either delayed- or non-union [57,58]. Age-related changes in matrix composition, disturbances of cell-matrix interactions, and alterations in growth factor concentration increase the likelihood of deviations from the normal wound healing sequence [59–63]. In animal models of fracture healing, increased age and related disease states are associated with loss of extracellular matrix regulation. For example, collagenous and fibrotic tissues established during early wound repair persist and prevent normal replacement by bone and cartilage tissues, resulting in delayed healing [31,44,64,65]. While the interactions between the extracellular matrix and surrounding tissues have been sufficiently characterized, the exact mechanisms underlying such sub-optimal cellular behavior in aged matrixes during fracture repair have yet to be discovered [61,66,67]. However, given the current research on the restoration of the extracellular matrix in other system, such findings may be readily applied in the context of bone regeneration [68–70].

Because of the multifaceted nature of bone regeneration, many questions surrounding fracture healing remain unanswered, regardless of age or outcome. So, to understand the process in older populations, a plethora of work must be undertaken to elucidate age-related changes in biological responses in addition to altered relationships between aged cell types. Overcoming these challenges is critical to the development of novel therapies targeted to fractures attributed to type II osteoporosis.

Future of osteoporotic fracture research – small animal model for metaphyseal fracture healing

Although the above observations nicely summarize the animal studies and filled in some of our current knowledge gaps in our understanding of osteoporotic fractures related to type I and type II osteoporosis, one phenomenon of osteoporosis is that it is mainly manifested by the microarchitectural deterioration of trabecular bone at the distal radius, proximal humerus and proximal femur [71,72]. This is one of the main reasons why osteoporotic fractures most frequently occur at these anatomical sites and in vertebra bodies which are also associated with a remarkable amount of trabecular bone [72–74]. There is also published data on differences in bone healing between the metaphyseal and diaphyseal region of long bones with less periosteal callus formation in the metaphysis than in the diaphysis [75].

Despite the high number of articles on the pathophysiology and microarchitectural bone alterations in osteoporosis, there is only limited data in fracture healing in non-osteoporotic vs. osteoporotic bone. A lot of knowledge on non-osteoporotic fracture healing has been generated from small animal studies in rats and mice. These experiments have frequently used the fracture model of Bonnarens and Einhorn with a midshaft fracture of the femur or tibia with internal fixation by intramedullary roding [76]. Several studies on

fracture healing in osteoporotic bone have also been conducted based on the diaphyseal model of Bonnarens and Einhorn with an obvious gap between experimental surgical methods in midshaft long bones that is somewhat deviated from the clinical relevance of metaphyseal fracture in patients [13,77–84]. Therefore, the conclusions of these studies are limited and more clinically relevant animal model focused on the metaphyseal bone area would make our understanding on fracture healing in osteoporotic bone more comprehensive.

Small animal models for metaphyseal fracture healing in osteoporosis must meet three general criteria. First, the metaphyseal region of a long bone is targeted and a complete discontinuity of this area is accomplished by osteotomy or other means. Second, the type of internal fixation should mimic as good as possible the clinical situation which means that mainly plate fixation techniques should also be used in animals. The third criterion is by far the most difficult one to achieve, which is an osteoporotic or at least osteopenic bone status in small animals comparable to the human situation. This bone mineral density reduction procedure should be carried out reflecting the underlying study aim focusing either on type 1 (post-menopausal) osteoporosis, primary type 2 (senile) osteoporosis or secondary osteoporosis. Possible ways of induction of osteoporosis with all pros and cons have recently been reviewed by Simpson and Murray et al. (2015) in this context [85].

The first model that mimicked those clinical properties on targeting metaphyseal fractures with plate fixation in small animals was introduced by Stürmer et al. (2010) in a study that was primarily dedicated on the effects of estrogen and raloxifene in the early phase of fracture healing in osteoporotic bone [86]. Surgical technique included an anterior–medial approach from the medial femur condyle to the middle of the tibia. A transverse osteotomy of the proximal tibia metaphysis was performed followed by plate fixation of the proximal tibia with a T-shaped titanium plate. As the animals underwent ovariectomy during the osteotomy procedure, osteoporotic bone status cannot be claimed for this series.

Alt's group recently published a rat model on the metaphyseal area of the distal femur with different gap sizes to mimic fracture defect healing in ovariectomized rats for the potential use of biomaterials to stimulate fracture healing [87]. In contract to the model Stürmer et al., the rats were ovariectomized 12 weeks before osteotomy leading to a significant reduction in bone mineral density compared to sham-operated animals at the time of distal femoral osteotomy. Furthermore, the distal femur was used allowing for a greater defect region compared with the proximal tibia metaphysis. The third difference was the wedge-shaped osteotomy in the femur with a lateral height of 3 or 5 mm in relation to the horizontal osteotomy without significant defect on the proximal tibia by Stürmer et al. This study showed that wedge shaped fracture defects with a lateral height of 3 mm was leading to stable bone healing after 6 weeks whereas 5 mm defects did not consolidate and can therefore be considered as a critical size fracture defect model.

As mentioned above, the study of Stürmer et al. [86] used ovariectomy at the time of osteotomy and phytoestrogen-free pelleted food for the duration of the study of 35 days which limits the effects of bone mineral density reduction to 35 days. The study design contained four different treatment groups: osteopenic control with ovariectomy (OVX) (group I), sham-operated animals without ovariectomy (group II), osteopenic animals with ovariectomy treated with estradiol benzoate (group III) and osteopenic animals with ovariectomy treated with raloxifene (group 4). After 35 days, all osteotomies had healed in all groups but the OVX group exhibited a significantly lower yield point compared to the sham animals in biomechanical testing. Regarding treatment effects, estrogen and raloxifene improved the biomechanical properties of bone healing compared to OVX with a denser trabecular network for estrogen treatment. Raloxifene greatly induced total callus formation in contrast to estrogen which mainly enhanced new endosteal bone formation.

Alt et al. performed a study on the comparison of fracture defect healing in 3 mm wedge shaped defects based on the above mentioned animal model between ovariectomized and non-ovariectomized rats in which both groups received a calcium-, phosphorus- and vitamin D3-, soy- and phytoestrogen-free diet [87,88]. After the evaluation period of 6 weeks, one of the two non-destructive three-point bending tests with at 3 mm lever span showed a significant reduction in the lower flexural rigidity in the OVX group compared to the sham group. However, the 10 mm lever test did not yield a statistical significant difference. This might be related to the fact that the bending test at 3 mm distance to the femoral condyles mimics more a shear test arrangement due to the close application of the load to the healing zone. The 10 mm test can be rather considered as a real bending test

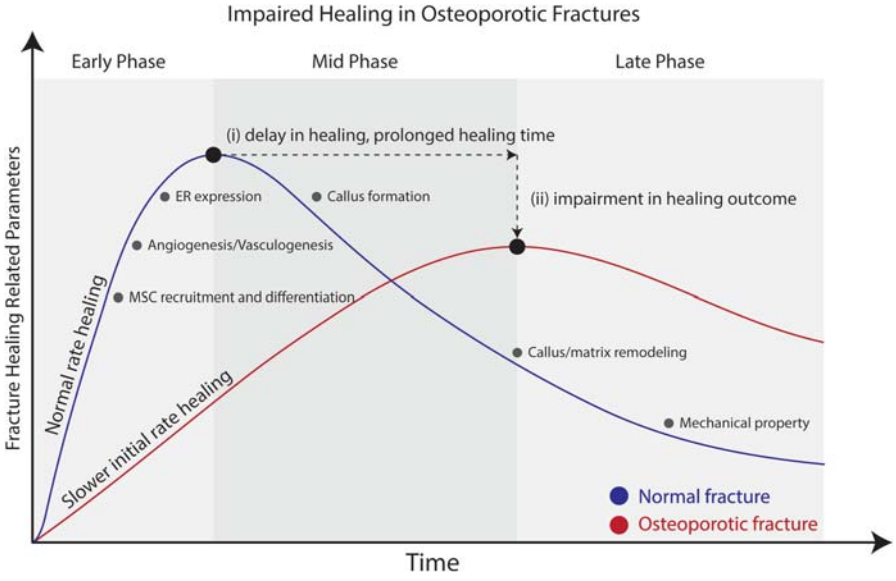

Fig. 1. Impairments in Osteoporotic fracture. Osteoporotic fracture healing often demonstrates (i) delayed healing and (ii) impairment in healing outcome. Factors that were observed to be impaired include MSC recruitment and differentiation, angiogenesis, vasculogenesis, and ER expression during the early phase of fracture healing. Callus formation capacity and the subsequent callus/matrix remodeling was also shown to be impaired during the mid to late phase of osteoporotic fracture healing. These impairments would ultimately determine the healing outcome in mechanical property of the healed bone.

revealing the flexural rigidity of the whole femur with the cortical bone as the major contributing structure. This might indicate a weaker effect of the ovariectomy on the cortical bone compared to the effects on healing of the osteotomy in the metaphyseal region.

Morphological assessment of fracture healing revealed bridging cortices and consolidation of the defect in both groups in both groups without detectable differences in total ossified tissue or vascular volume fraction. In histology, this bony bridging in the OVX group was rather in the shape of a bony cortex around the callus than a cortical bridging. Histology additionally showed differences in bone healing with a higher amount of cartilaginous remnant and more unmineralized tissue in the OVX rats compared to a more mature appearance of bone consolidation in the sham group.

Osteoporotic fractures mainly affect the metaphyseal part of long bones. There are relevant differences in the healing of metaphyseal versus diaphyseal healing patterns after fracture. Therefore, fracture healing studies for osteoporotic fractures should also focus on metaphyseal models with plate fixation of the distal femur or proximal tibia and not only on simple diaphyseal fracture models with intramedullary roding. Data of two independent studies suggest differences in fracture healing in metaphyseal fractures in ovariectomized rats versus non-ovariectomized rats.

Conclusion

As the world aging population continues to escalate and the prevalence of osteoporotic fracture is projected to increase substantially, the healing process and outcome of fractures in osteoporotic bone caused by postmenopausal estrogen deficiency (type I) or aging (type II) have been extensively studied in the past decade. The well-orchestrated healing process in osteoporotic bone seems to be having one or few of the instruments playing slightly out-of-tune. The expression of estrogen receptor was shown to be delayed during the healing process that correlated to impairment in callus formation capacity. Osteoporotic bone demonstrated no worse mechanical sensitivity during mechanical stimulation may suggest a promising therapeutic target for intervention. Other factors including progenitor cell recruitment, differentiation, and proliferation during the early phase of fracture healing; angiogenesis and vasculogenesis during the early to mid-phase of healing; the capacity of extracellular matrix production and callus formation during the mid-phase of healing; and finally the capacity of callus remodeling at later phase of the healing process were also found to be impaired in osteoporotic bone that are common to both type 1 and type 2 osteoporotic animal models (Figure 1). These factors are also highly promising therapeutic targets. Since many of these findings and knowledge were obtained from studying of mid-shaft femoral fracture in rats; hence, an osteoporotic fracture model at the metaphyseal region is suggested for future studies to broaden our understanding to the healing of trabecular bone dense regions that is mostly affected by osteoporosis and more clinically relevant.

Conflict of interest

The authors have no conflict of interest.

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When is the stability of a fracture fixation limited by osteoporotic bone?

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KEYWORDS

Fracture fixation
Osteoporotic bone
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Failure

ABSTRACT

This article is concerned with the search for threshold values for bone quality beyond which the risk of fixation failure increased. For trochanteric fractures we recognized a BMD lower than 250 mg/cm^3 as an additional risk for cut out. For medial femoral neck fractures since joint replacement surgery is available and produces excellent functional results, we see no indication for further differentiation or analysis of bone quality in relation to fracture fixation. In the area of osteoporotic vertebral body fractures, there are many experimental studies that try to identify BMD limits of screw fixation in the cancellous bone on the basis of QCT analysis. However, these values have not yet been introduced for application in clinical practice. In case of indication for surgical fixation, we favor minimally invasive, bisegmental, fourfold dorsal instrumentation with screw-augmentation for a T-value less than −2.0 SD (DXA analysis, total hip or total lumbar spine). For proximal humerus fractures, BMD value of 95 mg/cm^3 could be seen as a threshold value below which the risk of failure rises markedly. In relation to osteoporotic distal radius fractures, based on our clinical experience and scientific analyses there are virtually no restrictions as far as bone quality is concerned on the application of palmar locking implants in the surgical management of distal radius fractures. Optimization of preoperative diagnostics might help to revise the treatment algorithm to take bone density into account, thus reducing the risk of failure and, at the same time, acquiring additional data for future reference.

Introduction

Osteoporosis is a widespread disease process and is now not only prevalent in Europe and north America but has become a worldwide challenge [1] due to an increase in life expectancy. Orthopaedic traumatology is particularly impacted by this phenomenon for two reasons: firstly, fracture rates have increased markedly and, secondly, fracture treatment of osteoporotic bones differs in several ways from treatment of non-osteoporotic bones. Typical locations of osteoporotic fractures include the proximal femur, proximal humerus, distal radius and spine. Many fractures can be treated surgically or non-surgically so a choice has to be made between these options with their associated advantages and disadvantages. Ultimately, surgery may be unavoidable, especially for fractures of the lower extremities.

If the treatment of choice is surgical intervention, success depends on three important parameters: Selection of the ideal implant, best possible anatomical reduction, and correct positioning of the implant [2]. Slight deficits in any one of these three areas can generally be compensated for by non-osteoporotic bone during fracture healing. However, two main characteristics differentiate osteoporotic bone from the healthy skeleton: firstly, implant anchorage (generally in trabecular bone) tends to be insufficient [3], secondly, fracture healing takes longer due to a decelerated bone metabolism [4]. These factors combined repeatedly lead to fatigue failure that is manifest as screw migration through cancellous bone (cut out [3]) with resultant dislocation of the fracture and fixation failure, even when none of the three critical areas show any relevant deficits. This article is concerned with the search for threshold values for bone quality and/or bone density beyond which the stability of the osteosynthesis is limited and the risk of fixation failure increased. Identifying threshold values will make it possible to modify the treatment concept to accommodate individual bone quality and predict complication risk more accurately, e.g. in relation to non-surgical and surgical fracture treatment or joint replacement. The data are based on published literature and derived from the author's own experimental findings and clinical experience.

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Trochanteric femur fractures

Proximal femur fractures in the region of the trochanter are one of the most frequent and most serious osteoporotic fractures due to the lack of alternatives to surgical management. Surgical intervention is unavoidable in the majority of cases; joint replacement may be possible in principle, but will be a highly complex challenge; osteosynthesis often remains the best therapeutic option despite the presence of osteoporosis. Fixation failure often signals the end of patient mobility [5,6], whereby the appropriate fixation is physiologically destined to experience relatively high loads in the region of the hip [7]; in many cases it is not reasonable to expect partial loading given the reduced condition of general health typical of these patients. It is all the more important that proper consideration be given to the afore-mentioned key concerns in fracture management – reduction, appropriate choice of implant and correct implant placement. Fracture reduction and correct implant positioning are the responsibility of the surgeon for which he has some guiding criteria available [2]. With regard to the choice of implants, modern and clinically proven solutions are available from most manufacturers. In particular rotationally stable implants have clearly lowered complication rates in osteoporotic bone in recent years [8]. Nevertheless, failures that lead to cut out even where detailed analysis of the three key areas showed no relevant deficits can be clinically observed. In these cases, it can be assumed that bone quality had reached a critical threshold that limited the efficacy of fracture fixation.

Biomechanical experiments were employed to identify a possible threshold of bone mineral density for a reliable fixation of implants in the proximal femur [3]. First, we tested 30 proximal femurs from human body donors for bone mineral density (BMD) at the femoral head using quantitative computed tomography (QCT). We selected this region of interest because load transfer during weight bearing takes place at the interface between the cancellous bone of the femoral head and the femoral head screw. It is in this area that BMD is especially important for the stable anchorage of the load carrier. After determining BMD, osteotomy was performed to simulate an unstable trochanteric AO type 31 A2.3 fracture followed by intramedullary nailing with insertion of the most recent generation of nails (PFNA from Synthes, Trigen Intertan from Smith&Nephew and Targon PFT from Aesculap). After fracture fixation cyclic dynamic loading of the constructs was performed until failure. The primary endpoint of the study was calculation of the relative risk of cut out in relation to the BMD values (Figure 1). The incidence of cut-out for BMD less than 250 mg/cm^3 was 0.55 (5 of 9) and for BMD greater than 250 mg/cm^3 0.05 (1 of 21). Therefore, the risk of cut-out for BMD <250 mg/cm^3 was almost 11 times greater than for BMD >250 mg/cm^3. The conclusion can be summarized as follows. There is a very high risk of implant failure after surgical management of trochanteric fractures where BMD is below 250 mg/cm^3 in the region of the femoral head. A threshold value like this for bone density could be helpful, for example, when deciding for or against cement augmentation [9] at the bone-screw interface in the femoral head. Currently, there are no definitive decision-making criteria for implant augmentation [10] and widespread application of augmentation to all trochanteric fractures would not be advisable because of the associated complication risks as well as for socio-economic reasons. On the other hand, determining bone density in the region of the femoral head is not easy logistically. In principle, it is not very difficult to perform QCT, however, some institutions do not have the necessary infrastructure and the software of the CT manufacturers is often not sophisticated enough for this special application. Despite these constraints and based on our own experimental findings and data from the literature [11], a BMD threshold of 250 mg/cm^3 appears to be a clinically relevant values for the prediction of stability of intramedullary osteosynthesis of proximal femur fractures.

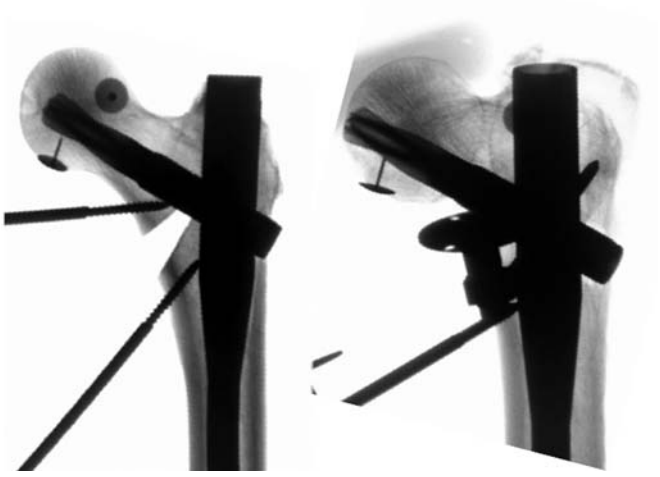


Fig. 1. Radiological images of a construct incorporating proximal femoral nail osteosynthesis (PFNA, DePuy-Synthes) before loading (left) and after 10,000 load cycles (right) at 2100N. It shows cut out typical of a clinical complication involving medialization of the PFNA blade, varus dislocation and collapse of the osteotomy gap, which corresponds to comminution in the clinical environment.

Medial femoral neck fractures

Medial femoral neck fractures occur at an incidence similar to that of trochanteric fractures and are likewise a typical osteoporotic fracture type. In practice, treatment depends on the classification of the fracture, whereby international and national directives for fracture management do not provide practical guidelines and leave the surgeon great freedom to make treatment decisions. Nevertheless, it can be broadly stated that stable femoral neck fractures should be treated by osteosynthesis [12] and unstable fractures by joint replacement [13]. Osteosynthesis of stable fractures is not susceptible to any relevant mechanical failures in the sense of cut-out or fracture dislocation [12], provided that the classification of the fracture as stable or unstable is correct. The risk of complications does however increase for unstable fractures, but since joint replacement surgery is available for unstable femoral neck fractures and produces excellent functional results [13], alloplastic treatment is a viable option for unstable fractures with osteoporosis. Given this situation, we see no indication for further differentiation or analysis of bone quality in relation to fracture fixation for medial femoral neck fractures.

Vertebral body fractures

Pathological vertebral body fractures without relevant trauma or after low energy trauma represent a major challenge in the context of osteoporosis. In many cases, non-surgical treatment is extremely promising and offers satisfactory functional outcomes [14]. However, in some cases surgery is indicated, either to alleviate pain or to reverse some marked deformity such as spinal canal stenosis, which is associated with pain and neurological deficits. This section is concerned with the challenges of screw fixation in osteoporotic vertebral bodies, but not with vertebroplasty or kyphoplasty, which represent more or less invasive approaches to pain therapy with low levels of evidence to date [15].

Typical failures of dorsal instrumentation are cut out and also pull-out of the pedicle screws [16]. In contrast to trochanteric fractures it is bone quality that is more frequently responsible for failure rather than reduction or precise screw placement, which is generally exactly transpedicular because of the anatomical features of the region. Various technical methods are available if the treatment of choice for osteoporotic vertebral fractures is dorsal instrumentation: Simple, bisegmental dorsal bridging of the fractured vertebra is the

cornerstone of surgical management and has a tolerable early complication rate [17]. Furthermore, there is an option to perform a four-segment bridging as an extension of dorsal instrumentation towards the cranial and caudal aspects by one segment. Cement augmentation of pedicle screws or even simultaneous kyphoplasty of the affected vertebrae are ways to support the ventral column and potentially preempt failure. Existing literature however does not reveal sufficient clinical data to answer the question of when the aforementioned adjuvant measures are indicated nor to solve the dilemma of which technical option will provide better protection from mechanical failure or the development of adjacent fractures [16] (Figure 2). The decision can only be based on subjective criteria and is dictated more by eminence and less by evidence-based criteria. The relevant literature provides certain hints for a correlation of BMD with mechanical stability related to screw anchorage. The standard work on this matter is that of Wittenberg et al. [18], which correlates pedicle screw fixation with bone density (QCT) in the experimental setting. A threshold value of 90 mg/cm^3 has been identified as a good predictor for failure. In a more recent study by Paxinos et al. [19] a BMD of 150 mg/cm^3 has been identified as the threshold value below which mechanical stability of dorsal instrumentation was reduced. This value was however based on in-vitro data, whereby it is close enough to the findings of Wittenberg et al for these data to be regarded as valid reference values. Furthermore, the literature offers numerous biomechanical analyses that correlate the fixation stability of vertebral derotation spondylodesis (VDS) with bone quality based on DXA or QCT. As might be expected the findings reveal a correlation between BMD and mechanical stability in pull-out testing, but a threshold value to indicate failure risk was not defined [20]. One of the biomechanical studies conducted at our institute [21] compared ventral cage spondylodesis with and without dorsal instrumentation. The study confirmed the assumption of higher stability for the combined procedure and also identified a BMD cut-off value below which the stability of isolated ventral stabilization is at risk. The value obtained from this study was 220 mg/cm^3, which is at about the same level as the threshold value identified for proximal femur fractures.

These values have been cited in a number of publications, but have not yet been introduced for application in clinical practice. The reasons for this might be that, as for proximal femur fractures, QCT is not possible at the pre-operative stage at most institutions. Even the suggestion of evaluating these values in the clinical setting, which is not happening at this time, may be considered by clinicians with scepticism.

At our institution we perform DXA for vertebral body fractures if the patient is in an age group typically susceptible to osteoporosis. If the indication for surgical stabilization is given, we favor minimally invasive, bisegmental, fourfold dorsal instrumentation with PMMA augmentation of all four pedicle screws for a T-value less than –2.0 SD (Figure 3). So far, we have been able to clearly reduce the risk of failure with this procedure. Nevertheless, this value is based on purely subjective criteria and clinical experience, whereby it does embrace the threshold stated in the national recommendations for medicinal therapy for osteoporosis [22].

