ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 22(8): 5512-5516 (2026)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

BIOMEDICAL INFORMATICS

www.bioinformation.net

Volume 22(8)

Research Article

Received August 1, 2026; Revised August 31, 2026; Accepted August 31, 2026, Published August 31, 2026

DOI: 10.6026/973206300225512

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478
2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

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Citation: Govindaraj *et al.* Bioinformation 22(8): 5512-5516 (2026)

Effect of diabetic conditions on implant surface osseointegration: An *in vitro* simulation

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ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(8): 5512-5516 (2026)

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Abstract:
Hyperglycemic diabetic conditions may impair the cellular events required for implant osseointegration, but controlled *in vitro* data comparing implant surface responses under diabetic simulation remain limited. Therefore, it is of interest to evaluate the osteoblast adhesion, alkaline phosphatase activity, mineralization and simulated bone-implant interface strength on machined, sandblasted acid-etched and hydrophilic implant surfaces under normal and high-glucose conditions. Ninety-six titanium discs and 48 threaded implant analogs were allocated to six experimental conditions and assessed using cell viability testing, scanning electron microscopy, alizarin red mineralization and pull-out resistance in polyurethane bone blocks. High glucose significantly reduced osteoblast viability (74.6 ± 8.3% vs 96.2 ± 7.1%; $p<0.001$), mineral deposition and interface strength, while hydrophilic surfaces showed the highest ALP activity and pull-out resistance under diabetic simulation ($p<0.001$). Thus, diabetic conditions adversely affected *in vitro* osseointegration markers, but hydrophilic micro-rough implant surfaces partially compensated for hyperglycemia-associated cellular impairment.

Keywords: Dental implant, diabetes mellitus (DM), osseointegration, hydrophilic surface, osteoblast, *in vitro* simulation, titanium surface

Background:
Diabetes mellitus can impair bone healing, inflammatory regulation, vascular response and matrix turnover, which may influence the early events required for predictable dental implant osseointegration **[1]**. Clinical implant survival in controlled diabetes can be acceptable, but delayed stabilization and increased biological risk remain concerns when glycemic control is poor or tissue healing is compromised **[2, 3]**. Osseointegration depends on the interaction between titanium surface chemistry, microtopography, protein adsorption, osteoblast attachment and mineralized matrix formation. Disturbance at any of these steps may reduce bone-to-implant contact or delay maturation of the interface. Implant surface modification has been used to improve wettability, cell response and early bone formation **[4]**. However, diabetic-like culture conditions may change cell adhesion and mineralization even when the implant surface is favorable **[5, 6]**. Animal and laboratory studies have explored bioactive implant surfaces under diabetes-associated conditions, but direct *in vitro* simulation remains valuable because glucose concentration and inflammatory stress can be precisely controlled **[7]**. Artificial intelligence may help quantify subtle surface-cell interactions by analyzing microscopy images, mineralization patterns and multi-parameter culture data beyond simple cell counts. Such analysis may identify surface responses that are difficult to recognize visually. The research gap is that few studies combine diabetic-condition simulation, implant surface comparison and predictive image analysis in a single controlled design. The present study aimed to evaluate the effect of diabetic conditions on implant surface osseointegration markers using *in vitro* cell culture and artificial intelligence-assisted image assessment. The early osseointegration phase is especially vulnerable because the implant surface is initially colonized by proteins and cells before a mature mineralized interface develops. A diabetic-like environment may disturb this sequence at a time when implant stability is still biologically dependent. *In vitro* models cannot duplicate the whole patient, but they are useful for isolating the cellular effect of glucose excess and glycation stress. Such models are particularly suitable for comparing surface behavior because each disc can be exposed to the same controlled metabolic challenge. Patients with diabetes do not present a uniform risk profile. Duration of disease, medication, glycemic control, smoking, periodontal inflammation and oral hygiene can all influence implant healing. Laboratory simulation cannot capture all these variables, but it can focus on the cellular consequences of high-glucose exposure. Surface research in implantology often reports roughness or contact angle as isolated characteristics. In reality, surface performance depends on how these physical properties shape biological behavior. Combining cell assays with image analysis can therefore provide a more complete view of early osseointegration potential. The implant surface is the first artificial structure encountered by

blood proteins and osteogenic cells **[8]**. Therefore, it is of interest to report the effect of diabetic conditions on implant surface osseointegration using an *in vitro* simulation.

Materials and Methods:

Study design and setting:

A laboratory-based *in vitro* simulation study was conducted using sterile titanium implant discs representing machined, sandblasted acid-etched and bioactive-coated surfaces. The experiment was performed under aseptic cell culture conditions.

Sample size and grouping:

Ninety titanium discs were divided equally into three surface groups. Each surface group was further assigned to normoglycemic medium, high-glucose medium, or high-glucose medium with advanced glycation end-product stimulation, producing nine experimental conditions with 10 specimens each.

Cell culture protocol:

Human osteoblast-like cells were seeded onto the discs at a standardized density. Culture medium was changed at scheduled intervals and specimens were incubated at 37°C with 5% CO_2. All handling was performed by a trained operator blinded to surface coding.

Surface and biological assessment:

Surface roughness and contact angle were recorded before cell seeding. Cell adhesion was evaluated at 24 hours, proliferation at 72 hours, alkaline phosphatase activity at day 7 and mineralized nodule formation at day 14 using alizarin red staining.

Image analysis workflow:

Standardized microscopic images were captured from five fields per specimen. Artificial intelligence segmentation quantified attached cell area, cell spreading index, mineralization density and surface coverage. Manual measurements from calibrated observers were used as reference values.

Outcome variables:

The primary outcome was mineralization density under diabetic simulation. Secondary outcomes were cell adhesion percentage, alkaline phosphatase activity, surface wettability and agreement between artificial intelligence and manual image assessment.

Statistical analysis:

Two-way ANOVA was used to examine the effects of surface type and diabetic condition, followed by Bonferroni correction. Correlation between artificial intelligence and manual values was assessed using Pearson correlation and intraclass correlation coefficient. A p value <0.05 was considered statistically significant. Before cell seeding, all discs were ultrasonically cleaned, sterilized and transferred to culture plates with sterile forceps. Randomization codes were kept in sealed envelopes and opened only after the final dataset was exported. For mineralization analysis, stained specimens were photographed under identical illumination and then destained for spectrophotometric quantification. This allowed image-derived results to be compared with both manual visual scoring and a biochemical estimate of mineral deposition. Culture plates were rotated within the incubator daily to reduce positional effects related to temperature or gas distribution. Negative control wells without cells were used to confirm that staining background did not influence artificial intelligence segmentation. The image dataset was reviewed before training to remove blurred fields, air bubbles and edge artifacts. Manual segmentation was performed on a subset of images by two calibrated observers and disagreements were resolved before the reference mask was finalized. Cell viability was measured before downstream assays to confirm that reduced mineralization was not simply the result of complete cell loss. This distinction allowed the study to separate survival from osteogenic maturation. The artificial intelligence output was reviewed at specimen level and not only at image-patch level. Specimen-level averaging was used for statistical comparison so that multiple images from the same disc did not artificially inflate the sample size.

Results:

High-glucose exposure significantly reduced cell viability, ALP activity and mineralized area in all surface categories. The negative effect was most pronounced on machined surfaces. Hydrophilic surfaces showed superior cell spreading and mineralization under both normal and high-glucose conditions. Pull-out resistance was also higher for hydrophilic and sandblasted acid-etched surfaces than for machined surfaces. The machine-learning classifier identified high-glucose exposure, mineralized area and wettability as the strongest predictors of impaired osseointegration response. High-glucose and advanced glycation conditions reduced cell spreading more markedly on machined surfaces than on hydrophilic micro-rough surfaces. The difference was visible by 24 hours and became more pronounced at the mineralization stage. The artificial intelligence segmentation model identified mineralized area and wettability category as leading predictors of favorable simulated osseointegration. Agreement with manual image assessment was strongest for mineralization and moderate for early cell-spreading morphology. The reduction in mineralized area was more pronounced when high glucose was combined with glycation stimulation, showing that a combined diabetic-like stressor produced a stronger inhibitory effect than glucose elevation alone. Cell viability and mineralization did not decline in exactly the same proportion. Some specimens retained moderate viability but showed marked reduction in mineralized area, indicating that high-glucose stress affected differentiation as well as survival. Baseline surface characteristics for the experimental groups are summarized in **Table 1**. Cellular viability, alkaline phosphatase activity and mineralized-area findings are presented in **Table 2**. Mechanical pull-out resistance and AI-based osseointegration-response outcomes are shown in **Table 3**.

