Journal of Biomechanics 115 (2021) 110138

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Reconstruction of proximal humeral fractures without screws using a reinforced bone substitute ☆

Luca Cristofolini [a,*], Maria Luisa Ruspi [a], Daniele Marras [a], Marco Cavallo [b], Enrico Guerra [b]

[a] Department of Industrial Engineering, School of Engineering and Architecture, Alma Mater Studiorum – Università di Bologna, Bologna, Italy
[b] Shoulder and Elbow Surgery, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

ARTICLE INFO

Article history:
Accepted 12 November 2020

Keywords:
Proximal humeral fracture
Osteoporotic multi-fragment fracture
Locking plate
Augmentation
Number of screws

ABSTRACT

Multi-fragment fractures are still a challenge: current clinical practice relies on plates and screws. Treatment of fractures of the proximal humerus has the intra-operative risk of articular damage when inserting multiple screws. Distal-varus collapse of the head is a frequent complication in osteoporotic patients. The aim of this biomechanical study was to investigate if an *Innovative-cement-technique* (the screws are replaced by injection of cement) provides the same or better stability of the reconstructed head compared to the *Standard-technique* (locking screws). A four-fragment fracture was simulated in twelve pairs of humeri, with removal of part of the cancellous bone to simulate osteoporotic "eggshell" defect. One humerus of each pair was repaired either with a *Standard-technique* (locking plate, 2 cortical and 6 locking screws), or with the *Innovative-cement-technique* (injection of a partially-resorbable reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP). Cement injection was performed both in the lab and under fluoroscopic monitoring. The reconstructed specimens were tested to failure with a cyclic force of increasing amplitude. The *Innovative-cement-technique* withstood a force 3.57 times larger than the contralateral *Standard* reconstructions before failure started. The maximum force before final collapse for the *Innovative-cement-technique* was 3.56 times larger than the contralateral *Standard-technique*. These differences were statistically significant. The *Innovative-cement-technique*, based on the reinforced bone substitute, demonstrated better biomechanical properties compared to the *Standard-technique*. These findings, along with the advantage of avoiding the possible complications associated with the locking screws, may help safer and more effective treatment in case of osteoporotic multi-fragment humeral fractures.

1. Introduction

Proximal humeral fractures affect approximately 66 out of 10,000 persons yearly (Lanting et al., 2008), accounting for about 10% of all fractures in elderly patients (Barrett et al., 1999; Palvanen et al., 2006; Singh et al., 2015). The golden standard for such fractures is fixation with locking plate with screws (Charalambous et al., 2007; Gavaskar et al., 2016; Rosengren et al., 2015; Schliemann et al., 2015). The second-generation of these locking devices overcame many drawbacks experienced with first-generation non-locking plates in elderly patients (Gavaskar et al., 2016; Olerud et al., 2011). However, locking plates create several problems, increasing with patients' age and fracture complexity (Berkes et al., 2013; Brunner et al., 2009; Schliemann et al., 2012; Sproul et al., 2011; Thanasas et al., 2009). This system is associated with intra-operative risks, chiefly cartilage damage while drilling or inserting the screws (incidence: 12–25% (Charalambous et al., 2007; Olerud et al., 2011)). This risk is higher in osteoporotic patients: due to the lack of bone in the center of the humeral head, the screws must be long enough to reach the subchondral bone, increasing the risk of cartilage perforation or prominence over the cartilage layer (Erhardt et al., 2012). Furthermore, four-parts fractures require a large number of screws to stabilize each fragment, multiplying the risks (Charalambous et al., 2007; Varga et al., 2018). Secondary loss of reduction is the most common post-operative failure mechanism (Schliemann et al., 2015). Bone quality, associated with medial comminution of the humeral neck undermines stability of fixation (Namdari

☆ Submitted as an Original Article for the SM Perren Special issue (ref: BM-D-20-00708).

* Corresponding author at: Department of Industrial Engineering, School of Engineering and Architecture, Alma Mater Studiorum – Università di Bologna, Viale Umberto Terracini 24-28, 40131 Bologna, Italy.
E-mail address: luca.cristofolini@unibo.it (L. Cristofolini).

https://doi.org/10.1016/j.jbiomech.2020.110138
0021-9290/© 2020 The Authors. Published by Elsevier Ltd.

et al., 2012; Schliemann et al., 2015). In fact, the low mechanical properties in low-density bone reduce the pull-out and cut-through strength of the screws (Fankhauser et al., 2003; Maldonado et al., 2003; Seebeck et al., 2004). The locking screws in the humeral head act as cantilevers connected to the plate on the lateral humerus; repetitive loading gradually induces the tip and thread of these screws to damage the osteoporotic bone, cutting-through the cancellous bone and leading to varus dislocation of head (Choma et al., 2011; Hertel, 2005; Jabran et al., 2018; Kammerlander et al., 2016). Acromial impingement is another frequent problem with plate fixation, affecting up to 21% of patients (Bachner et al., 2019; Kirchhoff et al., 2008).

Another critical point is the desire to early mobilize the shoulder and prevent disabling stiffness. Therefore, in patients with poor quality bone and multiple-fragment fracture, a higher number of screws is often required to obtain sufficient stability (Varga et al., 2018).

In order to overcome these problems, screw augmentation has been proposed, mainly with acrylic cement. Despite the initial concerns, cement has been proven not to cause thermal bone necrosis or cartilage apoptosis in these applications (Blazejak et al., 2013; Danesi et al., 2017). Biomechanical studies reported how screw augmentation is effective in stabilizing the fragments and preventing head migration when positioned in critical area (Kathrein et al., 2013). Nevertheless, to the Author's knowledge only few studies report clinical application of this technique in four-parts proximal humeral fractures, in relatively small studies (<100 cases) (Egol et al., 2012; Hengg et al., 2019; Katthagen et al., 2018; Knierzinger et al., 2020; Siebenburger et al., 2019). These papers often report complications such as screw penetration of the collapsed humeral head and avascular necrosis, even if incidence is reduced by the use of cement (Hengg et al., 2019; Knierzinger et al., 2020; Siebenburger et al., 2019). Polymethylmethacrylate (PMMA) cement in itself is unable to promote bone healing and does not address problems of vascularization. Calcium-phosphate cements are osteoconductive, but provide limited mechanical support, leading to risk of early fixation failure (Danesi et al., 2017). The need of conjugating the advantages of the different augmentation materials led to the development of innovative products. A combination of PMMA and beta-tricalcium-phosphate (beta-TCP) was introduced to provide adequate mechanical properties for initial fixation, and promote bone ingrowth with partial substitution of the cement over time. This composite material allows formation of interconnected porosity by resorption of the beta-TCP (Dall'Oca et al., 2014; Dall'Oca et al., 2017). Due to its open microporous structure, this cement allowed the blood vessels and bone cells to colonize superficially the gap left by the beta-TCP reabsorption, and it permitted the osteoblasts to re-create homogeneously the bone tissue at the bone-cement interface (Dall'Oca et al., 2014, 2017). Similar products have already been used in pre-clinical studies, showing biomechanical positive support to conventional plate and screw fixation (Kuang et al., 2018). This led to the idea to verify in a biomechanical setting if it would be reasonable to develop a construct with the positive aspects of cement augmentation without the drawbacks of screws presence in the long term. A recent *in vitro* biomechanical study reported encouraging results when the number of screws was reduced and replaced with a reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP (Cristofolini et al., 2020).