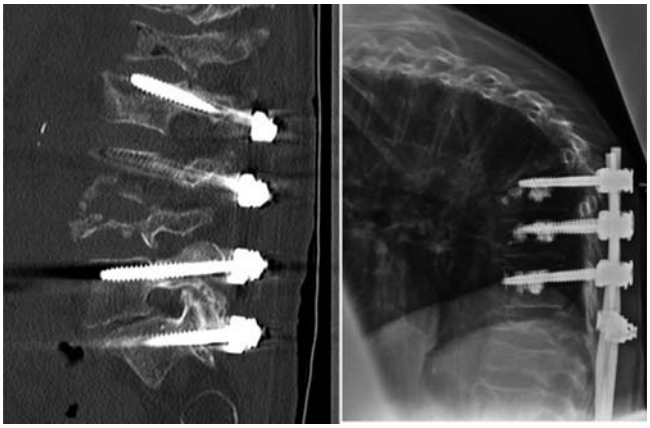
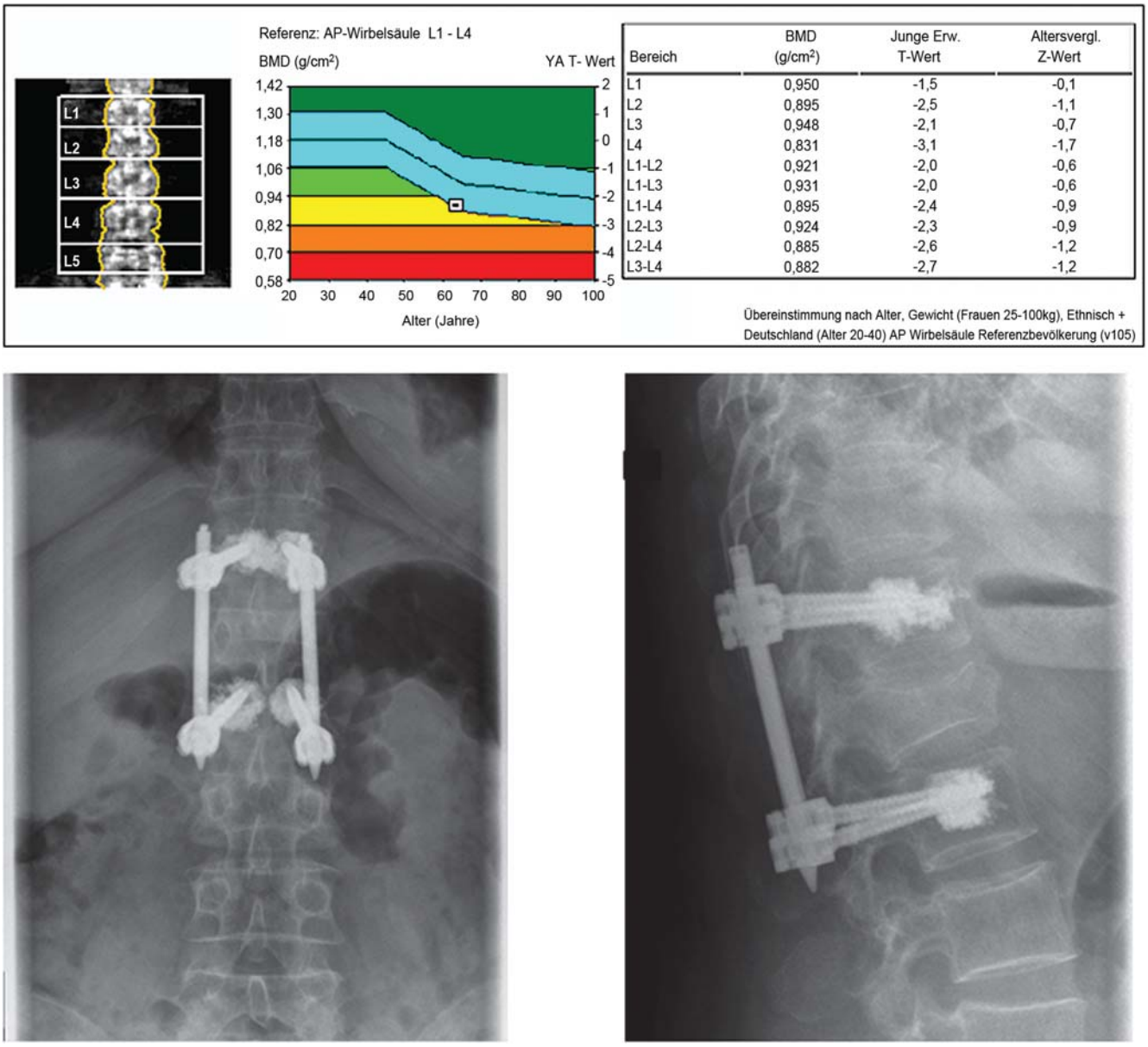


Fig. 2. Sectional CT imaging after surgical intervention for osteoporotic subsidence fractures. On the left side cut out of the cranial screws occurred despite the four segment bridging. On the right side another complication typical of extensive fusion is illustrated, namely, fracture of the adjacent cranial vertebral body.

Proximal humerus fractures

Proximal humerus fractures are another large group of injuries typical for osteoporosis. In many cases non-surgical management is possible and achieves acceptable or even very good functional outcomes [23,24]. However, in cases of severe dislocation or in unstable fractures surgical intervention must be considered [23]. The competing options today are locking screw plate fixation or intramedullary nailing. If the articular cartilage (joint) has extensive damage, joint replacement becomes an option to consider either as an anatomical joint prosthesis or as a reverse prosthesis [23]. Unfortunately, clearly defined decision-making criteria relevant to surgical, non-surgical treatment or even joint replacement have not yet universally agreed. In reality, current management of these fractures is dictated more by institutional circumstances and subjective criteria [23]. Although evidence-based research is sparse [25] this section addresses the search for threshold values relevant to osteosynthesis of proximal humerus fractures by plating or nailing. As for the proximal femur, early fixation failure in humerus fractures is manifested as screw cut out from the cancellous bone at the articular surface with consequent tilting of the cortex, generally into varus, and resultant fracture dislocation (Figure 4). Delayed failure in the form of humeral head necrosis is a different entity because it derives from fracture-related compromise of cortical vascularity. Early failure rates can be as high as 20% [26]. The quality of the fixation depends not only on the suitability of the implant and correct axial alignment of the reduction, but also on screw anchorage in the cortical bone. In contrast to the femoral head, the cancellous structure of the humeral head shows large local variations. At the periphery subchondral bone can be found which is very dense [27,28], and it is in this area that the implants should be anchored even though it is associated with the risk of intraarticular screw penetration. The central region of the humeral head may contain very little bone and provides almost no mechanical support for the anchorage of metallic implants. Due to this inhomogeneous nature of the trabecular bone in the humeral head it is difficult to interpret an overall BMD measurement.

Numerous biomechanical studies have compared different osteosynthesis procedures in cadaveric bones. The majority of studies found a strong correlation between failure and BMD, but since these series were comprised of approximately 6–8 pairs of bones only, it is not possible to determine a BMD cut-off value to predict failure. Fortunately, data from a prospective clinical study that investigated various parameters which were then compared with failure after surgical management of proximal humerus fractures are found in the literature [26]. As expected bone density expressed as BMD calculated from CT images strongly correlates with failure. The authors even state a BMD value of 95 mg/cm^3 as a threshold value below which the risk of failure rises markedly, whereby the precise algorithm for BMD computation from CT data is not expanded in detail in that publication. However, the same team has published a well designed and established method of calculating BMD from CT data for the contralateral limb [29]. The fact that the data cited above are based on a clinical study increases the statement validity of the values, making it easier to transfer theory into clinical practice. In addition, preoperative CT diagnostics for proximal humerus fractures are part of standard procedures in many institutions, which means that even the preoperative analysis of the predictive factor “osteoporosis”



Bereich	BMD (g/cm²)	Junge Erw. T-Wert	Altersvergl. Z-Wert
L1	0,950	-1,5	-0,1
L2	0,895	-2,5	-1,1
L3	0,948	-2,1	-0,7
L4	0,831	-3,1	-1,7
L1-L2	0,921	-2,0	-0,6
L1-L3	0,931	-2,0	-0,6
L1-L4	0,895	-2,4	-0,9
L2-L3	0,924	-2,3	-0,9
L2-L4	0,885	-2,6	-1,2
L3-L4	0,882	-2,7	-1,2

Fig. 3. Treatment algorithm in the presence of osteoporosis. In this 64-year old female patient we decided that her painful, progressive kyphosis was an indication for closed reduction and minimally invasive dorsal stabilization. Given the osteoporosis values from DXA testing and based on our hospital's in-house algorithm we decided on PMMA augmentation of the pedicle screws.

could be performed at many medical care centers without much additional work.

Distal radius fractures

Distal radius fractures in the elderly population have a second incidence peak [30] and, consequently, represent a frequent form of osteoporotic fracture after low energy trauma. Regardless of bone quality, surgical management of distal radius fractures has undergone extensive changes over the last four decades, progressing from casting, to K-wire fixation followed by dorsal plating and finally palmar locked plate fixation. According to current biomechanical studies the latter offers very good primary stability [31]. In the clinical setting, palmar plate fixation has also produced very good results in terms of stability and minimization of reduction loss [30] even in multifragmentary osteoporotic situations [32]. Based on our clinical experience and scientific analyses [30] there are virtually no restrictions as far as bone quality is concerned on the application of locking implants in the surgical management of distal radius fractures. The implantation of bone substitute materials, e.g. calcium phosphate, to augment the dorsal defect zone, for which there is no verifiable evidence [33], has become more or less obsolete with the advent of "modern" implants [34]. Nonetheless, if preoperative diagnostics and surgical planning identify contraindications to plate fixation, e.g. extensive comminution of the epiphysis and/or extremely distal fracture morphology, then transfixation of the joint is a very good alternative in terms of both reduction loss and long-term function of the wrist [35]. Since the fixation pins are inserted into the cortex, stability is less affected by osteoporosis. Given the good outcomes achieved with these two treatment methods it is still noteworthy that current studies report comparable or sometimes even better functional outcomes for conservative treatment compared with surgical joint reconstruction in the geriatric population [32,36]. These findings should be carefully considered when selecting the therapy regimen since they help to put

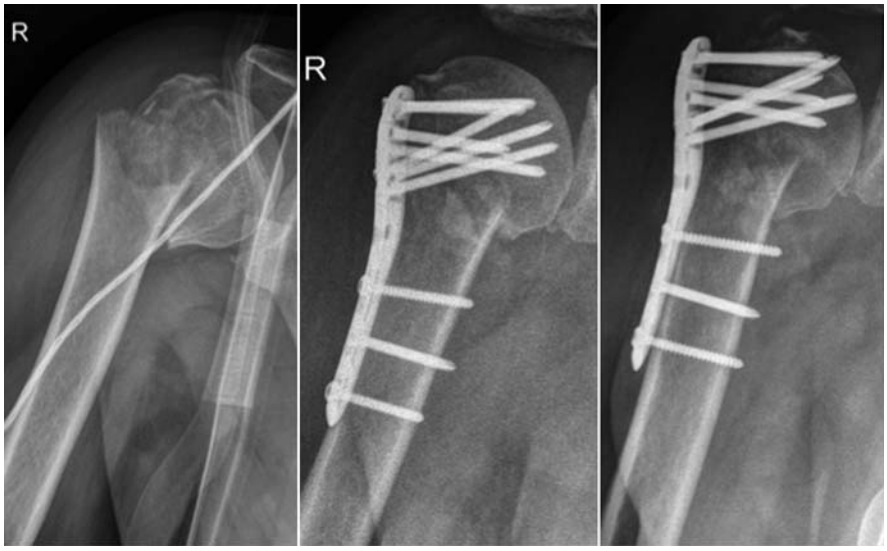


Fig. 4. Fracture treatment (left and middle) after 4 part humeral head fracture in a 72-year-old patient. Postoperative follow up with failure at 6 weeks postoperatively (right). Given insufficient reduction, lack of medial support and suboptimal placement of the implants failure related to bone quality was highly probable. Angular stability and bone quality in this case could not compensate for the reduction deficits.

the "problem of osteoporosis" better into perspective and reduce its relevance in the management of distal radius fractures.

Discussion

Osteoporotic fractures can occur in any bone from the dens to the foot. In addition to the injuries already described in this article, distal humerus fractures, insufficiency fractures of the pelvis, distal femur fractures around the knee, ankle fractures and periprosthetic fractures also present a great challenge to trauma surgery in the presence of osteoporosis [37–43]. In this article we have discussed the most common osteoporotic fractures, for which often different treatment options are available and we suggest that treatment decision can be based on bone density measurement. Bone density certainly influences the stability of surgical fracture fixation and this has been proven in numerous experimental biomechanical studies as cited above, but there are other reports based on clinical data that do not confirm an unequivocal relationship between osteoporosis and failure [44,45]. Two reasons may explain this lack of clinical evidence. The studies currently reported did not declare the analysis of an association between failure and bone density as a primary endpoint. The available data are the results of either retrospective analyses or secondary endpoints of prospective studies. Furthermore, the differences in definitions and test procedures for bone density across the various working groups do not permit the data to be brought together for the purpose of proper metaanalysis [44]. Another reason for the lack of evidence for an existing relationship between BMD and failure could be that other factors associated with the three key areas of "adequate reduction, implant positioning, and implant selection" may have a much greater influence on failure (Figure 4). In the "healthy" skeleton the biological repair processes at work in fracture healing can potentially compensate for deficits in the three key areas, but these mechanisms are very limited in the metabolism of osteoporotic bone.

With regard to low mineralization density the published literature offers insights into what "low" really means in the specific skeletal regions and what the threshold value is beyond which the risk of failure increases, whereby these BMD values that are generally derived from CT imaging have not found application in clinical routine despite the availability of the data. This is certainly due in part to the difficulties surrounding QCT testing in the preoperative setting but another reason for the absence of widespread application may be ignorance of the data, which is often obtained and disseminated only within the confines of academic institutions. Apart from BMD values good experience has been gained in the intraoperative evaluation of bone quality using the DensiProbe [46–48]. This instrument is a potentially handy tool in the intraoperative decision-making process, for example, when deciding whether cement augmentation is necessary or not. Although the body of data for the DensiProbe is very promising, this instrument has likewise failed to achieve widespread entry into clinical application beyond the walls of academic institutions.

Conclusion

It can be postulated based on our clinical and scientific experience coupled with research findings from the published literature that fracture fixation in osteoporotic bone is less promising if the osteosynthesis is suboptimal in an environment of weakened bone structure due to low mineralization density. Optimization of preoperative diagnostics might help to revise the treatment algorithm to take bone density into account, thus reducing the risk of failure and, at the same time, acquiring additional data for future reference.

Conflict of interest

The authors have no conflict of interest.

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Management principles of osteoporotic fractures

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KEYWORDS

Fixation
Osteoporotic fractures
Locked plating
Augmentation

ABSTRACT

Osteoporotic fractures are difficult to manage. They pose a number of difficulties to the surgeon arising from the underlying poor bone stock compromising the intention to achieve optimum fixation. Moreover, the frail elderly patients present with a variety of medical co-morbidities increasing the risk of developing perioperative complications. Despite these recognized challenges, there are currently a number of improving technologies and strategies at the surgeon's disposal to provide more confidence with fracture fixation and maximize the chance of success.

Challenges in the treatment of osteoporotic fractures

Over the next several decades, the increasing number of patients expected to experience osteoporotic fractures, the so-called "silver tsunami," is already being sensed by orthopaedic surgeons and others who provide care to elderly patients. These patients are characterized by physical frailty, medical co-morbidities, and general immobility. When fractures occur in these patients, fixation often rendered unpredictable by the poor holding power of internal fixation within osteoporotic bone [1]. These situations are also made more complex by their periarticular, periprosthetic, or even interprosthetic fracture locations [2,3]. The repair of these fractures require a thoughtful, and often unique, approach to maximize the strength of repair to allow patients to mobilize as soon as is feasible. Despite these recognized challenges, there are currently a number of improving technologies and strategies at the surgeon's disposal to provide more confidence with fracture fixation and maximize the chance of success.

Locked plating

One component of the pathological process in osteoporosis involves cortical thinning, which is often magnified in the metaphyseal or metadiaphyseal regions of long bones. Hence, osteoporotic fractures often occur in these regions. When these occur, the articular, or epiphyseal, fracture segment is often relatively small, making fixation with intramedullary nail interlocking screws problematic. Thus, plating of these fractures has historically been the technique of choice. With standard plating constructs, plating on one surface of a metaphyseal fracture (eccentric stabilization) can be particularly prone to fixation failure [4]. Mechanically, the ability of the screw head to toggle within the plate make it difficult for these implants to maintain coronal plane alignment, particularly with opposite-cortex comminution [5,6]. Because most plates are applied laterally, medial cortical comminution predisposes to reduction loss with varus deformity when standard implants are used (Figure 1).

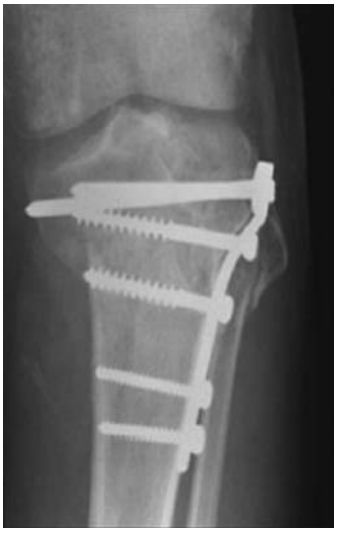

Fig. 1. Example of a proximal tibial metaphyseal treated with a lateral standard (non-locked) implant. Varus failure occurred.

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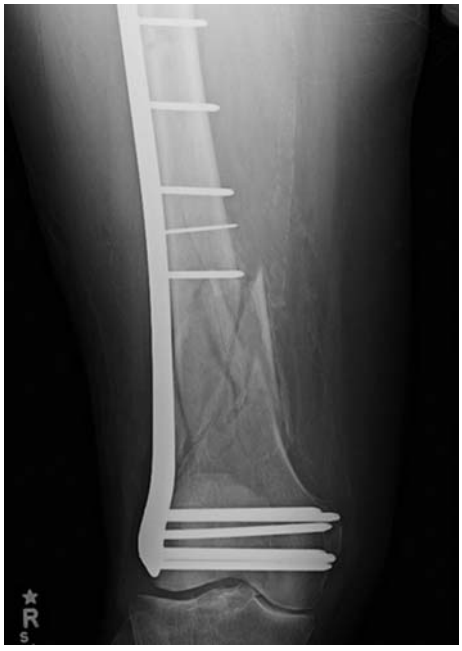

Fig. 2. Example of successful bridge plating of a comminuted metaphyseal supracondylar femur fracture in an elderly patient.

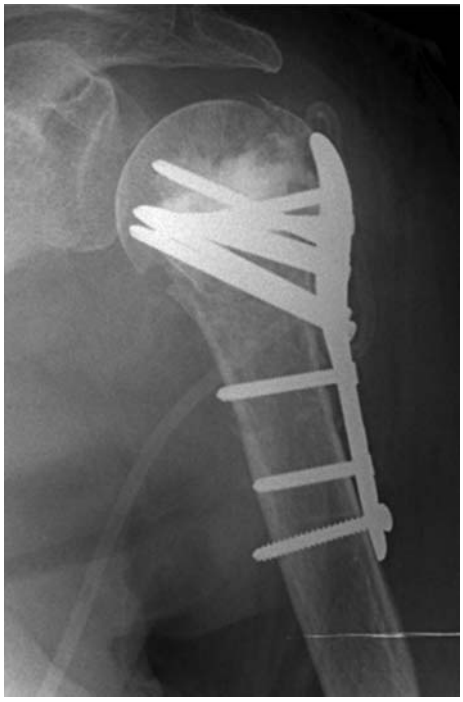

Fig. 3. One option for augmenting fixation in osteoporotic proximal humerus fractures is calcium phosphate application to fill the metaphyseal void and provide increased substrate for locked screw purchase.

Modern locked plating technology was introduced in the 1990's, in part to address the difficulties with treatment of osteoporotic metaphyseal fractures [7]. Locked plates allow the screw heads to thread into the plates, creating constructs that are "fixed-angle," which is theoretically better able to resist varus displacement of the fracture (Figure 2) [8]. These implants have provided an excellent tool to achieve stable fixation in many osteoporotic fractures [9,10].

Limitations of locked plating

Although the mechanical basis for locked plating seems ideally suited for the osteoporotic metaphyseal fracture, it has not turned out to be the panacea that was originally hoped. Most surgeons have transitioned to using locked plates for these fractures based on anecdotal observations of patient outcomes, but there is a paucity of clear, high-level evidence proving their benefit [11]. In addition, there are other limitations related to locked plating in this application. Even through the screw heads mechanically lock to the plate, in order for the fixation to remain stable, the screw shafts must remain securely anchored in the epiphyseal, periarticular bone segment [11]. For this to occur, there needs to be an adequate volume of bone with adequate quality to provide anchorage. Fractures that occur very distal, particularly in supracondylar femur fractures adjacent to a total knee arthroplasty, may have limited native bone stock available for placing effective locking screws. Additionally, severe osteoporosis, *e.g.* with trabeculae that are not visualized on CT scan and appear as a void, often precludes stable implant fixation. In these difficult situations, consideration can be given to augmenting the metaphyseal region with exogenous material such as "cement" bone void fillers to provide a mechanical substrate so the locked screws function as "rebar" to maintain fixation [12]. Commonly used augmentation material includes biological cements, such as calcium phosphate (Figure 3), fibular allografts (Figure 4), or polymethylmethacrylate (PMMA) [13].

Intramedullary nailing

Intramedullary nails have also evolved lately so that fracture fixation with a nail is more predictable than in the past. Similar to locked plates, intramedullary nails that are longer, have more screw options for fixing short osteoporotic segments, as well as fixed–angled capabilities are now available for treating difficult fractures such as those described here [14]. We have found in our practices that modern nails are quite effective for most of the fractures that are commonly treated with anatomically-contoured locked plates, the exceptions being comminuted articular fractures, those with one *very* short periarticular segment, or those with arthroplasty components that

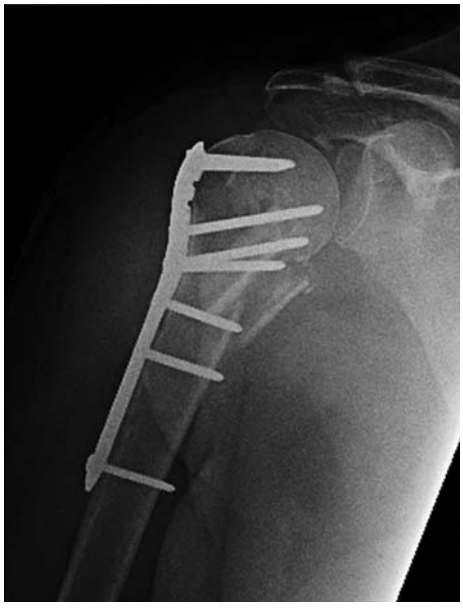

Fig. 4. Another option for augmentation in proximal humerus fractures includes use of a fibular strut allograft, which in this case functions as a medial cortical substitute to enhance overall construct stability [16].

preclude nailing. Using good surgical technique remains of critical importance in treating patients with osteoporotic fractures, as salvage after a surgical technical errors may be very difficult in this scenario. Steps such as getting a good starting point and reamer path, along with accurate fracture reduction, are key elements. Occasionally, repair of an osteoporotic fracture is either not indicated or not possible. In these cases, there remains a role for non-operative treatment or treatment with arthroplasty, respectively. The benefits of arthroplasty in the osteoporotic fracture patient are clear: the requisite for fracture healing and protected weight bearing is obviated. Potential risks for catastrophic failure (*e.g.* infection) and limited salvage options are inherent.

