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Low-dose Dexamethasone Primes the IGF-1 Receptor to Enhance Osteoblast Proliferation and Mineralization: A Mechanistic Strategy for Hepatic Osteodystrophy

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ABSTRACT

Background: *Hepatic osteodystrophy (HOD) compromises skeletal integrity and fracture healing in chronic liver disease through defects in vitamin D metabolism, calcium–phosphate homeostasis, and reduced endocrine insulin-like growth factor-1 (IGF-1) output. In surgical settings, glucocorticoids are commonly used for perioperative inflammation control, yet their dose-dependent effects on osteoblasts remain controversial, particularly in the context of HOD. We investigated whether clinically relevant low-dose dexamethasone (Dex) enhances osteoblast proliferation and matrix mineralization by upregulating the insulin-like growth factor-1 receptor (IGF-1R), thereby potentially enhancing cellular responsiveness to limited systemic or local IGF-1.*

Methods: *Human (hFOB1.19) and murine (7F2) osteoblasts were treated with calcitriol and Dex across a broad concentration range. Cell viability (MTT), proliferation markers (Ki-67, PCNA), receptor signaling (vitamin D receptor [VDR], glucocorticoid receptor [GR]/phosphorylated GR [p-GR], IGF-1R), osteogenic effectors (type I collagen, osteocalcin), and Alizarin Red S–detectable mineralization were quantified by qPCR, immunoblotting, and histochemical staining.*

Results: *Calcitriol increased osteoblast viability, whereas Dex exhibited a biphasic response: 1–10 nM enhanced viability, whereas ≥100 nM abrogated the low-dose increase and returned values toward baseline in both hFOB1.19 and 7F2 cells. Within this low-dose window, Dex increased Ki-67 and PCNA and—most notably—upregulated IGF-1R mRNA and protein after 48 h. Dex also modulated VDR and GR signaling, increased type I collagen and osteocalcin expression, and accelerated mineral deposition over 7–28 days, with mineralization patterns comparable to calcitriol.*

Conclusions: *Low-dose Dex reprograms osteoblasts toward proliferation and mineralization and elevates IGF-1R abundance, plausibly amplifying responsiveness to endocrine and paracrine IGF-1. These data support a testable perioperative strategy for HOD: vitamin D_3 repletion paired with carefully titrated low-dose Dex to potentially enhance osteoblast IGF-1 responsiveness via IGF-1R upregulation while minimizing glucocorticoid toxicity.*

Keywords

IGF-1 receptor, Hepatic osteodystrophy, Dexamethasone, Osteoblast.

Introduction

Hepatic osteodystrophy (HOD) is a frequent but under-recognised complication of chronic liver disease, characterised by osteopenia, osteoporosis, and delayed fracture healing. The liver–bone axis is disrupted by alterations in calcium–phosphate balance, vitamin D metabolism, and parathyroid hormone dynamics, ultimately compromising bone remodelling and structural integrity [1]. Clinically, these abnormalities translate into increased fracture risk, impaired implant integration, and prolonged functional recovery after orthopaedic or trauma surgery in patients with cirrhosis or chronic hepatopathy.

Classically, the somatomedin hypothesis attributes much of HOD to impaired growth hormone (GH)–IGF-1 signalling. The liver is the major source of circulating IGF-1, a key anabolic mediator for bone formation that supports osteoblast proliferation, differentiation, and matrix production [2-8]. In chronic liver disease, hepatic IGF-1 synthesis declines, serum IGF-1 levels fall, and bone mass and strength are reduced [4]. However, simple replacement of vitamin D or optimisation of calcium intake does not fully restore skeletal health in HOD, suggesting that endocrine IGF-1 deficiency is only part of the problem [1,9-17].