The aim of this study was to test the biomechanical validity of an innovative technique to repair humeral fractures, based on the injection of a partially-resorbable reinforced bone substitute to replace the screws normally used to stabilize the fragments. The hypothesis was that this technique would provide the same or better stability of the bone fragments compared to the standard technique. The focus was the risk of slippage of the reconstructed head in case of four-fragment fractures in proximal humeri with bone defects.

2. Materials and methods

2.1. Bone specimens

This Study was authorized by the Bioethics Committee of the University of Bologna (Prot. 68448, 10 May 2018). Twelve pairs of frozen humeri were obtained through an ethically-approved donation program (Anatomy Gifts Registry, Hannover, USA) (Table 1). In order to allow reproducible alignment, the humeri were cleaned removing all soft tissues and exposing the bone landmarks, which were used to identify the anatomical reference axes (Cristofolini, 2012). The distal portion of the intact humeri was resected. The diaphysis was potted using PMMA in an aluminum box. A fixed fraction of the humerus was left free (40% the biomechanical length of the intact humerus, Table 1) to grant comparable biomechanical conditions to the different humeri. Hydration was preserved wrapping the humeri in cloths soaked with physiological saline solution.

2.2. Fracture simulation

In all humeri, a four-fragment fracture (adapted from AO-11-C2 (Rüedi and Murphy, 2001)) was simulated. In order to allow consistent preparation of the fractures, the bones were processed in pairs, following well-defined resection planes, aligned with the previously-defined references, using custom-built cutting jigs (Fig. 1):

- 1st cut: the head was resected on a plane parallel to the end of the epiphysis.
- 2nd cut: the metaphysis was resected at the height of the end of the epiphysis.
- 3rd cut: the lateral fragment was cut in a frontal plane between greater and lesser tuberosity.

In addition, to simulate in a reproducible way the cases where the innovative technique is possibly indicated, a portion of the cancellous bone was removed to mimic lack of support due to severe osteoporosis ("eggshell defect") (Kamer et al., 2016). In both humeri of each pair, a hole was drilled in the cancellous bone under the drill press following a standardized procedure. In the head a ø30 mm bit was used, for a depth equivalent to 40% of the head diameter. Cancellous bone from the metaphysis was removed (ø20 mm bit) for a depth of 26–30 mm (the depth was adjusted in each pair to avoid compromising the cortical bone).

2.3. Surgical technique

The reconstructions of the fractured humeri were performed by an experienced shoulder surgeon (Fig. 2). The surgeon identified the optimal position of the plates, preparing the humeri in pairs, aiming to minimize inter-pair differences. One of the most common pre-contoured plates (Philos, DePuy-Synthes, Oberdorf, Switzerland) was used in conjunction with its locking and cortex screws. The recommended procedure was adapted for deployment in a laboratory setting. All the screws-hole were pre-drilled (ø2.5 mm) using the dedicated aiming device (Philos, DePuy-Synthes). The surgeon chose the length of each screw using the dedicated probe (Philos) following the standard procedure. A total of 6 plates (regular size) and 51 screws (ø3.5 mm) of titanium alloy were used for all the humeri. The locking screws were between 35, 40, 45, 50 mm; the cortex screws 28 and 34 mm. The plates and

Table 1
List of the humeri used in this study, including the donors' details and the biomechanical length of each bone specimen (defined as in (Cristofolini, 2012)). Two types of implant were prepared (*Standard-technique* and *Innovative-cement-technique*). No information about donor's laterality was available.

Donor	Cause of death	Sex	Ethnics	Age (years)	Height (cm)	Body weight (kg)	Side	Biomechanical length (mm)	Type of Reconstruction	Amount of cement injected (ml)	Preparation
#1	Renal Failure	F	Caucasian	56	163	204	L	300	*Standard*	–	In the lab
							R	315	*Innovative-cement*	10	In the lab
#2	Glioblastoma	F	Caucasian	62	163	113	L	332	*Innovative-cement*	15	In the lab
							R	335	*Standard*	–	In the lab
#3	Diabetes Complications	M	Caucasian	69	163	91	L	340	*Standard*	–	In the lab
							R	340	*Innovative-cement*	20	In the lab
#4	Pulmonary Fibrosis	F	Caucasian	70	175	136	L	295	*Innovative-cement*	20	In the lab
							R	300	*Standard*	–	In the lab
#5	Cardiogenic Shock	F	Black	66	170	136	L	340	*Standard*	–	In the lab
							R	340	*Innovative-cement*	20	In the lab
#6	Cardiac Arrest	F	Caucasian	50	158	136	L	310	*Innovative-cement*	20	In the lab
							R	305	*Standard*	–	In the lab
#7	Sepsis	F	Caucasian	75	167	144	L	313	*Innovative-cement*	14	Fluoroscope
							R	310	*Standard*	–	In the lab
#8	Respiratory Failure	F	Caucasian	58	162	142	L	306	*Innovative-cement*	20	Fluoroscope
							R	304	*Standard*	–	In the lab
#9	Cardiac Arrest	F	Caucasian	70	170	75	L	347	*Innovative-cement*	18	Fluoroscope
							R	348	*Standard*	–	In the lab
#10	Respiratory Failure	F	Caucasian	70	150	216	L	289	*Standard*	–	In the lab
							R	290	*Innovative-cement*	15	Fluoroscope
#11	Respiratory Failure	F	Caucasian	72	175	124	L	321	*Standard*	–	In the lab
							R	320	*Innovative-cement*	20	Fluoroscope
#12	Pneumonia	F	Caucasian	69	167	130	L	312	*Standard*	–	In the lab
							R	312	*Innovative-cement*	18	Fluoroscope
			Median	**69**	**165**	**136**	**–**	**313**	**–**	**19.0**	
			Range	**50–72**	**158–175**	**75–216**	**–**	**289–348**	**–**	**10–20**	

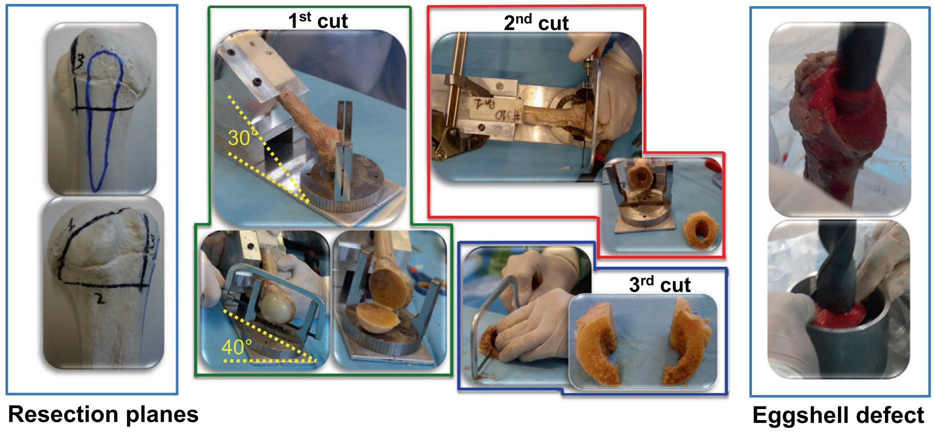

Fig. 1. Left: schematic view of the three resection planes to simulate a four-fragment fracture (left humerus: anterior and lateral views). Center: the steps of 1st, 2nd and 3rd cut to simulate a four-fragment fracture. Right: to mimic poor bone quality ("eggshell defect") the cancellous bone was removed by drilling the head and the metaphysis, without affecting the cortical bone.