A number of biomechanical studies have demonstrated that the stability of modern nails and plates in osteoporotic fracture models are comparable, although the characteristics of their respective "instabilities" are different [15,16]. Clinically, intramedullary nails have been shown to be effective for periarticular distal femur fractures in cohort studies [17,18]. Recently, a large prospective, randomized trial has shown that nails are at least as effective in treating distal femur fractures compared with plates [19]. Qualitatively, nails typically provide for abundant healing with symmetrical callus. Interestingly, there has been a recent push to create more symmetrically balanced constructs using plates in the form of dynamic plating [20], such that the mechanical environment more closely matches that of intramedullary nails.

Some surgeons have suggested further enhancement of fixation by using traditional concepts of plates and nails by using them together, such as overlapping them to stabilize an entire femur, thereby prophylactically preventing future periprosthetic fractures. Interprosthetic fractures have forced us to use creative solutions for working with and around pre-existing implants. It does not seem so far off where manufacturers design plates, nails, and even arthroplasties that might link together for these reasons. Additionally, changing the interface between the implants and the bone has and will continue to be a field of interest for surgeons treating osteoporotic fractures. Locally, bone cements and surface coatings are being used to improve fixation. For example, fenestrated screws are now approved by the U.S. Food & Drug Administration to apply with injectable calcium phosphate to augment the screw fixation.

Summary

It is clear that osteoporotic fractures create a number of challenges that will increasingly affect the practices of orthopedic surgeons. The current culture has arrived such that the energy and resources for dealing with these issues is increasing seemingly in proportion to the magnitude of the problem. Implants and techniques will likely continue to evolve to address many of the unique issues centered obtaining stable internal fixation in osteoporotic fractures.

Conflict of interest

Michael J. Gardner has received consulting fees from DePuy-Synthes, Pacira and KCI; royalties from Lippincott Williams & Wilkins and served as a speaker for KCI.

Cory Collinge has no conflict of interest.

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The use of augmentation techniques in osteoporotic fracture fixation

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ABSTRACT

There are an increasing number of fragility fractures, which present a surgical challenge given the reduced bone quality of underlying osteoporosis. Particularly in aged patients, there is a need for early weight bearing and mobilization to avoid further complications such as loss of function or autonomy. As an attempt to improve fracture stability and ultimate healing, the use of biomaterials for augmentation of osseous voids and fracture fixation is a promising treatment option. Augmentation techniques can be applied in various locations, and fractures of the metaphyseal regions such as proximal humerus, femur, tibia and the distal radius remain the most common areas for its use. The current review, based on the available mechanical and biological data, provides an overview of the relevant treatment options and different composites used for augmentation of osteoporotic fractures.

Introduction

Fragility fractures are of increasing importance in orthopaedic trauma surgery given the demographic changes of our aging population. The National Osteoporosis Foundation estimates that there are approximately 2 million osteoporosis-related fractures in the U.S. each year, while additional studies suggest that the worldwide burden is closer to 9 million [1,2]. Thus, a majority of fractures are associated with osteoporosis, which result in 36% of the annual in-patient care costs, or 860 million €, in Germany alone [1]. Over the next few decades the incidence of osteoporotic fractures is expected to increase [2]. In these fragility fractures, surgical treatment can be challenging given the reduced bone quality that particularly affects the frequently fractured metaphyseal regions such as the proximal humerus, proximal femur, distal radius, spine, and proximal tibia. Postoperative non-union, screw cut-out, and implant migration are common complications adversely affecting patient outcomes. In the elderly patient population susceptible to fragility fractures, full weight bearing and early mobilization are of paramount importance in order to avoid the significant peri- and post-operative complications associated with frequently present comorbidities. The one-year mortality of hip fractures for example is up to 30% [3].

While advances in implant design such as locked plates have addressed some of the challenging issues, there is still need to promote fracture biology, augment bone defects, and improve surgical fixation in the osteoporotic patient. The aim of this review is to provide an overview of a history of bone augmentation, clinical problems associated with osteoporotic fractures, and potential solutions to these challenges through the use of various augmentation techniques.

Mechanical and biological characteristics in osteoporotic fractures

Age-related resorption of calcium from bone results in thinning of both trabecular and cortical bone and an associated increase in bone diameter [2]. These anatomic changes have a direct effect on mechanical properties. As the density of bone decreases, there is a commensurate decrease in the yield stress, elastic modulus of cortical bone, and compressive strength of cancellous bone [2]. Additional cellular and physiologic changes in the bone contribute to an impaired healing potential; there is a decrease in the number, responsiveness, and activity of mesenchymal progenitor cells, and signaling molecules. There also is a decrease in vascularity and impaired osteoblast function that affect both endochondral and periosteal osteogenesis [3].

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A comprehensive strategy for improved treatment of osteoporotic fractures should address biological and mechanical issues, and include the stimulation of fracture repair, removal of inhibitors to bone healing, application of augmentation materials, and improvements in surgical implants.

Biological stimulation or induction of bone growth can be facilitated by local techniques, systemic methods, or physical means. At the time of surgery, bone marrow aspirates, platelet gels, and bone morphogenetic proteins (BMPs) can be placed at the fracture site and have been shown to improve healing response [4–6]. Administration of vitamin D, calcium, bisphosphonates and parathyroid hormone (PTH), have also been shown to increase fracture healing [7]. Finally, physical modalities such as ultrasound, direct electrical stimulation, pulsed electromagnetic fields, and extracorporeal shock waves have been reported to affect fracture repair [8].

There are many well-recognized inhibitors to bone healing, and every effort should be made to remove these inhibitors to improve healing in osteoporotic fractures. This includes limiting exposure to smoking, alcohol, potent anti-inflammatory medications, and steroids. Maximized control of medical issues such as malnutrition, diabetes, infection, thyroid disease, and hormonal problems is essential for optimizing bone healing.

Evolution of bone augmentation techniques

Bone augmentation with biomaterials was first described in 1984, when Deramond injected polymethyl methacrylate cement into a cervical vertebral body to treat a painful intravertebral haemangioma [9]. In the three decades that followed, many studies have been published describing and critiquing the biomechanical principles, preclinical animal experiments, surgical techniques, and clinical outcomes of bone augmentation of the vertebral column [10–13].

Although the 1987 publication by Galibert and Deramond stimulated the field of vertebral augmentation, the biomaterial used in their case (polymethylmethacrylate; PMMA) was not novel, having been introduced as early as 1877 by Fittig and Paul. PMMA became commercially available in 1936 as an alternative for glass under the name of plexiglas of perspex. The first clinical application of PMMA was in odontology, followed by ophtalmology (after it was discovered in the Second World War that small fragments of PMMA from shattered warplane canopies did not induce inflammatory reactions in the eyes of pilots), and most famously, as a bone-implant bonding material in hip replacement surgery in the early 1960s. General acceptance of PMMA as a biomaterial for intravertebral applications was not established until the late 1990s when the original French work was introduced to the English-speaking medical community by French Canadian Jacques Dion. This lead to an increased interest in minimally invasive procedures such as vertebroplasty (transpedicular injection of PMMA cement in the vertebral body) and kyphoplasty (injection of PMMA cement after inflation of a balloon(s) in the vertebral body) [11]. In the 2000s, the indications for these procedures expanded from primarily symptomatic osteoporotic vertebral compression fractures to painful spinal metastases, vertebral osteolysis in multiple myeloma, and traumatic burst fractures [14,15]. Although the precise working mechanism of spinal augmentation for most of these indications has not been fully elucidated, it was (and still is) generally believed that the resulting increase of mechanical stability (and thus less movement of microfractures) in intravertebral cancellous bone after cement injection led to an immediate and long-lasting decrease of pain. To the current authors best knowledge, Nakano and coworkers published the first series of patients undergoing vertebroplasty for painful osteoporotic vertebral compression fractures using a different (i.e. calcium phosphate) type of cement with the secondary goal of promoting physiological bone remodeling after stabilization [16]. Since the clinical results from this study were not different from the studies using PMMA cement, several hypotheses on the working mechanism for PMMA (including the effects of local toxicity or thermal damage from polymerizing methacrylate) were subsequently considered less plausible. Another topic of debate was the risk for adjacent level fractures after vertebroplasty or kyphoplasty to treat painful osteoporotic vertebral compression fractures. Although a definitive conclusion or consensus has not been achieved, most researchers and clinicians have agreed that mismatched elastic properties (i.e. Young's modulus) between augmented and non-augmented vertebral bodies plays an important role in the etiology of adjacent level fractures [17].

The examples above illustrate the urgent need for a wider range of biomaterials that are better designed for the specific clinical conditions, taking into account factors that include biocompatibility/degradability (especially for younger patients), stiffness (relative to patient's own bone mineral density), and safety (in case of cement leakage). Moreover, since biomaterials are increasingly being used for augmentation of methapyseal fractures of various anatomic locations (e.g. humerus, femur, distal radius, and tibial fractures), there is a growing number of scientific reports on that topic. In spinal surgery, these reports focus on the attempt to reinforce pedicle screws in the osteoporotic spine or to fill (large) voids in cages after reconstruction of spinal defects. Additionally, characteristics specific for the bone-implant interface, such as crack formation and propagation, are also gaining interest from researchers [18].

Augmentation of the spine

Several studies have shown that increased amounts of PMMA injected during procedures such as vertebroplasty and kyphoplasty are associated with higher stiffness, higher risk of cement leakage (the most frequent complication after vertebroplasty/kyphoplasty procedures), and potential exothermal damage while not improving clinical outcome. The optimum amount of cement injected should therefore relate to the least amount needed for clinical efficacy. It has been demonstrated in several studies that this minimum amount corresponds to approximately 15% of the vertebral volume to be treated [19]. Other factors associated with a lower risk of cement leakage have also been identified: using balloons (as in kyphoplasty procedures Figure 1a) prior to cement injection; employing large-diameter needles to keep injection pressure low; using high viscosity cement; and visualizing/monitoring the region of interest with high-quality fluoroscopy equipment. It must be noted that for good clinical results, the careful selection of patients supported by the appropriate imaging techniques is still of greatest importance. When augmenting pedicle screws with biomaterials, some principles from arthroplasty cementing techniques may apply, including achieving an even cement mantle between pedicle screw and cancellous bone and allowing for undisturbed polymerization of the cement mantle until plastic cement deformation is no longer present. In larger spinal defects (e.g. after gross resections or when filling metallic cages), the benefits of using biocompatible/degradable cements may be limited, considering the large distances and volumes involved with respect to potential vascular ingrowth necessary for bone remodeling and creeping substitution.

Augmentation techniques for the humerus

Fracture fixation of the proximal humerus in patients with reduced bone quality still poses a great challenge to the surgeon. Despite the development of new and improved implants, secure anchorage of the implants with screws or blades in the trabecular bone of the proximal humerus remains the weak link for fixation and is mainly responsible for implant-related mechanical failures. Initial attempts to improve screw fixation in the humeral head used fibular grafts to augment the trabecular bone of the humeral head [20]. Later, biomechanical [21] and clinical studies [22] reported improvement in implant anchorage by using calcium phosphate cements to augment the central void in the humeral head. Recent developments of cannulated and perforated

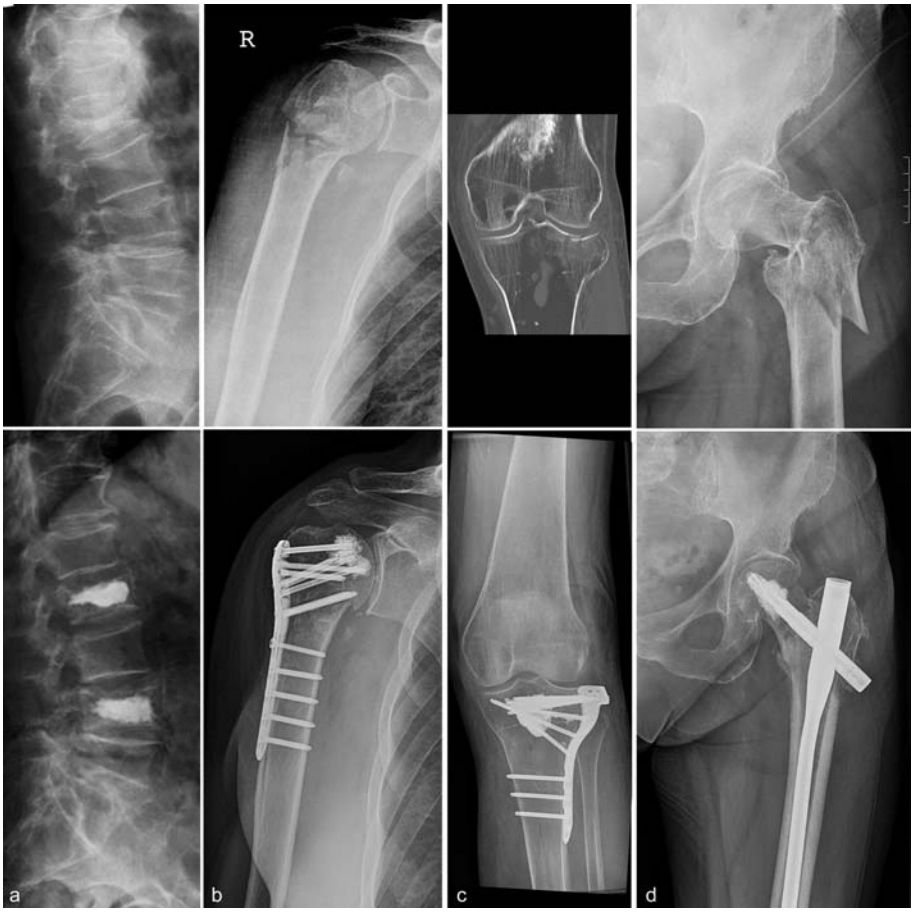

Fig. 1. Pre- and post-operative radiographs after operative treatment using different augmentation techniques. (a) vertebral fracture treated with PMMA kyphoplasty; (b) proximal humerus fracture treated with a PMMA augmented plate osteosynthesis (PHILOS ®); (c) proximal tibia fracture treated with internal fixation after filling of the subchondral void with calcium-phosphate cement; (d) trochanteric fracture treated with a PMMA augmented PFNA (Proximal Femur Nail Antirotation, Fa. Synthes).

screws in combination with angular stable plates enable fracture fixation in a conventional way and allow in-situ augmentation of the screws with polymethyl-methacrylate (PMMA) cement (Figure 1b).

In a biomechanical in-vitro study, the effect of in-situ augmentation on implant anchorage was investigated in a three part fracture model [23]. Fracture fixation was carried out using an angularly stable plate and cannulated screws to allow for the augmentation of the proximal screws with 0.5 ml of PMMA cement. Paired humeri (control and augmented) with reduced bone quality were used for two differently simulated loads (torsion and varus bending). Cyclic loading, with a constantly increasing load magnitude, to implant fixation failure was applied in both loading conditions. Compared to the contralateral control group, augmentation resulted in a significantly increased number of load cycles and failure for varus bending and torsional loading. While implant anchorage showed a strong correlation with bone quality in the control group, the augmented group showed no correlation between implant anchorage and bone quality. However, it was shown that the improvement of implant anchorage by augmentation (difference between control and augmentation) correlated with bone quality, and augmentation was most effective in low bone quality and negligibly effective in good bone quality (Figure 2).

Due to a non-uniform distribution of bone quality in the humeral head, investigators still debate which and how many screws are most beneficial for augmentation. In order to determine which screws had the least purchase and would benefit the most from augmentation, a study was performed evaluating the local bone quality in the humeral head by measuring the breakaway torque at the screw tip [24]. The screws in the anteromedial and anteroinferior aspects of the humeral head showed the lowest breakaway torques and were selected for augmentation with 0.5 ml of PMMA cement. Using a similar test setup for varus bending, the effect of in-situ augmentation of two screws with the lowest breakaway torque achieved almost the same stability as augmentation of the four most proximal screws.

Augmentation techniques for hip fractures

According to epidemiologic data, there is an increasing incidence of hip fractures, with an estimated 1.7 million fractures worldwide per year in 1990 to an expected number of 6.3 million per year in 2050 [25]. Given the importance of maintaining function and independence in the geriatric patient population, the use of PMMA for augmentation of fixation in hip fractures is of growing. The use of bone cement augmentation has been reported for plate, screw, and nail osteosynthesis in elderly patients [26,27], demonstrating increased bone-implant interface, improved implant anchorage, reduced screw cut-out, and improved early full-weight bearing [26,28]. The treatment of trochanteric fractures with a DHS (Dynamic Hip Screw) augmented with PMMA or a resorbable bone cement based on calcium phosphate has shown greater biomechanical strength, faster pain reduction, and improved healing compared to a control group [27].

In a clinical prospective study of 64 patients with 31-A2 and 31-A3 fractures of the proximal femur, treatment with a PMMA-augmented DHS showed good fracture consolidation without any adverse complications such as avascular necrosis of the femoral head [29]. However, intramedullary nailing was associated with improved biomechanical stability relative to extramedullary fixation techniques

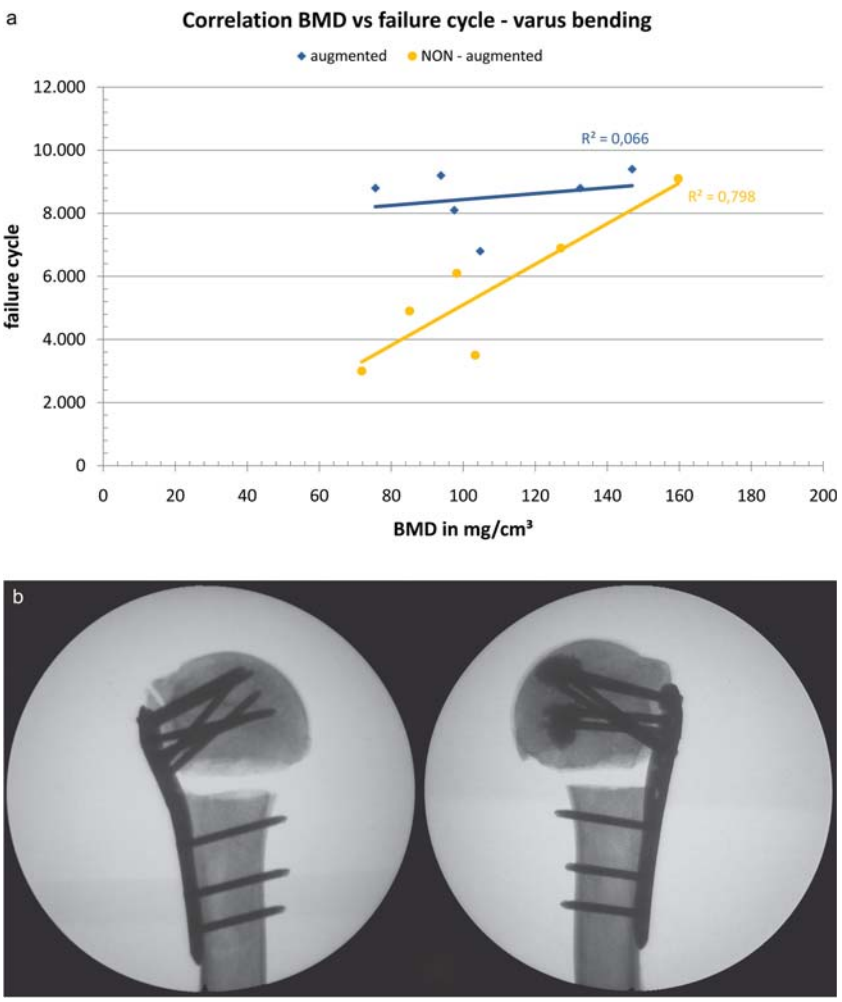

Fig. 2. Biomechanical analysis of cement augmented plate osteosynthesis in a proximal humerus fracture. (a) Graphic representation of the correlation of BMD vs. failure cycle and (b) Radiographic image of the model used for the mechanical testing [23].

[26], and the use of PMMA-augmented intramedullary nailing of proximal femur fractures is another potential area for improved fixation using augmentation techniques. Using a special high viscosity bone cement (Traumacem V+) applied via a PFNA blade, augmentation can be safely and effectively achieved using similar standard implantation techniques to the non-augmented device [28]. Instead of the conventional spiral blade (Figure 1d), a perforated spiral blade is used in cement-augmented PFNA nailing to better achieve dissemination of the cement in the femoral head. Prior to the introduction of cement using this technique, the possibility of intraarticular leakage into the hip joint should be evaluated by injecting a dissolved contrast agent, which can subsequently be cleared with a saline flush. After mixing a high viscosity bone cement (such as Traumacem V+) with a specially-designed cement kit, the bone cement is injected into the blade by using a trauma needle kit under fluoroscopic control. Approximately 3–5 ml of cement should be injected via the blade, not to exceed a maximum volume of 6 ml bone cement should not be exceeded. Hardening of the cement takes about 10–15 minutes [30]. In the intra- and post-operative radiographs, a central distribution of bone cement around the top of the spiral blade is desirable.

Augmentation techniques for tibia plateau fractures

Tibial plateau fractures make up about 2% of all fractures and about 10% of fractures in the elderly. This type of fracture usually results from direct axial compressive forces applied in conjunction with a valgus force. With increasing age, the subchondral bone and the underlying cancellous bone are less able to resist axial loading, resulting in a split or depressed fracture. The treatment goal, as with most intraarticular fractures, is to reestablish joint congruency, and restore range of motion, alignment, and stability. One of the major problems with fractures that involve a depressed articular fragment is to maintain the reduction of the fragment during the course of healing.

The classic method to support the elevated articular fragment is through filling of the subchondral void with autologous or allogenic bone transplant. However, conventional bone transplants are often weak, and weight-bearing during healing has to be restricted to prevent subsequent displacement of the fracture and avoid subsidence of the elevated articular fragment; full weight-bearing is usually restricted for 6–12 weeks post-operatively, including when bone graft is used [31–33]. In addition to the lack of adequate mechanical support during healing, autologous bone transplants are also associated with draw-backs related to donor-site morbidity that can be significant. As a substitute to autologous bone transplants, various biomaterials have been introduced for use in the filling of subchondral voids in tibial plateau fractures (Figure 1c).

Composites for subchondral void filling offer a variety of potential options with regards to their physical, mechanical, and biological properties. These materials frequently are available as preformed blocks that can be tailored to defects as well as substances that are injectable and self-hardening materials to fill bone voids intraoperatively. The mechanical property most often used to characterise the mechanical behavior of a bone graft substitute is compressive strength,

which is critical for avoiding subsidence. Material hardness is another relevant property that impacts shock absorbance in the subchondral bone. If a material is too hard, the mechanical environment for the overlying cartilage might be negatively affected. Even though the compressive properties are important, a fracture site is also subject to shear and bending forces. When using materials with low bending and shear resistance, it is necessary to use screws or other hardware to neutralize these forces to provide a mechanical construct that can withstand not only compression forces, but also shear and bending forces. When using bone graft substitutes, the available materials possess a wide variety of biological properties, which range from non-resorptive to gradually remodeling, to rapidly degrading characteristics. Bone graft substitutes should cause no or a very limited inflammatory reaction in the surrounding tissues following implantation. While many materials are biologically inert, it is common for many classes of materials to exhibit some osteoconductive properties while few provide an osteoinductive effect. The preferred material for a given clinical situation depends on a number of factors, which include type of injury, patient age, physical demands, bone quality, and surgeon experience.