At the cellular level, osteoblast responsiveness to IGF-1 depends not only on hormone concentration but also on IGF-1R abundance and downstream signalling competence. Yet, how osteoblasts adapt their IGF-1R expression under conditions of chronic IGF-1 scarcity remains poorly understood. In addition, glucocorticoids—routinely used perioperatively for anti-inflammatory and antiemetic purposes—have well-known catabolic effects on bone at high doses and with chronic exposure [18]. Paradoxically, glucocorticoids can also exert context- and dose-dependent trophic effects on osteoblasts, particularly when combined with osteogenic stimuli such as vitamin D_3 [19-22].

We therefore hypothesised that clinically relevant low-dose dexamethasone (Dex) might increase osteoblast IGF-1R expression and proliferation, thereby sensitising osteoblasts to limited IGF-1 and cooperating with vitamin D_3 to enhance matrix mineralisation. Using human (hFOB1.19) and murine (7F2) osteoblast models, we examined Dex dose–response relationships for cell viability, proliferation markers, VDR/GR signalling, IGF-1R expression, osteogenic gene expression, and functional mineral deposition, with the aim of defining a mechanistic rationale for a perioperative strategy in HOD.

Materials and Methods

Human fetal osteoblasts (hFOB1.19) and murine osteoblast-like cells (7F2) were cultured under standard osteogenic conditions as previously described for vitamin D–regulated osteoblast differentiation [19-22]. Cells were maintained in appropriate media supplemented with fetal bovine serum, antibiotics, and, where indicated, β-glycerophosphate and ascorbate to support matrix mineralisation.

Calcitriol ($1,25(OH)_2D_3$) and dexamethasone (Dex) were dissolved in suitable vehicles and diluted into culture media immediately before use. For viability and mechanistic studies, cells were treated with calcitriol or a range of Dex concentrations for 48 h. Dex doses included a "low-dose window" (1–10 nM) and higher concentrations up to 1000 nM to capture potential biphasic effects [18]. Vehicle-treated cells served as controls.

Cell viability was assessed after 48 h of treatment using the MTT assay. Absorbance values were normalised to vehicle controls and expressed as mean ± SEM. Experiments were performed in triplicate wells and repeated at least three times independently.

Total RNA was isolated from treated osteoblasts, and cDNA was synthesised using standard reverse transcription protocols. Quantitative PCR (qPCR) was performed to quantify transcripts encoding proliferation markers (Ki-67, PCNA), receptors (VDR, GR, IGF-1R), and osteogenic effectors (type I collagen, osteocalcin). Expression levels were normalised to housekeeping genes and reported as fold-change relative to controls.

Protein extracts were prepared from treated cells, separated by SDS-PAGE, and transferred to membranes for immunoblotting. Primary antibodies against Ki-67, PCNA, VDR, GR, p-GR, IGF-1R, type I collagen, osteocalcin, and GAPDH (loading control) were used. Bands were visualised with appropriate secondary antibodies and detection reagents, and densitometry was performed to quantify relative protein levels.

To assess functional mineralisation, osteoblasts were cultured under osteogenic conditions with calcitriol or Dex for 7–28 days. At each time point, cells were fixed and stained with Alizarin Red S to visualise and semi-quantify calcium deposition. Representative images were acquired at 40× magnification, and staining intensity was evaluated qualitatively across conditions.

Data are presented as mean ± SEM. Group comparisons were performed using one-way ANOVA with appropriate post-hoc tests (Fisher's LSD or Bonferroni) as indicated. A p value < 0.05 was considered statistically significant.

