



A next-generation Magnesium Phosphate composite exhibits superior biointegration and remodelling compared to conventional MPC in rat femoral defects

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Abstract

Critical-sized bone defects remain a major challenge in orthopaedic reconstruction because they lack the intrinsic capacity for complete regeneration, while many synthetic grafts fail to achieve optimal bioactivity, biodegradation, and host integration. This study evaluated the regenerative efficacy of a novel magnesium phosphate–triphasic silica-coated hydroxyapatite composite (MP–HASi) compared with conventional magnesium phosphate cement (MPC) in a rat femoral defect model. Bilateral unicortical femoral defects (2 × 6 mm) were surgically created in twenty-one adult male Wistar rats, with MPC implanted in the left femur (control) and MP–HASi in the right femur (test). Animals were euthanised at 2, 6, and 12 weeks for evaluation using serial radiography, gross morphology, histopathology, semiquantitative histomorphometry, and scanning electron microscopy. MP–HASi demonstrated earlier radiographic mineralisation from week 2, enhanced woven bone formation, accelerated cortical bridging, and more rapid graft–host integration than MPC. Histological and histomorphometric analyses revealed significantly reduced inflammatory and fibrotic responses, greater new bone formation, earlier maturation from woven to lamellar bone, and superior defect remodelling in the MP–HASi group throughout the study. By week 12, MP–HASi-treated defects exhibited complete lamellar bone reconstruction with complete biomaterial resorption, whereas MPC-treated defects retained residual graft material and showed incomplete remodelling. Scanning electron microscopy further confirmed intimate bone–material contact, abundant osteocyte lacunae, seamless interfacial integration, and synchronised biodegradation in the MP–HASi group. These findings demonstrate that MP–HASi provides superior osteoconductive and osteointegrative performance with coordinated resorption and bone remodelling, highlighting its potential as a next-generation synthetic bone graft substitute for the treatment of critical-sized osseous defects and supporting further evaluation in large-animal and translational preclinical models.

Keywords: Bone regeneration, magnesium phosphate cement, hydroxyapatite composite, osteointegration.

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Critical-sized bone defects resulting from traumatic injury, neoplastic excision, or reconstructive procedures remain a major clinical challenge because their intrinsic regenerative capacity is insufficient to restore structural and functional integrity. Autologous bone grafting is widely regarded as the clinical gold standard; however, its utility is restricted by donor-site morbidity, limited graft availability, and inconsistent biological performance, particularly in patients with systemic comorbidities or compromised healing potential (Roberts & Rosenbaum, 2012). These limitations underscore the need for synthetic graft substitutes that reliably support bone regeneration across diverse clinical scenarios.

Magnesium phosphate cement (MPC) has gained increasing attention as a translational biomaterial due to its rapid intraoperative handling characteristics, favourable compressive strength, and controlled bioresorption profile (Tian et al., 2024). Moreover, magnesium ion release has been shown to enhance osteoblast activity and promote apatite nucleation, biological effects that may be advantageous in the early phases of fracture repair or graft incorporation (Gelli & Ridi, 2023). Despite these advantages, existing MPC formulations demonstrate variable degradation kinetics and mechanical stability, which limit their predictability and impede clinical adoption for load-sharing applications.

Hydroxyapatite (HA), owing to its molecular similarity to native bone mineral, provides a stable osteoconductive scaffold, whereas silica has demonstrated robust osteoinductive effects, including accelerated mineralisation and improved early cellular response (Hing et al., 2006; Rao, 2020). Triphasic silica-coated HA scaffolds in particular have shown enhanced angiogenic and osteogenic activity (Dinesh, 2018), features that are critical for bridging larger defects and improving integration with host bone. Incorporating HA and silica into an MPC matrix offers a rational, biomimetic strategy for producing a composite with improved mechanical reliability, biologically favourable degradation, and enhanced regenerative potential—attributes directly aligned with clinical needs in orthopaedic reconstruction.

In this context, the present study evaluated a novel magnesium phosphate–triphasic silica-coated hydroxyapatite composite (MP–HASi) using a validated paired-limb rat defect model that minimises biological variability and enables high-resolution comparison of graft performance. Radiographic, histological, histomorphometric, and scanning electron microscopic analyses were employed to characterise the composite's osteogenic capacity, integration behaviour, and degradation profile. These data provide foundational evidence to support future translational development of MP–HASi as a next-generation bone graft substitute for repairing critical-sized defects in orthopaedic and trauma surgery.

Materials and methods

A controlled in vivo study was conducted using 21 adult male Wistar rats (8 weeks old; 150–200 g). The study was conducted in full compliance with CCSEA regulatory requirements and was approved by the Institutional Animal Ethics Committee (IAEC/COVAS/PKD/22/2/2024).

Bilateral standardised unicortical femoral defects (2 × 6 mm) were created in each animal. The left femur served as the control site and was filled with magnesium phosphate cement (MPC). In contrast, the right femur received the experimental magnesium phosphate–triphasic silica-coated hydroxyapatite composite (MP–HASi). Animals were monitored for 12 weeks, with radiographic, morphological, histological, histomorphometric, and ultrastructural analyses performed.

MP–HASi and MPC were prepared immediately prior to implantation. Powdered phases were mixed with their respective liquid components to achieve a homogeneous, injectable paste in accordance with the manufacturer's specifications.

Animals were randomly assigned to surgical order and fasted for one hour prior to anaesthesia. Hindlimbs were shaved and cleansed with soap and water, followed by 70% ethanol and povidone–iodine. Thirty minutes before induction, each animal received 2 mL sterile saline intraperitoneally.

Premedication consisted of buprenorphine (0.05 mg/kg SC). Anaesthesia was induced with a ketamine–xylazine combination (ketamine 30 mg/kg IP; xylazine 3 mg/kg IP). A stock mixture (ketamine 50 mg/mL; xylazine 100 mg/mL) diluted to 20 mL was administered at 0.1 mL/100 g body weight. Isoflurane (1–2% in oxygen) was used for maintenance.

A lateral approach to the femoral diaphysis was performed as described by Costa et al. (2011). After a linear incision over the lateral thigh, blunt dissection through the interval between the superficial gluteus and biceps femoris exposed the femur. Muscular attachments were elevated to isolate the cortical surface. A standardised unicortical defect (2 × 6 mm) was created using a 2-mm dental bur under continuous irrigation. Defects were filled with MPC or MP–HASi according to treatment allocation. Following the material setting, tissues were closed in layers using polyamide 3-0 in a simple continuous pattern.

Postoperative care included ceftriaxone (40 mg/kg IM twice daily for 7 days) and meloxicam (2 mg/kg SC for 5 days). Wounds were treated twice daily with povidone–iodine ointment. Skin sutures were removed on postoperative day 10. Animals were inspected daily for signs of infection, pain, or surgical complications.

Animals were euthanised at 2, 6, and 12 weeks

with an intraperitoneal overdose of 5% thiopentone sodium, in accordance with CCSEA euthanasia guidelines. Both femurs were excised, cleaned of soft tissue, and processed for radiographic, histological, and SEM evaluation.

Orthogonal radiographs were acquired immediately after surgery and at 2, 4, 8, and 12 weeks for radiographic evaluation. Healing was evaluated using a validated 0–4 scoring system reflecting graft–host integration, defect margin definition, and cortical continuity.

Grossly, the harvested femora were examined for cortical bridging, diaphyseal contour restoration, and macroscopic incorporation of the implanted materials.

For histology and histomorphometry, specimens were fixed in 10% neutral buffered formalin, decalcified, embedded, sectioned, and stained with haematoxylin and eosin and Masson's trichrome. Semiquantitative scoring assessed inflammatory infiltrates, vascularity, fibrosis, new bone type and quantity, and graft–host interface characteristics (Qiu et al., 2007). Five randomly selected fields at the defect centre and periphery were analysed at 400× magnification.

Scanning electron microscopy was performed on samples which were sputter-coated with gold–palladium (10 mA, 75 s) and examined using secondary electron imaging at multiple magnifications to characterise microarchitecture, mineralisation patterns, and bone–cement interface using a TESCAN VEGA 3 SEM.

Results and discussion

General observations

All 21 animals completed the study without intraoperative complications, postoperative morbidity, or biomaterial-associated adverse events. Incisions healed normally, and suture removal on postoperative day 10 was uneventful. No signs of infection, behavioural distress, or delayed wound healing were observed.

Radiographic evaluation

Serial radiographs demonstrated distinct material-dependent differences in the tempo and pattern of bone regeneration. Immediately postoperatively, both MPC and MP–HASi exhibited radiodensity comparable to native cortical bone, confirming accurate placement and defect standardisation.

By week 2, MP–HASi defects showed a measurable increase in radiodensity, reflecting early mineral deposition, whereas MPC-treated defects demonstrated minimal radiographic progression. This divergence widened by week 4, with MP–HASi exhibiting

robust early mineralisation and MPC showing only modest changes.

Both groups achieved radiographic cortical bridging by week 6. At week 8, a transient reduction in radiodensity was observed in both groups, consistent with early-stage remodelling; however, the change was more pronounced in the MP–HASi cohort, suggesting accelerated turnover.

At 12 weeks, complete radiographic union was observed in all animals. Residual radiopaque graft particles were still detectable in some MPC-treated defects, whereas MP–HASi-treated sites were radiographically indistinguishable from adjacent bone, indicating superior material resorption and integration.

Gross morphology

Time-dependent differences in graft incorporation were clearly evident. At week 2, MPC defects maintained a well-demarcated graft–host interface with no appreciable integration, while MP–HASi defects exhibited early marginal incorporation, particularly along caudal and distal cortices.

By week 6, MPC demonstrated only partial incorporation with persistent cortical discontinuity. In contrast, MP–HASi-treated defects showed extensive new bone formation and near-complete replacement of the composite material.

At week 12, MPC-treated sites displayed progressive—but still incomplete—defect bridging, with visible remnants of the original cement. MP–HASi-treated femora exhibited complete cortical restoration and seamless filling of the defect with newly formed bone, consistent with the radiographic findings.

Histopathological evaluation

Histological analysis revealed marked differences in the spatial organisation and quality of new bone.

By two weeks, MP–HASi specimens demonstrated reduced inflammation, minimal fibrosis, a narrower defect space, and a continuous band of woven bone spanning both cortices. MPC-treated defects exhibited a larger defect gap, pronounced inflammatory infiltrates, abundant fibrous tissue, and limited woven bone restricted to the margins. Masson's trichrome confirmed early osteoid deposition in MP–HASi and dense fibrous tissue in MPC. (Fig. 1)

During sixth-week observations, MP–HASi-treated defects exhibited well-organised lamellar bone extending toward the defect centre, indicative of accelerated maturation and reduced unfilled areas, whereas MPC sites showed improved bone organisation

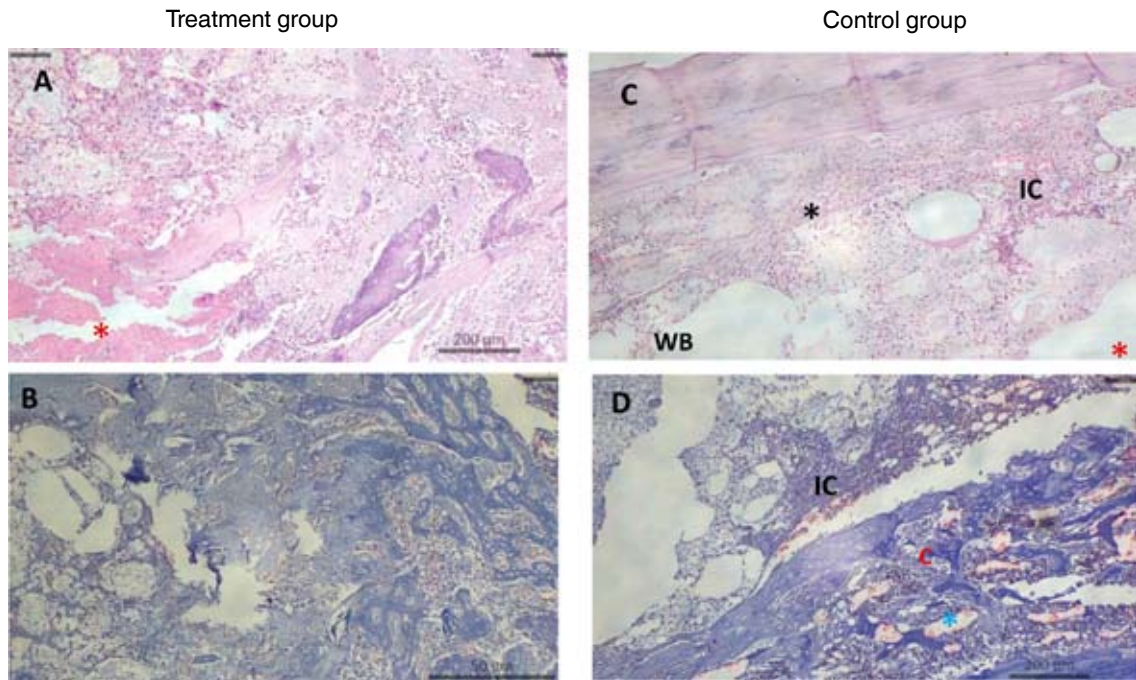


Fig.1 2nd week of bone healing- Treatment: A & B; Control: C & D

A. Defect (*) (x10, H & E) and woven bone deposition (**WB**). **B.** (**WB**) seen as light blue colour (x10, Mason's Trichrome). **C.** Fibrous callus (*) deposition around the defect area (x10, H & E), inflammatory cells (IC), woven bone and clearly visible defect area (*). **D.** Well organised collagen deposition (C) in defect site (x10, Mason's Trichrome) with vascularization (*) and inflammatory cells (IC).

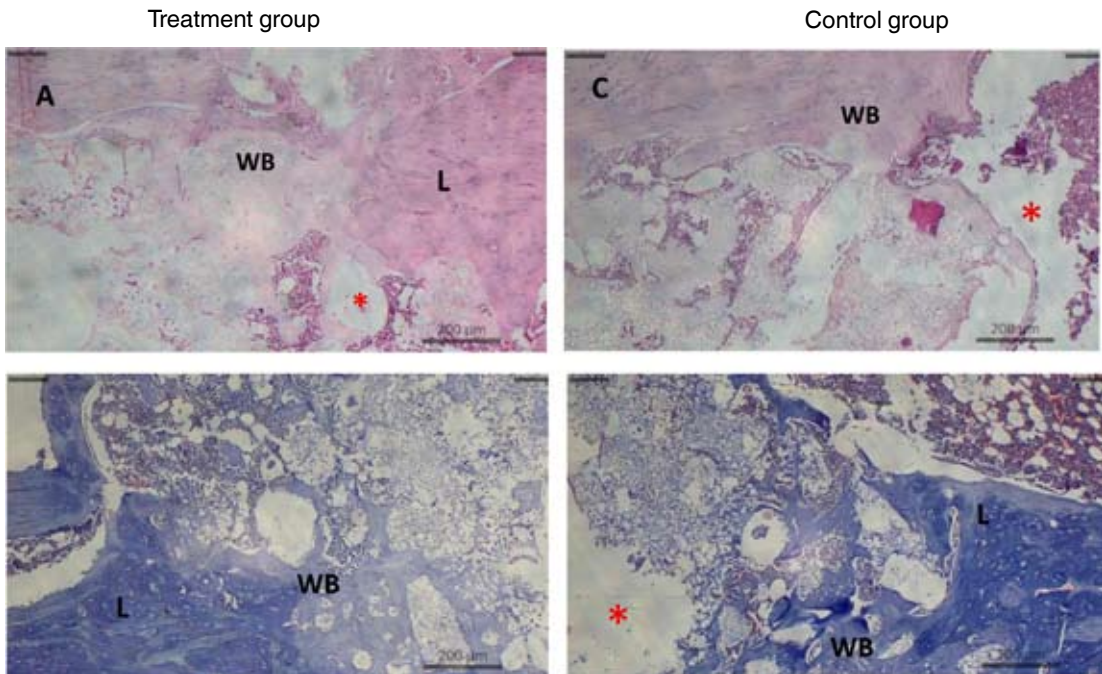


Fig. 2 6th week of bone healing: Treatment A & B; Control C & D

A. Filling of defect area with mixed scattered islands of woven bone (WB) with lamellar bone formation (L) (x10, H & E), defect site (*). **B.** Defect area filled with thick lamellar bone (L) with decreased scattered island of woven bone (WB light blue colour) (x10, Mason's Trichrome). **C.** Defect (*) filled by sheets of woven bone (**WB**) (x10, H & E). **D.** Lamellar (*) bright blue colour) with collagen deposition and woven bone (light blue colour) at defect site (*) (x10, Mason's Trichrome).

but retained central graft remnants and incomplete cortical bridging. (Fig. 2)

At 12 weeks, although both groups progressed to advanced healing, MP-HASi-treated sites exhibited nearly complete

lamellar bone formation, uninterrupted cortical continuity, and absence of fibrous tissue. In contrast, MPC-treated defects still demonstrated partial bridging, persistent central clefts, mixed woven-lamellar bone, and thin fibrous encapsulation around residual graft particles. Masson's

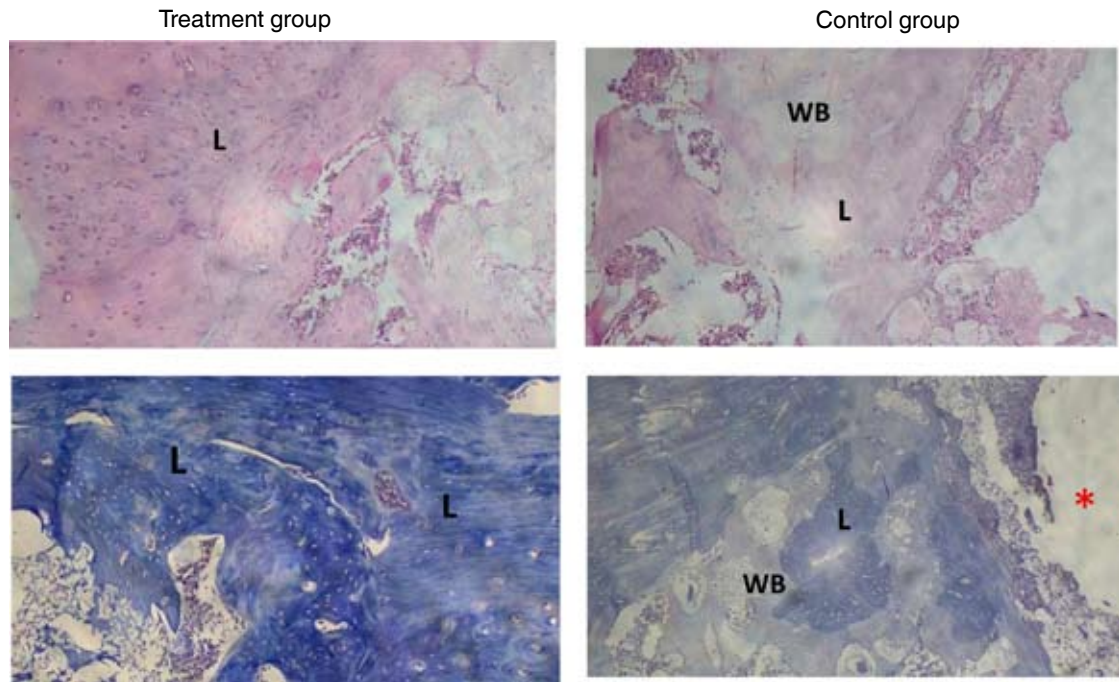


Fig. 3. 12th week of bone healing: Treatment A & B; Control C & D

A. complete bridging of defect with mature lamellar bone (L) (x10, H & E) which seems to me brighter due to more eosinophilic in nature. **B.** Mature lamellar bone (bright blue) completely bridging the defect site (x10, Mason's Trichrome). **C.** Diffused zone of lamellar bone with decreased amount of woven bone (WB) (x10, H & E). **D.** Lamellar bone (bright blue colour) with small amount of woven bone (WB) (appeared as light blue) with defect gap (*) (x10, Mason's Trichrome). D-defect

trichrome staining revealed dense, mature lamellar bone in the MP-HASi group, confirming superior mineralisation and structural integration. (Fig. 3)

Gross and histologic analyses revealed that MP-HASi not only accelerated early reparative processes but also fundamentally altered the quality of healing. Reduced early inflammation, diminished fibrosis, and more continuous woven bone formation at week 2 indicate a more permissive microenvironment for regeneration. By week 6, MP-HASi defects displayed organised trabecular formation and earlier lamellar transition, while MPC defects maintained unremodeled graft cores and incomplete cortical bridging—findings consistent with prior reports of slower MPC resorption and delayed remodelling (Rentsch et al., 2014; Gong et al., 2023). By week 12, MP-HASi-

treated defects exhibited robust lamellar maturation and seamless cortical continuity, attesting to the composite's capacity to support both early and late phases of bone regeneration.

Histomorphometric outcomes

Histomorphometric analysis demonstrated marked differences in the quality and progression of healing between groups. (Table 1)

Early vascularity was high in both groups, consistent with active reparative angiogenesis. Vascular scores gradually regressed to baseline by week 12, and no abnormal vascular patterns—such as excessive neovascularisation or avascular regions—were detected.

Table 1: Histomorphometric Scoring%

Parameter	MP-HASi Composite (Test)			MPC Cement (Control)		
	2 nd Week	6 th Week	12 th Week	2 nd Week	6 th Week	12 th Week
Inflammation	1.40 ± 0.51	2.60 ± 0.24	2.60 ± 0.24	0.60 ± 0.24	2.40 ± 0.24	2.60 ± 0.24
Vascularity	2.80 ± 0.37	1.80 ± .20	0.20 ± 0.2	3.00 ± 0.00	1.50 ± 0.32	0.20 ± 0.20
Fibrosis	2.20 ± 0.37	3.00 ± .00	3.00 ± 0.00	1.40 ± 0.4	1.40 ± 0.00	2.10 ± 0.24
New Bone Type	1.00 ± 0.00	1.00 ± 0.55	2.80 ± 0.20	0.20 ± 0.2	0.40 ± 0.24	2.00 ± 0.32
New Bone Quantity	1.40 ± 0.24	1.20 ± .49	2.60 ± 0.24	0.40 ± 0.4	0.80 ± 0.49	2.00 ± 0.00
Host bone integration	1.80 ± 0.73	2.60 ± .24	3.00 ± 0.00	1.40 ± 0.6	2.40 ± 0.24	3.00 ± 0.00
Total	10.6 ± 0.17	12.2 ± 0.4	14.2 ± 0.44	7.00 ± 0.42	8.9 ± 0.43	11.9 ± 0.41

At week 2, MP-HASi exhibited a lower inflammatory score compared with MPC, reflecting a more controlled early host response. Inflammation decreased progressively in both groups and was negligible in all specimens by week 12.

MPC-treated defects demonstrated persistent fibrous tissue from weeks 2 to 12, indicating a prolonged reparative phase. In contrast, MP–HASi defects showed markedly reduced early fibrosis with complete resolution by week 12, suggesting a more favourable microenvironment for bone deposition and remodelling.

At week 2, MPC defects generated small peripheral islands of woven bone, whereas MP–HASi defects developed broad, continuous spans of woven bone across the defect margins. By week 12, MPC sites retained mixed woven–lamellar architecture, while MP–HASi sites exhibited near-complete lamellar bone maturation, indicating more advanced structural remodelling.

MP–HASi-treated defects demonstrated stronger early cortical edge integration at week 2 compared with MPC. By week 12, although both groups achieved cortical continuity, MP–HASi consistently showed more uniform and complete bridging across specimens.

Total healing scores increased in a time-dependent manner for both groups; however, MP–HASi outperformed MPC at each time point. Overall, MP–HASi reduced early inflammation, enhanced osteogenesis, accelerated lamellar maturation, and improved structural integration compared with MPC.

Scanning Electron Microscopy

SEM provided ultrastructural confirmation of the superior osteointegration observed with MP–HASi.

At **2 weeks**, both groups exhibited interfacial gaps; however, MP–HASi defects showed earlier narrowing of the bone–material interface and closer apposition of new tissue to the composite surface, indicating more rapid initiation of osteointegration (Fig. 4).

At **6 weeks**, MPC-treated defects displayed initial ECM bridging but retained irregular, discontinuous

Fig. 4 (a) 2-week treatment group

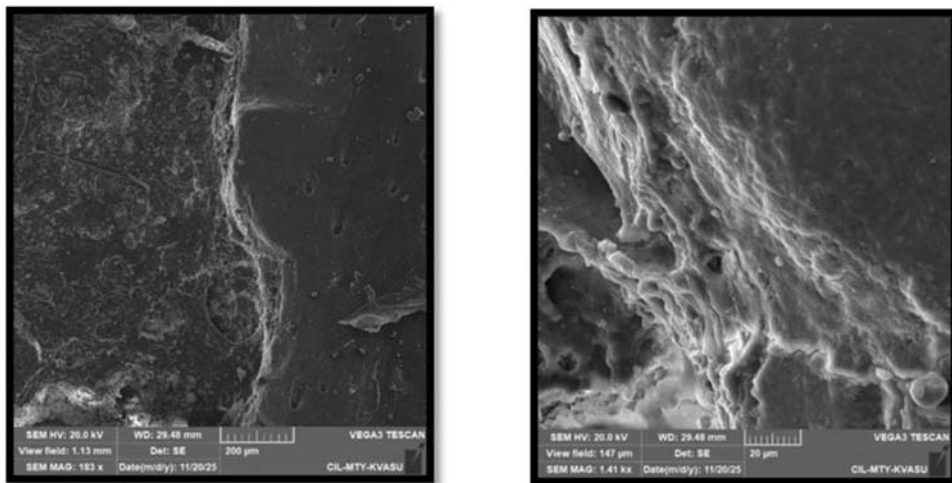


Fig. 4 (b) 2-week control group

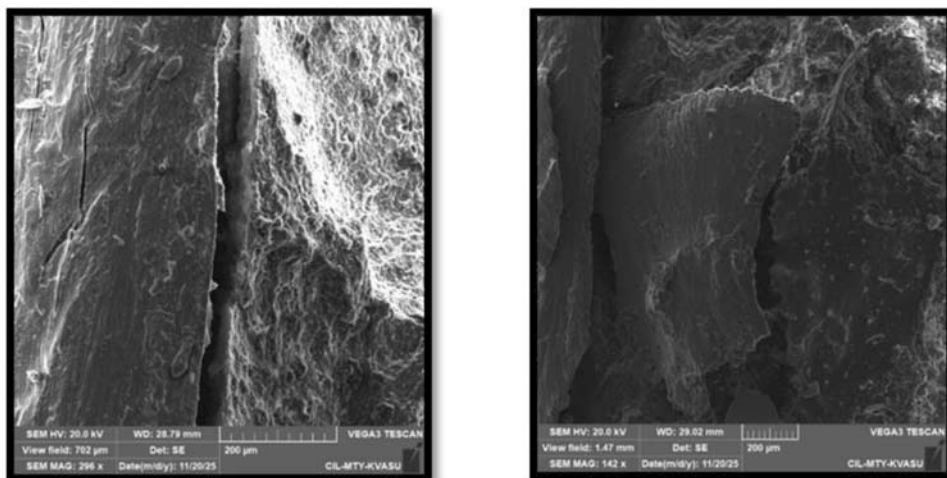


Fig. 4 a & b. Clear interfacial gaps observed. Treatment group showed earlier narrowing of the bone–material interface and closer apposition of new tissue to the composite surface.