Composites for augmentation

A variety of biomaterials are used for a range of clinical purposes, including augmenting vertebral bodies to resist axial loading, reinforcing implants at the bone-implant interface, and filling voids created by osteotomies, resections, and reconstructions. The characteristics of biomaterials are increasingly being individualized and are also starting to incorporate patient-specific parameters. Properties for an ideal bone substitute include: (1) void filling capacity; (2) structural support; (3) osteoconductivity; (4) osteoinductivity; (5) osteogenicity; (6) minimal morbidity; (7) cost-effectiveness; and (8) unlimited availability. There is currently no bone substitute that fulfills all of these requirements, and substitutes should be chosen based on the most critical need when treating a particular fracture (Table 1). In general it seems reasonable that the material should be replaced by bone over time. However, when used in osteoporotic fractures, mechanical competence over time is far more important than remodeling. This means that for osteoporotic fractures the most important characteristics for the ideal substitute seems to be offering mechanical stability while remodeling and replacement by host bone seems less important. As a result, the research field of augmentation composites is expanding rapidly. Of the various bone graft substitutes available at present, injectable calcium-phosphate compounds are by far the most widely documented for use in tibial plateau fractures. Based on published studies it seems that calcium-phosphate cement can be a good alternative to bone grafting for filling of a subchondral void in tibial plateau fractures. This section will summarize some of the recent developments in new composite technology and provide an overview of the available composites for osteoporotic bone augmentation.

Hydroxyapatite

In fractures that involve a metaphyseal defect, such as is present in many tibial plateau fractures, preformed blocks of hydroxyapatite can be used to fill the void. In a study by Bucholz et al. [34] published in 1989, forty patients with tibial fracture fractures were randomized to filling of the subchondral void with either contoured porous hydroxyapatite blocks combined with hydroxyapatite granules or autologous cancellous bone harvested from the ipsilateral iliac crest. All patients underwent conventional screw and plate fixation. Radiological and clinical assessments up to an average of 35 months did not reveal any significant differences between the two groups. Biopsies at the time of planned hardware removal in 7/20 patients in the hydroxyapatite group showed incorporation of the hydroxyapatite block by bone ingrowth with close apposition of new bone against the implanted block. There was no apparent evidence of implant resorption or inflammatory activity. The authors concluded that porous hydroxyapatite was an excellent osteoconductive scaffolding for bone ingrowth, and that the biodegradation occurred at an extremely slow pace.

PMMA

Injectable materials that harden in-situ, such as standard polymethylmetacrylate (PMMA), can be used to improve screw purchase in osteoporotic bone, fill subchondral voids in tibial plateau fractures, and augment metaphyseal fracture stabilization at other anatomical locations. Even though PMMA has been used successfully for augmentation in osteoporotic fractures, including hip and wrist fractures, [35–37], some clinicians still have concerns about using PMMA for augmentation in the treatment of fractures of the extremities. The perceived potential drawbacks include an exothermic reaction during curing, inability of the cement to be remodeled, risk of inhibiting fracture healing if interposed between fracture surfaces, and difficulty in removing the cement if revision surgery becomes necessary.

Temperature considerations in PMMA augmentation

PMMA polymerization may lead to the development of supraphysiological temperatures and harm the surrounding bone tissue and cartilage. In one basic research study, temperature was monitored in the proximity of in-situ PMMA augmented screws, the subchondral bone, and on the articular surface during augmentation of four screws in the humeral head [38]. Overall, only small temperature increases were reported. The temperature increase was highest at the screw tips and decreased with increased distance from the cement. The maximum temperature measured on the articular surface during polymerisation was 38.3°C. The highest temperature at the subchondral bone was 43.5°C, which is well below the stated threshold for necrosis and apoptosis of bone tissue in the literature.

Table 1.
Characteristics of bone augmentation materials.

	Void filler	Structural	Inductive	Conductive	Osteogenic	Low morb.	Low cost	Unlimited
ATBG								
S-ALG								
NS-ALG								
DBM								
CaP								
CaS								
PMMA								

ATBG = autologus bone graft, S-ALG = Structural Allograft, NS-ALG = Non Structural Allograft, DBM = Demineralized Bone Matrix, CaP = Calcium Phosphate, CaS = Calcium Sulfate, PMMA = Polymethylmethacrylate. Dark Pink = Strongly Advantageous; Salmon = Weakly Advantageous; Light Pink = Not Advantageous.

Another in vivo study investigated the effect of subchondral PMMA injections in sheep knees [39]. The subchondral bone tissue and joint cartilage were evaluated by high-resolution peripheral quantitative computed tomography imaging (HRpQCT), histopathological osteoarthritis scoring, and glycosaminoglycan content in the joint cartilage. Compared to the untreated control knee, no significant differences were found. The authors concluded that PMMA implant augmentation of metaphyseal fractures does not harm the subchondral bone plate or adjacent joint cartilage.

Bioglass

Various compositions of bioactive glass have been shown to be bone-bonding and osteoconductive, with potentially beneficial effects on bone formation and healing, angiogenic stimulation, and antibacterial activity [40,41]. Granules made of silicate glasses containing sodium, calcium and phosphate have been used for filling of the subchondral defects in tibial plateau fractures. In a randomized study, Heikkilä et al. [42] used bioactive glass granules or autologous bone to fill subchondral voids. At one year, there were no significant differences between groups in radiological, clinical, and subjective patient evaluations. In another prospective randomised study with 11-year follow-up, similar results were reported with no differences reported between bioactive glass and conventional autologous bone graft treatment groups [43].

Calcium sulphate cements

Injectable calcium sulphate has been used to fill subchondral defects in tibial plateau fractures in clinical series [44,45]. Although calcium-sulphate is brittle, injectable calcium-sulphate cements with compressive strengths similar to that of cancellous bone have been developed. Alpha and beta hemihydrate have been developed, with the α-form providing a more strength than the β-form, mainly due to differences in the density. Different products have quite different properties, with compressive strengths ranging from only a few MPa to almost 100 MPa, despite belonging to the same class of materials. Calcium sulphates degrade rapidly and independently from bone formation. Due to this rapid degradation, there is a risk that strength that the loss of strength will occur too rapidly. In a study evaluating calcium sulfate in a canine model, a material with an initial strength exceeding the strength of normal cancellous bone had a significantly decreased compressive strength at 26 weeks (only 0.6 Mpa) [46]. Additional studies comparing calcium-sulphate with other products and with autologous bone are needed in order to better define proper indications.

Calcium phosphate

So far, the most widely evaluated bone graft substitute for tibial plateau fractures is calcium-phosphate cement. Calcium-phosphate mimics the mineral phase of bone. Animal studies have shown that calcium-phosphate is osteoconductive and undergoes gradual remodeling over time, although this process seems to be very slow. When used in the injectable form, it cures in vivo without exothermic reaction to form an apatite that, within a few minutes, achieves compressive strength greater than normal cancellous bone. However, as for calcium-sulphate cements, there is a wide variation in strength as well as other properties between different products.

In two separate case series it was shown more than a decade ago that calcium-phosphate cement was a viable alternative for filling subchondral voids in tibial plateau fractures. Lobenhoffer et al. [47] used calcium-phosphate cement in combination with conventional hardware for fixation of 26 tibial plateau fractures. Patients were followed up to three years with radiological and clinical evaluations. The conclusion was that the material provided for a successful outcome with few complications. In another case series, calcium-phosphate cement was used in 49 patients to fill subchondral voids in combination with minimal internal fixation. At one year after the procedure, the authors found calcium-phosphate to be a useful alternative to bone graft in tibial plateau fractures [48]. In a randomized study comparing calcium-phosphate cement to autologous bone graft, the subsidence of the articular fragment was measured using radiostereometry. Despite more aggressive rehabilitation with full weight bearing at 6 weeks in the group treated with calcium-phosphate cement compared with 12 weeks in the group treated with autologous bone, the average subsidence was 1.41 mm in the group treated with calcium-phosphate cement compared with 3.88 mm when using autologous bone graft [49]. In another randomized study, 120 patients with a tibial plateau fracture were randomized to subchondral void filling with either calcium-phosphate cement or autologous bone graft. With a follow-up of up to one year, the investigators concluded that calcium-phosphate cement appeared to have less subsidence compared with autologous bone graft [50].

Biomechanical and clinical considerations

Based primarily on PMMA, the use of cements has become widespread for spinal augmentation. PMMA is biologically inert, does not result in a significant inflammatory reaction, and has the capacity to provide immediate multidirectional mechanical stability even before the polymerization process is completed. The stiffness of PMMA cement has been shown to range between cortical and cancellous bone [51]. This property may also result in osteoporotic fractures at levels adjacent to those augmented with PMMA, prompting researchers to develop PMMA-based cements with altered biomechanical properties to better approximate the decreased stiffness of osteoporotic cancellous bone. The stiffness of PMMA cement can be changed, for example, by adding compounds such as hydrogels, which influence the porosity of the end product, or by modifying the basic chemical components of the cement. Calcium phosphate cements have been shown to have comparable stiffness to PMMA-based cements during compression tests. However, under shear loads, calcium phosphate cements have been observed to fail early compared to PMMA-based cements in in-vitro tests. When injected into confined spaces, such as in simple vertebral compression fractures, this characteristic may have minimal clinical implications since shear loads in these relatively stable fracture configurations are small, and even in the presence of some cracks/fissures, the axial load bearing capacity may not be affected significantly. In applications where shear-stress, translation, and torque can be expected (for example in highly unstable spinal fractures or after pedicle screw reinforcement), calcium phosphate cements may be less suitable than PMMA cements unless they are protected by additional instrumentation. Some authors have, however, obtained good results for these challenging applications with calcium phosphate cements in both in vivo and clinical settings [51].

Several studies have recently been completed or are underway evaluating cement screw augmentation of angularly stable plate fixation in proximal humerus fractures. Similarly, there have been promising reports of the safe and effective use of PMMA in the augmentation of the proximal femoral nail antirotation (PFNA) device in a multi-center study [30,52].

Removal of augmented screws

Despite the promising mechanical results for in situ screw augmentation, complications such as infection, implant failure, and necrosis lead to the need for implant removal. Therefore, the removal of in situ PMMA augmented screws for angular stable plates of the proximal humerus was investigated in a laboratory setting [53]. Screw extraction torque was measured in 14 augmented screws and

compared to 14 control screws in the contralateral humerus. Additionally, frozen cut sections along the screw axes were carried out to macroscopically assess the integrity of the cement bone interface. Extraction torque for augmented screws was not increased compared to the control group and macroscopically there was no damage to the trabeculae within the humeral head due to screw removal. Therefore it was concluded that the removal of in situ PMMA augmented screws from an angular stable plate can be accomplished without additional damage to the bone-cement interface. These results are in accordance with clinical observations of implant removal in other anatomic locations following augmented screw fixation.

Conclusion and future directions

In summary, various treatment options for the use of augmentation in osteoporotic fracture fixation are currently available [54–59]. Different composites can be used for reconstruction of osseous defects in fragility fractures in different anatomic locations. Strengthening implant fixation through the use of materials such as PMMA have shown promising mechanical and clinical results, with a majority of these materials showing remarkable biocompatibility. Given the demographic changes of our aging population, the need for early weight-bearing and mobilization to avoid complications and the loss of function and independence in older patients is of great importance. Therefore, the need to develop biomaterials that improve fixation in osteoporotic bone is of great importance. Additional studies are necessary to evaluate the mechanical, clinical, and biomedical aspects of augmentation using different composites and in different injuries.

Conflict of interest

Dr. Christian Kammerlander has been involved in educational activities with DePuy Synthes. All other authors declare no conflict of interest.

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Periprosthetic fracture fixation in osteoporotic bone

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KEYWORDS

Periprosthetic fracture
Interprosthetic fracture
Nail
Plate
Cement augmentation

ABSTRACT

Fixation techniques of periprosthetic fractures are far from ideal although the number of this entity is rising. The presence of an intramedullary implant generates its own fracture characteristics since stiffness is altered along the bone shaft and certain implant combinations affect load resistance of the bone. Influencing factors are cement fixation of the implant, intramedullary locking and extramedullary or intramedullary localization of the implant and the cortical thickness of the surrounding bone. Cerclage wires are ideally suited to fix radially displaced fragments around an intramedullary implant but they are susceptible to axial and torsional load. Screws should be added if these forces have to be neutralized. Stability of the screw fixation itself can be enhanced by embracement configuration around the intramedullary implant. Poor bone stock quality, often being present in metaphyseal areas limits screw fixation. Cement augmentation is an attractive option in this field to enhance screw purchase.

Introduction

Since arthroplasty numbers are rising, the periprosthetic fracture fixation becomes more and more a concern [1]. Patient's condition and postoperative requirements render the treatment challenging. A high primary stability is needed due to the fact that partial weight bearing is impossible for many patients. Undiagnosed loosened prosthesis stems, being considered as stable during surgery contribute to the high failure rate actually reported for periprosthetic fracture osteosyntheses [2].

The main fixation techniques currently applied comprise revision surgery with conversion to a longer non-cemented prosthesis stem bridging the fracture zone, plate osteosynthesis and intramedullary nailing.

Although the choice of the fixation method is still individualized depending on the patient's condition and the surgeon's selection, certain biomechanical principles could be deducted from recent biomechanical studies. Varying fracture gap configurations fixed with different plate types and screw configurations have been widely investigated [3–6]. Vice versa, the type of implants and their configuration additionally affect fixation stability [7]. Apart from the working length of the implant, additional factors have to be taken into account, since intramedullary and extramedullary implants are both interacting in a fixed periprosthetic fracture [8]. Interprosthetic fractures, sometimes requiring a fixation in-between two prosthesis stems represent a separate category [9].

Osteoporotic bone quality is a special concern in metaphyseal fracture locations like periprosthetic fractures of the distal femur at non-constrained bicondylar total knee arthroplasties [10]. Screw purchase in this almost cancellous bone area is limited. Implant augmentation is an option to enhance fracture fixation [11].

Current mechanical aspects of periprosthetic fracture fixation are summarized in this article, focusing on implant mechanics and their affection of bone strength as well as the use of augmentation in periprosthetic fracture fixation at the distal femur.

Biomechanics of periprosthetic fracture fixation

Bone quality, stability of the stem anchorage and fracture pattern have direct impact on periprosthetic fracture fixation strategy. Periprosthetic fractures with intact stem anchorage are the domain of osteosynthesis. They are often located around the tip of the stem where the bending stiffness drops, since the bone is not splinted by the prosthesis stem any more. Simple fractures with closed fracture gap and medial cortical support allow partial load transfer via the cortex. In open fracture gap situations like comminuted fractures without medial cortical support a single lateral plate might not be stable enough for weight bearing and a stiffer plate or a double plating construct has to be

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used to prevent implant fatigue failure [6,12]. A finite element analysis study has shown, that anterolateral double plating as well as long stems equalize implant stress distribution, increases construct stiffness and reduces interfragmentary movements at the fracture gap [13].

Not requiring intraosseous anchorage, cerclage wires are almost independent from local bone quality [14]. Their force transmission runs centripetally to the loop, fixing radially displaced fragments. Cerclages are ideally suited for centripetal fracture reduction and fracture fixation on the level of the stem, since an intramedullary splinting is present [15]. Due to the fact that the long bone shaft is not an idealized round tube, the cerclage effects an uneven pressure distribution on the bony surface with high pressure values at the deflection edges [16]. Comparable to the point contact fixation of modern plating systems the cerclage spans from edge to edge with non-loaded zones in-between (Figure 1). The contact surface of a tightened 1.5 mm wire or 1.7 mm cable cerclage ranges from 0.30 to 0.36 mm [14]. In congruently reduced shaft fractures, it is unlikely to produce a fracture or grade cutting by cerclage tightening, since the cortex withstands static concentric pressure [16]. Loading the cerclage fixation revealed no microfracturing at the shaft cortex [16]. The groove formation, the so called biological loosening of a cerclage [15] is induced by the micro movement of an already loosened cerclage and not by the weakness of the cortex itself [15–17]. Instead of cortical bone resorption, a bony ingrowth was observed for well tightened cerclages [16–18]. Noteworthy loss of pretension almost occurs at the twist. Apart from using a larger wire diameter, pretension could be influenced by the twisting procedure. Highest pretension is obtained when the twist is formed under permanent traction by the pliers, the twist is plastically deformed at the end of the twisting procedure, wire ends are cut outside the twist and when the twist is bent forward at the end of the procedure [19]. Backward bending should be avoided, since 90% of the pretension gets lost throughout this manoeuver. When plastic deformation of the twist is accomplished, the twisting procedure has to be stopped before twisting off the wire [19]. Cable cerclages, closed by a crimp achieve higher pretension values compared to wire cerclages. Looping the wire cerclage twice around the bone before closure effects pretension values comparable to a cable cerclage of the same diameter looped once. According to the tackle principle, the twist is less loaded in the double looped configuration and a higher amount of travel is needed to provoke loosening of the cerclage [20]. Ogden proposed a plating construct with cerclage fixation on the level of the stem and bicortical fixation in the opposite fracture fragment [21]. Clinical results of this construct exhibited an overall complication rate of 30% [21] comparable to the failure rate of allograft struts (24%) placed on the lateral and anterior aspect of the long bone shaft and fixed by cerclages [22]. If load is applied in axial direction and torsion, the bone slides under the cerclage [14] if it is not maintained by the interdigitation of the fracture fragments. To add stability in axial direction and torsion, cerclage-plate constructs should be combined with locking screws [5,14].

Screws could be either placed monocortically or bicortically within the narrow bone corridor lateral to the prosthesis stem. Tangential intracortical screw placement which reduces fixation strength has to be avoided during bicortical screw insertion [5,23]. In conventional nonlocking plates, the screw insertion angle could be varied within the plate hole allowing bicortical screw placement. The fixation principle of nonlocking screws, requiring a tight frictional coupling at the plate-bone interface is not suited for osteoporotic bone [24,25]. Multiaxial locking screws are one solution of this shortcoming [26]. Broader plates with laterally placed screw holes [6] or attachment plates shifting the screw entry point to the lateral allow an embracement configuration of the bicortical locking screws, a very effective way to enhance fixation stability (Figure 2) [5,27]. Compared to cerclages combined with monocortical locking screws, the shaft embracement of bicortical locking screws realized by the locking attachment plate provides superior stability especially in fractures with lacking cortical support [27].

Under axial compression force, orthogonal to the screw shaft axis, monocortical and bicortical locking screws of the same diameter achieve comparable fixation strength [14]. In both, most of the load is transferred at the near cortical hole. An ovoid enlargement of the near cortical hole and a longitudinal fissure of the near cortex was observed during failure. Since the fissure is located below the osteosynthesis plate, it could not be detected on conventional radiographs. Detection of the ovoid hole enlargement on radiographs is sometimes possible by meticulous analysis [14]. The neutralization of torsional forces requires bicortical fixation in both, the proximal and the distal fracture fragment [14].

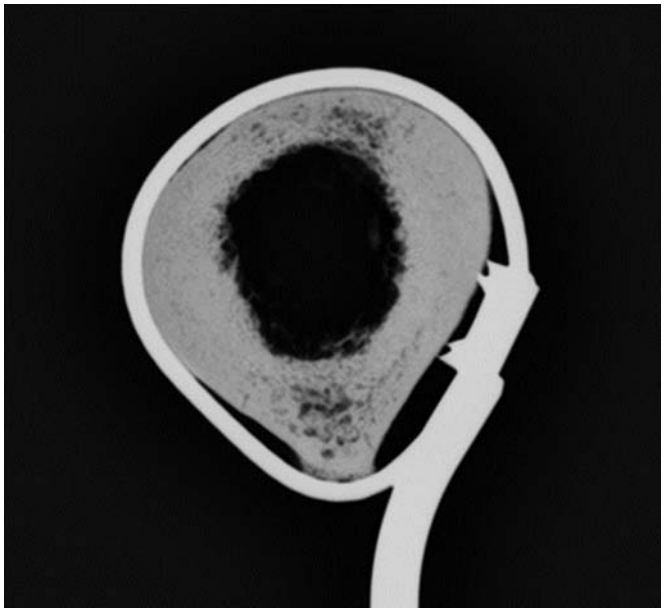

Fig. 1. Cerclages, being deflected at the edges of the bone and providing a point contact fixation with non-contact zones in-between.

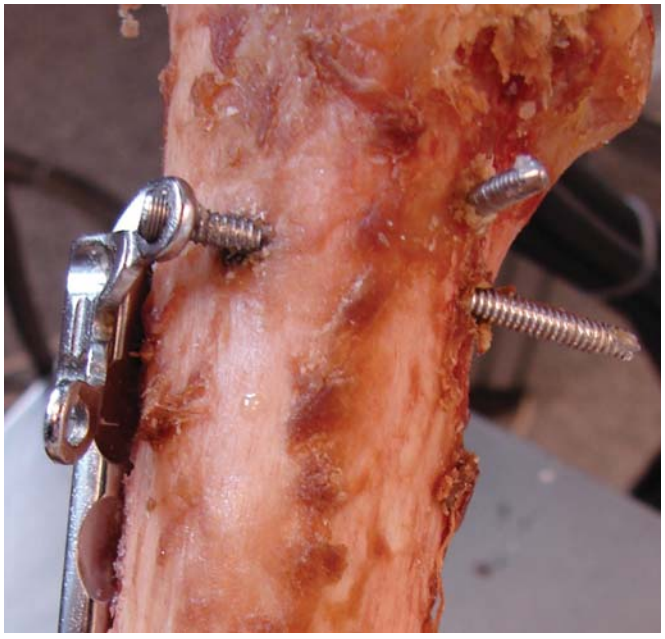

Fig. 2. Plates, shifting the screw entry point more laterally and allowing an embracement configuration of the locking screws around the intramedullary implant.

Up to now, it remains controversial, if screws could be anchored in the cement mantle of cemented stems without damage of its integrity provoking loosening of the stem [28]. The potential of this option has not been investigated in detail jet. In osteoporotic bone, a screw placement in the cement mantle would enhance screw purchase [28].

According to the actual consensus, a stem replacement is considered the best treatment option in case of stem loosening (Vancouver type B2 fractures). In case of modest bone stock (Vancouver type B3), treatment might end up at megaprostheses, whose surgery is very consuming for the patient. In this context, screw fixation in the prosthesis stem might be an idea worth considering [29]. Although this technique is not yet established, prototype tests show promising results, rendering the fixation independent of the surrounding bone and allowing a minimal invasive surgery. Drilling the metal stem requires special drill bits and a suction and collection system to remove the metal debris, which would induce stem loosening, if kept in situ. Future stem designs could provide holes for intraprosthetic screw connection to avoid the drilling procedure.