Results

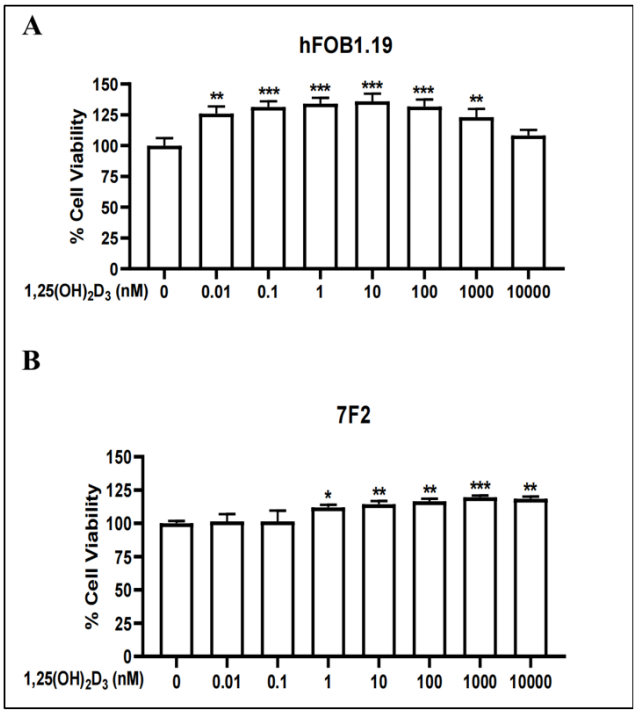

Figure 1: $1,25(OH)_2D_3$ enhances osteoblast viability in human hFOB1.19 and murine 7F2 cells.

A) hFOB1.19 and (B) 7F2 cells were treated with increasing concentrations of 1,25(OH)$_2$D$_3$ (0–10,000 nM) for 48 h, and cell viability was assessed by MTT assay. Data are expressed as percentage of vehicle-treated controls (mean ± SEM). 1,25(OH)$_2$D$_3$ significantly increased cell viability over a wide concentration range without evident toxicity at the highest dose.

Treatment with 1,25(OH)$_2$D$_3$ for 48 h significantly increased osteoblast viability in both hFOB1.19 and 7F2 cells over a broad concentration range (0.01–10,000 nM). In hFOB1.19 cells, 0.01–1 nM 1,25(OH)$_2$D$_3$ elevated viability to approximately 120–135% of control and remained above baseline up to 1,000 nM, with no cytotoxicity observed even at 10,000 nM (Figure 1A). 7F2 cells showed a similar but slightly blunted response, with significant increases in viability at 1–10,000 nM (Figure 1B).

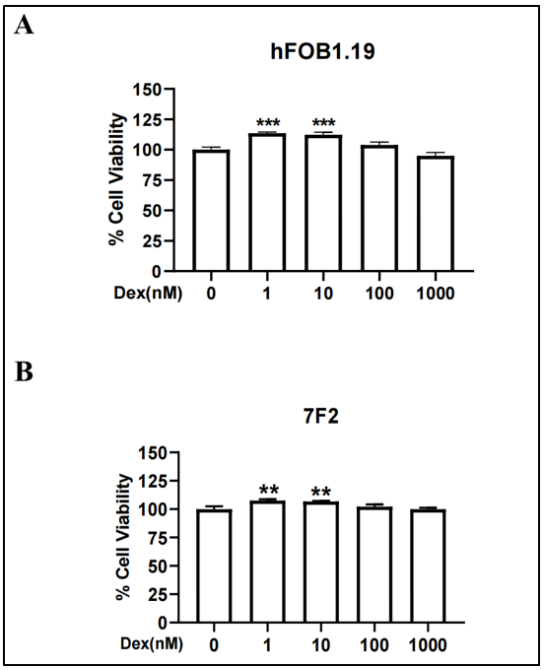

Figure 2: Low-dose dexamethasone increases osteoblast viability, whereas higher doses abrogate this effect.

(A) hFOB1.19 and (B) 7F2 osteoblasts were treated with dexamethasone (Dex; 0–1000 nM) for 48 h, and cell viability was assessed by MTT assay. Data are expressed as percentage of vehicle-treated controls (mean ± SEM). Low-dose Dex (1–10 nM) significantly increased cell viability in both cell lines, while higher concentrations (100–1000 nM) failed to further enhance viability and tended to return values toward baseline, indicating a biphasic response. Statistical analysis was performed by one-way ANOVA followed by Fisher's LSD (*p < 0.05, **p < 0.01, ***p < 0.001 vs. control).