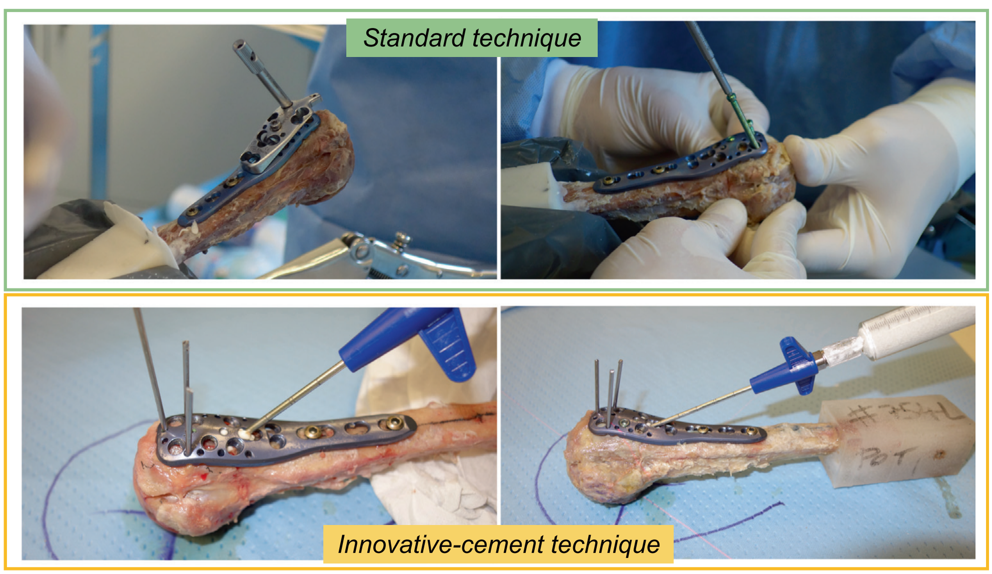

Fig. 2. Comparison between the two reconstruction techniques tested in this study. Top: preparation of the holes and insertion of the locking screws in the humeral head for the *Standard-technique*. Bottom: injection of the cement (the fragments were temporarily kept in place by Kirschner wires and a plate) for the *Innovative-cement-technique*.

screws were carefully checked before re-use following a validated procedure to exclude critical damage of the threads, or bending (Danesi et al., 2011). One humerus of each pair was randomly assigned to one of these two techniques:

- *Standard-technique:* In each specimen the distal portion of the Philos plate was fixed with two cortex screws (distally); six holes were prepared for the proximal locking screws (Fig. 3a). To enable reproducible and accurate preparation, the screw holes were drilled using the plate as a guide, before simulating the fracture. The plate and screws were then implanted after fracture simulation (see below).
- *Innovative-cement-technique*: The innovative treatment was performed after reduction of the fragments. In order to keep all the fragments in place, a plate was temporarily fixed to the diaphysis with two cortex screws; Kirschner wires (ø1mm) were inserted proximally before injecting the cement. A reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP (Cal-CEMEX, Tecres, Sommacampagna, Italy) was injected into the humeral head (Fig. 3b). The monomer and powder were mixed in the dedicated kit (Shakit, Tecres) for 2 min. The cement was delivered 4 min using the proprietary kit (Xtruder) through the central hole of the Philos plate, in order to reach the eggshell defect. As a first part of the study, the surgeon injected cement in six humeri in the laboratory: the amount injected was chosen based on the volume of the bone cavity: no leakage of cement was observed through the bone fractures. For the remaining six, the surgeon injected the cement under a fluoroscope (Vision-FD Vario-3D, Ziehm-Imaging, Nuremberg, Germany), and stopped injection based on cavity filling, as it would happen during real surgery (Fig. 4). The quantities of cement injected in laboratory (10–20 ml) and under the fluoroscope (14–20 ml) were not significantly different (Table 1). The cortex screws, plates and wires were removed from the *Innovative-cement* specimens before the mechanical test.

To allow the cement to season before mechanical testing, the specimens were stored for 48 h at 37 °C in physiological saline solution (additivated with 0.18% methyl-4-hydroxybenzoate to avoid degradation). This corresponds to the earliest time when a patient would load the operated limb (Doshi et al., 2017).

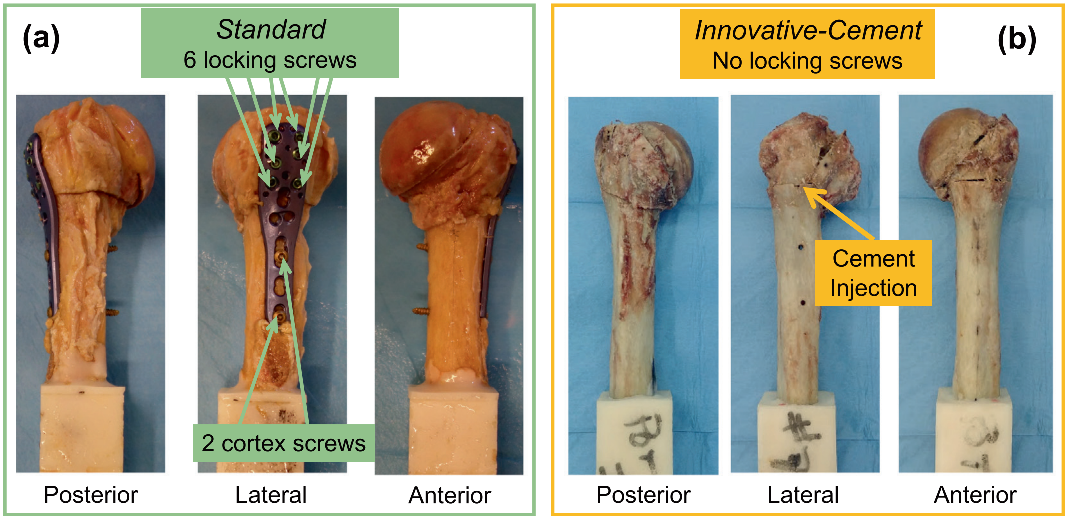

Fig. 3. Pair of humeri (anterior, lateral and posterior views) after simulation of fracture and reconstruction with the *Standard-technique* (on the left, (a)) and with the *Innovative-cement-technique* (on the right, (b)).

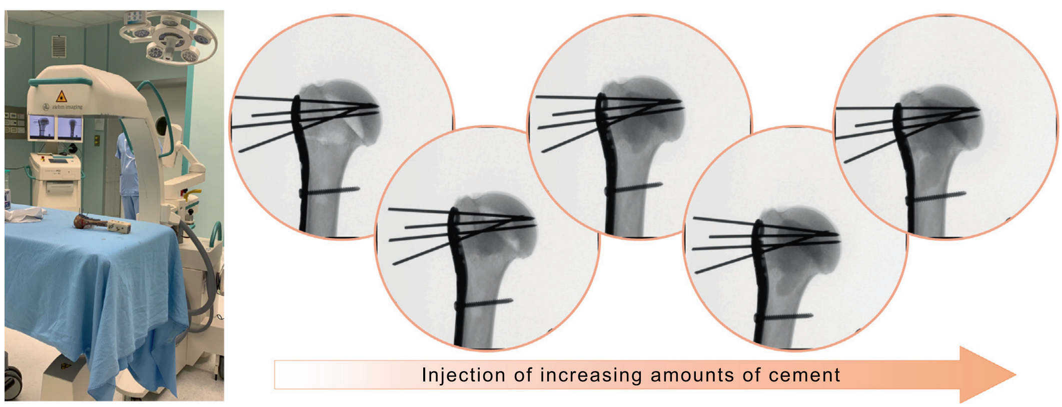

Fig. 4. Left: injection of the cement under the fluoroscope to monitor the flow of the cement in the *Innovative-cement-technique*. Right: the fluoroscopic images showing the amount and the distribution of cement at different steps of the injection (from left to right). The cement first spread into the head of the humerus filling the entire cavity. When the head of the humerus was completely full, the cement filled the diaphyseal cavity of the humerus. The images show also the plate and the Kirschner wires temporarily used to hold the fragments in place during cement injection.