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Table 1: Experimental groups and baseline surface characteristics

Group	Surface	Glucose condition	Water contact angle (°)	Ra roughness (μm)
M-NG	Machined	5.5 mM glucose	78.4 ± 6.2	0.42 ± 0.08
M-HG	Machined	25 mM glucose + AGE	79.1 ± 6.7	0.43 ± 0.07
SLA-NG	SLA	5.5 mM glucose	54.8 ± 5.9	1.56 ± 0.21
SLA-HG	SLA	25 mM glucose + AGE	55.2 ± 6.1	1.58 ± 0.24
H-NG	Hydrophilic SLA	5.5 mM glucose	18.6 ± 3.7	1.61 ± 0.22
H-HG	Hydrophilic SLA	25 mM glucose + AGE	19.4 ± 4.1	1.63 ± 0.23

Table 2: Cellular markers of simulated osseointegration

Group	Cell viability (%)	ALP activity (U/mg protein)	Mineralized area (%)	p value
M-NG	88.5 ± 7.8	18.4 ± 3.2	24.7 ± 5.1	<0.001
M-HG	64.2 ± 7.5	10.6 ± 2.8	13.1 ± 4.6	
SLA-NG	96.2 ± 7.1	25.8 ± 4.1	36.9 ± 6.4	
SLA-HG	75.5 ± 8.4	17.9 ± 3.6	24.5 ± 5.2	
H-NG	103.4 ± 8.6	31.2 ± 4.7	44.8 ± 7.2	
H-HG	84.7 ± 8.9	23.6 ± 4.0	33.5 ± 6.1	

Table 3: Mechanical and AI-based osseointegration-response outcomes

Group	Pull-out resistance (N)	Favorable response n (%)	AI probability score	p value
M-NG	214.6 ± 36.7	10 (62.5)	0.61 ± 0.15	<0.001
M-HG	151.8 ± 31.2	4 (25.0)	0.36 ± 0.14	
SLA-NG	298.4 ± 42.5	14 (87.5)	0.78 ± 0.11	
SLA-HG	226.3 ± 38.9	9 (56.3)	0.57 ± 0.16	
H-NG	336.1 ± 46.8	15 (93.8)	0.85 ± 0.10	
H-HG	271.5 ± 41.7	12 (75.0)	0.72 ± 0.13	

Discussion:

The study showed that diabetic-condition simulation significantly reduced osteoblast attachment, alkaline phosphatase activity and mineralized matrix formation on titanium surfaces. Bioactive-coated specimens retained comparatively better biological performance than machined surfaces under high-glucose stress **[9]**. These findings are consistent with the biological expectation that hyperglycemic environments disturb osteoblast differentiation, increase oxidative stress and alter extracellular matrix maturation. The implant surface can support attachment, but it cannot fully overcome an unfavorable metabolic microenvironment **[10]**. The greater resilience of bioactive-coated discs may be related to improved wettability and surface chemistry that supports protein adsorption and early cell spreading. Under compromised conditions, such surface advantages may become more important than under normal culture conditions **[11]**. Artificial intelligence-assisted image analysis showed strong agreement with manual evaluation and provided additional measures of cell spreading and mineralization density. This suggests that digital segmentation can reduce observer variability and capture spatial features that are not represented by bulk biochemical assays **[12]**. The findings should be interpreted cautiously because *in vitro* diabetic simulation does not reproduce immune cells, vascular supply, mechanical loading, medication effects, or systemic metabolic fluctuation. Implant healing in patients is more complex than osteoblast behavior on a disc surface. Even with these limitations, the work supports the concept that glycemic stress can influence the earliest implant-surface biological events. It also suggests that surface selection may be particularly relevant in medically compromised situations where healing margins are narrow. Future studies should incorporate macrophage-osteoblast co-culture, dynamic glucose fluctuation, inflammatory cytokines and animal validation. External testing of artificial intelligence image tools across microscopes and staining protocols will also be needed before routine laboratory adoption. The results suggest that a favorable implant surface can moderate, but not completely neutralize, the adverse influence of diabetic-like culture conditions. This distinction is important because implant success in diabetes depends on both local surface design and systemic biological control. The hydrophilic surface advantage observed in this experiment is compatible with the idea that initial wetting and protein distribution influence cell attachment. Under high-glucose stress, any improvement in early spreading may help maintain later alkaline phosphatase activity and mineral nodule formation. Artificial intelligence image analysis may be particularly useful in this field because cellular responses are spatially heterogeneous. Two specimens can have similar biochemical values but different distribution of cells and mineral deposits and spatial distribution may influence true interface maturation. The distinction between high glucose alone and high glucose with glycation stress is important because diabetic complications are not caused by glucose concentration only. Protein modification and inflammatory signaling also contribute to impaired tissue repair. The findings suggest that hydrophilic micro-rough surfaces may be useful in compromised healing, but they should not be seen as a substitute for medical stabilization. Local surface advantages are most likely to succeed when systemic conditions are also controlled. External validation is essential because image segmentation can be influenced by microscope type, staining intensity and culture density. A model trained in one laboratory may require recalibration before being used elsewhere, especially when the visual appearance of mineralization differs. This separation between viability and mineralization is important. A cell may remain alive but function poorly and implant integration depends on matrix formation rather than survival alone. The

artificial intelligence model helped visualize this distinction by identifying regions with spread cells but limited mineral deposition. Such spatial interpretation can complement biochemical assays that average the entire specimen surface. A future model could integrate surface roughness maps with biological images. This would allow investigators to determine whether certain microtopographic regions are more resistant to diabetic-like stress than others. The interaction between surface and medium was statistically significant, confirming that the effect of diabetic simulation depended on implant surface characteristics. This interaction is clinically relevant because surface choice may matter more in compromised healing than in ideal biological conditions. The laboratory model also highlights why implant planning in diabetic patients should include both medical and local factors. Even when an implant surface is designed for rapid integration, a compromised cellular environment can reduce the expected biological response. Surface wettability emerged as an important contributor in the artificial intelligence analysis, but it should be interpreted alongside roughness and chemistry. A hydrophilic surface may improve early protein distribution, yet mineralization still depends on the metabolic capacity of attached cells. The study design deliberately used controlled discs rather than threaded implants for cellular assessment. This improved imaging consistency and allowed reliable surface comparison, although threaded implant geometry should be tested in future experiments. For clinical translation, the outcome should not be interpreted as a direct prediction of implant failure. Instead, it indicates how diabetic-like conditions can influence early biological markers that are necessary for successful osseointegration. The combined use of biochemical assays and artificial intelligence-assisted microscopy may become useful for screening future surface modifications intended for medically compromised patients. The broader principle that osseointegration is influenced by implant-surface characteristics is well established **[13]**. These observations are consistent with established implant-surface classification concepts and recent evidence that surface modification can enhance osseointegration under diabetic conditions **[14, 15]**. Contemporary literature also emphasizes the importance of systemic diabetes management for implant outcomes **[16]**, while emerging biomaterial research suggests that multifunctional titanium-surface coatings may improve osseointegration in diabetes **[17]**.

Conclusion:

High-glucose diabetic simulation reduced osteoblast viability, alkaline phosphatase activity, mineralization and simulated implant interface strength. Hydrophilic micro-rough implant surfaces showed the most favorable biological and mechanical behavior under both normal and diabetic conditions. These findings support careful surface selection and glycemic-risk consideration during implant planning, while emphasizing the need for *in vivo* and clinical validation.

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