



Augmenting a dynamic hip screw with a calcium sulfate/hydroxyapatite biomaterial

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ABSTRACT

Internal fixation failure in hip fractures can lead to reoperation. Calcium sulfate/hydroxyapatite (CaS/HA) is a biomaterial that can be used for augmenting fracture fixation. We aimed to determine whether an injection of 2 ml CaS/HA increases the fixation of a dynamic hip screw inserted in synthetic and human trabecular bone. The study consists of two parts: 1) synthetic bone blocks ($n = 74$), with three subgroups: empty (cannulated screw, no injection), cannulated, and fenestrated; and 2) osteoporotic human femoral heads ($n = 29$), with the same subgroups. The heads were imaged using μ CT. Bone volume fraction, insertion angle, and head diameter were measured. Pullout tests were performed and peak force, stiffness, and work were measured. The fenestrated group showed increases in pullout strength compared to no injection in the synthetic blocks. The cannulated group showed a higher pullout strength in low-density blocks. In the femoral heads, the variation was larger and there were no significant differences between groups. The bone volume fraction correlated with the peak force and work, and the insertion angle correlated with the stiffness. CaS/HA can improve the fixation of a dynamic hip screw. For clinical use, spreading of the material around the threads of the screw must be ensured.

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1. Introduction

More than 500,000 hip fragility fractures were recorded in 2017 in Europe alone, and the number is expected to increase with 28% by 2030 [1]. Approximately half of the hip fractures are trochanteric and half cervical [2]. In order to preserve the hip joint, internal fixation using hip screws is preferred over total hip arthroplasty for younger patients with minimally displaced cervical neck fractures, as they generally also have a higher bone density [3]. In the elderly, with exception for nondisplaced fractures, hip arthroplasty is preferred due to fewer complications. In a review of the outcome of internal fixation of nondisplaced femoral neck fractures, reoperation rates varied from 8% to 19%, most of which, were

converted to total hip arthroplasty [4]. The most common reasons for failed trochanteric fracture osteosynthesis are device cut-out, with penetration of the screw through the femoral head, or extensive distal sliding, leading to reoperation rates up to 10% in unstable fractures [5].

Injection of polymethylmethacrylate (PMMA) around the screw has been shown to significantly increase the initial fixation of hip fractures stabilized with a sliding hip screw [6]. The increased fixation was particularly evident in osteoporotic bones. Injection of PMMA around a dynamic hip screw improved clinical outcomes for intertrochanteric fractures in elderly patients [7]. However, PMMA comes with drawbacks. The setting temperatures are high enough to cause femoral head osteonecrosis and it is non-resorbable, which complicates revision surgery [8]. As an alternative to PMMA, ceramic materials like calcium phosphates (CaP) have been investigated [9]. For example, CaP increased the pullout strength of various fixation devices used for femoral neck fractures in synthetic low-density bone blocks [10]. In a clinical trial, CaP has been shown to improve radiological outcome of screw fixation of unstable trochanteric fractures [11].

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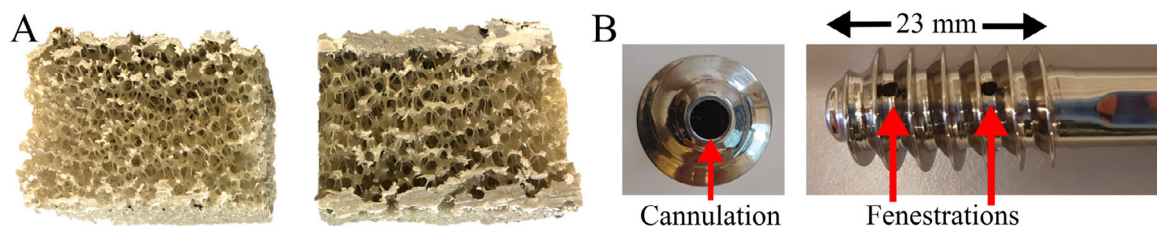


Fig. 1. A) Low (left) and high (right) density synthetic bone blocks. B) A cannulated dynamic hip screw with fenestrations on the sides.

Calcium sulfate/hydroxyapatite (CaS/HA) is an alternative to PMMA with initial mechanical properties similar to CaP [12–14]. CaS/HA may be preferred over CaP because of its biphasic nature. The CaS phase, embedding micro-HA particles, resorbs within 6–8 weeks thereby increasing the osteoconductivity of the biomaterial and leaving the hydroxyapatite particles as a scaffold for bone ingrowth [15]. Simultaneously, the CaS phase can be used for initial controlled delivery of drugs such as antibiotics and bone active molecules [16,17]. CaS/HA has been used in clinical practice in, for example, vertebroplasties, wrist osteotomies and tibial condyle fractures [18–20]. The biomaterial is injectable and its low viscosity ensures good distribution into the trabecular bone [21]. It has been shown that CaS/HA in trabecular bone allows new bone formation around the screw without hampering fracture healing [17]. Therefore, we hypothesize that an injection of CaS/HA would help anchor the osteosynthesis device and stabilize internal fixation of a hip fracture in osteoporotic trabecular bone by creating a strong interface between the threads of the fixation device and the surrounding bone.