2.4. Biomechanical test

The biomechanical test was similar to a recent study (Cristofolini et al., 2020) and allowed comparing the two reconstruction techniques (*Standard-technique* vs. *Innovative-cement-technique*). One of the most common mechanisms of failure is a distal sliding of the humeral head with respect to the humeral diaphysis. For this reason, all the humeri were tested imposing a cyclic force of increasing magnitude with a specific loading direction. Due to repetitive axial loading, the screws gradually cut into the cancellous bone causing the sliding of the head (Brianza et al., 2010; Lescheid et al., 2010). To test this scenario, the distal end of the humerus was fixed to the load-cell of the testing machine (Mod.8800, Instron, Canton, USA; Fig. 5). A vertical force (aligned with the axis of the humerus) was applied to the humeral head by the actuator. The biomechanical test was the worst-case-scenario: a force aligned with the humeral axis elicits the highest risk of distal slippage of the humeral head (Anglin et al., 2000; Westerhoff et al., 2009).

A cyclic force was applied at 1 Hz: the baseline was constant (80 N) while the amplitude started from 60 N, and increased at each cycle by 1% of current amplitude until failure. The force and displacement were measured with a high-performance datalogger (PXIe-6341 + PXIe-8135, National-Instruments, Austin, USA).

2.5. Identification of failure

To quantitatively and objectively measure the strength of the reconstructions, failure was defined when the distal migration of the head exceeded 5.0 mm with respect to the initial condition of the test. The migration of the head was measured through the displacement of the actuator since the humeri were aligned with the testing machine (Fig. 6). This is consistent with the criterion indicated by Neer et al, where a displacement of 5.0 mm or more was considered an indication for surgical treatment for humeral head fractures (Neer et al., 1982) (Fig. 7). A first failure event was defined as a change of slope in the force-displacement curve. This would correspond to an initial migration of a reconstructed humeral head in a shoulder patient. To identify such a transition in an operator-independent way, the first failure event was defined similar to the identification elastic limit in material testing: the initial slope of the force-displacement curve was first identified; a line with a 0.2 mm offset was then drawn; the intersection of the offset line with the force-displacement plot defined the end

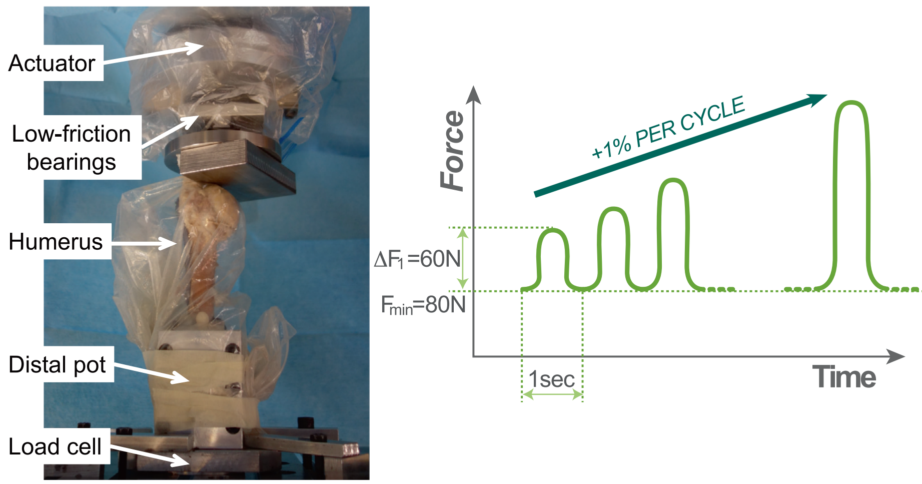

Fig. 5. Left: Overview of the test setup, showing a reconstructed left humerus (wrapped in a plastic bag to prevent leakage of fluids), and the system for application of the force (actuator and low-friction bearings); the load cell is below the distal aluminum pot. A metal plate was used to ensure that the force was applied to the humeral head (and not to the greater tuberosity). Right: The diagram explains the load profile (of increasing amplitude) applied during the mechanical cyclic test. A cyclic compressive force was applied at 1 Hz. The baseline force was constant (80 N), while the amplitude increased at each cycle by 1% of the current amplitude, starting from an amplitude of 60 N for the first cycle. The entire test lasted between 152 and 412 cycles (between 2 and 7 min).

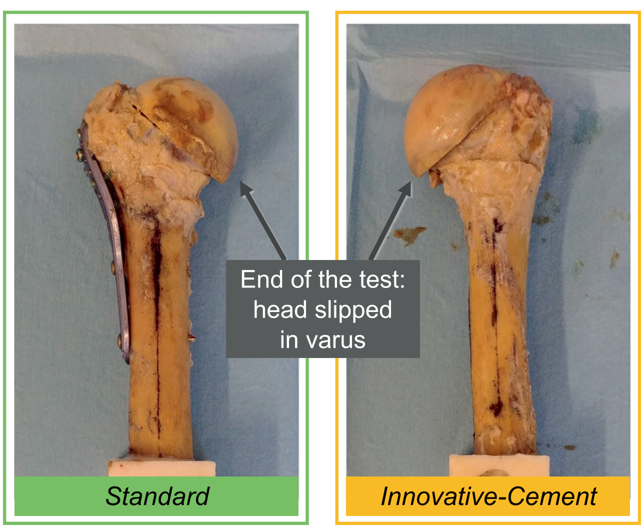

Fig. 6. Pair of humeri, reconstructed with the two different techniques (left: *Standard-technique,* right: *Innovative-cement-technique*) after the biomechanical test. In both cases there was a distal migration of the head which lead to failure.

of the linear region (first failure). Additionally, the maximum force was defined as the largest force recorded from the beginning to the test. This corresponds to the maximal force that can be resisted by the reconstructed humerus before gross failure occurs.

2.6. Measurement of the curing temperature

In order to measure the temperature increase due to cement curing, twelve specimens were instrumented with four thermocouples (three in the head, one in the metaphysis) prior to cement injection. More details are reported in the Supplementary materials.

2.7. Statistics

To ensure that the two preparations with the *Innovative-cement-technique* (cement injections in laboratory and under the fluoroscope) were comparable, a F-test was performed. As the laboratory-prepared and the fluoroscope-prepared specimens were not statistically different, the two sub-groups were pooled together for a total of twelve pairs. The F-test was used also to compare the variance of the two reconstruction techniques. The Wilcoxon signed-rank two-sided non-parametric test was used to compare the strength of the paired samples. All statistical analyses were performed with Matlab 2018 (MathWorks, Natick, MA, USA).

3. Results

3.1. Distribution of the injected cement

For all the specimens reconstructed with the *Innovative-cement-technique*, the cement injected through the hole first spread into the head of the humerus filling the entire cavity (Fig. 4). Subsequently, when the head of the humerus was completely full, the additional cement injected flowed to the diaphyseal cavity of the humerus. No leakage of cement was observed between the fragments, both for the fluoroscope and for the laboratory preparations.