Low-dose Dex promoted osteoblast proliferation, as reflected by increased expression of cell-cycle markers. In hFOB1.19 cells, Dex at 10 nM significantly upregulated Ki-67 and PCNA mRNA compared with vehicle, whereas 1 nM produced a modest, non-significant trend (Figure 3A,B). Western blotting confirmed higher Ki-67 and PCNA protein levels after 1–10 nM Dex, with densitometric analysis showing a clear increase in PCNA and a variable but overall upward shift in Ki-67 (Figure 3C–E). A similar pattern was observed in 7F2 cells: 10 nM Dex significantly elevated Ki-67 transcripts, and both 1 and 10 nM Dex increased Pcna mRNA (Figure 3F,G). Correspondingly, Ki-67 and PCNA protein abundance rose in a dose-dependent manner, with densitometry revealing up to ~4–6-fold increases over control at 10 nM Dex (Figure 3H–J). Together, these data indicate that low-dose Dex (1–10 nM) drives a pro-proliferative response in both human and murine osteoblasts.

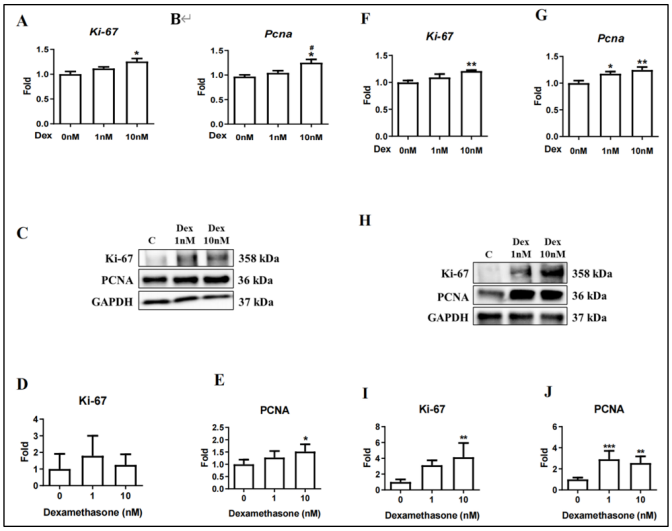

Figure 3: Low-dose dexamethasone increases proliferation markers in human and murine osteoblasts.

(A,B) hFOB1.19 cells were treated with Dex (0, 1, or 10 nM) for 48 h. Ki-67 and PCNA mRNA levels were quantified by qPCR and expressed as fold-change relative to vehicle-treated controls. Dex at 10 nM significantly increased both Ki-67 and PCNA transcripts.

(C) Representative Western blots showing Ki-67 and PCNA protein expression in hFOB1.19 cells after treatment with 1 or 10 nM Dex; GAPDH served as a loading control.

(D,E) Densitometric analysis of Ki-67 and PCNA protein levels in hFOB1.19 cells, normalised to GAPDH and expressed as fold-change vs. control. Low-dose Dex produced a consistent increase in PCNA protein and a variable upward trend in Ki-67.

(F,G) 7F2 cells treated with Dex (0, 1, or 10 nM) for 48 h showed significantly higher Ki-67 and Pcna mRNA levels, particularly at 10 nM Dex.

(H) Representative Western blots of Ki-67 and PCNA protein in 7F2 cells following Dex treatment; GAPDH is shown as a loading control.

(I,J) Densitometric quantification of Ki-67 and PCNA protein expression in 7F2 cells, normalised to GAPDH. Low-dose Dex markedly increased both markers, with the largest effects observed at 10 nM. Data are presented as mean ± SEM; one-way ANOVA with Bonferroni post-hoc test was used for multiple comparisons (*p < 0.05, **p < 0.01, ***p < 0.001 vs. 0 nM Dex).

Low-dose Dex induced modest but cell type–dependent changes in

VDR and GR signaling. In hFOB1.19 cells, Dex (1–10 nM, 48 h) did not significantly alter Vitamin D receptor or GR mRNA levels (Figure 4A, B). Western blot analysis showed only minor, non-significant changes in VDR protein abundance and in the p-GR/GR ratio (Figure 4C–E), suggesting limited remodeling of nuclear receptor signaling at this dose range in human osteoblasts.

In contrast, 7F2 cells displayed a clearer response. Dex at 10 nM significantly increased GR mRNA, whereas VDR transcripts showed a mild upward trend (Figure 4F,G). At the protein level, 10 nM Dex markedly enhanced VDR expression and increased the p-GR/GR ratio (Figure 4H–J), consistent with activation of GR and upregulation of VDR in murine osteoblasts. These findings indicate that low-dose Dex can reconfigure VDR/GR signaling in a species-dependent manner, providing a receptor context that may favor subsequent osteogenic responses.

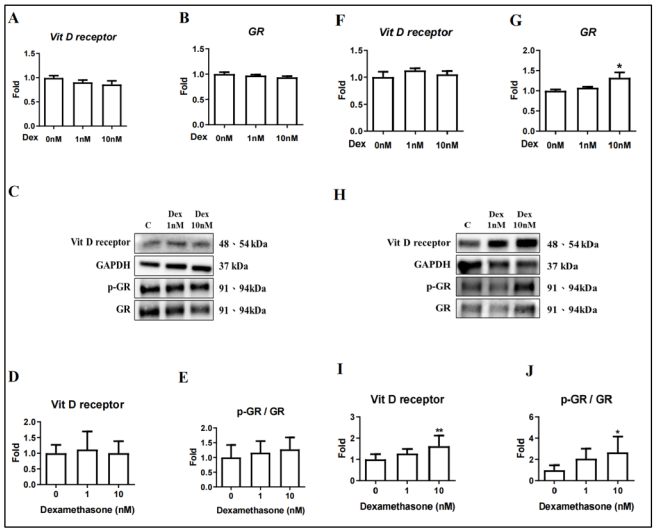

Figure 4: Effects of low-dose dexamethasone on vitamin D receptor (VDR) and glucocorticoid receptor (GR) signalling in osteoblasts.

(A,B) hFOB1.19 cells were treated with Dex (0, 1, or 10 nM) for 48 h. Vitamin D receptor and GR mRNA levels were quantified by qPCR and expressed as fold-change relative to vehicle-treated controls. No significant changes were observed.

(C) Representative Western blots of VDR, phosphorylated GR (p-GR), total GR, and GAPDH (loading control) in hFOB1.19 cells after Dex treatment.

(D,E) Densitometric analysis of VDR protein and the p-GR/GR ratio in hFOB1.19 cells, normalised to GAPDH or total GR and expressed as fold-change vs. control.

(F,G) 7F2 cells treated with Dex (0, 1, or 10 nM) for 48 h showed a significant increase in GR mRNA at 10 nM Dex, with a modest trend toward higher VDR transcripts.

(H) Representative Western blots of VDR, p-GR, GR, and GAPDH in 7F2 cells.

(I,J) Densitometric quantification of VDR protein and the p-GR/GR ratio in 7F2 cells, demonstrating significant increases at 10 nM Dex. Data are presented as mean ± SEM; one-way ANOVA with Bonferroni post-hoc test was used for multiple comparisons (*p < 0.05, **p < 0.01 vs. 0 nM Dex)

Low-dose Dex robustly upregulated IGF-1 receptor expression in both human and murine osteoblasts. In hFOB1.19 cells, 10 nM Dex significantly increased IGF-1R mRNA to ~1.3–1.4-fold of control, whereas 1 nM produced a modest, non-significant rise (Figure 5A). 7F2 cells showed a similar dose-dependent pattern, with a significant increase in Igf1r transcripts at 10 nM Dex (Figure 5B). Western blotting confirmed higher IGF-1R protein abundance after low-dose Dex in both cell types (Figure 5C,D). Densitometric analysis revealed that 10 nM Dex elevated IGF-1R protein to approximately 3–4-fold in hFOB1.19 cells and about 2-fold in 7F2 cells relative to untreated controls (Figure 5E,F). These findings indicate that low-dose Dex substantially enhances IGF-1R availability on osteoblasts, thereby potentially increasing the capacity for IGF-1 signalling under low-ligand conditions.

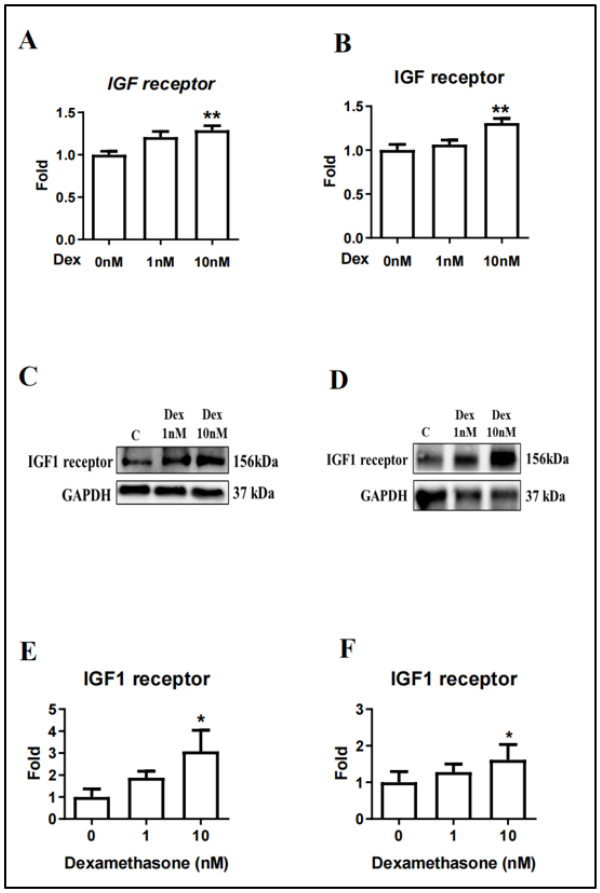

Figure 5: Low-dose dexamethasone upregulates IGF-1 receptor expression in osteoblasts.

(A, B) hFOB1.19 (A) and 7F2 (B) cells were treated with Dex (0, 1, or 10 nM) for 48 h. IGF-1 receptor (IGF1R) mRNA levels were quantified by qPCR and expressed as fold-change relative to vehicle-treated controls. Dex at 10 nM significantly increased IGF1R transcripts in both cell lines. (C, D) Representative Western blots showing IGF-1R protein expression in hFOB1.19 (C) and 7F2 (D) cells after treatment with 1 or 10 nM Dex;

GAPDH served as a loading control.
(E, F) Densitometric analysis of IGF-1R protein levels in hFOB1.19 (E) and 7F2 (F) cells, normalised to GAPDH and expressed as fold-change vs. control. Low-dose Dex, particularly at 10 nM, induced a marked increase in IGF-1R protein abundance. Data are presented as mean ± SEM; one-way ANOVA with Bonferroni post-hoc test was used for multiple comparisons (*p < 0.05, **p < 0.01 vs. 0 nM Dex).

This increase occurred in the absence of exogenous IGF-1, highlighting a receptor-centric adaptation that could compensate for reduced endocrine IGF-1 in HOD. Low-dose Dex also enhanced osteogenic matrix protein expression. In hFOB1.19 cells, Dex at 10 nM modestly increased Collagen I mRNA and significantly upregulated osteocalcin transcripts compared with control (Figure 6A,B). