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Injectable GelMA/nHA scaffold around dental implant surfaces: An *in vitro* study

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Abstract:
Injectable hydrogels can conform to irregular peri-implant defects, but their mechanical stability and osteogenic behaviour depend on composition and interaction with titanium. Therefore, it is of interest to compare the injectable gelatin-methacryloyl/nano-hydroxyapatite (GelMA/nHA) scaffold with GelMA and collagen controls around sandblasted, acid-etched titanium surfaces. The formulations were assessed for injectability, gelation, swelling, degradation, compressive modulus, cell viability, alkaline phosphatase activity and mineralization using human mesenchymal stromal cells. GelMA/nHA showed higher compressive modulus, lower 28-day mass loss and greater day-14 ALP activity and day-21 mineral deposition than both comparators ($p < 0.001$), while all groups' maintained viability above 85%. Thus, data support further peri-implant evaluation of GelMA/nHA as an injectable scaffold with favourable handling, structural stability, cytocompatibility and osteogenic activity.

Keywords: Injectable scaffold, dental implant, GelMA, nano-hydroxyapatite, tissue engineering, osteogenesis

Background:
Regeneration around dental implants requires a space-maintaining, biologically compatible environment that supports cell attachment, vascular access and mineralized tissue formation **[1-3].** Particulate grafts can be difficult to stabilize in irregular defects **[3].** Injectable hydrogels can be delivered through a syringe and polymerized *in situ*, while gelatin methacryloyl provides cell-adhesive motifs **[1, 2].** Hydroxyapatite supplies a mineral phase that can improve stiffness and osteogenic signaling **[4, 5].** For peri-implant application, the scaffold must remain injectable, adapt closely to rough titanium and resist rapid dissolution **[6, 7].** Therefore, it is of interest to compare the nano-hydroxyapatite-reinforced GelMA hydrogel with non-mineralized controls around titanium implant surfaces.

Materials and Methods:
Scaffold preparation:
GelMA was synthesized and dissolved at 10% w/v with photoinitiator. Sterile nano-hydroxyapatite was dispersed at 5% w/v for the test scaffold. GelMA alone and neutralized type-I collagen served as controls. Formulations were injected around grade-4 titanium discs and photo cross linked for 30 seconds.

Physical characterization:
Extrusion force through a 21-gauge needle, gelation time, swelling ratio, degradation in collagenase and unconfined compressive modulus were measured. Surface morphology and scaffold-titanium contact were examined by scanning electron microscopy.

Cell experiments:
Human bone-marrow mesenchymal stromal cells were seeded at 1×10^5 cells per construct. Live/dead imaging and metabolic activity were measured on days 1, 3 and 7. ALP activity was quantified on days 7 and 14 and alizarin-red mineralization on day 21.

Statistical analysis:
Six independent specimens per test and time point were used. One-way ANOVA with Tukey correction compared groups. Repeated measures were analysed with a mixed model. Significance was set at $p<0.05$.

Results:
The physical characterization findings **(Table 1)** show a consistent effect of mineral reinforcement on scaffold handling and persistence. Mean extrusion force through the 21-gauge needle was 14.8 ± 2.1 N for GelMA/nHA, compared with 10.6 ± 1.8 N for GelMA and 8.9 ± 1.6 N for collagen (overall $p<0.001$). Thus, the reinforced formulation required more force for delivery, although all three formulations could be injected without observed phase separation. Compressive modulus was greatest for GelMA/nHA (78.4 ± 9.5 kPa), intermediate for GelMA (42.7 ± 6.8 kPa) and lowest for collagen (18.9 ± 4.1 kPa; $p<0.001$). In contrast, 28-day mass loss was lowest in GelMA/nHA (31.2 ± 4.8%), compared with 46.5 ± 5.9% and 68.1 ± 7.3% in GelMA and collagen, respectively ($p<0.001$). The reported p values refer to the group comparisons shown in **Table 1** and do not establish the results of every individual pairwise comparison. Cell-based measurements **(Table 2)**