3.2. Failure mechanism

For both types of reconstruction, our test elicited the expected type of failure: a progressive varus-distal collapse of the humeral head respect to the diaphysis (Fig. 6). The force-displacement plots had a monotonic trend until failure for all the specimens (Fig. 7). In several specimens of both types of reconstruction, the force showed a second increase after a migration of several millimeters was reached: this was associated with a compaction of the fragments.

Each group showed a typical and consistent failure mechanism (Table 2):

- The *Standard-technique* (i.e. repaired with 6 locking screws) failed progressively, starting at a force (first failure) that was lower than the maximum peak. The maximum force was 1.36 times larger (median of 12 specimens) than the first failure.
- For the *Innovative-cement-technique* (i.e. with injection of the cement, and tested without any plate or screws), failure was more progressive than with the *Standard-technique,* with the force still increasing after the first failure. The maximum force was 1.58 times larger (median of 12 specimens) than the first failure.

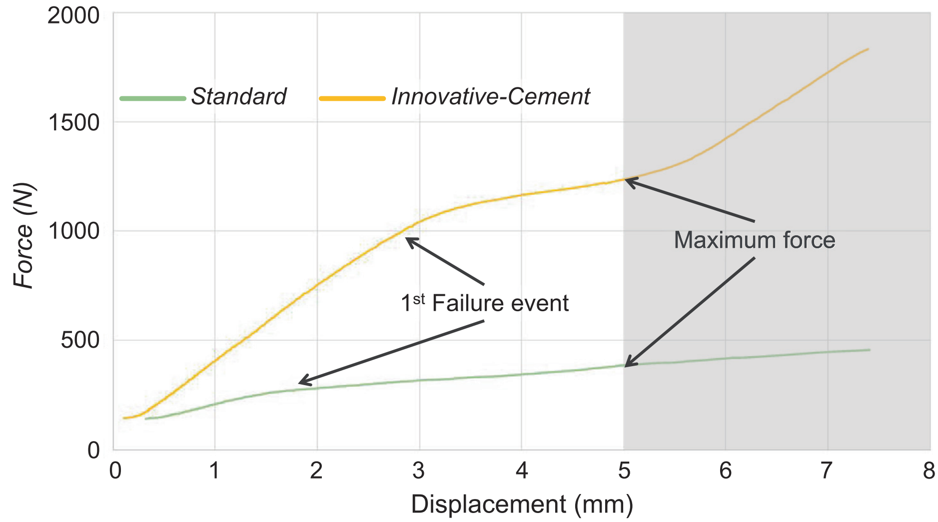

Fig. 7. Typical force-displacement plots throughout the mechanical destructive test for the *Standard-technique* and for the *Innovative-cement-technique*. The envelope of the load peaks is shown. While the criterion for failure was a migration of 5.0 mm, the test was extended as far as 8.0 mm to ensure that failure became clear in all specimens.

Table 2
The values of force at 1st failure and maximum force are reported for each specimen both for *Standard-technique* and *Innovative-cement-technique*. For the *Innovative-cement-technique*, also the normalized values are reported, as a fraction of the contralateral specimens prepared with the *Standard-technique*.

Standard-technique

Donor #	*Force at 1st failure (N)*	*Maximum force (N)*
#1	347	504
#2	383	511
#3	303	383
#4	468	626
#5	464	804
#6	368	603
#7	185	269
#8	276	385
#9	425	437
#10	323	594
#11	329	394
#12	–*	154
Median	**347**	**470**
Range	**185–468**	**154–804**

Innovative-cement-technique

Donor #	*Force at 1st failure (N)*	*Maximum force (N)*	*Force at 1st fail as fraction of Standard-technique*	*Max Force as fraction of Standard-technique*
#1	919	1294	2.65	2.57
#2	1644	2520	4.29	4.93
#3	1111	1834	3.67	4.79
#4	1757	2912	3.75	4.65
#5	1582	1995	3.41	2.48
#6	1372	2331	3.73	3.87
#7	514	686	2.78	2.55
#8	1021	1231	3.70	3.20
#9	296	1066	0.70	2.44
#10	1154	1933	3.57	3.25
#11	898	1537	2.73	3.90
#12	564	633	–*	4.11
Median	**1066**	**1685**	**3.57**	**3.56**
Range	**296–1757**	**633–2912**	**0.70–4.29**	**2.44–4.93**

Note * missing data due to data recording problems during the mechanical test.

3.3. Strength of the reconstructions

The force at first failure of the *Innovative-cement-technique* (range: 296–1757 N) was 3.57 times larger (median of the ratio) than the contralateral *Standard-technique* (range: 185–468 N) (Table 2). This difference was statistically significant (Wilcoxon signed-rank, $p = 0.002$). Similarly, the maximum force of the *Innovative-cement-technique* (range: 633–2912 N) was 3.56 times larger than the contralateral *Standard-technique* (range: 154–804 N) (Table 2). This difference was statistically significant ($p = 0.00049$). Remarkably, all of the *Innovative-cement-technique* specimens were at least as strong as the contralateral *Standard-technique* (Fig. 8).

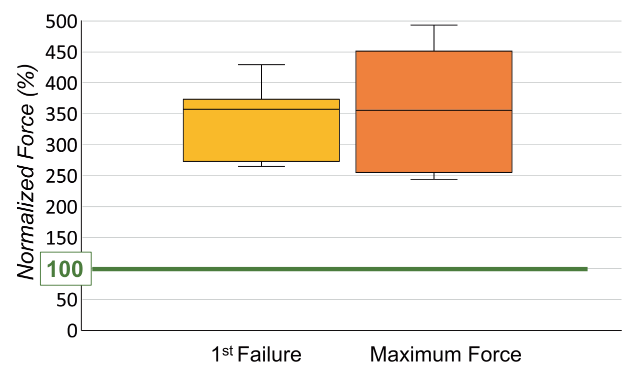

Fig. 8. The strength measured of the *Innovative-cement-technique* was normalized in comparison with the corresponding value measured for the *Standard-technique*. The force to reach first failure event and the maximum force are reported (box-and-whiskers plot with quartiles over 12 pairs of specimens). Values of 100% indicate that the *Innovative-cement-technique* was as strong as the contralateral *Standard-technique*; values larger than 100% indicate that the *Innovative-cement-technique* was stronger.

The inter-specimen variability (coefficient of variation = standard deviation/mean = 23–42%) was similar for the *Standard-technique* and the *Innovative-cement-technique* both for the force at first failure and for the maximum force (F-test, $p > 0.1$).

3.4. Curing temperature

The peak temperature at the cement-bone interface during cement curing was 59.2 °C; it exceeded 45 °C for 10′12″, and 48 °C for 7′25″ (mean of 12 specimens). More details are reported in the Supplementary materials.

4. Discussion

Treatment of multi-fragment fractures of the proximal humerus in osteoporotic patients often leads to dissatisfactory results (Brunner et al., 2009; Hertel, 2005; Owsley and Gorczyca, 2008). Locking plates represent a milestone for these fractures, but still outcomes need to be improved due to the difficulties for the surgeon to achieve a good reduction and a stable fixation on osteoporotic bone. In fact, fractures in elderly patients are often comminuted with bone impaction, where after an anatomic reduction, bone stock supporting the screws and other fragments is missing from the central part of the humeral head. For this reason, different cements based on PMMA and on calcium-phosphate were proposed, reporting positive results (Blazejak et al., 2013; Kammerlander et al., 2016; Röderer et al., 2013). PMMA provides adequate strength immediately (Kammerlander et al., 2016) and no concerns seems to be justified relating to the curing temperature when used for screw augmentation (Blazejak et al., 2013; Kammerlander et al., 2016). However, PMMA inhibits healing when interposed between fractures rims. Recently, bioactive cements have been introduced for augmentation at different sites (Kuang et al., 2018), showing positive biological results *in vitro* (Lu et al., 2001). Calcium-sulphate cements are biologically better than PMMA, but they lose mechanical property too rapidly, due to their fast degradation (Urban et al., 2004). A reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP was introduced to promote bone ingrowth with partial substitution of the cement over time, while granting adequate short- and long-term mechanical support (Dall'Oca et al., 2014; Dall'Oca et al., 2017), helping to partially rehabilitate the space that would be occupied by the screws with conventional technique.

To test if this *Innovative cement-technique* provides the same or superior strength compared to *Standard-technique*, 12 pairs of cadaveric humeri reconstructed with both techniques were tested to failure. All the specimens showed a clinically relevant failure mechanism. The biomechanical test showed that, before failure initiated, the fractured humeri reconstructed with the *Innovative-cement-technique* withstood a significantly larger force (3.57 times) compared to the *Standard-technique*. Similarly, the *Innovative-cement-technique* withstood a significantly larger maximal force (3.56 times) compared to the *Standard-technique*, before catastrophic failure occurred. This confirms that the *Innovative-cement-technique* may better prevent both early post-operative head migration and gross failure due to loads typical of early loading.

Biomechanical studies showed that augmentation increases the mechanical properties of plate fixation (Jabran et al., 2018; Kammerlander et al., 2016). No technique is completely satisfactory yet. In fact, different conclusions are found in the literature comparing the outcome of augmented and non-augmented plate-and-screw fixation: the clinical studies reported always an incidence of screw penetration at follow up over 12 months also with augmented screws (Hengg et al., 2019; Siebenburger et al., 2019). This led to the idea to verify in a biomechanical setting if it would be reasonable to develop a construct with the positive aspects of cement augmentation without the drawbacks of screws presence in the long term.

The aim of the surgeon is to allow patients to recover functionality as soon as possible, and to minimize the limitations caused by the fracture. An important and critical motor task for a patient with upper limb surgery is raising up from seated using the arm support (Brianza et al., 2010; Lescheid et al., 2010). This action causes a peak force of about 1.8 times the body weight (Anglin et al., 2000), that means 1413 N for an 80 kg patient. The failure strength measured in this study matches positively this requirement: in fact, the maximum force for the *Innovative-cement-technique* was 1686 N, whereas the *Standard-technique* could only resist 471 N, confirming that the innovative reconstruction may allow a patient to raise the functional level in the post-operative period. Similar considerations apply to other activities: abduction of the straight arm causes a resultant force at the glenohumeral joint of 600 N, lifting a weight of 1.1 kg a force of 2070 N, wheelchair propulsion a force of 1900 N (Bergmann et al., 2007). Therefore, these actions would not represent a risk of failure for the *Innovative-cement-technique*, but some of these would be critical with the *Standard-technique*.

A limitation of this study is the focus on the possible slippage of the reconstructed head as failure mechanism. The most challenging load for this specific scenario was simulated aligning the force with the humeral axis. Since the angle spanned by the force for different activities like abduction, external rotation and internal rotation is large (30–95°) (Westerhoff et al., 2009), multiple failure scenario not simulated in this study are possible, due to loading in different directions. The mechanism investigated in the present study was chosen because it was reported to be the most common failure scenario in elderly patients (Hertel, 2005).

Another limitation relates to the repositioning of fragments after fracture simulation: the reconstructions performed in the lab represents an ideal condition that might not always occur in real patients where soft tissues prevent direct visibility of entire fragments. However, as the same condition applies to both techniques, comparisons between the two techniques are possible.

The donors were possibly younger than the target patients for this treatment. This would result in better bone purchase of the screws in the *Standard-technique* (i.e. overestimating the strength) and worse interdigitation of the cement in the bone, due to higher bone density (i.e. an underestimation of the strength of the *Innovative-cement-technique*). Therefore, considering that paired humeri were tested, if there was a bias this could only make the *Innovative-cement-technique* seem less advantageous than it would be indeed in lower-quality bone. DXA-based measurements of bone quality in the proximal humerus have been found to be scarcely reproducible (Oh et al., 2014), and sub-optimal predictors of the fracture risk (Skedros et al., 2016). BMD was not directly measured in our specimens. The eggshell defect created to simulate the osteoporotic setting was another simplification: due to the impossibility to obtain multiple paired specimens with comparable grade of osteoporosis, a defect was reproducibly created in all the heads following an anatomical study (Kamer et al., 2016).

The *Innovative-cement-technique* offers significant potential benefits in terms of reconstruction strength and avoidance of screws-related risk factors in particular subgroups of patients. In fact, avoiding the use of plate and screws would prevent complications such as screw protrusion on the humeral head, screws cut off or secondary protrusion at follow-up after a humeral head collapse (e.g. due to osteonecrosis), and acromial impingement of the plate.

The cement adopted in this study is partially-resorbable and is able to fill the defect, providing good support of the fragments and encouraging bone integration in the cement over time. This is possibly advantageous in case of head osteonecrosis: the presence of cement instead of the screws in the subchondral bone would prevent rapid scratching damage of the glenoid cartilage, giving the surgeon more time to see if revision is required. Furthermore, in osteoporotic patients with proximal humerus fracture the risk of re-fracture is higher (Jung et al., 2019). The cement used in the innovative technique cannot be easily removed. However, in this case a new fixation with conventional Philos technique is possible, because the described cement can easily be drilled to host the screws.

Moreover, the specific properties of the reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP used in this study are expected to promote bone formation. In fact the osteoconductivity due to the with beta-TCP, and the size and morphology of the pores in the PMMA after dissolution of the mineral component, promote significant apposition of new bone (Dall'Oca et al., 2014, 2017). This cement has a relatively low curing temperature as the beta-TCP serves as a ballast. The temperature increase measured during cement curing could raise some concern, as it could cause partial osteonecrosis (Blazejak et al., 2013). This issue requires further investigation (which is beyond the scope of the present biomechanical study).

5. Conclusions

The innovative technique, based on injection of a reinforced bone substitute consisting of PMMA additivated with 26% beta-TCP without the use of plate and locking screws, showed positive results, demonstrating better biomechanical properties compared to the *Standard-technique*. These laboratory findings, along with the advantages of not using screws, may help the surgeon perform a procedure that is surgically safer, and more effective for the patient. Further studies are necessary to confirm the clinical validity of these laboratory findings, and to verify if it would be clinically possible to perform a fracture fixation with a temporary plate, cement and no screw as the results of this study suggest.

Funding

The Department of Industrial Engineering of the School of Engineering and Architecture, Alma Mater Studiorum – Università di Bologna received from Tecres SpA (Sommacampagna, Verona, Italy) research funds and the test specimens for this study.

Ethical approval

This study is based on humeri from human donors, which were obtained through an international ethically-approved donation program (Anatomy Gifts Registry, Hannover, USA). This Study was authorized by the Bioethics Committee of the University of Bologna (Prot. 68,448 of 10 May 2018).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The Authors wish to thank dr. Renzo Soffiatti and dr. Roberta Tosato for the valuable technical advice about the cement; dr. Federico Morosato for the help with the preparation of the specimens; dr. Marco Palanca for the help and advice about the mechanical tests; Roberto Rotini, MD, and Alessandro Marinelli, MD, for the stimulating discussions; Antonio Micoli for the support during temperature measurements. Tecres SpA (Sommacampagna, Verona, Italy) is gratefully acknowledged for the financial support.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbiomech.2020.110138.

References

Anglin, C., Wyss, U.P., Pichora, D.R., 2000. Glenohumeral contact forces. Proc. Inst. Mech. Eng. H: J. Eng. Med. 214, 637–644.

Bachner, E.M., Schmidt, E.C., Chin, M., Namdari, S., Baxter, J.R., Hast, M.W., 2019. Parameterization of proximal humerus locking plate impingement with in vitro, in silico, and in vivo techniques. J. Shoulder Elbow Surg. 28, 1183–1192.

Barrett, J.A., Baron, J.A., Karagas, M., Beach, M.L., 1999. Fracture risk in the U.S. Medicare population. J. Clin. Epidemiol. 52, 243–249.

Bergmann, G., Graichen, F., Kaab, M., Rohlmann, A., Westerhoff, P., 2007. In vivo glenohumeral contact forces – measurements in the first patient 7 months postoperatively. J. Biomechanics 40, 2139–2149.

Berkes, M.B., Little, M.T., Lorich, D.G., 2013. Open reduction internal fixation of proximal humerus fractures. Curr. Rev. Musculoskeletal Med. 6, 47–56.

Blazejak, M., Hofmann-Fliri, L., Buchler, L., Gueorguiev, B., Windolf, M., 2013. In vitro temperature evaluation during cement augmentation of proximal humerus plate screw tips. Injury 44, 1321–1326.

Brianza, S., Plecko, M., Gueorguiev, B., Windolf, M., Schwieger, K., 2010. Biomechanical evalutaion of a new fixation technique for internal fixation of three-part proximal humerus fractures in a novel cadaveric model. Clin. Biomech. (Bristol, Avon) 25, 886–892.

Brunner, F., Sommer, C., Bahrs, C., Heuwinkel, R., Hafner, C., Rillmann, P., Kohut, G., Ekelund, A., Muller, M., Audigé, L., Babst, R., 2009. Open reduction and internal fixation of proximal humerus fractures using a proximal locked plate: a prospective multicenter analysis. J. Orthop. Trauma 3, 163–172.

Charalambous, C.P., Siddique, I., Valluripalli, K., Kovacevic, M., Panose, P., Srinivasan, M., Marynissen, H., 2007. Proximal humeral internal locking system (PHILOS) for the treatment of proximal humeral fractures. Arch. Orthop. Trauma Surg. 127, 205–210.

Choma, T.J., Frevert, W.F., Carson, W.L., Waters, N.P., Pfeiffer, F.M., 2011. Biomechanical analysis of pedicle screws in osteoporotic bone with bioactive cement augmentation using simulated in vivo multicomponent loading. Spine 36, 454–462.

Cristofolini, L., 2012. Anatomical Reference Frames for Long Bones: Biomechanical Applications. Springer, New York, New York, NY, pp. 2971–2999.

Cristofolini, L., Morellato, K., Cavallo, M., Guerra, E., 2020. Reconstruction of proximal humeral fractures with a reduced number of screws and a reinforced bone substitute. Med. Eng. Phys. 82, 97–103.

Dall'Oca, C., Maluta, T., Cavani, F., Morbioli, G.P., Bernardi, P., Sbarbati, A., Degl'Innocenti, D., Magnan, B., 2014. The biocompatibility of porous vs non-porous bone cements: a new methodological approach. Eur. J. Histochem. 58, 2255–2256.

Dall'Oca, C., Maluta, T., Micheloni, G.M., Cengarle, M., Morbioli, G., Bernardi, P., Sbarbati, A., Degl'Innocenti, D., Lavini, F., Magnan, B., 2017. The biocompatibility of bone cements: progress in methodological approach. Eur. J. Histochem. 61, 2673–2674.

Danesi, V., Cristofolini, L., Stea, S., Traina, F., Beraudi, A., Tersi, L., Harman, M., Viceconti, M., 2011. Re-use of explanted osteosynthesis devices: a reliable and inexpensive reprocessing protocol. Injury 42, 1101–1106.

Danesi, V., Faldini, C., Cristofolini, L., 2017. Methods for the characterization of the long-term mechanical performance of cements for vertebroplasty and kyphoplasty: critical review and suggestions for the test methods. J. Mech. Med. Biol. 17, 1–33.

Doshi, C., Sharma, G.M., Naik, L.G., Badgire, K.S., Qureshi, F., 2017. Treatment of proximal humerus fractures using PHILOS plate. J. Clin. Diagn. Res.: JCDR 11, RC10-RC13.

Egol, K.A., Sugi, M.T., Ong, C.C., Montero, N., Davidovitch, R., Zuckerman, J.D., 2012. Fracture site augmentation with calcium phosphate cement reduces screw penetration after open reduction-internal fixation of proximal humeral fractures. J. Shoulder Elbow Surg. 21, 741–748.

Erhardt, J.B., Stoffel, K., Kampshoff, J., Badur, N., Yates, P., Kuster, M.S., 2012. The position and number of screws influence screw perforation of the humeral head in modern locking plates: a cadaver study. J. Orthop. Trauma 26, e188–e192.

Fankhauser, F., Schippinger, G., Weber, K., Heinz, S., Quehenberger, F., Boldin, C., Bratschitsch, G., Szyszkowitz, R., Georg, L., Friedrich, A., 2003. Cadaveric-biomechanical evaluation of bone-implant construct of proximal humerus fractures (Neer Type 3). J. Trauma Acute Care Surg., 345–349

Gavaskar, A.S., Karthik, B.B., Tummala, N.C., Srinivasan, P., Gopalan, H., 2016. Second generation locked plating for complex proximal humerus fractures in very elderly patients. Injury 47, 2534–2538.

Hengg, C., Nijs, S., Klopfer, T., Jaeger, M., Platz, A., Pohlemann, T., Babst, R., Franke, J., Kralinger, F., 2019. Cement augmentation of the proximal humerus internal locking system in elderly patients: a multicenter randomized controlled trial. Arch. Orthop. Trauma Surg. 139, 927–942.

Hertel, R., 2005. Fractures of the proximal humerus in osteoporotic bone. Osteoporosis Int.: A J. Established Result Cooperation Eur. Found. Osteoporosis Natl. Osteoporosis Found. USA 16 (Suppl 2), S65–S72.

Jabran, A., Peach, C., Ren, L., 2018. Biomechanical analysis of plate systems for proximal humerus fractures: a systematic literature review. Biomed. Eng. 17, 47.

Jung, H.S., Nho, J.H., Ha, Y.C., Jang, S., Kim, H.Y., Yoo, J.I., Park, S.M., Lee, Y.K., 2019. Incidence of osteoporotic refractures following proximal humerus fractures in adults aged 50 Years and older in Korea. J. Bone Metab 26, 105–111.

Kamer, L., Noser, H., Popp, A.W., Lenz, M., Blauth, M., 2016. Computational anatomy of the proximal humerus: an ex vivo high-resolution peripheral quantitative computed tomography study. J. Orthop. Translat. 4, 46–56.

Kammerlander, C., Neuerburg, C., Verlaan, J.-J., Schmoelz, W., Miclau, T., Larsson, S., 2016. The use of augmentation techniques in osteoporotic fracture fixation. Injury 47, S36–S43.