In this study, we aimed to determine whether an injection of CaS/HA increases the immediate fixation of a dynamic hip screw (DHS) used in femoral neck fractures. The hypothesis was first tested in a model of low- and high-density synthetic bone blocks, and secondly in osteoporotic human femoral heads harvested from patients with low energy fractures operated with a total hip arthroplasty.

2. Materials and methods

To investigate the increase in immediate fixation that CaS/HA (Cerament™ Bone Void Filler, Bone Support AB) could offer, DHS's (115 mm, Auxein Medical, Haryana, India) either cannulated (hollow) or fenestrated (along the threads) were used. All CaS/HA injections were performed by mixing the material according to the manufacturer's guidelines and injecting it through a 14 Gauge needle ($\varnothing = 2$ mm, length = 80 mm) placed in the burr canal of the DHS.

The study was divided into two parts. In the first part, the material density was controlled by using synthetic open cell foam blocks (Sawbones Europe, Malmö, Sweden) specifically designed to mimic the properties of cancellous bone. In the second part, femoral heads intraoperatively harvested and banked from patients that sustained a low energy hip fracture and were undergoing hip replacement surgery were used.

2.1. Synthetic bones

Synthetic bone blocks with two densities were used; 1) low-density blocks (15% bone volume fraction (BV/TV)) mimicking osteoporotic bone and 2) high-density blocks (31% BV/TV) mimicking healthy bone (Fig. 1A). All blocks were cut to a size of $6 \times 5.5 \times 4$ cm using a hand saw and divided in three groups 1) empty, 2) cannulated, and 3) fenestrated (Table 1). In the empty and cannulated groups, cannulated DHS's were used and in the fenestrated group

Table 1

Number of samples per group, both for the synthetic bone blocks and the human femoral heads.

	Empty	Cannulated	Fenestrated
Low-density synthetic bone	N = 15	N = 15	N = 8
High-density synthetic bone	N = 14	N = 14	N = 8
Human femoral heads	N = 11	N = 10	N = 8

cannulated DHS's with 6 fenestrations (holes with $\varnothing 1.5$ mm) inside the threads were used (Fig. 1B). In all groups, a 3 cm deep hole with 6 mm diameter was predrilled in the center of the block and a shallow hole of 10 mm diameter was drilled in the same location to improve the ease and consistency of the screw insertion. In the empty group, the DHS was completely inserted (30 mm) in the drilled canal. In the cannulated group, the DHS was first inserted 20 mm, after which 2 ml CaS/HA was injected and the screw was inserted an additional 10 mm to a depth of 30 mm. In the fenestrated group the DHS was inserted completely (30 mm) and 2 ml CaS/HA was injected. The injections were performed in batches of four blocks at the time.

2.2. Human femoral heads

Human femoral heads ($n = 29$) were harvested and banked at the Kaunas University Hospital, Lithuania, from patients that were undergoing partial or total hip replacement following a low energy cervical neck fracture. Following the hip replacement procedure through anterolateral approach all femoral heads were extracted using a T-handle femoral head cork screw extractor (Zimmer Biomet). The patients gave their informed consent to the retention and use of their tissue in accordance with hospital guidelines and the relevant EU legislation.

The heads were imaged using μ CT (U-CT system, MILabs, Utrecht, The Netherlands) (x-ray voltage: 65 kVp, current 0.13 mA, 40 μ m isotropic voxel size) together with two hydroxyapatite phantoms (250 and 750 mg/cm³) for calibration of bone density. The femoral head and the hole left by the extractor screw were segmented after scaling down the images 4 times (voxel size 160 μ m) (Seg3D2, University of Utah, Salt Lake City, USA). The segmented images were used to plan the DHS insertion site (Fig. 2). The aim was to find a location for insertion as close to the center of the fractured surface while not covering or completely covering the extractor hole. The fracture surface of the femoral heads was cut flat using a diamond band saw (Exact Technologies Inc, Oklahoma City, USA) to ensure an even force distribution around the DHS during pullout. The femoral heads were not cut if they were so small that cutting would mean that the DHS could not be inserted to the planned depth.

