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ORIGINAL ARTICLE

Safety and feasibility of calcium sulfate/hydroxyapatite with zoledronic acid for the augmentation of helical blades in trochanteric fractures: A randomized pilot study

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Fixation failure in osteoporotic trochanteric fractures (TFs) is a common complication. Mechanical failure rates are highly variable, ranging from lower baseline reoperation and revision rates of 3% to 20% in registry studies and meta-analyses, to extreme complication rates of up to 47% revision in other reported series.[1-5] Suboptimal surgical fixation in frail with osteoporotic patients is the primary driver of these complications.[6,7] Polymethyl-methacrylate (PMMA) cement augmentation of the screw canal has shown to be efficient in reducing mechanical

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ABSTRACT

Objectives: This study aims to evaluate the feasibility, safety, and peri-implant bone formation of augmenting a proximal femoral nail (PFN) helical blade with a calcium sulfate/hydroxyapatite (CaS/HA) biomaterial combined with systemic zoledronic acid (ZA).

Patients and methods: This single-center, two-arm, parallel-group, randomized-controlled pilot study included a total of 20 patients with osteoporotic trochanteric fractures (TFs) between December 2023 and January 2025. The patients were randomized into a control group receiving standard PFN or an intervention group receiving PFN augmented with CaS/HA biomaterial. All patients received cefazoline and doxycycline for infection prophylaxis. On postoperative Day 7, both groups received a single intravenous infusion of ZA. The primary outcome was the change in bone mineral density (BMD) defined by previously published peri-implant regions-of-interest at one week and six months postoperatively. Secondary outcomes included tip-apex distance (TAD) for assessing blade migration and the Harris Hip Score (HHS) for functional evaluation.

Results: Of a total of 20 patients included in the study, 6 were male and 14 were female with a median age of 81 (range, 65 to 90) years. Regarding intervention delivery, all 10 randomly assigned patients received their intended treatment. While 19 of the 20 randomly assigned patients received the intended treatment; one patient died within the first week and did not receive ZA. The required data for clinical analysis (change in peri-implant BMD, TAD, fracture union, and HHS) could only be extracted for five patients in the control group and five patients in the intervention group. There were no intraoperative complications, and no adverse effects related to the CaS/HA biomaterial were reported. Ten patients were included for the outcome analysis. The intervention group demonstrated a more pronounced increase in peri-implant BMD compared to controls. Additionally, TAD changed more in the control group. Functional evaluation revealed that the intervention group demonstrated a slightly greater HHS improvement.

Conclusion: Our study results suggest that augmentation using the CaS/HA and ZA is a feasible and safe procedure for patients with osteoporotic TF. Preliminary findings indicate a potential trend toward enhanced peri-implant bone formation in the intervention group.

Keywords: Augmentation, bisphosphonate, bone mineral density, calcium sulfate, hydroxyapatite, intertrochanteric fractures, proximal femoral nail.

complications in several trials, but lacks concrete evidence and has not gained widespread clinical acceptance. The method has risks such as vascular leakage, thermal necrosis and more difficult revisions.[8-10] An alternative to PMMA is augmenting the screw canal using resorbable osteoconductive bioceramics that set *in situ* at isothermic temperature and gradually are replaced by bone. Calcium phosphates (CaP) or biphasic combinations with calcium sulfate/hydroxyapatite (CaS/HA) have been tested in fixation of intertrochanteric hip fractures in cadavers, as well as in clinical pilot series.[11,12]

The CaS/HA by itself can be used to bind systemically administered bisphosphonates to the hydroxyapatite. Zoledronic acid (ZA), a third-generation bisphosphonate, administered systemically, causes high local accretion to apatite deposited at a bone-implant interface.[13,14] With the hypothesis that bisphosphonates would decrease the resorption of the bone around the screw, a recent clinical proof-of-concept study evaluated whether CaS/HA augmentation and targeted ZA would improve fixation of TF using dynamic hip screws (DHSs).[12] The use of CaS/HA combined with ZA, administered during the hospital stay, has been shown to be safe and enhanced peri-implant bone formation and material remodeling and presents a promising complementary approach, addressing improved immediate mechanical fixation, long-term biological bone enhancement and even the prevention of secondary osteoporotic fractures.[15-17] This addresses a significant gap in care, as it has been reported in a single-center study that less than 20% of patients may be receiving antiresorptive treatment,[18] despite modern osteoporosis fracture care increasingly incorporating early bisphosphonates treatment recommended by fracture liaison services (FLSs).[19]

Building on the previously demonstrated feasibility and safety of the concept with DHS,[12] in the present study, we hypothesized that a PFN with a helical blade would achieve comparable results. We, therefore, aimed to evaluate the feasibility, safety, and peri-implant bone formation in a clinical pilot study applying an earlier described method with CaS/HA and systemic ZA in patients with osteoporotic TF, using the helical blade in proximal femoral nail (PFN).

PATIENTS AND METHODS

Study design and study population

This single-center, two-arm, parallel-group, randomized-controlled pilot study was conducted at Aksaray University Faculty of Medicine, Department of Orthopedics and Traumatology between December 2023 and January 2025. Reporting was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot and feasibility trials. Initially, patients aged between 65 and 90 years, with acute, unilateral, low-energy, stable pertrochanteric fragility fractures (AO/OTA types 31A1.2 and 31A1.3) who were deemed to be eligible for PFN surgical procedure were screened. Those who were classified as having a high fracture risk and a low mortality risk according to the Fracture and Mortality Risk Evaluation (FAME) Index[20] were included. Exclusion criteria were as follows: having a history of a previous ipsilateral hip or pelvic fracture; acetabular involvement of the current fracture; a history of local malignancy; irreversible coagulopathies; dialysis dependence or elevated serum creatinine levels (> 1.4 mg/dL); hypo- or hypercalcemia (< 8.5 mg/dL or > 10.5 mg/dL, respectively); hyperthyroidism or thyroid adenoma; ongoing systemic corticosteroid therapy; concurrent medical treatment for osteoporosis; and an inability to understand the study procedures due to impaired communication. Recruitment feasibility was demonstrated by successfully enrolling the target of 20 eligible patients until January 2025. A total of 99 patients were excluded due to being over the age 90 (n = 4), 31.A3 type fracture (n = 32), having high mortality risk (n = 16) and low fracture risk (n = 12) according to FAME Index, concurrent osteoporosis treatment (n = 13), high creatinine levels (n = 8), ongoing corticosteroid therapy (n = 4), and declining to participate (n = 10). The study was ended as planned in July 2025 after final follow-up was performed. A written informed consent was obtained from each patient. The study protocol was approved by the Aksaray University Clinical Research Ethics Committee (Date: 14.09.2023, No: 2023/17-02). The study was conducted in accordance with the principles of the Declaration of Helsinki. An independent clinical research organization (Ascot Science, İstanbul, Türkiye) was responsible for monitoring the trial to ensure data integrity and adherence to the protocol.

Randomization

A target sample size of 20 participants (10 per group) was chosen without a formal sample size calculation for this proof-of-concept feasibility study to estimate outcome variability and

identify procedural challenges in a clinical setting. Participants were randomized in a 1:1 ratio to the intervention or the control group, using sealed, sequentially numbered, opaque envelopes, by a researcher who was not involved in participation recruitment. The envelope was opened by the study coordinator to reveal the group assignment preoperatively. The study was originally designed as double-blind, with participants and evaluating investigators unaware of the group allocation; however, blinding of the surgical team and for radiological and bone mineral density (BMD) outcome evaluations was not possible due to radiopaque material.

Surgical technique and rehabilitation

All included patients were treated with a PFN with a fenestrated helical blade (TIPMED Medical Device Manufacturing Ltd. Co., İzmir, Türkiye) following Association of Osteosynthesis (AO) principles, under routine anesthesia by a single senior surgeon. Totally, 2 g of cefazolin was administered as infection prophylaxis 1 h preoperatively, combined with 100 mg of oral doxycycline, administered 2 h preoperatively and 6 h postoperatively. The control group received the standard surgical procedure without CaS/HA material or any type of augmentation. For the patients randomized into the experimental group, a regulatory approved CaS/HA material CERAMENT™ (BONESUPPORT AB, Lund, Sweden) consisting of 60% CaS and 40% HA and iohexol iodine for radiopacity was purchased. The surgical method for insertion was similar to the procedure previously described for DHS by Markeviciute et al.[12] The essential steps for injecting the CaS/HA material through the cannulated PFN blade were as follows: (1) A standard canal for the PFN blade was prepared using a 10-mm drill, (2) the blade was partially inserted into the proximal femur (approximately 3 cm away from its final position), (3) a long cannula connected to a syringe containing the CaS/HA paste was introduced, (4) the prepared CaS/HA paste (3 mL) was injected into the reamed cavity in front of the blade. The blade was, then, advanced into its final position following the standard PFN practice. Both arms received standard thromboprophylaxis and full weight bearing was allowed postoperatively. On postoperative Day 7, all patients in both groups received a single 5 mg/100 mL intravenous infusion of ZA (Ronidro™, VEM Pharmaceuticals, İstanbul, Türkiye) over 30 min. As all patients were normocalcemic at baseline and maintained adequate dietary calcium, prophylactic pharmacological supplementation was not administered. Patients were monitored clinically for symptomatic hypocalcemia post-infusion and instructed to report any relevant symptoms.

Outcome measures

Feasibility outcomes included recruitment rates, the technical success of the intraoperative CaS/HA injection, participant retention over six months, and the practical viability of tracking peri-implant BMD via dual-energy X-ray absorptiometry (DXA) scanning. Safety was evaluated by monitoring intraoperative complications and material-related adverse events. All patients, including the patients that were excluded for reasons other than mortality, were contacted six months postoperatively to investigate whether any complications occurred.

The primary outcome was the change in peri-implant BMD measured by DXA (GE LUNAR 8743; GE Healthcare, Madison, WI, USA), in

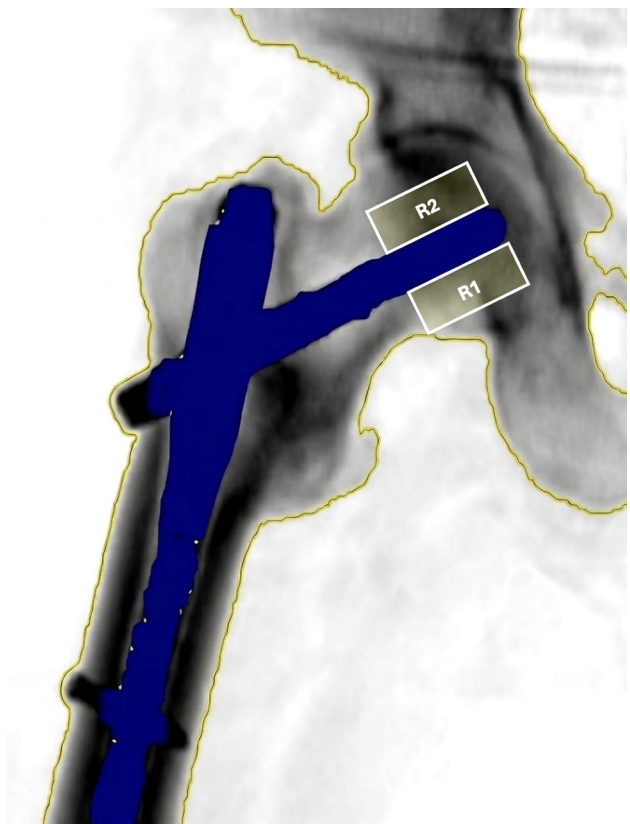

FIGURE 1. Definition of regions of interest (ROIs) for peri-implant bone mineral density analysis. The image illustrates region 1 (R^1) ROI and region 2 (R^2) surrounding the proximal femoral nail helical blade. These specific regions were used to quantify the percentage change in peri-implant bone density between one-week and six-months post-operation.

standard scan mode, within the two regions of interest (ROIs) also used by Markeviciute et al.[12] in a previous study (Figure 1). The ROIs were manually adjusted using enCORE software (GE Healthcare, Madison, WI, USA) after excluding the metal implant and related artifacts. Measurements were obtained at two time points: one week and six months postoperatively.

Secondary outcomes included tip-apex distance (TAD)[21] assessed by computed tomography (CT) scan at the same time points, via multiplanar reconstruction (MPR) using RadiANT DiCOM Viewer (version 2025.2, Medixant, Poland) by two authors independently. Inter-rater reliability between the two authors was evaluated using the intraclass correlation coefficient (ICC) for TAD measurements. Additional evaluation of quality of reduction according to the Baumgartner's Reduction criteria[21] and material leakage as defined by radiopaque material observed on an area outside of initial injection, was also assessed during this evaluation by the same authors on one-week CT images. Nonunion was defined definitively by the absence of bone union on the six-month CT and was evaluated by two authors. The Harris Hip Score (HHS) was evaluated at the aforementioned time points. The incidence of any mechanical complications during six-months follow-up was also reported.

Statistical analysis

Statistical analysis was performed using the Jamovi version 2.6 software (The Jamovi Project, Sydney, Australia).[22] Complication and mortality analyses were conducted on an intention-to-treat basis, including all 20 randomized participants in the group to which they were allocated. However, due to expected attrition in this frail demographic, BMD, radiological and functional outcomes were evaluated using an available-case analysis. Given the pilot nature of this study, all analyses of clinical outcomes were considered exploratory, and no statistical conclusions were drawn. Continuous variables were presented in median (min-max), while categorical variables were presented in number and frequency. In addition, 95% confidence intervals (CIs) were omitted, as the low number of patients per arm is insufficient to reliably calculate or report them.

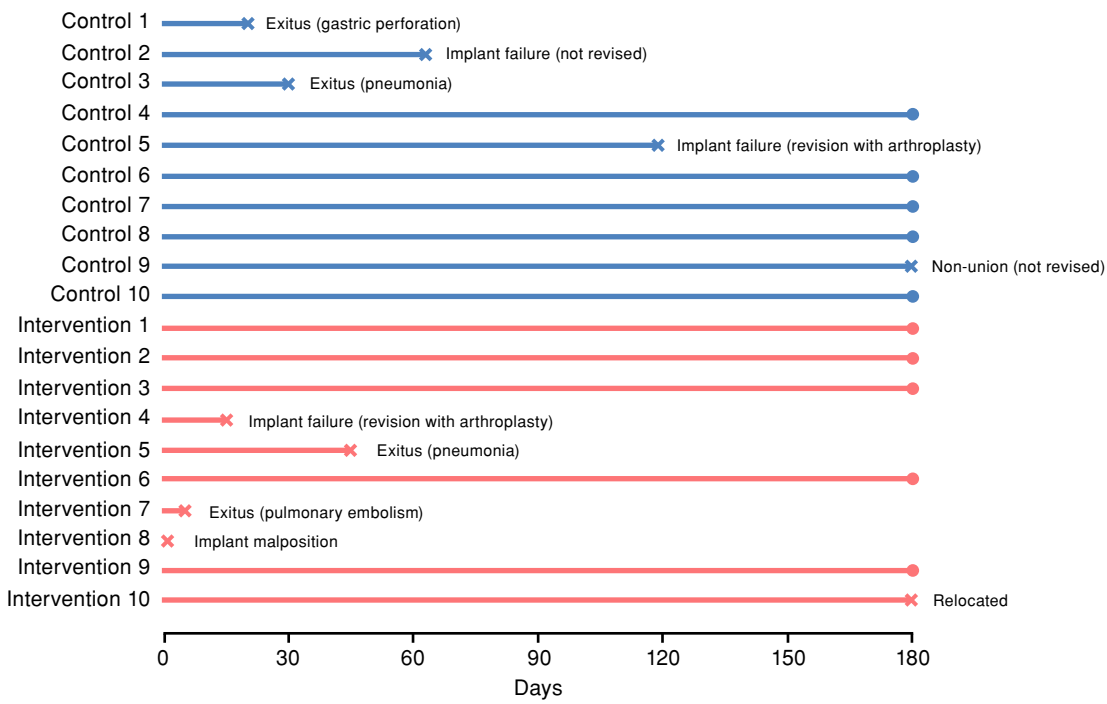

FIGURE 2. Patient follow-up timeline and causes of attrition. The diagram illustrates the 180-day follow-up trajectories for all 20 randomised patients in the control (blue) and intervention (red) groups. Lines terminating in a circle indicate patients who successfully completed the six-months follow-up and were included in the final analysis. Lines terminating in an "x" denote patients who dropped out or were excluded, with the specific clinical reasons and their approximate timing annotated.