Kathrein, S., Kralinger, F., Blauth, M., Schmoelz, W., 2013. Biomechanical comparison of an angular stable plate with augmented and non-augmented screws in a newly developed shoulder test bench. Clin. Biomech. 28, 273–277.

Katthagen, J.C., Lutz, O., Voigt, C., Lill, H., Ellwein, A., 2018. Cement augmentation of humeral head screws reduces early implant-related complications after locked plating of proximal humeral fractures. Obere Extrem. 13, 123–129.

Kirchhoff, C., Braunstein, V., Kirchhoff, S., Sprecher, C.M., Ockert, B., Fischer, F., Leidel, B.A., Biberthaler, P., 2008. Outcome analysis following removal of locking plate fixation of the proximal humerus. BMC Musculoskelet Disord. 9, 138.

Knierzinger, D., Crepaz-Eger, U., Hengg, C., Kralinger, F., 2020. Does cement augmentation of the screws in angular stable plating for proximal humerus fractures influence the radiological outcome: a retrospective assessment. Arch. Orthop. Trauma Surg. 140, 1413–1421.

Kuang, G.M., Wong, T.M., Wu, J., Ouyang, J., Guo, H., Zhou, Y., Fang, C., Leung, F.K.L., Lu, W., 2018. Augmentation of a locking plate system using bioactive bone cement-experiment in a proximal humeral fracture model. Geriatr. Orthop. Surg. Rehabil. 9, 2151459318795312.

Lanting, B., MacDermid, J., Drosdowech, D., Faber, K.J., 2008. Proximal humeral fractures: a systematic review of treatment modalities. J. Shoulder Elbow Surg. 17, 42–54.

Lescheid, J., Zdero, R., Shah, S., Kuzyk, P.R.T., Schemitsch, E.H., 2010. The biomechanics of locked plating for repairing proximal humerus fractures with or without medial cortical support. J. Trauma Acute Care Surg. 69, 1234–1242.

Lu, W., Cheung, K., Luk, K., Holmes, A., Zhu, Q., Leong, J., 2001. Bioactive bone cement as a principal fixture for spinal burst fracture: an in vitro biomechanical and morphologic study. Spine 26, 2684–2690.

Maldonado, Z.M., Seebeck, J., Heller, O.W., Brandt, D., Hepp, P., Lill, H., Duda, G.N., 2003. Strining of the intact and fractured proximal humerus under physiological-like loading. J. Biomech. 36, 1865–1873.

Namdari, S., Voleti, P.B., Mehta, S., 2012. Evaluation of the osteoporotic proximal humeral fracture and strategies for structural augmentation during surgical treatment. J. Shoulder Elbow Surg. 21, 1787–1795.

Neer, C.S., Watson, K.C., Stanton, F.J., 1982. Recent experience in total shoulder replacement. J. Bone Joint Surg. 64, 319–337.

Oh, J.H., Song, B.W., Kim, S.H., Choi, J.A., Lee, J.W., Chung, S.W., Rhie, T.Y., 2014. The measurement of bone mineral density of bilateral proximal humeri using DXA in patients with unilateral rotator cuff tear. Osteoporosis Int.: A J. Established Result Cooperation Eur. Found. Osteoporosis Natl. Osteoporosis Found. USA 25, 2639–2648.

Olerud, P., Ahrengart, L., Ponzer, S., Saving, J., Tidermark, J., 2011. Internal fixation versus nonoperative treatment of displaced 3-part proximal humeral fractures in elderly patients: a randomized controlled trial. J. Shoulder Elbow Surg. 20, 747–755.

Owsley, K., Gorczyca, J.T., 2008. Displacement/screw cutout after open reduction and locked plate fixation of humeral fractures. J. Bone Joint Surg. Am. 90, 233–240.

Palvanen, M., Kannus, P., Niemi, S., Parkkari, J., 2006. Update in the epidemiology of proximal humeral fractures. Clin. Orthop. Relat. Res. 442, 87–92.

Röderer, G., Scola, A., Schmölz, W., Gebhard, F., Windolf, M., Hofmann-Fliri, L., 2013. Biomechanical in vitro assessment of screw augmentation in locked plating of proximal humerus fractures. Injury 44.

Rosengren, B.E., Karlsson, M., Petersson, I., Englund, M., 2015. The 21st-century landscape of adult fractures: cohort study of a complete adult regional population. J. Bone Miner. Res. 30, 535–542.

Rüedi, T.P., Murphy, W.M., 2001. AO Principles of Fracture Management. Georg Thieme Verlag, Stuttgart.

Schliemann, B., Seifert, R., Rosslenbroich, S.B., Theisen, C., Wahnert, D., Raschke, M.J., Weimann, A., 2015. Screw augmentation reduces motion at the bone-implant interface: a biomechanical study of locking plate fixation of proximal humeral fractures. J. Shoulder Elbow Surg. 24, 1968–1973.

Schliemann, B., Siemoneit, J., Theisen, C., Kosters, C., Weimann, A., Raschke, M.J., 2012. Complex fractures of the proximal humerus in the elderly–outcome and complications after locking plate fixation. Musculoskelet Surg. 96 (Suppl 1), S3–S11.

Seebeck, J., Goldhahn, J., Stadele, H., Messmer, P., Morlock, M.M., Schneider, E., 2004. Effect of cortical thickness and cancellous bone density on the holding strength of internal fixator screws. J. Orthop. Res.: Off. Publ. Orthop. Res. Soc. 22, 1237–1242.

Siebenburger, G., Helfen, T., Biermann, N., Haasters, F., Bocker, W., Ockert, B., 2019. Screw-tip augmentation versus standard locked plating of displaced proximal humeral fractures: a retrospective comparative cohort study. J. Shoulder Elbow Surg. 28, 1326–1333.

Singh, A., Adams, A.L., Burchette, R., Dell, R.M., Funahashi, T.T., Navarro, R.A., 2015. The effect of osteoporosis management on proximal humeral fracture. J. Shoulder Elbow Surg. 24, 191–198.

Skedros, J.G., Knight, A.N., Pitts, T.C., O'Rourke, P.J., Burkhead, W.Z., 2016. Radiographic morphometry and densitometry predict strength of cadaveric proximal humeri more reliably than age and DXA scan density. J. Orthop. Res.: Off. Publ. Orthop. Res. Soc. 34, 331–341.

Sproul, R.C., Iyengar, J.J., Devcic, Z., Feeley, B.T., 2011. A systematic review of locking plate fixation of proximal humerus fractures. Injury 42, 408–413.

Thanasas, C., Kontakis, G., Angoules, A., Limb, D., Giannoudis, P., 2009. Treatment of proximal humerus fractures with locking plates: a systematic review. J. Shoulder Elbow Surg. 18, 837–844.

Urban, R.M., Turner, T.M., Hall, D.J., Infanger, S.I., Cheema, N., Lim, T.-H., Moseley, J., Carroll, M., Roark, M., 2004. Effects of altered crystalline structure and increased initial compressive strength of calcium sulfate bone graft substitute pellets on new bone formation. Orthopedics 27, s113–s118.

Varga, P., Inzana, J.A., Gueorguiev, B., Sudkamp, N.P., Windolf, M., 2018. Validated computational framework for efficient systematic evaluation of osteoporotic fracture fixation in the proximal humerus. Med. Eng. Phys. 57, 29–39.

Westerhoff, P., Graichen, F., Bender, A., Halder, A., Beier, A., Rohlmann, A., Bergmann, G., 2009. In vivo measurement of shoulder joint loads during activities of daily living. J. Biomech. 42, 1840–1849.