The same groups were created as for the synthetic bone blocks (Table 1). However due to the smaller size of the femoral heads the insertion depth was reduced. In each group, a 20 mm deep hole with 8 mm diameter was predrilled. In the empty and fenestrated group, the DHS was inserted 20 mm, and in the fenestrated group 2 ml CaS/HA was injected. In the cannulated group, the cannulated

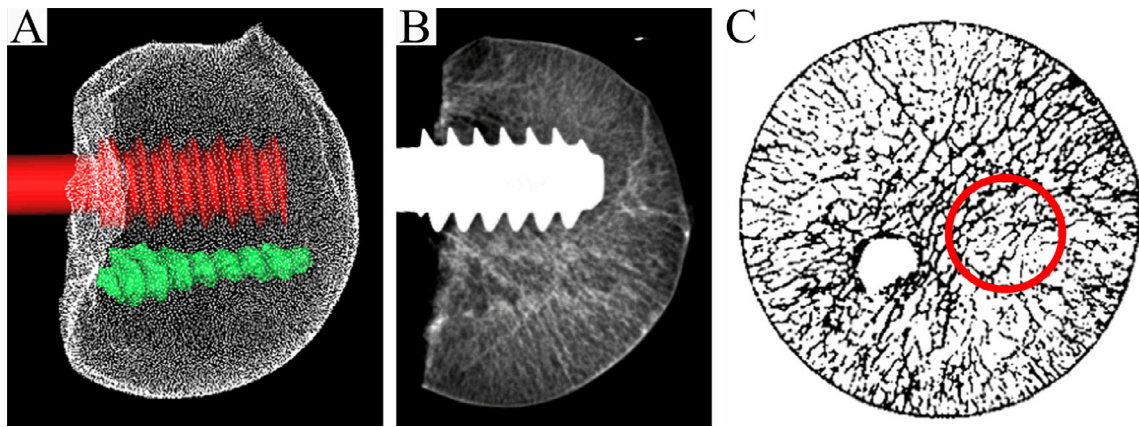


Fig. 2. The screw insertion was first planned based on the μ CT images. B) Actual insertion location is exemplified based on radiograms. C) μ CT image highlighting the region where the DHS was inserted and the BV/TV quantified.

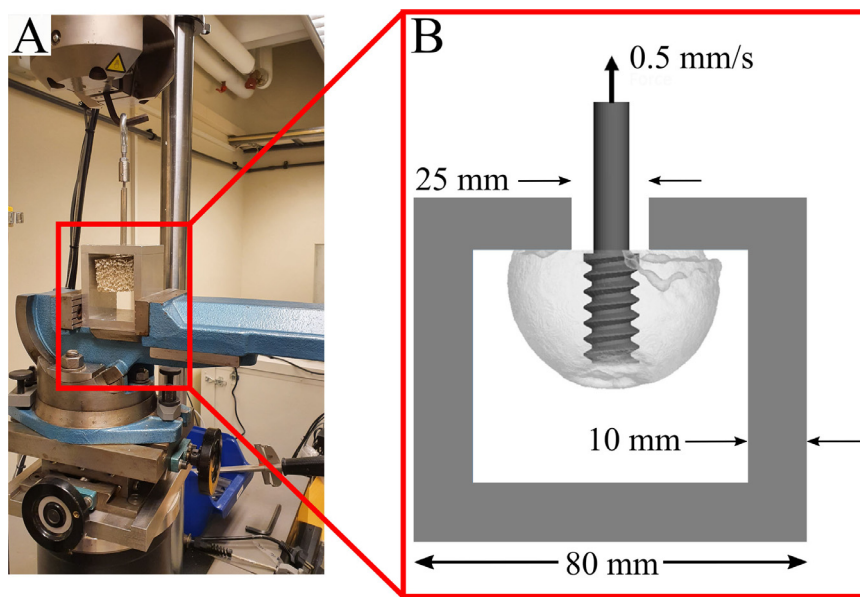


Fig. 3. A) A photo of the complete pullout setup. B) A schematic of the pullout setup with the human femoral heads

DHS was first inserted 10 mm, and 2 ml CaS/HA was injected after which the screw was further inserted another 10 mm to a total depth of 20 mm. After insertion of the screws, radiograms were taken (Discovery XR656, GE, Chicago, USA) to confirm the position of the screws and the spreading of the CaS/HA.

The BV/TV was measured in several steps. First, the μ CT images were resliced so the axial slices were perpendicular to the axis of the screw. Second, a region of interest (ROI) was selected at the location of screw insertion (Fig. 2C). In case the DHS insertion site covered the hole left from the extraction, this hole was excluded from the ROI. Lastly, the image was segmented using a threshold of 450 mg/cm^3 and the BV/TV was determined in the ROI.

The gross insertion angle was measured from two photos of the femoral head and the screw after insertion. With the screw upright one photo was taken from the front. The femoral head and screw were then rotated 90 degrees and another photo from the same position was taken. By measuring the angle between the screw and the femoral head surface, the insertion angle could be calculated. From the two angles a plane was defined, parallel to the cut surface on the femoral head. The angle between the normal to this plane and the DHS was the final insertion angle.