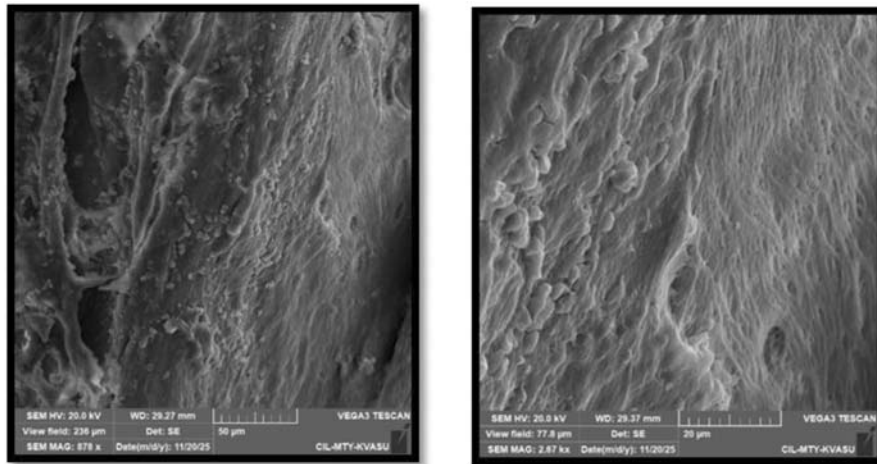
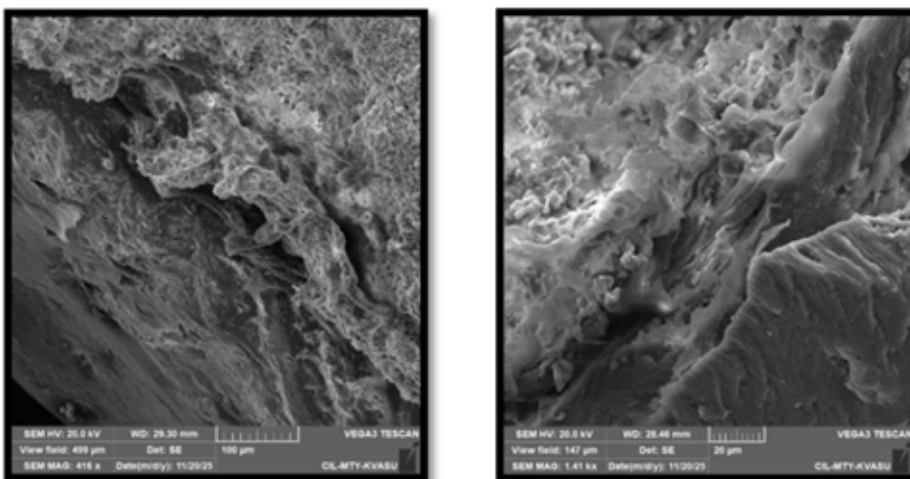
Fig 5. (a) 6-week treatment group**Fig 5. (b)** 6-week control group

Fig. 5 a & b. Initial ECM bridging in control group with irregular, discontinuous interfaces. Treatment group demonstrates uniform ECM deposition, smoother interfacial transitions, and early osteocyte lacunae formation.

interfaces. In contrast, MP–HASi defects demonstrated more uniform ECM deposition, smoother interfacial transitions, and early osteocyte lacunae formation—hallmarks of active bone deposition and early matrix organisation (Fig. 5).

At **12 weeks**, MPC defects continued to exhibit partial integration with persistent small particulate remnants and variable matrix organisation. MP–HASi specimens, however, presented a well-organised lamellar structure, advanced matrix remodelling, and seamless graft–host continuity. The absence of visible residual material further supported the composite’s controlled and biologically synchronised biodegradation (Fig. 6).

Collectively, SEM findings validated the histological results, demonstrating that MP–HASi supported more rapid and more structurally coherent bone–material integration than MPC.

The successful repair of critical-sized bone defects remains a major clinical challenge, necessitating

biomaterials that provide structural support while actively coordinating biological regeneration. Although magnesium phosphate cement (MPC) offers advantages over traditional calcium phosphate-based substitutes—including rapid intraoperative handling, favourable compressive strength, and intrinsic bioactivity mediated by magnesium ion release (Tian et al., 2024; Gelli & Ridi, 2023)—current formulations exhibit variable degradation kinetics and incomplete integration. These limitations highlight the need for next-generation composites with improved biological performance and more predictable remodelling behaviour.

Enhancing MPC with hydroxyapatite (HA) and silica (Si) presents a rational strategy to overcome these constraints. HA provides a chemically familiar, osteoconductive scaffold that mimics native bone mineral, while silica has been widely shown to stimulate osteogenic differentiation, accelerate mineral nucleation, and promote early vascularisation (Hing et al., 2006; Dinesh, 2018; Rao et al., 2021). Triphasic silica coatings further enhance

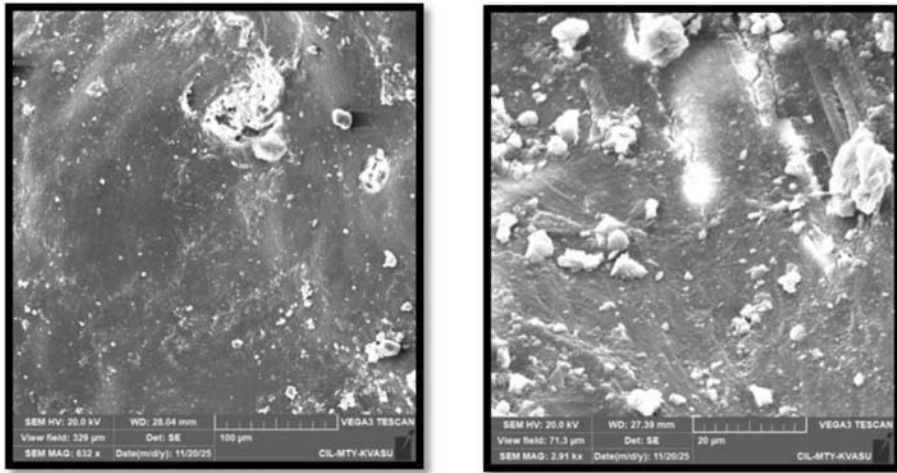
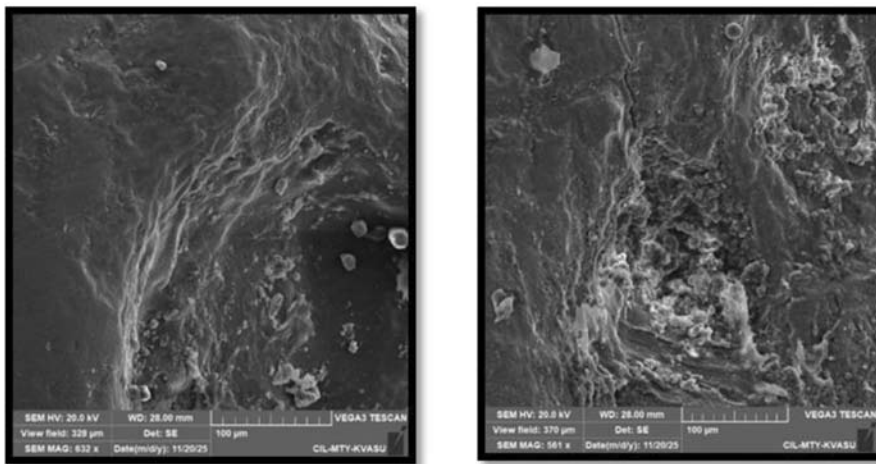
Fig 6. (a) 12-week treatment group**Fig 6. (b)** 12-week control group

Fig. 6 a & b. Control group exhibits partial integration with persistent small particulate remnants and variable matrix organisation. Test Group showed a well-organised lamellar structure, advanced matrix remodelling, and seamless graft–host co

cellular recruitment and angiogenic signalling, indicating strong potential for synergistic interactions when combined with a bioactive magnesium-based matrix.

In the present study, the novel MP–HASi composite demonstrated clear improvements over conventional MPC in all evaluated domains of bone repair. Early radiographic increases in radiodensity in the MP–HASi group reflect enhanced mineral deposition, concordant with prior literature on silica-mediated bioactivity (Nair et al., 2008; Rao et al., 2021). By week 12, the absence of residual material in MP–HASi defects—contrasting with discernible remnants in MPC-treated sites—indicates a more synchronised degradation-and-replacement profile, a critical attribute for defect substitution materials intended for clinical use.

SEM analyses provided ultrastructural validation of these observations. MP–HASi promoted earlier establishment of intimate bone–material contact, smoother interface transitions, and abundant lacunar architecture—

hallmarks of functional osteointegration (Brueckner et al., 2019; Shah et al., 2019). In contrast, persistent particulate remnants and irregular matrix deposition in MPC-treated sites reflected slower biodegradation and less efficient cellular remodelling. The microstructural features of MP–HASi, including its porosity and surface chemistry, likely facilitated enhanced cellular infiltration and angiogenesis (John et al., 2008), accelerating the progression from woven to mature lamellar bone. Taken together, these findings suggest that MP–HASi's regenerative superiority arises from synergistic interactions among its constituents.

- Magnesium ions stimulate early osteoblast activity and mineral precursor formation.
- Hydroxyapatite provides an osteoconductive scaffold that guides organised bone deposition.
- Silica enhances osteoinductive signalling, accelerates mineral nucleation, and promotes angiogenic coupling.

The integration of these mechanisms results in more rapid mineralisation, enhanced structural integration, and a remodelling pattern more closely aligned with native bone biology than conventional MPC.

Conclusion

This study demonstrates that the triphasic silica-coated hydroxyapatite-reinforced magnesium phosphate composite (MP-HASi) provides substantial regenerative advantages over conventional MPC for the treatment of critical-sized bone defects. MP-HASi facilitated earlier mineralisation, attenuated inflammation and fibrosis, improved graft-host integration, and supported rapid transition to mature lamellar bone. Its coordinated biodegradation, matching the tempo of new bone formation, further underscores its suitability as a bioactive, osteoconductive bone graft substitute.

These findings establish MP-HASi as a strong candidate for translational development in orthopaedic trauma and reconstructive surgery. Future work should include long-term biomechanical testing, evaluation in load-bearing defect models, and comparative assessment against clinically established alloplastic grafts to support progression toward clinical application.

Conflict of interest

The authors declare that there exists no conflict of interest

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