Osteosyntheses of Vancouver type A_G fractures (fractures of the greater trochanter) exhibit a high failure rate [30]. Current fixation techniques include cerclages, tension band wiring and plates, but often provide unidirectional stability in the laterosuperior direction. Most of the biomechanical studies support this misunderstanding by focusing on a one-dimensional load application. Tension forces of the gluteus sling muscles acting on the greater trochanter are multidirectional, especially in activities like stair climbing and rising from a chair [31]. Recent clinical and biomechanical data revealed that double plating on the anterior and lateral aspect of the greater trochanter improves fixation strength and lowers failure rates [32,33].

How do implants affect bone strength?

The number of orthopedic implants continuously rises, especially in the hip and knee, which impacts the stability of the affected bones. Considering a scenario with a single proximal prosthesis in the femur, changes in the stiffness of the bone increases the risk for a fracture of the femur of up to 30% [9,34]. If, at the same time, another intramedullary force carrier (i.e. a nail) is implanted on the ipsilateral side next to a proximal prosthesis the risk for interprosthetic fracture further increases (Figure 3). Compared to an unoperated native femur only half the force is required to induce a fracture to the operated femur [9]. Thus, this combination represents one of the highest risk for a fracture. It is somewhat different when two cemented stems from a hip and knee prosthesis come to lie in the femur. Own biomechanical studies have shown that in this scenario, the risk for a fracture is different. This may be due to the locking screws of the nail, which represent a "locus of minor resistance" because of their transmitted stress riser to the cortex. The distance between these cemented implants does not seem to play an important role. Much more important is the cortical thickness of the femur that has major influence on fracture risk [35]. The risk of suffering from a fracture between a proximal prosthesis and an extramedullary implant for example a locking plate is significantly lower. It can be concluded that an extramedullary plate might be biomechanically advantageous for the treatment of supracondylar femoral fractures in the presence of a hip prosthesis at the proximal side.

There is abundant clinical evidence that loosened prostheses, either cemented or uncemented increases the risk for a fracture around the prostheses [36]. However, this scenario is difficult to simulate in

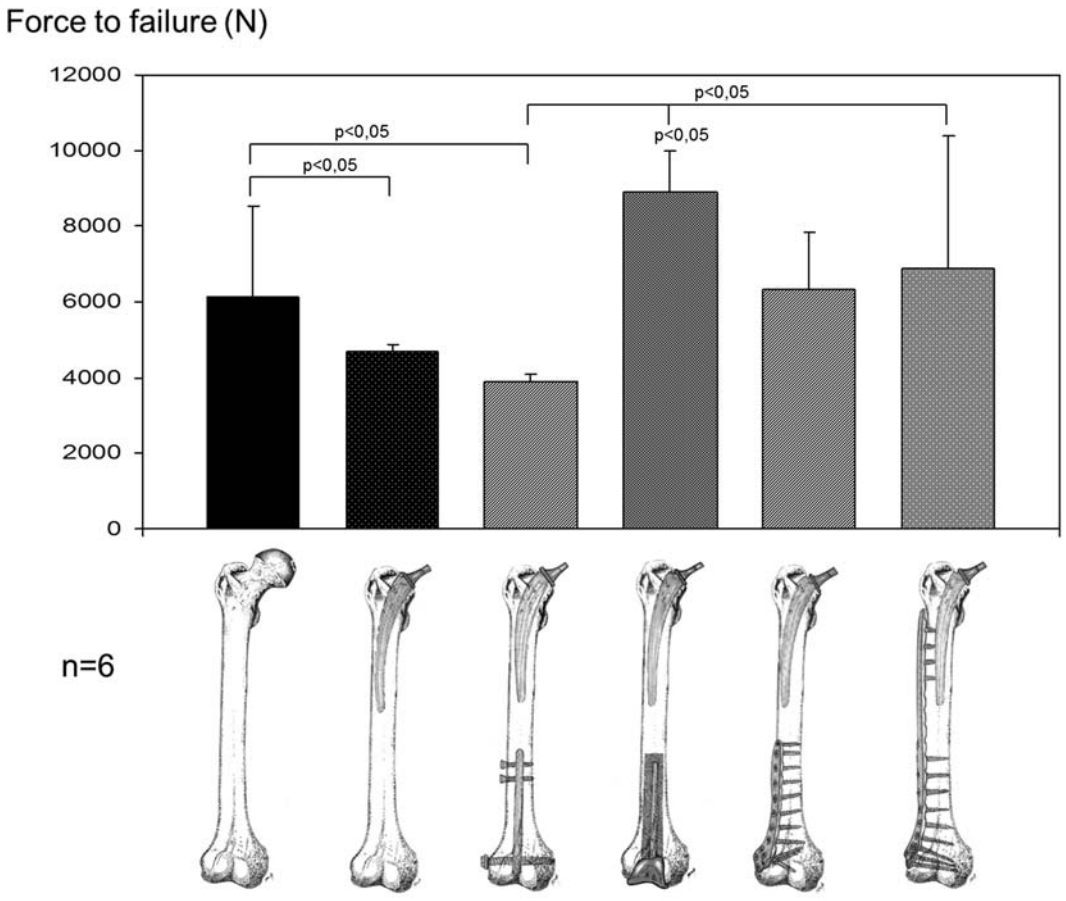

Fig. 3. Fracture strength. Average load to failure in different groups in a biomechanical testing. The required fracture force further decreases considerably if a retrograde nail was implanted. A constrained knee prosthesis did not show this effect; the large cement mantle imparts a very high required fracture force. With extramedullary locking stable plates in the distal femur, the risk for a fracture is not as high as with a retrograde nail.

biomechanical experiments because loosening of the stem over time cannot be modeled adequately.

Which therapeutic possibilities do we have for interprosthetic fractures? Numerous articles came up for periprosthetic fractures around a hip replacement or knee prosthesis, which deal with the various modes of treatment of these injuries. These include the stabilization of non-stable-angle plates, angle-stable plates, cerclage wires, additional allogeneic bone or exchange of the prosthesis [37–39]. It could be shown that the stabilization with locking plates is superior to all other methods, as long as the prostheses are not loose [40–41]. If the prosthesis is loose, replacement might be the most favorable treatment option [42]. Treatment strategies for injuries between two implants on the femur are very limited. Apart from specific risks that are related to the bone quality, general risk factors such as the general condition of the often elderly patients plays also a significant role. In addition, the particularly difficult perfusion status of the bone increases the risk of delayed fracture healing or nonunion.

It has been shown that comparable to periprosthetic fractures in interprosthetic fractures also some of the prosthesis are loose [43]. In such cases, the prosthesis has to be replaced. But in these particular cases, we have implants on the proximal and on the distal side and under certain circumstances this can lead to a replacement of the whole femur [44]. McLean et al. report on 5 patients with complete exchange of the femur after periprosthetic fracture, with good results [42]. Usually, however, plate fixation is sufficient. Mamczak et al. describe a series of 25 patients with 26 interprosthetic fractures within 20 years that were treated with plate osteosynthesis [45]. Here, in 17 cases the distal metaphyseal part of the femur was affected while only nine times the diaphysis below the hip prosthesis was involved. This observation was made also by other authors, which observed most fractures in the supracondylar region [46]. Mamczak et al. have had no non-unions and all patients were started full weight bearing after 13 weeks [45]. The authors state that gentle surgical technique and overlapping of the plate to the proximal and distal end of the prosthesis to bridge the stress riser are most important. A recommendation how far the plate should overlap the end of the prosthesis is not given. In this context, the term “stress riser” is well known in the literature, but precise criteria could not yet be established. Our own biomechanical studies indicate that the distance between the implants is less important than the cortical thickness [35]. Hou et al. report a series of 13 patients within six years [47]. Here, in four cases, the prosthesis on one side was loose and needs to be replaced by a longer prosthesis. This was possible without coming into conflict with the opposite prosthesis. All other cases were treated with locking plate osteosynthesis only. Unfortunately, there is no more information regarding the localization of the fracture in this paper. The plates were so long that they exceeded the end of the prosthesis more than twice the diameter of the diaphysis. Important for the consolidation of fractures using a plate osteosynthesis is the length of the implant-free zone in the femur bone. If this is particularly short and the biological architecture is already disturbed in many parts of the femur, this can have a significant effect on fracture healing. Soenen et al. Suggest, based on their experience in a multi-center study of 14 patients that have been classified with the Vancouver classification, to expand this classification for these specific injuries and call these Vancouver type D fractures [44]. In all 6 cases that were classified as Vancouver type D, after primary care with plate osteosynthesis they noticed bone healing disorders that needed revision either with an additional bone grafting or complete femur replacement [44]. Platzer et al. in a series of 23 patients in 16 years also mainly used plate osteosynthesis [48]. In 4 patients with a loose prosthesis a replacement has been performed. In 3 out of 19 cases, there was a delayed fracture healing or nonunion. Also a very successful series of instrumentation with locking plate osteosynthesis has been reported by Sah et al. in 22 patients over 4 years [49]. Additional cancellous bone chips were used and placed an average of 3 cerclage in the field of hip prosthesis in 7 patients in 6 cases. The cerclage wires were used only additive in all cases. The localization of the fractures were again mainly supracondylar.

Take together our data from biomechanical studies and clinical reports from the literature suggest variable effects of implants to the stability of the affected bone. Biomechanical studies have shown that a hip prosthesis alone increases the risk for a fracture significantly. With an ipsilateral retrograde nail the risk of fracture is double as high for the femur, as without an implant. Therefore, extramedullary implants seem to be superior for distal periprosthetic fractures. The situation is different with 2 cemented prostheses on the same side [7]. Here, the risk for a fracture is not as high as long as both prostheses are fixed. The influence of interprosthetic distance is not as high as one might suppose. The most important point is also not total bone density (BMD), but the cortical thickness. These observations should be taken into account when surgery is done at the distal end of the femur in the presence of a hip prosthesis. If an interprosthetic fracture appeared and there is no loosening of the stems the stabilization with locking plates seems to be the method of choice. This could be confirmed by the data from present clinical and biomechanical studies [9,24,44,48,49].

Augmentation as treatment option in periprosthetic distal femur fractures

Osteoporotic fractures are an unsolved problem in today’s orthopedic and trauma surgery [50–58]. Fractures of the distal femur are associated with major complications (e.g. thrombosis, embolism, immobilization) [50,59]. Especially the periprosthetic distal femur fractures present surgeons with a major challenge in implant fixation and implant anchorage. Thereby, the metaphyseal part is the most difficult, due to the restricted space and the poor bone stock quality. Periprosthetic distal femur fractures can be treated using different implant options. Retrograde intramedullary nailing is only possible, if the type of knee prosthesis allows nail insertion. Another concern of intramedullary nailing is the methaphyseal fixation with only a few locking bolts. This may cause secondary loss of fixation and malalignment or implant loosening (Figure 4). The gold standard in the treatment of periprosthetic distal femur fractures is the angular stable plate fixation. But also this technique has problems in screw placement and anchorage due to the prosthesis and poor bone quality.

In our group we investigated the implant augmentation as one option to enhance implant fixation in distal femur fractures. In order to improve the screw anchorage bone cement was used to increase the load-bearing surface and thus reduce complication rate, avoiding revision surgery, and allowing earlier mobilization of the patients.

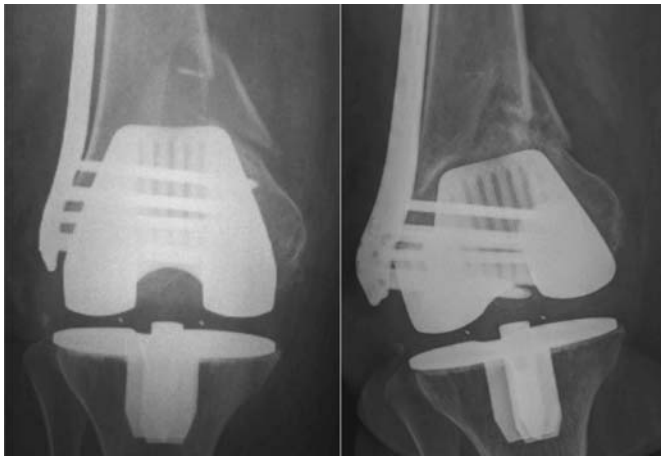

Fig. 4. Periprosthetic distal femur fracture of an 80-year-old patient after low energy trauma. Postoperative x-ray in ap-view after angular stable plate fixation (left) and 3-month postoperative follow-up showing the varus-failure with screw “cut-out” into the knee joint (right).

Implant augmentation has been shown to increase anchorage between the implant and the bone, additionally it can rule out the influence of osteoporosis. Certain biomechanical studies could proof the benefit of augmentations techniques in osteoporotic fracture fixation [60–62]. Clinically implant augmentation was introduced for the treatment of osteoporotic proximal femur fractures and proximal humerus fractures [63].

In our first study we investigated the potential of implant augmentation in the treatment of osteoporotic distal femur fractures [11]. Therefore we used 12 custom made artificial osteoporotic bone models of the distal femur. In both groups ($N = 6$ per group) an AO 33 A3 extraarticular fracture with a fracture gap of 15 mm (representing a comminution zone) was created. The proximal part of the femur was replaced by a 3rd generation composite bone (Sawbones, Malmö, Sweden). Fixation in the proximal part was performed in a rigid manner to focus biomechanics on the distal/metaphyseal fixation. Fracture fixation was performed using a standard angular stable plate (locking compression plate for the distal femur, LCP DF, DePuy Synthes, Solothurn, Switzerland). For distal fixation seven 5 mm self-tapping locking screws were used. In the augmented group prior to screw insertion 1 ml of PMMA based (polymethylmetacrylate) bone cement (Traumacem V+, DePuy Synthes, Solothurn, Switzerland) was injected using a side opening cannula. Cement injection was performed into the medial part of the bone samples from dorso-caudal to anterior-caudal. After cement curing biomechanical testing was performed using a servohydraulic material testing machine (Instron 8874, Instron, High Wycombe, Bucks, United Kingdom). Cyclic axial loading was performed with a frequency of 2 Hz and a peak load of 500 N for 45,000 cycles. Afterwards specimens were loaded with 750 N peak load until failure.

From the test machines transducers system time, cycle, axial load and axial displacement were recorded with a frequency of 50 Hz. Axial stiffness was calculated from the load displacement curves. Furthermore, the displacement was calculated for selected cycles.

The mean axial stiffness was 102.5 N/mm in the non-augmented group compared to 139.7 N/mm for the augmented group. This difference was statistically significant with $p = 0.04$. The displacement after 45,000 cycles was significant lower for the augmented group (0.68 mm) compared to the non-augmented (2.28 mm; $p = 0.001$).

The results of this study showed a promising potential of locked plate augmentation as an option in the treatment of severe osteoporotic distal femur fractures. The augmented group showed significantly higher axial stiffness and less displacement as well as a significant higher number of cycles until failure. From these results we concluded that implant augmentation has the potential to increase construct stability and therefore can reduce complication rate (secondary loss of reduction, implant loosening).

In the second study we investigated the influence of bone quality on the effect of implant augmentation [64]. In several biomechanical studies using human osteoporotic specimens augmentation has been shown that the lower the bone mineral density, the greater the advantage of augmentation [60,61]. In the previously performed investigation we found a significant reduction of cut-out due to augmentation in artificial osteoporotic femora. The aim of this second study was to investigate the influence of bone quality on the impact of augmentation in a distal femoral fracture model. Therefore, we used 8 artificial osteoporotic and 8 non-osteoporotic specimens of the distal femur; 4 of each quality were augmented and 4 not. The implants, instrumentation, test-setup and biomechanical testing was equal to the first study. Additionally a 3D motion tracking system (Optotrak Certus Motion Capture System; Northern Digital Inc., Waterloo, Canada) was used to determine interfragmentary movements.

The mean axial stiffness was comparable within both, the non-augmented (osteoporotic 103 N/mm (SD 17) vs. non-osteoporotic 103 N/mm (SD 12; $p = 0.944$)) and augmented groups (osteoporotic 140 N/mm (SD 23) vs. non-osteoporotic 136 N/mm (SD 28; $p = 0.845$)). Augmentation therefore increases axial stiffness significantly about 36% in the osteoporotic group ($p = 0.043$) and not significantly about 32% in the non-osteoporotic group ($p = 0.084$). The mean displacement was significant lower for the augmented osteoporotic group after 45,000 cycles compared to the non-augmented osteoporotic group ($p \leq 0.017$; Figure 5). Augmentation reduced cut-out in the osteoporotic specimen about 67%. In the non-osteoporotic group displacement showed no statistical significant difference, the augmentation showed no influence to the cut-out of the screws after 45,000 cycles ($p \geq 0.9$). Furthermore, the screw removal torque was measured after biomechanical testing. With 3.3 Nm (SD 0.84) the augmented group showed a significant higher screw removal torque. In the non-augmented group a mean torque of 1.9 Nm (SD 0.93) was necessary to remove the screws. These 72% increase in peak torque were found to be statistically significant ($p \leq 0.01$) but no problems occurred during screw removal. The maximum torque measured was 6.1 Nm. In this study implant augmentation significantly increases mechanical stability in osteoporotic bone. Mechanical stability was comparable to non-osteoporotic bone model; therefore, implant augmentation has the potential to rule out the influence of osteoporosis in the treatment of distal femoral fractures. We found no biomechanical benefit of augmentation in non-osteoporotic bone samples.

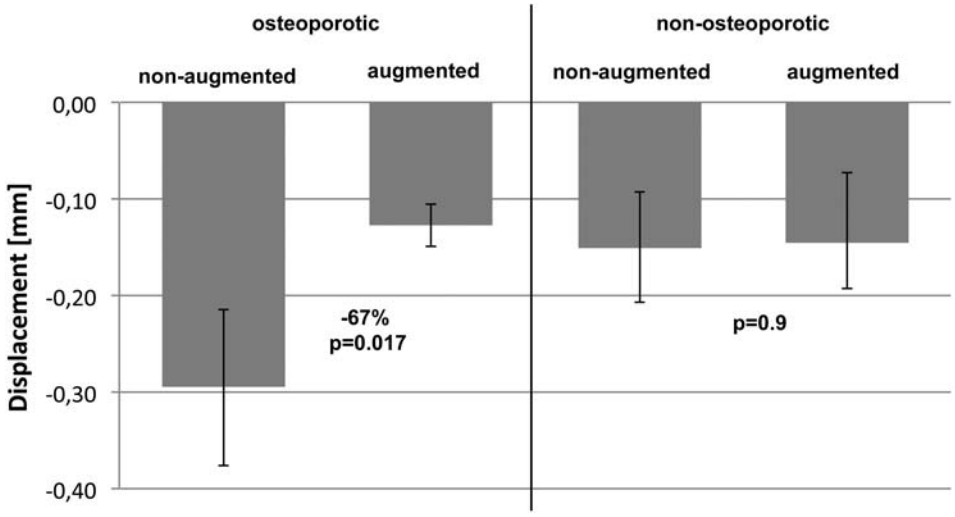

Fig. 5. Mean cut-out in mm after 45,000 cycles for the osteoporotic and non-osteoporotic specimens with standard deviation.

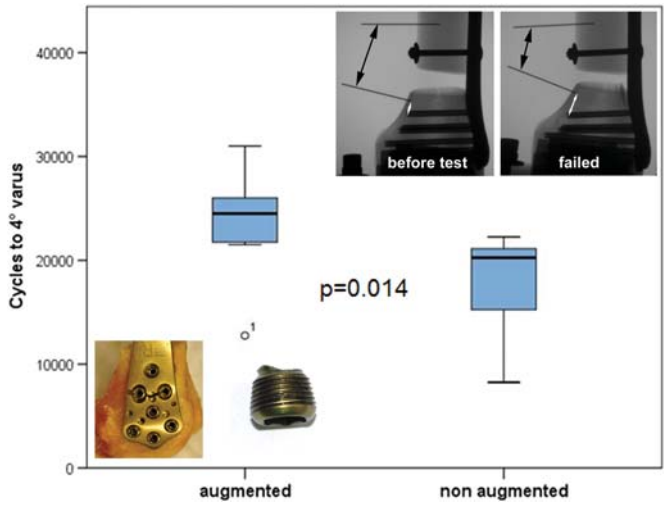

Fig. 6. Number of cycles to failure (4> varus displacement) for the augmented and non-augmented specimens, including the modes of failure: non-augmented specimens failed by cut-out (upper right corner) and augmented failed by plate and/or screw breakage (lower left corner).

In the last study on the topic of implant augmentation for the treatment of osteoporotic distal femur fractures we used human specimens and modified screws to establish and investigate a clinically applicable procedure [65]. Therefore, seven pairs of fresh frozen human distal femur specimens with low bone mass (mean age 87 years, all female) were used. Prior to any testing bone mineral density (BMD) was measured using QCT. In accordance with the previous studies the LCP distal femur with an AO 33 A3 fracture model was used. The femoral shaft has been replaced by a PMMA part and the plate was fixed in rigid manner. In contrast to the previous studies cannulated and perforated screws (four 1.1 mm holes in 10 and 15 mm distance from the screw tip) were used. Thus, cement injection could be performed after instrumentation through the screw shaft. Testing was performed with a comparable setup; the force maximum started at 750 N and was increased at 0.05 N per cycle. To determine failure x-rays in antero-posterior direction were performed every 250 cycles. Biomechanical testing showed no significant difference for initial axial stiffness (augmented 385.5 N/mm vs. non-augmented 366.7 N/mm; $p = 0.444$). The mean number of cycles to failure was 23483 (SD 5715) for the augmented vs. 17643 (SD 5483) for the non-augmented group (Figure 6). This difference was statistically significant ($p = 0.011$). Furthermore, the mode of failure changed significantly from cut-out in the non-augmented group to implant failure (plate and/or screw breakage) in the augmented specimens (Figure 6).

In summary of the above-presented studies [11,64,65] cement augmentation of an angular stable locking plate shows beneficial mechanical characteristics in osteoporotic distal femur fracture fixation. This method can enhance bone-implant anchorage significantly and therefore has the potential to increase stability and avoid complications (e.g. secondary loss of reduction, mal-union, non-union, cut-out). This treatment option is not only possible for osteoporotic fractures, but also for the treatment of periprosthetic distal femur fractures with a well-fixed prosthesis and the possibility for fracture fixation. The additive augmentation is a further option for surgeons to enhance stability and reduce complications in osteoporotic – and only osteoporotic – distal femur fractures. In our opinion it is a meaningful salvage procedure for particular patients with severe osteoporotic/periprosthetic fractures.

Conclusion

Periprosthetic fractures continue to be a hot topic and to generate a lot of interest in the field of trauma surgery. Several options exist in periprosthetic fracture fixation: Cerclages are ideally suited to fix radially displaced fragments around an intramedullary implant, but they are susceptible to axial load and torsion. Due to the bony surface geometry, cerclages provide a point-contact fixation and do not compromise periosteal blood supply. Bicortical locking screw fixation is effective but difficult on the level of the prosthesis stem. Inserted in the embracement configuration around the intramedullary implant, bicortical locking screws provide stable fixation in all load directions. Double plating is another method to enhance construct stability.

Intramedullary implants increase fracture risk. The combination of a retrograde nail and a hip endoprosthesis doubles the fracture risk compared to a non-instrumented femur, whereas the combination of two cemented well-fixed arthroplasty stems does not. Extramedullary implants seem favorable for distal periprosthetic fracture fixation. Concerning stability of the interprosthetic region, cortical thickness of the femoral shaft is the more contributing factor compared to interprosthetic distance.