The head diameter was measured from the 3D segmentation of the μ CT. After aligning the segmentation with the DHS, it was ro-

tated to get a top view (looking down the DHS). From this view, three measurements of the diameter were made. Each measurement was approximately 60 degrees rotated from the previous. The average of the three measurements was taken as the head diameter.

2.3. Pullout test

Pullout tests were performed using a custom pullout setup (Fig. 3). A metal box with two open sides and a hole in the top was clamped to the bottom of the loading device (Instron® 8511.20, Instron Corp). A digital acquisition system was used (Isi-DAQ-STD-8D, Isi-Sys GmbH) to sample the analogue recordings of the applied force (load cell M211-112, Sensor-Data Technologies, Inc.). The DHS with the bone attached was put through the hole from the bottom. A custom-made ring was screwed into the end of the DHS. A hexagonal Allen key was clamped on the top of the loading device to which the ring connected to the DHS was applied. With the DHS now suspended from the Allen key, the box was moved to center the DHS inside the hole using an adjustable XY stage. The loading device was moved until the bone was in contact with the top of the box, and then loading at a displacement rate of 0.5 mm/s was performed until failure.

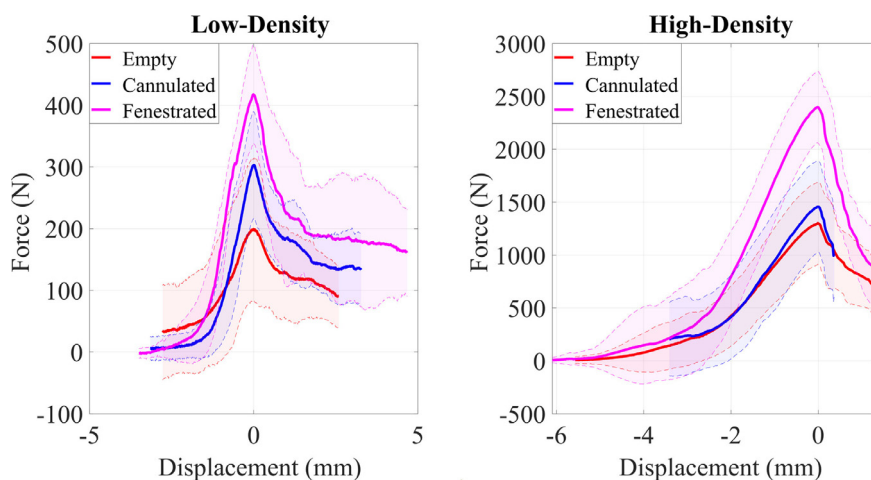


Fig. 4. Force-displacement curves for all sawbones, shown as mean (solid lines) and standard deviations (shaded area). To obtain a representative measure for the mean and standard deviation of the curves the displacement to peak force was first subtracted from each individual curve centering the peak at 0 mm displacement.