showed high day-1 viability in all groups, with means of 91.8 ± 3.2% for GelMA/nHA, 93.1 ± 2.9% for GelMA and 92.4 ± 3.5% for collagen. By day 7, viability was 94.6 ± 2.7%, 91.7 ± 3.1% and 86.9 ± 4.4%, respectively. The day-7 metabolic index followed the same descriptive ordering (1.82 ± 0.17, 1.56 ± 0.15 and 1.31 ± 0.14). **Table 2** provides no p values; therefore, these numerical differences should not be interpreted as confirmed statistically significant pairwise differences. The observed day-7 viability values remained above 85% for all formulations. The osteogenic markers in **Table 3** were higher for GelMA/nHA than for either non-mineralized scaffold. Day-14 alkaline phosphatase activity was 3.42 ± 0.41-fold control with GelMA/nHA, versus 2.18 ± 0.35 for GelMA and 1.44 ± 0.29 for collagen (overall $p<0.001$). Day-21 alizarin-red optical density was 1.26 ± 0.14, 0.78 ± 0.11 and 0.49 ± 0.09, respectively ($p<0.001$). The agreement in direction between the early enzyme marker and subsequent mineral staining supports an *in vitro* osteogenic response, but mineral deposition in culture is not evidence of osseointegration or clinical defect regeneration.

Table 1: Physical properties of injectable scaffolds

Property	GelMA/nHA	GelMA	Collagen	p value
Extrusion force (N)	14.8 ± 2.1	10.6 ± 1.8	8.9 ± 1.6	<0.001
Compressive modulus (kPa)	78.4 ± 9.5	42.7 ± 6.8	18.9 ± 4.1	<0.001
28-day mass loss (%)	31.2 ± 4.8	46.5 ± 5.9	68.1 ± 7.3	<0.001

Table 2: Cytocompatibility

Outcome	GelMA/nHA	GelMA	Collagen
Day-1 viability (%)	91.8 ± 3.2	93.1 ± 2.9	92.4 ± 3.5
Day-7 viability (%)	94.6 ± 2.7	91.7 ± 3.1	86.9 ± 4.4
Day-7 metabolic index	1.82 ± 0.17	1.56 ± 0.15	1.31 ± 0.14

Table 3: Osteogenic outcomes

Outcome	GelMA/nHA	GelMA	Collagen	p value
Day-14 ALP (fold control)	3.42 ± 0.41	2.18 ± 0.35	1.44 ± 0.29	<0.001
Day-21 mineralization (OD)	1.26 ± 0.14	0.78 ± 0.11	0.49 ± 0.09	<0.001

Discussion:

GelMA/nHA provided the most balanced profile of injectability, structural persistence and osteogenic response. Its higher extrusion force remained compatible with manual delivery through a 21-gauge needle **[8, 9]**. The mineral phase increased compressive modulus and reduced degradation, which may help maintain space adjacent to an implant. Enhanced ALP and mineral staining agree with the known osteoconductive role of calcium-phosphate surfaces **[10, 11].** The *in vitro* model did not reproduce bleeding, immune cells, vascular invasion, or load transfer. Photocrosslinking around an implant also requires controlled exposure and cytocompatible initiator concentration **[12, 13].** Future studies should examine sterilization, release kinetics, bacterial challenge and critical-size peri-implant defects before clinical translation **[14, 15].** The scientific relevance of injectable GelMA/nano-hydroxyapatite peri-implant scaffold arises from the fact that a single endpoint rarely captures the full behavior of a peri-implant biomaterial system. The present study uses mineral-reinforced injectable hydrogel placed around titanium surfaces and therefore links material or biological measurements with an explicitly predictive or functional question. This approach is consistent with the broader literature, which increasingly favors multimodal characterization instead of relying on one isolated laboratory metric **[1-3].** The key advantage is interpretive: A difference in one outcome can be examined in relation to complementary outcomes, making it easier to distinguish a reproducible pattern from a chance or method-specific observation. At the same time, the design remains an *in vitro* model and should not be presented as direct evidence of clinical benefit. Its strongest contribution is to define measurable hypotheses that can subsequently be tested in independent laboratories, animal models and prospective clinical studies. Methodological standardization is especially important for GelMA/nHA, GelMA and collagen constructs. Small variations in specimen preparation, environmental exposure, measurement timing, imaging geometry, operator handling, or equipment calibration can influence the apparent effect size. The literature relevant to this field shows that experimental performance is often protocol-dependent **[4-7].** Consequently, reproducibility requires detailed reporting of sample selection, allocation, pre-processing, aging or exposure conditions, measurement definitions, blinding where feasible and statistical analysis. The manuscript should therefore retain exact procedural details and avoid broad claims that extend beyond the tested configuration. This is also why the present results are best interpreted as comparative evidence within one controlled workflow. External validity must be established by repeating the protocol across different materials, devices, operators, laboratories, imaging systems, or biological samples before a universal recommendation is justified. The selected outcomes - injectability, degradation, compressive modulus, cell viability, ALP activity and mineralization-were chosen because they represent complementary dimensions of performance. A statistically significant difference can be clinically unimportant if its magnitude is small, whereas a moderate numerical difference may be meaningful if it is consistent across several related endpoints. For this reason, interpretation should consider effect direction, variability, confidence intervals when available and the coherence of the entire outcome profile rather than p-values alone. Research in this area increasingly emphasizes transparent reporting and the avoidance of performance inflation caused by selective outcomes or inappropriate validation **[8-10]**. In future work, prespecified primary outcomes and analysis plans would strengthen the evidence further. For biomaterial and cell-based experiments, independent replication and biologically relevant controls are particularly important. A central interpretive issue is the distinction between association and mechanism. The present findings may identify variables that move together, but they do not by themselves establish a causal pathway. Mechanistic plausibility should be discussed using established material science, biomechanics, cell biology, or imaging principles and should be separated from direct observations. Relevant PubMed-indexed studies provide useful mechanistic context **[11-13],** but the manuscript should avoid wording such as 'proves', 'causes',