Cement augmentation enhances angular-stable screw purchase in the osteoporotic periprosthetic distal femur. Especially, if plate fixation of an osteoporotic periprosthetic distal femur fracture with a well-fixed femoral component is considered, cement augmentation of the locking screws increases construct stability and reduces failure rate.

Conflict of interest

The authors have no conflicts of interest.

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Managing Vancouver B1 fractures by cerclage system compared to locking plate fixation – a biomechanical study

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KEYWORDS

Periprosthetic femoral fracture
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Revision surgery
Total hip arthroplasty
Complication

ABSTRACT

With increasing life expectancy and number of total hip arthroplasties (THA), the need for revision surgery is increasing too. The aim of this study was to evaluate the optimal fracture treatment for a clinically characteristic Vancouver B1 fracture. We hypothesized that locking plate fixation has biomechanical advantages over fixation with a simple cerclage system. Additionally, we hypothesized that removal of the primary short stem and revision with a long stem would show biomechanical benefit.

The biomechanical testing was performed with a static and a dynamic loading protocol on twenty 4th Generation sawbones. These were divided into four different groups ($n = 5$ each). In group 1, the primary uncemented short stem remained and the fracture was stabilized with a locking plate. In group 2, the primary stem remained and the fracture was stabilized with a cerclage stabilization system containing two stabilizers and four cerclages. In group 3, the primary stem was replaced by an uncemented long revision stem and the fracture was fixed with a locking plate. In group 4, the short stem was replaced by a long revision stem and the fracture was fixed with the cerclage system.

Static testing revealed that the revision of the short stem with the long stem caused a 2-fold ($p < 0.001$, ANOVA) increase of axial stiffness. In dynamic testing, the number of cycles to failure was 4 times ($p < 0.001$, ANOVA) higher with the long revision stem. Compared to locked plating cerclage wiring demonstrated a 26% more cycles to failure ($p = 0.031$, ANOVA). The load to failure was 91% larger ($p < 0.001$, ANOVA) with the long revision stem and 11% smaller with locked plating ($p < 0.001$, ANOVA).

In conclusion, the present biomechanical study indicates that periprosthetic Vancouver B1 fractures can be sufficiently fixed by simple cerclage systems. Revision with a long replacement stem provides a superior mechanical stability regardless of type of osteosynthesis fixation and is therefore a viable method in Vancouver B1 cases. A disadvantage of the cerclage system compared to plating is that an increased subsidence of the short stem was observed.

Introduction

With the increasing number of hip arthroplasties and the growth in life expectancy, the need for revision surgery after periprosthetic fractures is rising [1–3]. Additionally, a rise of intraoperative fractures has been reported with the introduction of uncemented stems, often as a consequence of the effort to obtain sufficient press fit. The incidence for intraoperative fractures with cemented hips was described in 1992 by Kavanagh et al. as 0.1–1%, which is considerably lower than the incidence for non-cemented hips of 5.4% [4].

Revision surgery can be challenging, particularly in osteoporotic bone and with elderly patients, who require stable fixation and rely on immediate weight bearing capacity of the revision. Although complications during revision surgery are rare, they result in severe morbidity and mortality [2]. About 80% of all periprosthetic fractures represent Vancouver B1 fractures [1] with a stable implant and a fracture line at the tip of the prosthesis. Typically, the fracture is a spiral fracture, extending over a large part of the prosthesis (Figure 1). In contrast, biomechanical studies on periprosthetic fractures typically simulate the fracture situation with a short transverse [5–8] or a short oblique

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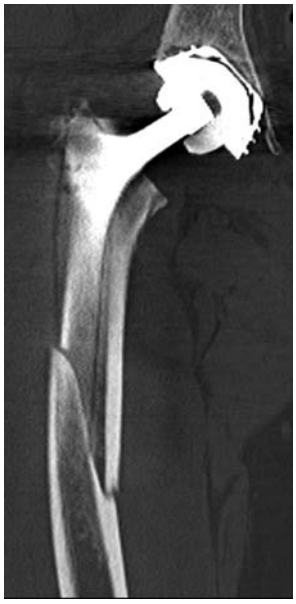

Fig. 1. CT scan of a patient with a characteristic periprosthetic spiral type fracture, Vancouver B1.

fracture [9–12]. In clinical reality, these fracture patterns are rarely seen and it remains unclear if these short fracture patterns accurately represent the clinical situation or not.

Periprosthetic fracture fixation aims for the restoration of limb function with successful bone healing and immediate load bearing capacity [3,13]. The best technique for achieving this goal is still discussed controversially. Plate fixation [5,14–19], cerclages [6,11,13,19–24], a combination of a non-locking plate with an allograft strut [12,20,25–26] and even external fixation have been described [27]. Moreover, the technique for fracture fixation depends on whether the periprosthetic fracture occurred around a cemented or an uncemented stem. Most biomechanical studies were performed with cemented stems [6,10,11,17,28–31]. However, clinically periprosthetic fractures, which show a different biomechanical performance, frequently occur in non-cemented situations. Findings from early biomechanical studies comparing strength in cemented and uncemented stems suggested a much larger load to failure for cemented stems [32]. For the stability of osteosynthetic fixation of cemented stems, biomechanical and clinical studies have reported that plate fixation yields favorable outcomes when compared to either the combination of cable fixation and a plate or just cable fixation [9,10,13,28].

To our knowledge, no biomechanical evidence exists for preferring plate over cable fixation for typical spiral periprosthetic fractures in uncemented stems. The first aim of our study was to assess the stability and strength of a clinically relevant Vancouver B1 periprosthetic fracture fixed by either a long bridging plate construct or by a cerclage technique with titanium straps. We hypothesized that locking plate fixation has biomechanical advantages over fixation with a simple cerclage system. In order to achieve maximum fixation stability, we also compared both osteosyntheses after replacing the short stem with a long revision stem. Thus, the second aim of our study was to assess the mechanical difference between a fixed short stem and a fixed long revision stem. We hypothesized that removal of the primary short stem and revision with a long stem would show biomechanical benefit.

Materials and methods

The aim of the study was to compare locking plate fixation versus a cerclage system and short stems versus long stems for their effectiveness in managing a typical periprosthetic spiral femoral fracture. Biomechanical testing was performed with static loading to assess the stiffness of the fixation constructs and cyclic loading to assess the failure strength and the cycles to failure. Twenty femur sawbones were divided into four groups: (1) short stem with plate fixation ($n = 5$), (2) short stem with cerclage system ($n = 5$), (3) long stem with plate fixation ($n = 5$), (4) long stem with cerclage system ($n = 5$).

Sample preparation

A standard femoral neck osteotomy was performed with an oscillating saw in twenty sawbones (#3406 left femur large with 16 mm channel, 4th Generation; Malmö, Sweden). Half of the sawbones were reamed and implanted with a cementless standard straight short stem (AnaNova Solitär, ImplanTec, Mödling, Austria) according to the manufacturer's recommendations. The other half of the sawbones were implanted with a cementless long revision stem (Modular Plus, Smith and Nephew, Schwechat, Austria) after preparing the medullary canal with a conical spiral reamer. After stem implantation, the composite bones were potted distally into an aluminum pot with polymethylmetacrylat (PMMA, Gößl & Pfaff, RenCast FC 53 A/B). For proximal fixation, the prosthesis cup was embedded with PMMA into an aluminum cylinder.

The pattern of the spiral fracture was investigated through an analysis of CTs and plain radiographs of 30 patients with Vancouver B1 fractures undergoing revision surgery at our institution (Figure 1). The average length of the fracture line was 14 ± 2.2 cm and was on average extending from 10 cm proximal to 4 cm distal of the stem. This characteristic fracture line was drawn on the sawbones with a custom made template. After temporary removal of the stems, the fracture line was milled using a milling machine (Deckel FP2, Friedrich Deckel Aktiengesellschaft, München), a rotary indexing table, and a 2 mm diameter cutter (Figure 2).

The stems were then re-implanted into the osteotomised sawbones with press fit stability. The proximal and distal sawbone fragments were placed with cortical contact. The primary short stems were carefully hammered into the sawbones. To implant the long revision stems, which consist of two components and a multi-conical coupling screw, the distal anchoring module was implanted first. After that, the proximal module was implanted and secured with the screw according to the manufacturer's recommendations. In ten sawbones, the fracture fixation was performed using a non-contact bridging left periprosthetic proximal femur plate with 15 holes and a length of 324 mm (NCB[1] Plating System, Zimmer Biomet, Vienna, Austria). The screw placement was performed by angulating the screws around the implant shaft in an unlocked manner followed by locking, utilizing locking-caps. Approximately 30° angulation was allowed in all directions. We placed five proximal screws (4 mm diameter cortical screws: 1 × 50, 1 × 46, 1 × 42, 1 × 34, 1 × 32 mm) and four distal screws (5 mm diameter cortical screws: 4 × 42 mm). Ten sawbones were provided with the Compression Cerclage Bands (CCG® System,

Fig. 2. Fourth generation sawbone model after osteotomy of the femoral neck and creation of a standardized characteristic 14 cm spiral fracture using a template and milling machine.

ImplanTec, Mödling, Austria), which consist of titanium bands and stabilizers. The stabilizers were locked to the sawbones by little spikes along the edges and firmly attached by compression bands according to the manufacturer's recommendations. Two stabilizers and four cerclages were used for each sawbone construct (Figure 3a–d).

Test setup

The biomechanical test was performed on a servo-hydraulic testing machine (Instron 8874, Instron Ltd., High Wycombe, United Kingdom, Figure 4). Distally, the embedded bone implant construct was rigidly fixed to the machine frame with an angle of six degrees between the femur shaft and the machine axis in the lateral direction. This was achieved by rotating the vice in the frontal plane to simulate an axial load along the mechanical axis of the leg (Mikulicz-line). Proximally, the force application at the femoral head was performed through an artificial acetabular cup which was embedded in an aluminum cylinder. The cylinder was connected to the actuator of the testing machine, including a biaxial load cell (Instron Dynacell, measuring range ±10 kN, ±100 Nm, Instron Ltd., High Wycombe, United Kingdom). To avoid undesirable constraint forces, movements of the test samples in the transversal plane were allowed due to the use of a cross table, attached to the load cell and the aluminum cylinder. To record the movement of the fragments, markers were fixed to the proximal and distal bone fragments. An additional reference marker was installed for software orientation.

Test procedure

The samples underwent a cyclic testing protocol with an increasing axial load level and testing was performed until failure. In a first step, the specimens were preconditioned for 100 cycles at a sinusoidal cyclic load between 50 and 500 N and a frequency of 2 Hz to allow for the samples to settle. Then, three quasi-static ramps were performed stroke controlled with a ratio of 0.02 mm/s to stress the specimens up to 500 N for the determination of initial axial construct stiffness. Stiffness was determined from the linear portion of the load-deformation curve. After that, the constructs resumed fatigue loading by first ramping the 500 N lower level set point. Cyclic sinusoidal fatigue loading then followed with an initial 2000 N upper load, increasing the upper load by 150 N every 500 cycles until failure. Failure of the periprosthetic fracture construct was defined as breakage of the bone, breakage of the plate or the cerclage system or 30 mm axial actuator displacement.

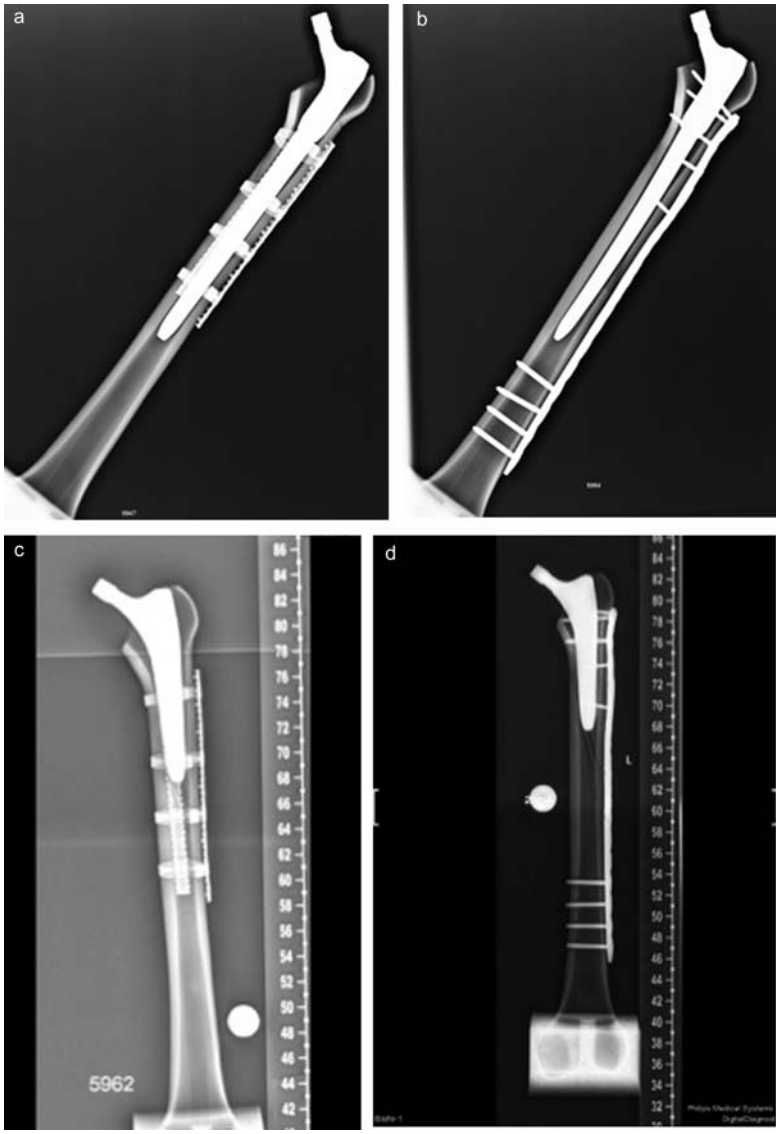

Fig. 3. (a) X-ray long revision stem/cerclage. (b) X-ray long revision stem/plate. (c) X-ray short primary stem/cerclage. (d) X-ray short primary stem/plate.

Fig. 4. Test setup for cyclic fatigue testing of periprosthetic fracture fixation using a servo- hydraulic testing machine (Instron 8874, Instron Ltd., High Wycombe, UK).

Data were recorded with the testing machine software (WaveMatrix V1.5, Instron Ltd., High Wycombe, United Kingdom). The movements in space were calculated with a three dimensional motion analysis video system (Pontos V6.3, GOM, Braunschweig, Germany), tracking the markers of the bone fragments. The minimum and maximum load amplitudes were held for five seconds to take a picture with the Pontos video system at the beginning of each load step.

The Initial stiffness, cycles to failure, load to failure, the movement of the stem in relation to the proximal fragment and the relative motion between the distal and proximal fragment were determined and statistically analyzed (IBM SPSS Statistics 19, Chicago, IL). Data acquired by Pontos were matched with the Instron data using Microsoft Excel (Microsoft Corporation, Redmond, USA) and were synchronized using a timed trigger. For the statistical analysis, a univariate analysis of variance (ANOVA) was performed to determine the influence of the type of stem construct and type of osteosynthesis separately. In addition, a Student's t-test for independent samples was executed to identify differences among the four groups. Results are presented as the mean value ± SD. Significance levels of $p < 0.05$ were indicated by *.

Results

Static testing revealed that the revision of the short stem with the long stem caused a 2-fold ($p < 0.001$, ANOVA) increase of axial stiffness. No consistent effects on axial stiffness were observed when comparing plating and cerclage wiring (Figure 5). In dynamic testing, the number of cycles to failure was 4 times higher ($p < 0.001$, ANOVA) with the long revision stem compared to a short stem. Compared to locked plating cerclage wiring demonstrated a 26% larger number of cycles to failure ($p = 0.031$, ANOVA). The analysis of fatigue strength revealed that the constructs with the long modular stem demonstrated a 91% higher ($p < 0.001$, ANOVA) load to failure compared to bones with short stems. Compared to cerclage wiring plating had an 11% smaller load to failure ($p < 0.001$, ANOVA, Figure 5). Individual differences in static and fatigue mechanical performance are depicted in Figure 5.

Dislocations of the fragments and the stem were analyzed at 1000 cycles of loading. The relative motion between the distal and proximal fragment was at least 8 times larger, when a short stem was used ($p < 0.001$, ANOVA). Similarly the movement after plate fixation was at least twice as large, than after cerclage wiring ($p = 0.001$, ANOVA). In contrast, the subsidence of the stem was significantly smaller with plating, compared to cerclage wiring ($p = 0.001$, ANOVA, Table 1).

Failures of the constructs during cyclic fatigue loading were characteristically different among the four groups. The long stems (Figure 6a, b), as well as the short stems in combination with titanium bands (Figure 6c), failed through an additional fracture in the area of the tip of the implant. The usage of a short stem and plate showed a different fracture pattern. Four of those samples broke transversely to the bone axis and proximal to the tip of the stem (Figure 6d) while one specimen failed at the most proximal screw of the distal locking screws.

Discussion

The findings of our biomechanical tests on clinically characteristic spiral Vancouver B1 fractures indicated that osteosynthesis with plate fixation has no biomechanical advantages over the use of a simple cerclage system. On the contrary, the cerclage constructs demonstrated a larger stiffness, larger strength and more cycles to failure compared to the plate constructs.

While our findings did not demonstrate any biomechanical advantages of plate fixation, the review of Pike et al. recommended the stabilization of B1 fractures with either compression or locking plates, but not cable-plate devices [13]. Studies performed on additional cable-stabilizer devices mostly advise against these cable-plate systems. For example, Tadross et al. suggested based on clinical findings, that the Dall-Miles Cable system (Stryker Howmedica, Mahawah, NJ) may not provide sufficient stability on its own [22]. A further cable plate fixation system, the Odgen Construct, demonstrated less stiffness than locked plating, but had a similar strength and did not cause any catastrophic failure, as the locked plating constructs did [28]. In 2015, Lewis et al. compared synthetic femurs with cemented THAs and Vancouver B1 fractures fixed with the NCB plate system against other fixation methods such as a cable plate device and found that the cable constructs exhibited lower failure forces compared to the NCB plate system [33].

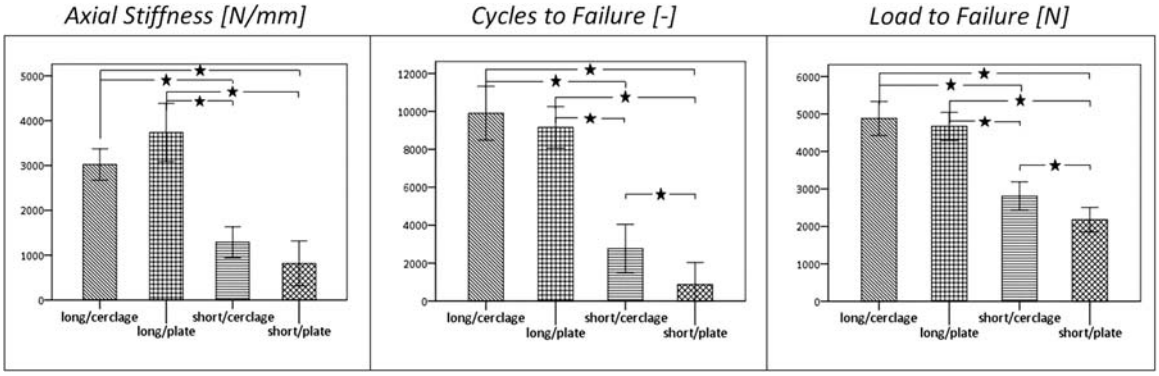

Fig. 5. Axial stiffness, cycles to failure and load to failure for the tested groups with different stem/osteosynthesis combinations (Mean value ± 1 SD). *: indicating significant ($p < 0.05$) differences in the Student's t-test.

Table 1.
Relative movements of the stem and fragments in axial direction after 1000 cycles (mean ± SD).

	Movement proximal to distal fragment [mm]	Movement stem to proximal fragment [mm]
Long stem/cerclage	0.1 ± 0.1	1.1 ± 1.1
Long stem/plate	0.2 ± 0.1	0.3 ± 0.2
Short stem/cerclage	0.8 ± 0.1	3.2 ± 1.1
Short stem/plate	4.1 ± 1.8	0.5 ± 1.7

While the differences in the stability of the osteosynthesis were apparent with a short stem implanted, the long stem increased stiffness and strength such that differences between osteosynthesis techniques were no longer discernible. The influence of stem length on the performance of cemented hip-arthroplasty was also investigated by Moroshima et al. 2013. Their results showed that sawbones break at a statistically significantly lower torque to failure when a shorter stem is used in comparison to a stem with a conventional length and the same offset [31]. In 2011, Rupprecht et al. determined that the femoral stem itself significantly reduces the fracture strength by 32%. But in their study a cemented THA was investigated [30]. In 2014, Moazen et al. used a finite element model to demonstrate that in treatment of B1 fractures, a single locking plate can be used without complications if partial weight bearing is followed. In the case of B2 fractures, long stem revision and bypassing the fracture gap by two femoral diameters is recommended. But considering the risk of single plate failure, long stem revision could be considered in all comminuted B1 and B2 fractures. Double plating was also described as an alternative [7,34]. Clinical data suggest a higher failure rate for ORIF in B1 fractures compared to the revision in the case of B2 fractures. In clinical practice the intraoperative evaluation of the classification within the Vancouver system is very difficult and often leads to wrong results. If a B2 fracture is treated like a B1 fracture, failure of the osteosynthesis can follow frequently [35].

The present study has its strengths and limitations. To our knowledge it was the first study simulating a clinically characteristic fracture with an obtuse fracture angle. The aim of our study was to investigate a clinically typical fracture pattern because the effectiveness of fracture fixation is also dependent of the fracture location and fracture angulation. Leonidou et al. developed a simplified parametric finite element model of a cemented total hip replacement for the management of Vancouver B1 fractures. Through the evaluation of different fracture angles they found, that for poor bone quality and obtuse fracture angles, alternative management methods such as single locking plates might be required as the fixation might be under higher risk of failure [36]. To our knowledge it was also the first biomechanical study to compare the Gundolf cerclage system (CCG) with a locking plate system for the management of Vancouver B1 fractures. Compared to other cerclage systems the CCG system has a broad contact surface which could be responsible for different biomechanical performance. Another unique feature of the CCG system is the presence of spikes along the stabilizers, which penetrate the cortical bone and should prevent the CCG system from slipping out of position. There was no breakage of the cerclages in the CCG system during testing. In contrast, breakage of cable wires is reported frequently.

As a limitation of this study it was not possible, based on the test conditions of synthetic femurs, to investigate the cutting of cerclages into the bone. It is observed that common cable wires can cut into the bone. This problem has not been noticed with the use of the CCG System in former clinical studies [24,37]. It was described that the CCG System allows for controlled compression of the titanium bands. A previous study of Lindtner et al. with histological investigations three weeks postoperatively showed that the osteoblastic line on the inner side of the titanium band and the surface of the femur provides evidence of the tendency towards union or bone healing. There was no evidence of necrosis, although the titanium band was positioned firmly on the bone, which was demonstrated in a microradiography [24,37]. The broad contact face of the titanium bands is intended to not constrict the bone and to not disrupt the blood flow. The intention of the stabilizers is to give initial stability to the bone and strengthen it through osseointegration of the rough titanium surfaces [38]. As mentioned above, it was not possible to investigate biological conditions within this biomechanical study.