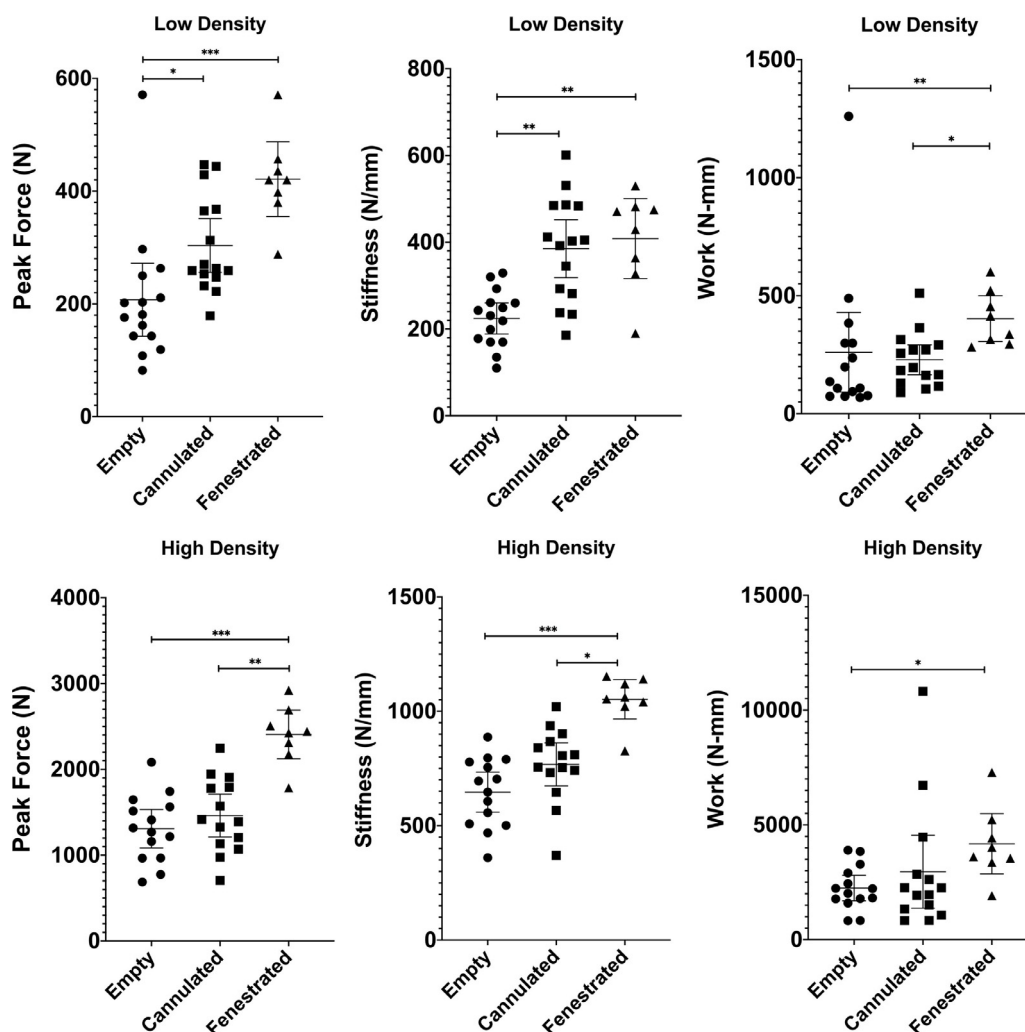


Fig. 5. Mechanical testing data from the synthetic bones, showing peak force, stiffness and work to peak force for both low density (top row) and high density (bottom row) samples. The graph shows individual data points, mean values and standard deviations. Statistical significance is indicated according to: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

2.4. Data analysis

In both synthetic bones and the femoral heads, the force-displacement curves were analyzed by measuring the peak force, the stiffness in the linear region, and the work to peak force. Statistical comparisons of the mechanical parameters between the

groups were made using a Kruskal-Wallis test. A Dunn's post-hoc test for multiple comparison was performed for the synthetic bones. In the femoral heads, the effect of the BV/TV, insertion angle, and head diameter on the mechanical parameters of the pull-out was investigated per group using linear regression analysis. For all comparisons a p -value below 0.05 was considered significant.

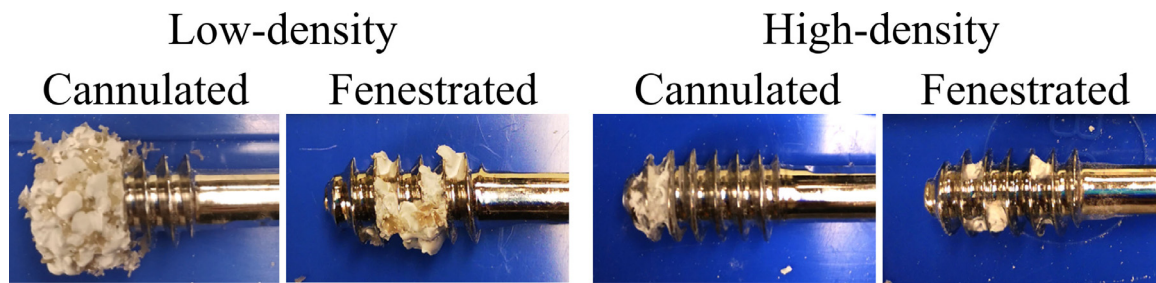


Fig. 6. Examples of pulled-out screws from low- and high-density synthetic bones with cannulated and fenestrated screws, indicating differences in how the material surrounded and attached to the screw during the pullout.

Table 2

Median (range) of the patients' age, BMI, and bone structural parameters for the mechanically tested samples in each group.

	Age (years)	BMI (kg m ⁻²)	BV/TV	Insertion angle (°)	Head diameter (mm)
Empty (N = 11, 1 male)	82 (68–94)	25 (23–30)	0.26 (0.15–0.36)	8 (2–18)	48 (42–55)
Cannulated (N = 7, 1 male)	85 (68–90)	25 (23–31)	0.26 (0.25–0.32)	8 (3–13)	50 (46–56)
Fenestrated (N = 6, 2 male)	89 (82–93)	24 (19–28)	0.32 (0.21–0.36)	8 (4–21)	48 (44–55)

3. Results

3.1. Synthetic bone blocks

From the force-displacement curves it was observed that the fenestrated group had the strongest fixation regardless of the density of the blocks (Fig. 4). The load-response of the cannulated group also differed from the empty group for the low-density blocks. In general, the peak forces were substantially lower in the low-density blocks compared to the high-density blocks. Another noticeable difference was that the displacement at peak force was significantly different between the low-density blocks (approximately 2 mm) and high-density blocks (approximately 4 mm).

3.1.1. Low-density synthetic bones

The peak force was higher in the cannulated (46% ($p = 0.03$)) and the fenestrated groups (103% ($p = 0.0001$)) compared with the empty group (Fig. 5, top). Despite a 39% difference in peak force between the cannulated and fenestrated group, it was not statistically significant. The stiffness was higher in the cannulated (72%, $p = 0.0003$) and fenestrated groups (82%, $p = 0.0005$), compared to the empty group. The work was higher in the fenestrated group compared with the empty (55%, $p = 0.009$) and the cannulated (76%, $p = 0.03$) groups, respectively (Fig. 5, top).

3.1.2. High-density synthetic bones

The fenestrated group demonstrated a higher peak force than the empty (72%, $p < 0.0001$) and cannulated groups (65%, $p < 0.0001$) (Fig. 5, bottom). No difference was observed in peak force

between the empty and the cannulated group. Similarly, the stiffness was higher in the fenestrated group, compared to the empty (63%, $p < 0.0001$) and the cannulated groups (37%, $p = 0.01$). The work was significantly higher in the fenestrated compared to the empty group (86%, $p = 0.03$) (Fig. 5, bottom).

In both the high and low-density synthetic bone blocks, 2 ml of CaS/HA biomaterial was injected successfully. After the screws were pulled out from the blocks a difference was observed in if, and in what way the material remained attached to the screws (Fig. 6). In the low-density blocks a larger amount of CaS/HA and synthetic bone was still attached to the screw, whereas, in the high-density blocks very little to no synthetic bone came out with the screw and nearly all injected CaS/HA material remained in the blocks. In comparison, in the empty group the DHS was in all specimens pulled out without any synthetic bone left in its threads.

3.2. Human femoral heads

Five femoral heads were excluded from further analysis because the DHS lost the grip during insertion ($n = 1$ in the cannulated group and $n = 2$ in the fenestrated group) or after insertion of the CaS/HA ($n = 2$ in the cannulated group). The patients' age, BMI, and bone structural parameters for the mechanically tested samples in each group are reported in Table 2.

The radiograms showed that the screws were inserted into the femoral heads, with the last thread not covered by bone (Fig. 7). The injected CaS/HA was clearly visible on the radiogram. In all specimens in the cannulated group, the majority of the CaS/HA was mainly deposited at the tip of the DHS and some entered the proximal threads of the screw. In the fenestrated group the CaS/HA

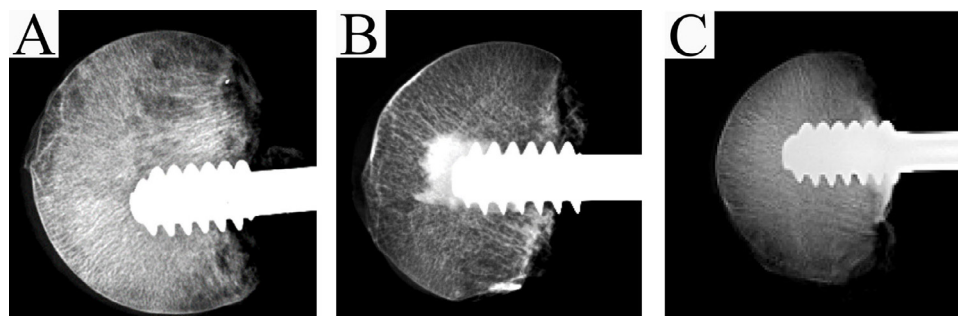


Fig. 7. Radiograms of the human femoral heads from A) the empty group, B) the cannulated group after CaS/HA injection, and C) the fenestrated group after CaS/HA injection.

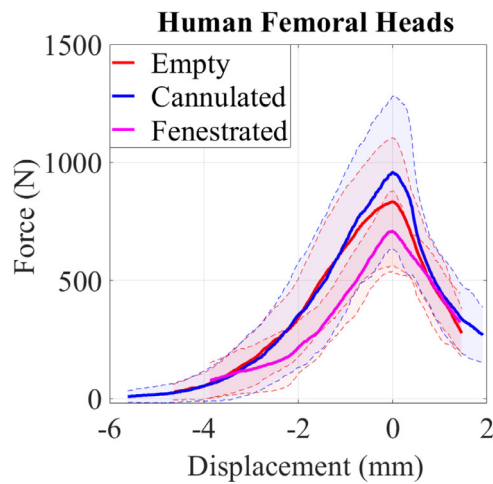


Fig. 8. Force-displacement curves for all human femoral heads, shown as mean (solid lines) and standard deviations (shaded area). To obtain a representative measure for the mean and standard deviation of the curves the displacement to peak force was first subtracted from each individual curve centering the peak at 0 mm displacement.

flowed out from the fenestrations closest to the surface of the bone after which it spread further on the cut surface leaving no visible CaS/HA deeper in the femoral head.

The force-displacement curves show the largest apparent difference between the cannulated and fenestrated group (Fig. 8). The cannulated and empty group largely follow the same trend, with a slightly lower average peak force for the empty group. The statistical comparison did not show any differences in mechanical parameters (Fig. 9).

Linear regression analysis of the influence of BV/TV, insertion angle and head diameter on the mechanical parameters showed few significant correlations. In the empty group, a higher BV/TV lead to a higher pullout strength ($R^2 = 0.58$, $p = 0.006$) and higher work to peak force ($R^2 = 0.39$, $p = 0.04$). In the cannulated group, the insertion angle correlated with the stiffness ($R^2 = 0.70$, $p = 0.02$). In the fenestrated group, no significant correlations between parameters were found.

4. Discussion

This study investigated if addition of CaS/HA can increase the fixation of a DHS. In the tests with the synthetic bone blocks, it

was shown that the injection of CaS/HA through the fenestrated screw resulted in the highest increase in pullout strength compared to no injection in both low-density (103% increase) and high-density (72% increase) material. The approach of injecting a CaS/HA biomaterial through a cannulated screw led to a 46% strength increase in the low-density synthetic bone. However, in the test with human femoral heads, no differences were observed between groups.

In the pullouts with the low-density blocks, the residual CaS/HA in the threads of the screw suggest that in the cannulated group the bone around the injected region breaks, whereas in the fenestrated group the CaS/HA itself breaks. For the high-density blocks, the CaS/HA breaks before the bone in both groups, however the small residual amount in the fenestrated group suggests that the CaS/HA creates a stronger interface between the screw and the surrounding material. This idea is further supported by the difference in peak forces between the cannulated and fenestrated groups.

In the human femoral heads, no clear difference could be observed between any of the groups. There are several likely reasons that can explain this lack of a difference: First, filling the femoral heads with CaS/HA increased the force required to insert the DHS in the cannulated group. It is possible that this additional force increased the damage to the trabeculae. This theory is supported by the low amount of CaS/HA around the threads after pullout in the high-density blocks (Fig. 6) and the lack of CaS/HA visible between the threads of the DHS on the radiograms (Fig. 7). This difficulty did not occur with the synthetic blocks which likely comes from the lack of other biological material (i.e., fibrin, bone marrow, and fatty tissue), making it easier for the CaS/HA to spread through the trabecular structure. Similarly, because living bone has circulating biological material, CaS/HA can spread through the trabecular structure more easily in a clinical situation.

Second, in all cases, during injection of the mixture of CaS/HA in the femoral heads the material started flowing backwards before 2 ml had been injected. This is largely due to the caliber of the needle, which was smaller than the internal screw canal, and resistance in the femoral head. With nearly 1 ml CaS/HA left inside the DHS, this leaves only about 1 ml in the bone void with most deposited at the tip of the DHS in the cannulated group and at the surface of the bone in the fenestrated group. In both groups little CaS/HA was deposited between the threads of the screw as seen in the radiograms (Fig. 7). This early backflow in the femoral heads can also be attributed to the presence of other biological tissue. To increase the amount and spreading of CaS/HA into the femoral heads and prevent backflow of the low-viscosity material a different injection technique is required. In previous research it has been

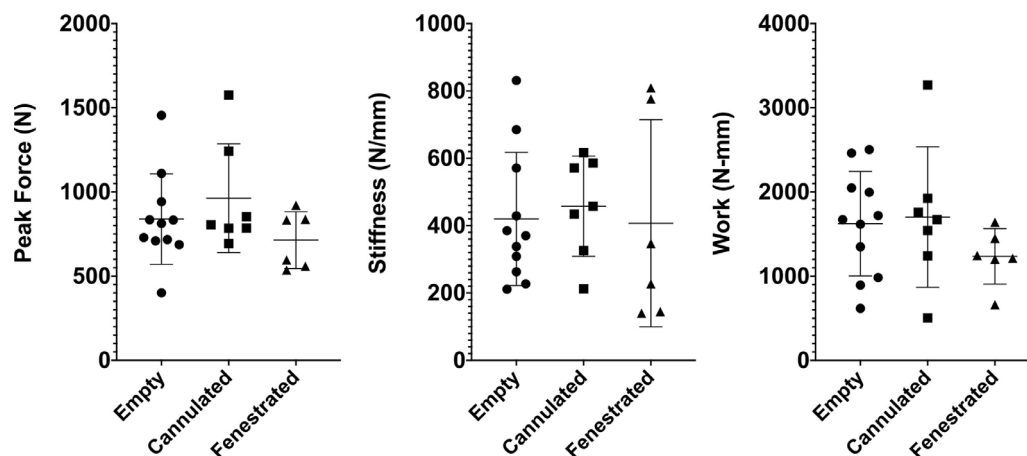


Fig. 9. Mechanical testing data from the human femoral heads, showing peak force, stiffness and work to peak force. The graph shows individual data points, mean values and standard deviations.

shown that spreading of CaS/HA in the femoral head is achievable [21]. In the case of internal fixation, this can also be improved by using a nozzle matching the diameter of the cannula and, after finalizing the injection, by inserting a rod in the nozzle compressing out the remaining CaS/HA in front of the screw.