RESULTS

Of a total of 20 patients included in the study, 6 were male and 14 were female with a median age of 81 (range, 65 to 90) years. Baseline patient demographics are summarized in Table I. Regarding intervention delivery, all 10 randomly assigned patients received their intended treatment, indicating the technical feasibility of injecting the CaS/HA material through the cannulated PFN blade was high. Participant retention and follow-up tracking revealed a high attrition rate characteristic of this frail demographic. While 19 of the 20 randomly assigned patients received the intended treatment; one patient died within the first week and did not receive ZA. The required data for clinical analysis (change in peri-implant BMD, TAD, fracture union, and HHS) could only be extracted for five patients in the control group and five patients in the intervention group. Attrition was driven by mortality from other medical causes (n = 4), fixation failure (n = 3), non-union (n = 1), implant malposition (n = 1), and loss to follow-up due to relocation (n = 1) (Figure 2). The practical feasibility of capturing measurement data via DXA was confirmed for the retained cohort, allowing for successful ROI analysis despite the presence of metal implants. The intervention demonstrated a favorable initial safety profile. There were no intraoperative complications, and none of the patients required transfusions. The early postoperative period was free from systemic complications such as cardiorespiratory complications, renal impairment, delirium, or venous thromboembolism and wound-related complications such as surgical site infection, hematoma, or wound discharge). No adverse effects due to CaS/HA application were noted; the material remained within the canal, and no contrast agent was observed leaking into the surrounding vasculature.

The analysis of peri-implant BMD change showed both baseline BMD and BMD increase was more pronounced in the intervention group in R1 ROI and R^2 ROI (Figure 3). The range of change was markedly higher in the control group (Table II).

Immediate postoperative CT evaluation showed immediate postoperative TAD was similar between the groups; however, it changed more in the control group (Table III). Inter-rater reliability was excellent for both time points (ICC = 0.925 and 0.942, respectively).

Serial imaging revealed progressive remodeling of the material into a pattern suggestive of trabecular bone within the experimental group by the six-month follow-up. This material-bone integration is demonstrated in the radiographs and oblique axial views of representative cases at one week and six months (Figure 4).

From one week to six months postoperatively, the median HHS in the control group increased from 22 (range, 21 to 25) to 58 (range, 32 to 62), representing a median change of 33 points (range, 10 to 41). On the other hand, the intervention group progressed from a one week median HHS of 37 (range, 21 to 40) to 72 (range, 62 to 89) at six months, yielding a

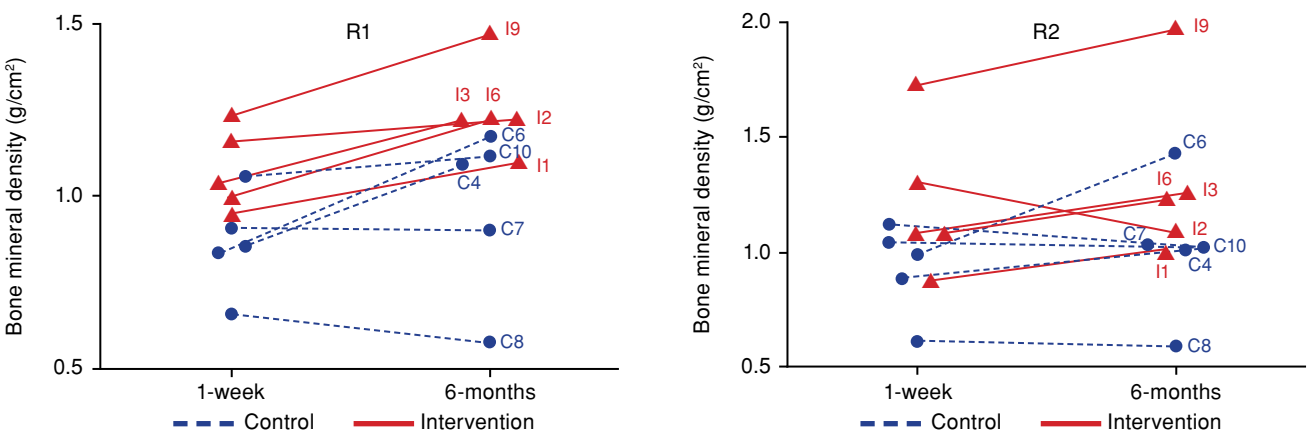

FIGURE 3. Individual trajectories of included patients' bone mineral density (g/cm^2) from 1-week to 6-months across Region of Interest R1 and R2. Blue dashed lines with circles indicate the control group; red solid lines with triangles indicate the intervention group.

C, control; I, intervention. Numbers denote patient numbers in the study.

TABLE I
Baseline demographics, clinical follow-up characteristics, and reasons for exclusion from the final analysis for the control and intervention groups

	Control group (n = 10)			Intervention group (n = 10)		
	n	Median	Range	n	Median	Range
Age (year)		82	71-90		77.5	65-86
Sex						
Female	6			8		
Body mass index (kg/m^2)		24.5	19.5-29.8		23	17-28.7
ASA score						
1	0			0		
2	6			7		
3	4			3		
4	0			0		
Fracture type						
31.A1.2	5			4		
31.A1.3	5			6		
Reduction quality						
Good	6			7		
Acceptable	4			2		
Poor	0			1		

ASA, American Society of Anesthesiologists.

TABLE II
Percentage change in peri-implant bone mineral density

	Control group (n = 5)		Intervention group (n = 5)	
	%	Range	%	Range
R1	5.6	–11.5-36.8	17.7	5.3-23.2
R2	–0.8	–8.9-43.8	13.7	–16.2-15.7

Regions of interest (R1, R2) from one-week to six-months postoperatively.

TABLE III
Median tip-apex distance (TAD) measurements and absolute change for both groups at one-week and six-months postoperatively

	Control group (n = 5)		Intervention group (n = 5)	
	TAD (mm)	Range	TAD (mm)	Range
One-week	24.8	20.6-25.4	20.7	11.6-24
Six-months	25.1	20.9-27	21.2	13-25
Absolute change in TAD ($\Delta\chi$)	2.6	0.3-4.4	0.5	0.4-1.4

median functional improvement of 41 points (range, 30 to 51).

Fixation failure due to blade cut-out was observed in both the control (n = 2) and intervention (n = 1) groups. One patient in each group underwent revision hemiarthroplasty; however, a second patient in the control group declined a second procedure. One patient in the control group developed a non-union, but also refused revision (Figure 2).

DISCUSSION

In the present study, we evaluated the feasibility, safety, and peri-implant bone formation in a clinical pilot study applying an earlier described method with CaS/HA and systemic ZA in patients

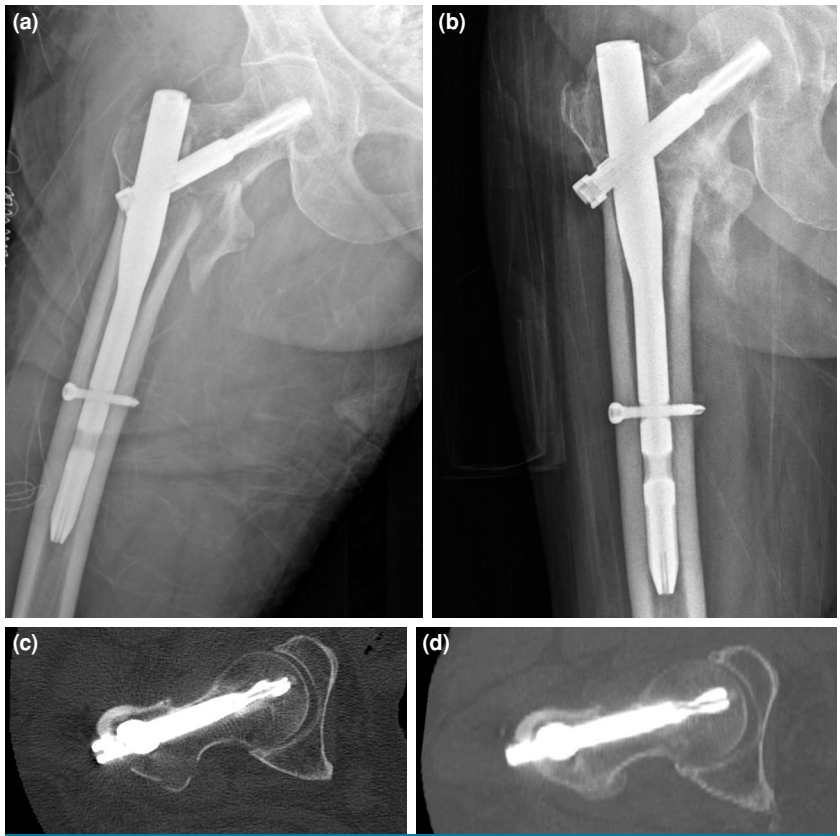

FIGURE 4. Radiographic and CT evaluation of fracture healing and biomaterial integration in representative cases. Radiographs show the CaS/HA material clearly visible around the helical blade at one-week **(a)**, progressing to a completely healed fracture with excellent remodelling and a structure consistent with trabecular bone in the femoral neck at six-months **(b)**. Oblique axial CT views at one-week **(c)** and six-months **(d)** highlight the progressive material-bone integration.
CT, computed tomography; CaS/HA, calcium sulfate/hydroxyapatite.

with osteoporotic TF using the helical blade in PFN. The principal finding of this pilot study was that augmentation using the CaS/HA and ZA was a feasible and safe procedure for patients with osteoporotic ITF. Although the small exploratory cohort precludes drawing definitive conclusions, preliminary data suggest a trend toward enhanced peri-implant bone formation in the intervention group, as evidenced by more pronounced regional increases in BMD. While these outcomes align with our prior DHS study,[12] the magnitude of the effect appears larger, a variance that may be attributable to the distinct design differences between the helical blade and a standard lag screw. Although initial peri-implant BMD measurements are confounded by the inherent radiopacity of the biomaterial, this early artifact renders our long-term observations more conservative. The CaS phase and iohexol dissolve rapidly, leaving the HA to act as an osteoconductive scaffold. Since the one-week baseline was already artificially inflated, the sustained increase against an elevated baseline supports the hypothesis of progressive bone remodeling and osseointegration. This potential benefit is accompanied by observations of reduced blade migration and fewer mechanical complications. It is of utmost importance to note that while baseline TAD differed numerically between the cohorts, all placements were securely within the established < 25 mm safe threshold. These variations can be considered within standard radiographic error margins, establishing a comparable clinical baseline between the groups. Furthermore, the intervention demonstrated a favorable initial safety profile, with no material-related complications such as wound discharge, allergic reactions, vascular leakage, or systemic adverse events observed in this cohort.

While PMMA-augmentation improve mechanical stability of PFNs, physiological loading can cause cement-bone fatigue cracks.[23-25] Consequently, bioactive CaP is being investigated as an alternative. Although initially mechanically inferior to PMMA, CaP eliminates these risks, promotes gradual bone ingrowth, and ultimately improves fracture fixation stability while reducing complication rates.[10,26,27]

Our approach utilized a biphasic CaS/HA composite, which combines a resorbable CaS embedding an osteoconductive microparticulate HA, allowing new bone ingrowth, while avoiding risks associated with PMMA.[28,29] This resorption of CaS and exposed microparticulate HA component, creates an accretion platform for systemically administered ZA given as a standard intravenous infusion during the first postoperative week.[13,14,29-31] Through calcium ion release, CaS facilitates early apatite precipitation deposited in a collagen network, facilitating ZA accretion and early bone ingrowth.[30-32] Consequently, the material is transformed from a passive void filler into a bioactive platform with accretion of bisphosphonate at the bone-implant interface.[29,30] Given that FLS initiatives currently recommend in-hospital administration of systemic bisphosphonates following osteoporotic fracture operations actively, our strategy of leveraging this standard of care by biologically activating a local bone cement offers a highly compatible and promising integrated solution for future osteoporotic fracture management.[15-17,19] A recent study translated this concept to a human proof-of-concept study using DHS fixation, which showed that CaS/HA augmentation followed by systemic ZA was safe and led to increased peri-implant bone-mineral density within six months.[12] As reported in a recent conference abstract, a biomechanical study in osteoporotic sawbones with CaS/HA augmentation in a gamma nail lag-screw led to a 650% increase in the peak extraction force compared with the non-augmented controls.[33] A critical distinction in our study is the use of a PFN with a helical blade, which compacts cancellous bone during insertion, rather than inserting the screw in a predrilled cavity to its final position. These design distinctions influence cement distribution; specifically. Mitsuzawa et al.[34] demonstrated that while lag screws allowed for a significantly larger total PMMA volume due to the void created by pre-drilling, the helical blade resulted in a distinct distribution pattern with greater penetration depth in the anterior and caudal directions. This variance was attributed to the blade's mechanism of compacting the cancellous bone, which creates a denser interface that limits total volume but directs flow differently than the void-filling nature of screw augmentation. In the present study, we hypothesized that the compaction of cancellous bone by the blade created a denser trabecular bed, which, when interdigitated with the CaS/HA, provided a stable composite and scaffold for systemically recruited ZA.