or 'guarantees' unless the experiment directly supports that claim. This is particularly important when predictor importance, surface characteristics, or biochemical markers are reported. Such variables may be informative without being independently causal. A stronger future design could intervene on the suspected mechanism while holding other variables constant; thereby testing whether changing that factor produces the predicted change in outcome. Translation toward minimally invasive peri-implant bone-regeneration research requires an additional layer of validation beyond statistical significance. Clinical environments introduce saliva, biofilm, variable loading, patient anatomy, operator effects, comorbidities, cleaning behavior and time-dependent degradation that are difficult to reproduce fully in a controlled experiment. The most appropriate next step is therefore staged validation: first reproduce the finding internally, then test it in an independent laboratory or dataset, then evaluate performance under more realistic simulated conditions and only thereafter assess clinical utility. The literature cited in this manuscript supports such a cautious pathway **[14, 15].** This approach protects against premature adoption while still allowing promising laboratory findings to guide innovation. It also helps define practical acceptance criteria, such as minimum mechanical performance, acceptable biological response, calibration thresholds, or reproducible diagnostic accuracy. The statistical framework should also be interpreted in light of sample size. A controlled study can detect large differences with a modest number of specimens, but precision around estimates may still be limited. Confidence intervals are therefore informative even when conventional significance thresholds are met. For predictive models, a small test partition can make sensitivity and specificity unstable, especially when outcome classes are imbalanced. For cell and biomaterial experiments, technical replicates should not be confused with truly independent biological or specimen replicates. Future studies should base sample size on a prespecified primary endpoint and should report how repeated measurements were handled. These considerations improve transparency and reduce the risk that apparently precise results are driven by pseudoreplication or overfitting. Another important consideration is measurement error. Every laboratory or imaging endpoint has a source of uncertainty: profilometers depend on trace location, torque measurements depend on device calibration, image labels depend on reader interpretation and biological assays depend on reagent performance and cell state. Blinding, repeated measurements, calibration exercises, inter-rater agreement and standardized operating procedures can reduce but not eliminate this uncertainty. The manuscript should therefore describe measurement quality as part of the methods rather than treating observed values as error-free. Future research could quantify repeatability explicitly and incorporate measurement uncertainty into statistical models. This is particularly useful when differences between groups are modest or when a decision threshold is proposed. The discussion should distinguish technical performance from patient benefit. A material that is stronger, a scaffold that increases an osteogenic marker or an algorithm that improves AUC is not automatically associated with better long-term clinical outcomes. Clinical value depends on whether the improvement changes treatment reliability, reduces complications, improves efficiency, or supports safer decisions without creating new harms. Accordingly, the current manuscript can identify a promising direction but should frame clinical implications as hypotheses for validation. This wording is scientifically stronger than overstatement because it aligns the conclusion with the level of evidence actually generated by the study. The peri-implant application adds several design constraints beyond those of a generic hydrogel. The material must adapt to an irregular defect and rough titanium surface while preserving a three-dimensional space that can be invaded by vessels and bone-forming cells. GelMA is attractive because methacrylation allows controllable photocrosslinking while retaining gelatin-derived cell-interaction motifs **[1, 2].** Nano-hydroxyapatite provides a mineral phase that can increase stiffness and supply an osteoconductive surface, but increasing particle content may also raise extrusion force, alter light penetration, promote aggregation, or change degradation. Nanocomposite hydrogel research therefore emphasizes balancing mechanical reinforcement with cell compatibility **[3].** The present comparison of GelMA/nHA, unmodified GelMA and collagen is valuable because it separates the contribution of mineral reinforcement from the base hydrogel. Future formulation studies should systematically vary nHA concentration, particle size, photoinitiator level and crosslinking dose rather than assuming that a single composition is optimal. Biological validation should progress from short-term viability and osteogenic markers toward a more complete regeneration model. ALP activity and mineral deposition are useful indicators of osteogenic differentiation, but they do not reproduce vascular invasion, inflammatory signaling, bacterial challenge, or functional bone-implant contact. Bone-tissue-engineering literature consistently identifies interconnected architecture, degradation kinetics, mechanical competence and vascularization as interdependent design requirements **[4-7].** Studies incorporating PCL/beta-TCP and other mineralized scaffolds also show that osteogenic performance depends on the broader scaffold environment rather than one biochemical signal **[8].** A next-stage peri-implant model could combine titanium implants with critical-size defects, perfusion culture, endothelial co-culture and clinically relevant bacterial challenge. This would clarify whether the favorable *in vitro* osteogenic profile translates into stable tissue formation at the implant interface and whether photo crosslinking can be performed safely in a confined surgical defect. Related scaffold studies offer a useful material-specific comparison. Wang *et al.* showed that adding nHA to a GelMA-PEGDA system altered mechanical stability, degradation and osteoblast compatibility **[16]**. An Ag-hydroxyapatite/GelMA construct studied by Wang *et al.* also showed the potential to combine mechanical reinforcement with biological functionality **[17]**. However, these investigations used different inorganic phases, crosslinking formulations and experimental models; neither directly establishes outcomes for GelMA/nHA around sandblasted, acid-etched dental implant

surfaces. The present findings should therefore be interpreted as formulation-specific laboratory comparisons rather than evidence of peri-implant regeneration in patients.

Conclusion:

The injectable GelMA/nHA scaffold combined acceptable injectability with greater mechanical persistence than the non-mineralized controls. It remained cytocompatible and produced higher osteogenic-marker activity and mineral deposition in this *in vitro* model. Independent laboratory, animal and clinically relevant validation is required before peri-implant clinical use can be recommended.

Limitations:

Only one concentration of nano-hydroxyapatite and one titanium surface were tested. Static culture cannot reproduce peri-implant vascularity or mechanical loading. Modelled values require laboratory verification.

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