Third, the variation in femoral heads was very large, including both men and women, ages ranging from 68–94, BV/TV ranging from 0.15 to 0.36, and differences in location of the hole left by extraction screw and the fracture pattern. Due to the large variation in femoral head sizes it was not possible to fully insert the DHS in all cases. Therefore, the insertion depth for all femoral heads was reduced. This means that the remaining distance to the cortical bone was different for each sample and that direct comparison of the mechanical parameters from the femoral heads with the synthetic blocks is not possible. Since the subchondral bone is typically denser, it is possible that this factor also contributed to the variation in mechanical properties. Additionally, the decreased insertion depth may have led to a decreased magnitude of all mechanical parameters. By increasing the insertion depth, it is likely that the load-response would be more similar to the synthetic bones.

Although there were no significant differences between the human femoral head groups, looking at the average load curves it appears that the stability of the screws in the fenestrated group is slightly lower. This apparent difference likely comes from the difference in age between the groups (Table 2). Looking at the cannulated and empty groups 4 out of the 5 highest measured pullout forces came from patients below 80 years old, while the youngest patient in the fenestrated group was 82 years old. The BV/TV in the fenestrated group was not lower and cannot fully explain the difference between the load curves. However, we expect that the average bone quality of the femoral heads in this group was lower.

There was a significant correlation between the BV/TV and pullout strength and work to peak force of the bone and between the stiffness and insertion angle. Another study comparing screw pullout strength to BV/TV in femoral heads has also shown that in femoral heads with double the BV/TV the increase in pullout strength more than doubled [22]. The effect of the insertion angle on the stiffness follows logically from the requirement of also straightening the screw during the pullout. This effect has previously been seen in pedicle screws [23]. In a clinical setting the stiffness will likely no longer depend on the insertion angle because the opposite fracture surfaces are largely aligned, but the correlation does explain the differences in the context of the current pullout set-up.

In another study where similar cannulated screws and synthetic bone blocks with similar densities (0.128 g/cm³, 0.192 g/cm³, and 0.288 g/cm³) were used, CaP led to an increase in pullout strength in the low-density blocks, but a decrease in pullout strength in the high-density blocks [24]. The authors speculated that this was due to the loss of material and the holding power caused by predrilling, which was not performed in their control group. Pullout tests on suture anchors using paired osteoporotic cadaveric humeral bone with or without CaP have shown that CaP can significantly increase the strength of these anchors [25]. It has to be mentioned that for this type of implant the pullout forces are typically only in the range of 50–500 N. In pullout tests with fenestrated pedicle screws CaP has performed similar to PMMA, reaching a force increase of 73% compared to the control group with as little as 1.5 ml CaP [26]. These studies also support that CaS/HA improves screw fixation at different locations in osteoporotic bone.

In this study, the focus was on initial stabilization of the screw fixation, but long-term stabilization is also expected. Positive clinical outcomes, where CaS/HA without the inclusion of drugs was used for stabilization, have already been seen for tibial plateau fractures, wrist osteotomies and vertebroplasties [18–20]. More re-

cently, it has also been shown that CaS/HA is an excellent carrier of bone anabolic and antiresorptive drugs, which can aid in bone healing and enhance implant anchorage to bone [16]. The inclusion of micro-HA particles even allows for improved implant anchorage with the use of systemic zoledronic acid [27]. The HA particles acted as a recruiting platform for the drug and promoted peri-implant bone formation around a threaded polymer screw. In combination with the results shown in this study, this strongly implies that augmentation using CaS/HA can aid in stabilization of internal fixation of a hip fracture, leading to an improved clinical outcome.

To conclude, a 2 ml injection of CaS/HA has the potential to improve the initial fixation of a DHS in low density bone. When considering the use of CaS/HA for clinical application special attention needs to be focused on the injection method to ensure spreading of the CaS/HA into the threads and surrounding bone of the DHS. This could be achieved by using other injection devices and techniques allowing for more controlled delivery of the CaS/HA biomaterial at the interface of the DHS and surrounding low-quality bone.

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Declaration of Competing Interests

Lars Lidgren is a board member of Bone Support AB, Sweden and Orthocell, Australia.

Ethical Approval

All human material has been obtained from patients with informed consent according to bone biobank rules in the EU and by following hospital guidelines at the Kaunas University Hospital, Lithuania.

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