We decided to use synthetic femurs because they have less interspecies variability of physical properties than bone of human donors. This increases comparability and avoids inherent variability in bone quality, geometry and the potential presence of preexisting damage [35,39, 40]. Recent industrial developments and an increasing number of mechanical tests have led to the development of synthetic bones with similar mechanical qualities to human bones. The sawbones fourth generation synthetic femurs used in our study have been used in many previous studies. The mechanical properties of these femurs are well known and these synthetic bones are the most similar to real bones that are used in in vitro mechanical tests [41]. However, as periprosthetic fractures typically occur in bones of elderly individuals with diminished material, properties, and increased fragility, the sawbone specimens may result in an overestimation of the load to failure and consequently in the number of load cycles to failure. Sawbones might also have better screw purchase than normal bone. Although the sawbone specimens were considerably stronger compared to human bone we could not produce any plate breakage, in contrast to previous biomechanical studies [42]. Also no pullout of the screws has been observed neither with the proximal screws (4 mm cortical) nor with the distal screws (5 mm cortical).

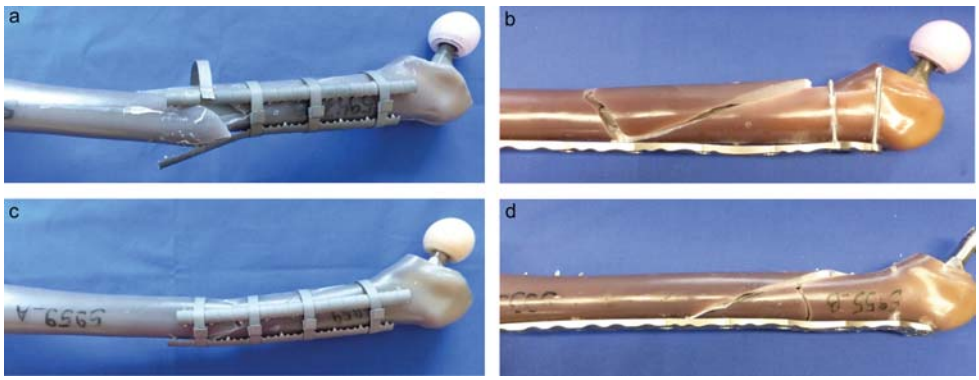

Fig. 6. (a) Typical Breakage of the "long stem/cerclage" samples. (b) Typical Breakage of the "long stem/plate" samples. (c) Typical Breakage of the "short stem/cerclage" samples. (d) Typical Breakage of the "short stem/plate" samples.

Furthermore, the setting in this study does not represent the soft tissue with peripheral muscle and ligaments which may affect the biomechanical characteristics. The fixation methods were easier to perform due to the missing soft tissue when compared to the in vivo environment. Only the initial stability of the constructs was evaluated, simulating the early healing stage where no osseointegration is seen. At this stage the interfragmentary stiffness is negligible and the constructs stiffness is only dependent on the implant fixation [9,43]. In vivo the strength of the construct would increase over time, as bone remodeling occurs [41]. However, no conclusion can be drawn about other clinical data such as blood loss, the prolongation of the operation time related to the removal of the stem out of the medullary space, the soft tissue damage, or hardware prominence because of the lack of in vivo conditions within this biomechanical study.

Even though all stems were implanted with press fit stability, axial pressure during biomechanical testing caused subsidence of the stem within the proximal fragment of the sawbones. Among the different groups a difference in the distance of subsidence was observed. The lowering of the stem was six times larger when a short stem combined with a cerclage system was used compared to using a short stem secured by a plate, which was statistically significant. The long modular revision stem groups also showed lowering effects but without statistically significant differences between groups. The edges of the long modular stem are sharp and have a double profile, which should prevent the stem from sinking and rotating and they increase the area of contact with the bone. The modular system provides the possibility of changing the proximal module while the distal module remains in the femur. This feature represents a revision option where it is not necessary to remove the entire stem. In order to remove the stem the femoral canal would have to be opened which would influence operation time, the risk of fracture and blood loss. Further clinical studies are needed to demonstrate the clinical relevance of stem subsidence and to assess if it can lead not only to leg length inequality, but even to luxation of the total hip arthroplasty [24].

Conclusions

Periprosthetic fractures are difficult to treat and ongoing research how to achieve optimum fixation is desirable. The present biomechanical study indicates that periprosthetic Vancouver B1 fractures can be sufficiently fixed by simple cerclage systems. Revision with a long replacement stem provides a superior mechanical stability regardless of type of osteosynthesis fixation and is therefore a viable method in Vancouver B1 cases. A disadvantage of the cerclage system compared to plating is that an increased subsidence of the short stem was observed.

Conflict of interest

The authors have no conflict of interest relating to this manuscript. Implants were kindly donated by Zimmer Biomet GmbH Vienna, Austria and Implantec GmbH Mödling, Austria.

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Bone formation and degradation behavior of nanocrystalline hydroxyapatite with or without collagen-type 1 in osteoporotic bone defects – an experimental study in osteoporotic goats

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KEYWORDS

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Biomaterial

ABSTRACT

The intention of the current work is to assess new bone formation and degradation behavior of nanocrystalline hydroxyapatite with (HA/col-1) or without collagen-type I (HA) in osteoporotic metaphyseal bone defects in goats. After ovariectomy and special low-calcium diet for three months, 3 drill hole defects in the vertebrae of L3, L4, L5, 4 drill hole defects in the right and left iliac crest and 1 drill hole defect at the distal femur were created in three Chinese mountain goats with a total of 24 defects. The defects were either filled with one of the biomaterials or left empty (empty defect control group). After 42 days, the animals were euthanized and the samples were assessed for new bone formation using high-resolution peripheral quantitative computed tomography (HR-pQCT) and histomorphometry with 2 regions of interest. Detail histology, enzymehistochemistry and immunohistochemistry as well as connexin-43 in situ hybridization and transmission electron microscopy were carried out for evaluation of degradation behavior of the materials and cellular responses of the surrounding tissue in respect to the implants. HR-pQCT showed the highest BV/TV ratio ($p = 0.008$) and smallest trabecular spacing ($p = 0.005$) for HA compared to the other groups in the region of interest at the interface with 1 mm distance to the initially created defect. The HA/col-1 yielded the highest connectivity density (Conn.D) ($p = 0.034$) and the highest number of trabeculae (Tb.N) ($p = 0.002$) compared to the HA and the control group. Histomorphometric analysis for the core region of the initially created defect revealed a statistically higher new bone formation in the HA ($p = 0.001$) and HA/col-1 group ($p = 0.001$) compared to the empty defect group including all defect sites. This result was confirmed for site specific analysis with significant higher new bone formation for the HA group for vertebral defects compared to the empty defect group ($p = 0.029$). For the interface region, no statistically significant differences were found between the three groups ($p = 0.08$). Histology revealed a good biocompatibility without inflammatory reaction for the HA- and HA/col-1 implants with a higher fragmentation of the HA-implant compared to the HA/col-1 biomaterial and formation of new bone in the region between the biomaterial fragments by osteoblasts. Fragmentation was shown by transmission electron microscopy to be caused by multinuclear osteoclast-like cells with degradation of the implant via intracellular incorporation of degraded implant material particles. In conclusion, both nanoparticulate HA with and without collagen type-1 showed better new bone formation compared to untreated drill hole defects in metaphyseal regions of this osteoporotic Chinese mountain goat model with good biocompatibility.

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Introduction

Osteoporosis and particularly osteoporotic fractures have a high impact both on the quality of life of patients and on the financial aspects of Western health care systems. Biomaterials have gained interest to enhance bone healing in osteoporotic fractures and to improve treatment outcome [1].

Among many other materials hydroxyapatite and namely nanoparticulate hydroxyapatite is a potential candidate as bone substitute material in osteoporotic bone for improvement of bone healing due to its osteoconductive effects. Nanoparticulate hydroxyapatatite with needle shaped HA crystals with a size of around 20 nm has already been investigated in experimental and clinical settings for dental and orthopaedic applications [2–10]. In general, good new bone formation via osteoconductivity with this type of nanoparticulate hydroxyapatite was reported. In all the above mentioned studies physiological and not osteoporotic bone was investigated.

Collagens represent 25–35% of the total body proteins and can be found in cartilage, bone and in almost all types of soft tissue [11]. Among 28 known different collagen types, collagen type-I is the most abundant in the body and in bone representing more than 90% of the organic mass in bone [12]. Collagens contain sections with the amino sequence arginine, glycine, aspartic (RGD) which was discovered as a small peptide ligand with high affinity to integrins increasing the adhesiveness of surface implants for osteoblasts via binding to those transmembrane integrin receptors [13]. Facilitated cellular attachment of pre-osteoblasts on collagen via RGD-peptides with theoretical enhancement of new bone formation is therefore of interest in the use of collagens in composite biomaterials [14].

The intention of the current study is to assess new bone formation and degradation behavior of nanocrystalline hydroxyapatite with or without collagen-type I in osteoporotic bone defects in metaphyseal bone defects in osteoporotic goats. The hypothesis is that both nanoparticulate hydroxyapatite and nanoparticulate hydroxyapatite with collagen-type I enhance new bone formation compared to empty control defects and that the additional use of collagen type-I improves new bone formation compared to plain nanoparticulate hydroxyapatite.

Materials and methods

Study design

There were three different treatment groups: group I: empty defect, group II: nanoparticulate hydroxyapatite, group III: nanoparticulate hydroxyapatite + collagen type I. In three osteoporotic Chinese mountain goats, a total of 24 bone defects were created that were either filled with nanoparticulate hydroxyapatite or nanoparticulate hydroxyapatite + collagen type I or were left empty after randomisation (Table 1). In each animal, 2 defects in the left iliac crest, 2 defects in the right iliac crest, 1 defect in the left distal femur, 1 defect in the third lumbar vertebra, 1 defect in the fourth lumbar vertebra and 1 defect in the fifth lumbar vertebra were created with a total of 8 defects per animal. Animal Research Ethics approval was obtained from the Animal Experimentation Ethics Committee of the Chinese University of Hong Kong before start of surgeries (Ref: 08/029/MIS).

Table 1
Study design with treatment protocol for each of the 24 defects.

	Goat 1	Goat 2	Goat 3
Right iliac crest #1	Empty	HA	HA + Col-type-I
Right iliac crest #2	Empty	HA	HA + Col-type-I
Left iliac crest #1	HA	HA + Col-type-I	Empty
Left iliac crest #2	HA	HA + Col-type-I	Empty
Left distal femur	Empty	HA	HA + Col-type-I
Lumbar vertebra 3	HA	HA + Col-type-I	Empty
Lumbar vertebra 4	HA + Col-type-I	Empty	HA
Lumbar vertebra 5	Empty	HA	HA + Col-type-I

Nanoparticulate hydroxyapatite

The hydroxyapatite (HA) used in the present study is a fully synthetic injectable nanocrystalline paste (Ostim®, aap Biomaterials GmbH, Dieburg, Germany) and consists of a suspension of pure hydroxyapatite in water prepared by a wet chemical reaction. The needle shaped HA crystals with a size of 21 nm in a-direction and of 36 nm in c-direction form agglomerates. Phase purity of the HA was determined by X-ray-diffraction which shows conformity with pure HA and an average crystallite size of 18 nm. The atomic ratio of calcium: phosphorus is 1.67. Ostim® paste does not harden after application into the bone and is free of endothermical heating in contrast to calcium phosphate bone cements.

Collagen was derived from split skin of pigs and purified by a multi-stage process including acidic and alkaline treatment. Precipitated hydroxyapatite was prepared in a suspension of purified collagen to which phosphoric acid and calcium oxide were added under constant stirring. The composite was dried, milled and mixed with pure hydroxyapatite to yield a composite containing hydroxyapatite and collagen a ratio of 80/20 and a solids content of 34.5

All materials were filled in 2 ml syringes and sterilized by gamma-irradiation.

Animals

According to previously established animal model [15–17], three female skeletally mature Chinese mountain goats were used for this study. The ages of the animal were at least 3 years old and skeletal maturity was confirmed by growth plate closure at the distal femora and proximal tibia by radiography. The goats were housed in air-conditioned and dark-light cycle-controlled partitions and were cared for by qualified veterinarians at the Laboratory Animal Service Centre, The Chinese University of Hong Kong, during the entire study.

Anaesthesia

All surgical operations were performed under general anaesthesia. Sedation was introduced by a mask at 5% isoflurane (VCA ISO, Halocarbon Laboratories, South Carolina, USA), immediately followed by standard tracheal intubation using a laryngoscope. Maintenance was kept at 1–2% of isoflurane with respiration monitored (apAlert RM5, MBM, Coorparoo, QLD, Australia) throughout all procedures including ovariectomy operations, Bone Mineral Density (BMD) scanning and bone defect creation [15,17,18].

Induction of osteoporosis by ovariectomy and low-calcium diet

Bilateral ovariectomy was performed under general anaesthesia with standard aseptic surgical technique. Postoperatively, all animals received regular analgesics with a 0.5 ml intramuscular injection of Temgesic (Reckitt & Colman Products, Ltd., Hull, UK) every 6 h for 2 days. The ovariectomized goats were fed with a low-calcium diet containing 50% of food pellet with 0.2% calcium (Glen Forrest Stockfeeders, Glen Forrest, Australia) plus 50% Wheaten Chaff with 0.3% calcium (O'Driscoll, Greerock, Australia) after the operation. All goats were kept for 6 additional months until development of osteoporosis prior to receiving bone defect creation. Osteoporosis was confirmed by BMD scanning by peripheral quantitative computed tomography (pQCT, Stratec, XCT2000L, Germany) at each calcaneus according to our established protocol [15].

Surgical procedure for drill hole defects

After general anaesthesia, the lumbar spine, iliac crest and left distal femur region were shaved, disinfected and subsequently was draped in sterile manner. An incision to the skin was made at the midline laterally to the spine where the spinous process, transverse process, and the pedicles of the L2-L5 were located. Further incisions were made to allow parapedicular access of the vertebral body to create a bone defect with 5 mm diameter using a saline-cooled trephine (DBCS; Biomet Deutschland, Berlin, Germany). The defects were either filled with the respective biomaterial or left empty according to the study protocol. For the distal femur and the iliac crests, skin incision and dissection of the subcutaneous tissue followed by incision of the fascia was performed and cylindrical defects with a diameter of 8 mm with the DBCS (DBCS1; Biomet Deutschland, Berlin, Germany) were created. Then defects were treated according to the study protocol as well. The wounds were closed with multilayer sutures and draped in sterile manner. Postoperatively, infrared light was used to prevent hypothermia. The animals were allowed full weight bearing and free access to water and goat diet.

Harvesting of specimens

The goats were sacrificed at the end-point of six weeks (42 days) post-bone defect surgery. Euthanasia was carried out by intravenous overdose pentobarbital (Dorminal 20%, Alfasan, Kuipersweg 9, Woerden, Holland) at 50 mg/kg of body weight. Each of the defective sites were carefully removed including the lumber vertebral bodies from L3 to L5, left and right illac crests, and left femoral condyle. Samples were immediately fixed in 9% buffered formalin for five days and preserved in 70% ethanol thereafter.

High-resolution peripheral quantitative computed tomography (HR-pQCT) of bone specimens

Each sample was subjected to HR-pQCT (XtremeCT, Scanco Medical, Brüttisellen, Switzerland). Scanning was performed covering the entire bone defect at the defective site using 59400 V and 900 µA, creating reconstructed two-dimension images at resolution of 41 micrometers. The region of interested was defined at the host bone-defect/biomaterial interface [16], and selected as a ring shaped hollow cylinder (Figure 1) with 1 mm offset thickness and 2 mm in depth, across all defective sites with various treatments methods. Three dimensional reconstructions and the histomorphometric parameters were evaluated by the standard algorithms in the built-in software with segmentation threshold set at 1.2/2/124. Bone volume (BV) was the volume of pixels with density higher than or equal to the threshold, and that tissue volume (TV) was the volume of the region of interest. The mean of the following parameters: Apparent bone mineral density (BMD), BV to TV ratio (BV/TV), Trabecular Number (Tb.N), Trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp), and Connectivity Density (Conn.D) were compared between groups and difference between groups were tested using Kruskal-Wallis test with confidence intervals at 95%.

Histology and histomorphometry

Both quantitative and qualitative histology was performed for determination of new bone formation and local tissue reactions of the different implants, respectively. For histological examinations in light microscopy, decalcified and undecalcified samples were used that were brought into 4% paraformaldehyde solution after explantation and Micro-CT analysis. Samples for decalcification were incubated in 10% EDTA (Carl Roth GmbH, Karlsruhe, Germany), embedded in paraffin and cut into 5 µm sections with a Leica RM2155 microtome (Leica, Wetzlar, Germany). Undecalcified samples were embedded in methyl methacrylate and sawed into 20 µm sections using the method of Donath and Breuner [19]. Subsequently, the sections were stained with toluidine blue and hematoxyline-eosin.

Histomorphometry was carried out on the hematoxyline-eosin sections. New bone formation was determined using a light microscope (Axiophot-2, Zeiss, Jena, Germany) and digital image software (Media Cybernetics; Silver Spring MD, USA) for quantitative assessment. Two different region of interest (ROI) were defined:

1. Initial defect region
2. Host bone-defect/biomaterial interface region with a distance of 1 mm to the initially created defect. This region corresponded to the ROI analysed by HR-pQCT (see section 2.8).

The area of newly formed bone was then divided by the respective ROI area, giving the percentage of new bone formation in relation to the entire area.

Statistical analysis was done using one way variance analysis with SPSS for Windows (Version 16), allowing direct comparison between the different implants. As normal distribution could not be assumed, Kruskal-Wallis-H-Test and subsequent Mann-Whitney-U-Test was performed. P-values < 0.05 (marked by *) were considered to be statistically significant and p-values < 0.01 (marked by **) were defined as statistically high significant. This analysis was done for all defects of each treatment group including spinal, iliac crest and femur defects as well as separately for spinal defects and separately for iliac crest defects. Due to the limited number of $n = 2$ for distal femur defects per treatment group this site specific comparison was not possible.

For further histological biocompatibility assessment, the sections were studied qualitatively using detailed histology with the focus on the appearance of newly formed bone, osteoclast-like cells, fragmentation of implants, and integrity of bone marrow.

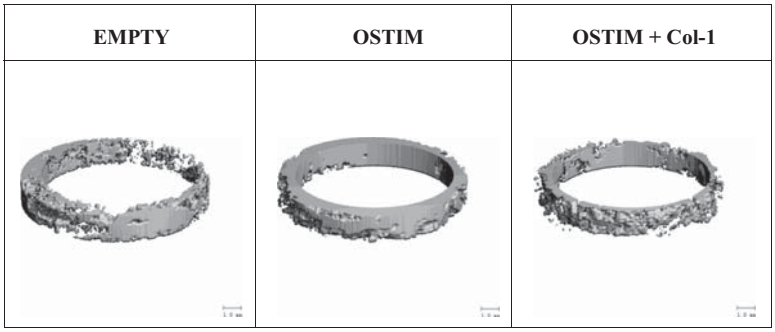

Fig. 1. 3D reconstructed images of the region of interest for high-resolution peripheral quantitative computed tomography (HR-pQCT) of the defective bone sites representing a ring shaped hollow cylinder with 1 mm offset thickness and 2 mm in depth at the host bone-defect/biomaterial interface.

Enzymehistochemistry – tartrat-resistant acid phosphatase (TRAP)

Enzymatic detections of tartrate-resistant acid phosophatase (TRAP) activity was performed by incubation of the slices in a solution of naphtol AS-BI-phosphate (7-bromor-3-hydroxy-2naphthoic-oanisidide phosphate, Sigma-Aldrich, Steinheim, Deutschland) and fast red violet LB salt (5-chloro-4-benzamido-2-methylbenzenediazonium chloride hemi [zinc chloride] salt, Sigma-Aldrich) in 0.2 M acetate buffer (pH 5.0) containing 50 mM tartaric acid for 20 min at 37°C. Then the slices were counterstained with hematoxyline. As negative control slices were incubated in 0.2 M acetate buffer (pH 5.2) for 20 min.

Immunohistochemistry for collagen type-1, CD68, osteocalcin, osteopontin, and eNOS

After deparaffination of tissue sections the endogenous peroxidase was blocked by incubation in 3% H_2O_2 in Tris-NaCl buffer (pH 7.4) with 0.025% Triton-X-100 (TBS). After rinsing with TBS the samples were incubated overnight at 4°C with the following primary antibodies in dilution buffer (Dako, Glostrup, Denmark): (a) CD68 (1:5 diluted; Dako), (b) Osteocalcin (1:50; R&D Systems, Minneapolis, MN, USA), eNOS (1:500; BD Biosciences, Heidelberg, Deutschland). After several washing steps with TBS sections were incubated for 30 min at room temperature with a biotinylated anti-mouse secondary antibody (1:400; Dako), rinsed again and labelled with the ABC complex/horseradish peroxidise labelled avidin (Dako) for another 30 min. The cromogen Nova Red (Vector laboratories, Burlingame, California, USA) was used for visualization of the peroxidise activity. Counterstaining of nuclei was done with hematoxylin (Shandon Scientific Ltd, Cheshire, UK).

Connexin-43 in-situ hybridization

DIG-labelled cRNA-probes were generated from a 137 bp PCR-product of the coding region of human Connexin-43 gene that was cloned in pGEM®-T (Promega, Mannheim, Germany) and transformed in Escherichia coli XL1-Blue (Stratagene, Heidelberg, Germany). After extraction of the plasmids by column purification (Qiagen, Hilden, Germany) the vectors were digested with NcoI and NotI (New England Biolabs, Frankfurt, Germany) for the production of sense- and antisense-cRNA. cRNA-probes were generated by using 10x RNA-DIG-labelling-Mix (Boehringer, Mannheim, Germany) and RNA-polymerase T7 and SP6 (Promega).

cRNA-probes were used for in-situ hybridization of deparaffinized sections that were permeabilized in proteinase K (20 µg/ml; Sigma, Deisenhofen, Germany) for 25 min at 37°C, postfixed in 4% paraformaldehyde, exposed to 20% acetic acid and prehybridized in 20% glycerol. For hybridization the cRNA-probes were diluted in 1:25 in hybridization-buffer containing 50% deionized formamide, 10% dextran sulphate, 2x standard saline citrate (SSC), 1x Denhardt's solution, 10 µg/ml salmon sperm DNA (Sigma), and 10 µg/ml yeast t-RNA (Sigma). Hybridization was performed overnight at 40°C in a humidified chamber. After washing sections were incubated overnight at 4°C with anti-DIG Fab-antibody conjugated to alkaline phosphatase (Boehringer Mannheim). After development of staining with nitro-blue-tetrazolium/5-bromo-4-chloro-3-indolyl-phosphate (BCIP/NBT; KPL, Gaithersburg, MD, USA) sections were mounted with glycerine gelatine (Merck, Darmstadt, Germany). Sense-cRNA probes were used as negative controls for each test.

Electron microscopy

For ultrastructural examinations, small samples were postfixed with 4% paraformaldehyde, 2% glutaraldehyde, 0.04% picric acid in 0.1 M phosphate buffer (pH 7.2, PB) for 6 hours (h) at 4°C, carefully washed with PB and incubated in 1% osmium tetroxide for 2 h. After repeatedly washing in PB, specimens were dehydrated in a series of graded ethanol and embedded in Epon (Serva, Heidelberg, Germany). Polymerization was performed at 60°C for 20 h. Semithin and ultrathin sections were cut with a diamond knife on an Ultracut (Reichert-Jung, Germany). Ultrathin sections (70–90 nm) were counterstained with uranylacetate and lead citrate (Reichert Ultrastainer, Leica, Germany) and examined in a Zeiss EM 109 transmission electron microscope.

Results

Induction of osteoporosis and clinical observation

BMD at the left calcaneus ($n = 3$) dropped from 439.8 ± 50.5 mg/mm^3 to 334.3 ± 40.1 mg/mm^3, and at the right calcaneus from 441.3 ± 45.0 mg/mm^3 to 335.3 ± 37.3 mg/mm^3 6 months after ovariectomy indicating an osteoporotic bone status with a loss of 24 ± 2% of the initial BMD.

Full-weight bearing was achieved in all three cases in the first post-operative days and all goats survived the entire observation period without any wound healing disturbance or other problems.

High-resolution peripheral quantitative computed tomography (HR-pQCT)

In general, it was observed that the bone defects filled with the injectable nanocrytalline hydroxyapatite with our without collagen type I showed higher bone volume with increased trabecular number and decreased trabecular spacing compared to the empty defect control group (Figure 2). This finding was confirmed by micro-CT histomorphometric parameters with HA exhibiting the highest BV/TV ratio ($p = 0.008$) and smallest trabecular spacing (Tb.Sp) ($p = 0.005$) compared to the other groups in the region of interest at the interface with 1 mm distance to the initially created defect (Table 2). The HA/col-1 yielded the highest connectivity density (Conn.D) ($p = 0.034$) and the highest number of trabeculae (Tb.N) ($p = 0.002$) compared to the HA and the control group.

Histomorphometry

Histomorphometric analysis for the core region of the initially created defect revealed a statistically higher new bone formation in the HA ($p = 0.001$) and HA/col-1 group ($p = 0.001$) compared to the empty defect group including all defect sites (Figure 2A). There were no significant differences between the HA- and the HA/col-1 group ($p = 0.15$). These results were confirmed for site specific analysis with significant higher new bone formation for the HA group for vertebral defects compared to the empty defect group ($p = 0.029$) (Figure 2B). There were no significant differences for new bone formation at the iliac crest ($p = 0.119$).

For the interface region, no statistically significant differences were found between the three groups including all defects ($p = 0.08$) (Figure 2C).

Histology

Defects of the empty control group were found either to be filled with granulation tissue or with lipid rich bone marrow with an accumulation of multinuclear cells degrading bone marrow fat cells (Figure 3). Bone lining cells of the surrounding trabecular bone turned into active osteoblasts with production of collagen into direction of the defect.

Defects filled with HA showed a good biocompatibility without inflammatory reaction and a high fragmentation of the implant that was related to some site-specific differences (Figure 3). HA implants in iliac crest defects were more fragmented than in the vertebrae. Fragmentation was shown to be caused by multinuclear cells with

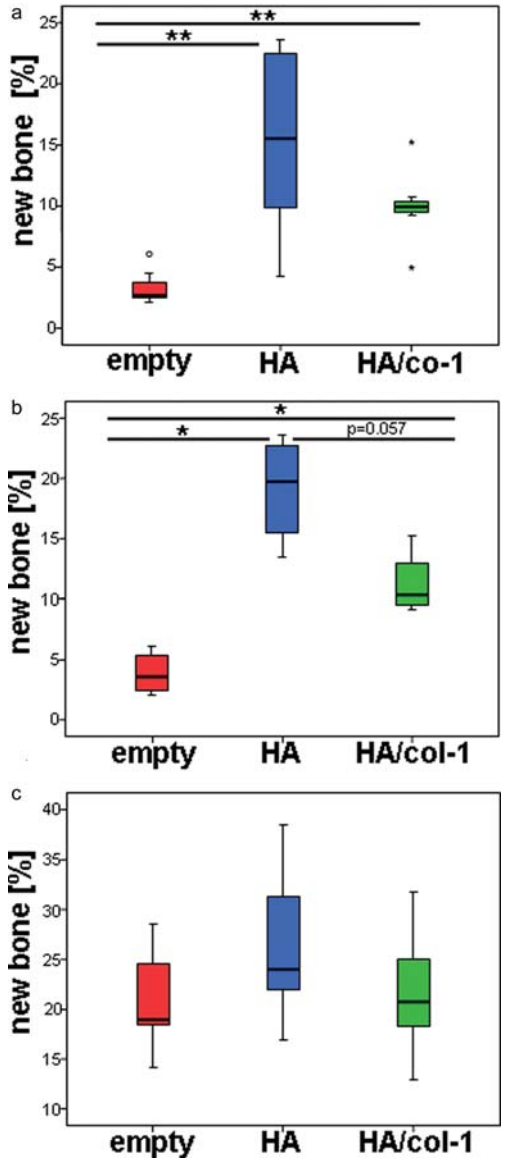

Fig. 2. Histomorphometrical results for the defect region including all anatomical sites (**a**), for lumbar vertebrae defects (**b**) and for the interface region with a 1 mm distance to the initially created defect including all defects (**c**). (*p < 0.05, **p < 0.01)

degradation of the implant. Multinuclear cells were followed by osteoblasts, fibroblasts and new blood vessels. HA fragments were surrounded by newly formed bone and multinuclear cells. Osteocytes were enclosed in newly formed bone that was encircled by osteoblasts and bone lining cells. High amount of blood vessels, fibrous tissue and the formation of bone marrow was observed in the lacunae between the HA fragments.

The HA/col-1 implants were also free of surrounding inflammatory tissue reaction but revealed less fragmentation compared to HA-implants (Figure 3). Most multinuclear cells were found on the surface of the implant and only a few of them were penetrating into the implant. A small rim of new bone covered by osteoblasts was also localised on the surface of implant and fragments. The implant was surrounded by fibrous tissue. The HA/col-1 implants were more fragmented in the iliac crest than in the vertebrae as described for the HA implants.

Immuno-, enzymehistochemistry and in situ hybridization

Osteoblasts were identified using immunohistochemistry with an antibody against osteocalcin and *in situ* hybridization for connexin-43 (Figure 4). Samples with HA implant showed a higher amount of osteoblasts than samples with HA/col-1 implant. In the controls with empty defects only a few osteoblasts were observed at the host bone interface. In addition to osteoblasts, osteocytes surrounded by calcified bone matrix showed also a positive connexin-43 labelling.

Newly formed bone was detected by collagen-type I immunohistochemistry. High amounts of collagen-I immunoreactivity around fragments of HA implants were found. TRAP could be seen within the cytoplasm of mononuclear macrophages and multinucleated cells. The same cell types were also positively stained for CD68 immunohistochemistry. Osteoclast-like cells were localized along the surfaces of HA particles which had not been covered by newly formed bone and within the granulation tissue. eNOS immunoreactivity labelled sprouting endothelial cells as well as osteoclast-like cells where the staining was localized in the resorbing region. This labelling also showed that newly formed blood vessels were localized in direct vicinity of resorbing multinuclear cells. In controls with empty defects, immunohistochemistry, TRAP and connexin-43 in-situ hybridization no positive staining was detected.

Transmission electron microscopy

Transmission electron microscopy showed that multinuclear cells localized at the interface of both the HA and HA/col-1 implants were able to incorporate degraded implant material particles (Figure 5). Multinuclear cells localised at the HA and HA/col-1 interface showed osteoclast-like properties such as exhibition of several nuclei and usual cell organelles and formation of sealing zones at the circumference of the ruffled border. At the sealing zone, pseudopodia-like plasmaprotrusions were formed to anchor the cell to the implant. Those osteoclast-like cells formed several short but wide plasma protrusions on the apical side. In the HA/col-1 group, osteoclast-like cells exhibited frequently more cell nuclei but the sealing zone was less developed compared to the HA group. Frequently, remnants of the HA implant were found between ruffled borders invaginations in the cytoplasm and in phagosomes but not in the nuclei.

Discussion

The current study revealed a statistically significant higher new bone formation in the defect region of the HA and the HA/col-1 group including all anatomical sites compared to the empty defect group in this osteoporotic animal model in Chinese mountain goats by

Table 2
Histomorphometric parameters evaluated by HR-pQCT expressed in mean ± SD, shown with p-values of Kruskal-Wallis test between groups.

	BMD (mmHA)	BV/TV (1)	Conn.D. (1/mm^3)	Tb.N (1/mm)	Tb.Th (mm)	Tb.Sp (mm)
Empty	618.8 ± 29.0	0.32 ± 0.22	2.09 ± 1.41	1.86 ± 0.45	0.32 ± 0.09	0.59 ± 0.17
HA	650.3 ± 19.3	0.58 ± 0.10	3.42 ± 1.26	2.40 ± 0.14	0.44 ± 0.11	0.41 ± 0.04
HA/Col-1	639.6 ± 27.8	0.42 ± 0.11	4.62 ± 2.45	2.47 ± 0.27	0.36 ± 0.08	0.42 ± 0.06
p-value	0.067	0.008*	0.034*	0.002*	0.055	0.005*

*$p < 0.05$.

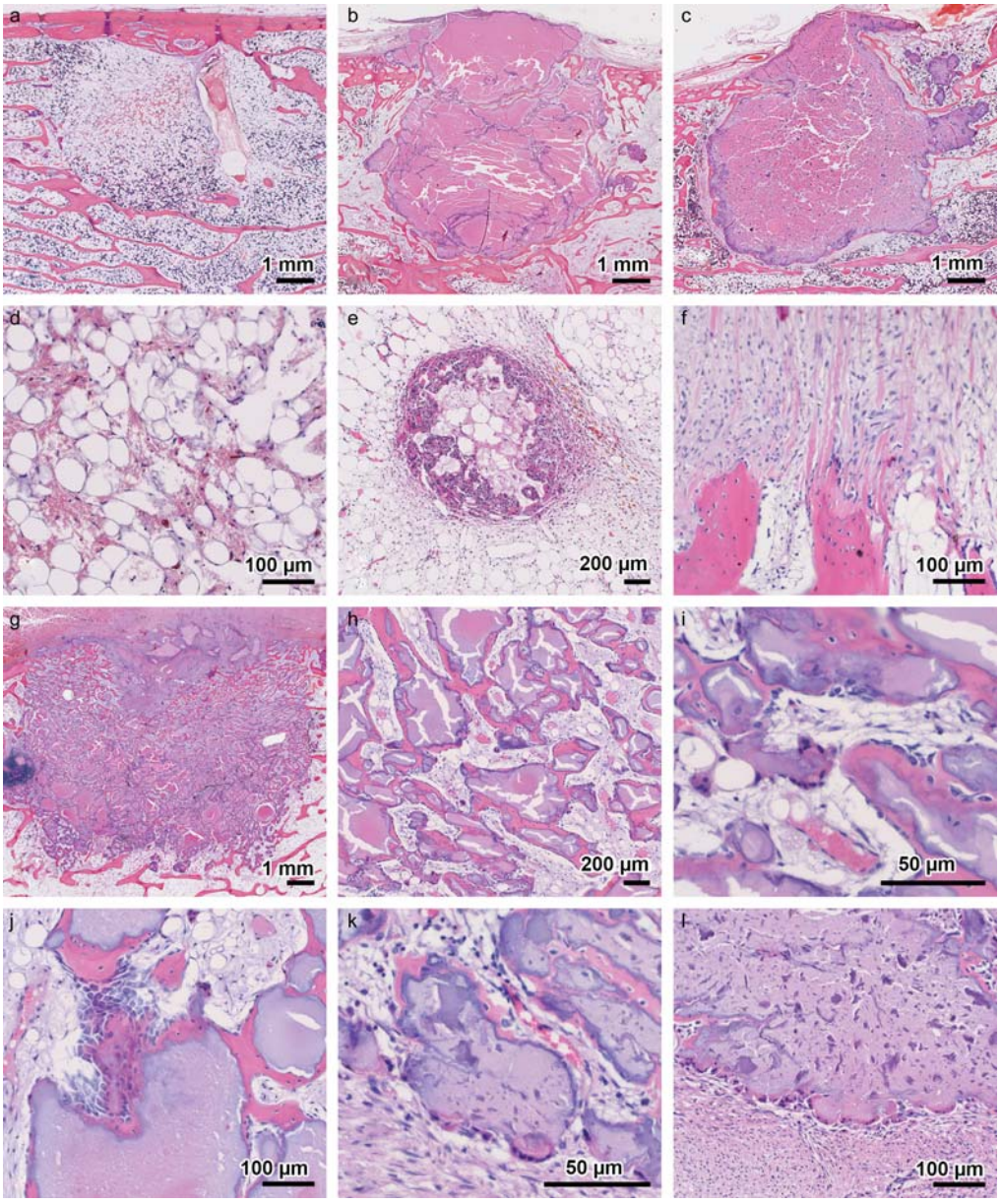

Fig. 3. Histological analysis of defects in the vertebrae of the lumbar spine of the empty defect group (**a**), HA implant (**b**), and HA/col-1 implant (**c**) group. Empty defects were mostly filled with bone marrow (**d**). Some empty defects showed an accumulation of multinucleated body giant cells and macrophages that were arranged as a circle with centred fatty bone marrow (**e**). Host bone trabeculae at the edge of empty defects were covered with osteoblasts forming new collagen fibers into direction of the defect (**f**). Overview of iliac crest defect filled with HA (**g**) with high fragmentation as shown in (**h**) in higher magnification. HA fragments were surrounded by newly formed bone covered with osteoblasts and in addition by some multinucleated macrophages (**i**). Accumulation of active osteoblasts at the interface of a HA fragment (**j**). Higher magnification of a HA/col-1 implant with high fragmentation but fragments were covered only with a small discontinuous rim of osteoid and osteoblasts (**k**), and a high number of multinucleated foreign body giant cells (**l**).

histomorphometry. There were no significant differences between the HA and the HA/col-1 group for this overall evaluation. HA could also show enhanced new bone formation for site specific analysis for vertebrae defects compared to the empty defect group. This confirms findings of other *in vivo* studies on the osteoconductive properties of the used nanocrystalline hydroxyapatite [2–10] which can be explained by the almost identical calcium/calcium phosphate ratio of human hydroxyapatite to the 1,67 ratio of this biomaterial [20]. Missing differences between the HA- and the HA/col-1 group suggest that the idea of enhancing adhesiveness of the biomaterial to osteoblasts via transmembrane integrin receptors via collagen-type I failed in the current study. However, it is difficult to assess if another HA/col-type-I ratio or other modifications might have had an effect which remains a question for potential further studies.

Histology revealed good biocompatibility with the absence of inflammatory reactions both for HA- and HA/col-type I implants confirming the results of other authors in physiological bone status in maxillofacial [6] and long bone defects [7–8]. Analysis of the degradation behaviour revealed higher fragmentation in the HA- compared to the HA/col-type I group with multinuclear osteoclast-like cells penetrating into the defect. In both groups, a considerable amount of implant remnants could be observed as HA- or HA/col-type I fragments that were surrounded by newly formed bone within the defect after 6 weeks suggesting an incomplete degradation of the two materials after 6 weeks. This is in line with findings from authors that also reported incomplete resoprtion of this nanocrystalline HA after several weeks [5,8,9]. Fragmentation was shown by transmission electron microscopy to be caused by multinuclear osteoclast-like cells

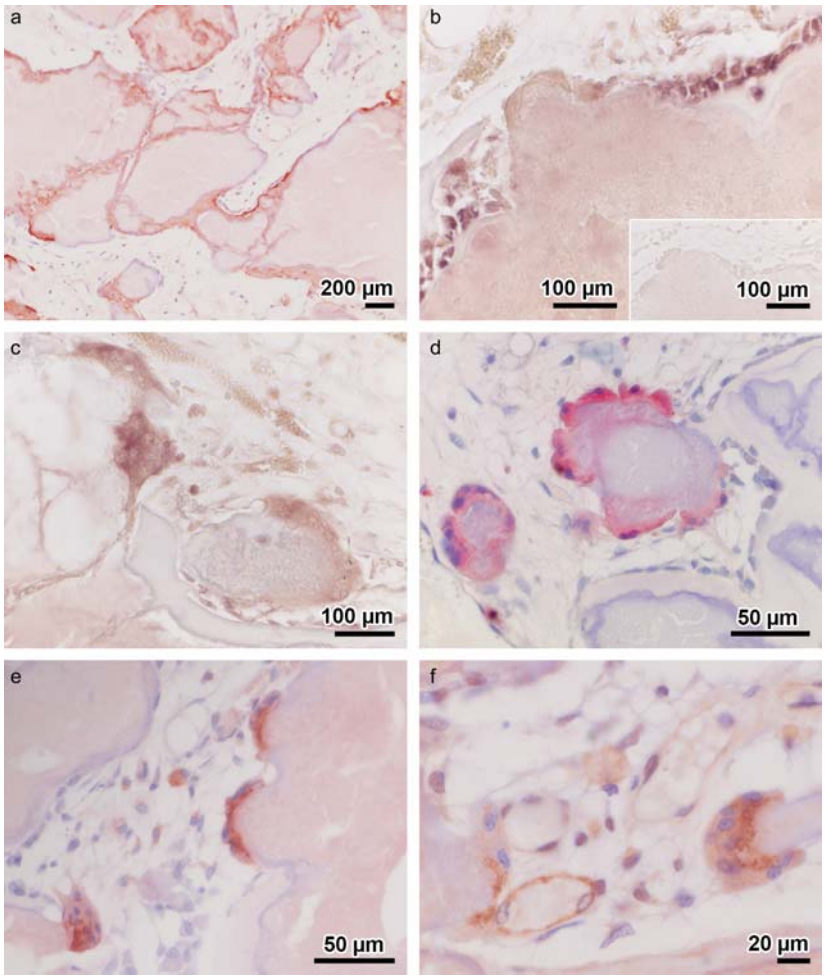

Fig. 4. Enzyme-, immunohistochemistry, and in-situ hybridization. Osteoid surrounding single HA fragments was identified by collagen type I immunoreactivity (**a**). The implants were covered with osteoblasts determined by connexin-43 in-situ hybridization (**b**). Inset in (b): negative control. Connexin-43 mRNA was also found in osteoclast-like cells at the HA/col-1 implant (**c**). Osteoclast-like cells were also identified by TRAP enzyme histochemistry as shown here for the HA implant (**d**). In addition, osteoclast-like cells were determined by CD68 immunohistochemistry as shown here at the bone-HA interface (**e**). eNOS immunoreactivity was used for identification of osteoclast-like cells as well as newly formed blood vessels in the granulation tissue between the implant fragments (**f**).

with degradation of the implant via intracellular incorporation of degraded implant material particles. For both the HA- and the HA/col-1 treated animals, remnants of the HA implant were frequently found between ruffled borders invaginations in the cytoplasm and in phagosomes but not in the nuclei.

Differences in the histomorphometric evaluation of new bone formation between high-resolution peripheral quantitative computed tomography (HR-pQCT) and "classical" histomorphometry are of importance. The first method was unable to distinguish between the used HA- or HA/col-1 implant from bone which made a reliable evaluation of new bone formation within the material impossible. This is due to the fact that the used HA in the implants closely mimics human HA limiting the value of CT methods if such implants are used. Therefore, the interface region was investigated by HR-pQCT and histology with a distance of 1 mm to the initial defect. HR-pQCT revealed the highest BV/TV ratio and smallest trabecular spacing for the HA group and the highest connectivity density and highest number of trabeculae for the HA/col-1 group suggesting better new bone formation compared to the empty defect. However, "classical" histomorphometry failed to show any significant enhancement of bone formation at the interface region between the groups.

The results of the current work are based on an established large animal model with induction of a significant loss of the BMD by ovariectomy and low-calcium diet in Chinese goats. The observed reduction in BMD in this work with a decrease of BMD measured in the calcanaeus of 24 ± 2% are comparable to similar studies using the same animal model [15]. As most osteoporotic fractures affect trabecular bone of the metapyhseal area of long bones, the metaphyseal regions of lumbar vertebrae, of the iliac crest and of the distal femur were selected for the current work. However, the study is limited by the small number of animals and the low number of the specific defects. Furthermore, only drill hole defects but no fractures were created in the current study which limits its conclusions for the potential enhancement of these two materials on fracture healing in osteoporotic fractures [21].

Conclusion

In conclusion, both nanoparticulate HA with and without collagen type-1 showed better new bone formation compared to untreated drill hole defects in metaphyseal defects of the lumbar spine, the iliac crest and in the distal femur of this osteoporotic Chinese mountain goat model. Both materials showed good biocompatibility without any inflammatory reaction and degradation via osteoclast-like multinuclear cells with intracellular uptake of the material into these cells.

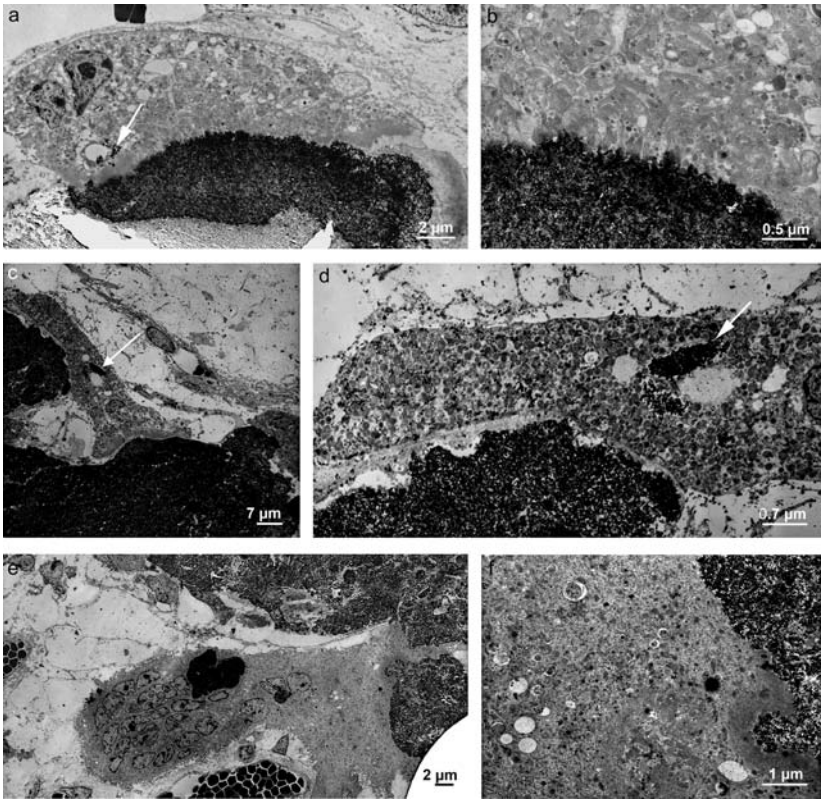

Fig. 5. Transmission electron microscopy. Osteoclast-like cell localized in vicinity to a HA fragment with intracellular uptake of HA fragments (arrow) (**a**) and formation of a ruffled border like resorption zone (**b**). Intracellular accumulation of HA remnants (arrows) by an osteoclast-like cell in vicinity to a HA fragment at lower (**c**) and higher magnification with distribution of implant remnants within the entire cytoplasm (**d**). Osteoclast-like cell in the vicinity to a HA/col-1 implant with a high number of nuclei (**e**) and only a small contact zone without formation of a ruffled border (**f**).

Conflict of interest

The authors have no conflicts of interest.

Acknowledgment

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