While assessing the BMD around the blade was the primary aim, the concurrent use of doxycycline in our pilot study warrants discussion as a complementary biomodulation strategy. Despite standard cephalosporin prophylaxis, deep infections are still being reported up to 3% with high associated mortality.[35,36] Therefore, we leveraged the implanted biomaterial as a recruiting moiety for systemically administered doxycycline, a second-generation tetracycline (TET).[30] It has been previously demonstrated that TET rapidly accretes to locally implanted HA, retaining efficacy against *Staphylococcus aureus (S. aureus)*.[37] This finding is consistent with historical data, notably Torsten André's[38] 1956 description of TET binding to human bone and Perrin's[39] 1965 identification of its specific attachment to calcium and phosphate groups. The clinical relevance of this strong affinity for bone mineral was further highlighted in a 1993 study on femoral neck fractures, where authors observed that patients receiving TET for bone labelling had significantly fewer deep infections.[40] Doxycycline's effective serum concentration and long half-life make it ideal for converting the apatite biomaterial into a drug-recruiting moiety to prevent colonization. To prevent confounding variables, this regimen was administered uniformly to both cohorts. We believe simultaneously addresses the broader vulnerabilities of fragility fracture patients by offering bone penetrance and extended protection without the nephrotoxic and catheter-related risks of prolonged intravenous therapies. However, while providing a localized safety margin here, routine adoption must be weighed against global antimicrobial resistance concerns.

The main limitation to this feasibility study is its small sample size. In addition, our cohort experienced a 20% mortality rate within six months. Despite employing eligibility criteria for low mortality risk using the FAME index, this rate reflects the general trend in similar

cohorts.[41] Given its pilot nature, the study cannot be powered to detect statistically significant differences in rare clinical failure rates, such as screw cut-out or reoperation, and obviously unlike in preclinical models, we could not perform histological analysis at the implant site to confirm the biological mechanism. Finally, we only included pertrochanteric fractures with intact lateral wall. Therefore, the clinical reflection of this method on unstable fractures may have demonstrate different characteristics.

In conclusion, our study results support the feasibility and preliminary safety of using CaS/HA and ZA to deliver early mechanical support via a resorbable biomaterial and at the same time create a targeted area with accretion of systemic ZA enhance local bone formation. Although the study was not designed to evaluate clinical efficacy, these preliminary findings provide a rationale for further investigation. Future studies involving larger, adequately powered cohorts are warranted to determine the clinical effectiveness of this approach, ideally as nested studies within established fragility fracture or hip fracture registries.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: D.B.R., L.L., V.T., E.A.S.: Idea/concept; H.Y., D.B.R, L.L, V.T., E.A.S.: Design; D.B.R., L.L., M.T., T.T., E.A.S.: Control/supervision; H.Y., D.B.R., M.T., S.G., E.A.S.: Data collection and/or processing; H.Y., D.B.R, L.L., S.G, E.A.S.: Analysis and/or interpretation; H.Y., D.B.R, V.T., E.A.S.: Literature review; H.Y., E.A.S.: Writing the article; D.B.R., L.L., M.T., S.T., T.T., V.T.: Critical review; D.B.R., L.L., M.T.: References and fundings; D.B.R., L.L., M.T., T.T., E.A..: Materials; H.Y.: Performing the surgeries.

Conflict of Interest: D.B.R., M.T., and L.L. are co-founders and hold stocks in Moroxite AB, a non-listed company based in Lund, Sweden. Moroxite AB has not had any role in study design, data analysis, or manuscript preparation. The remaining authors declare no conflict of interest.

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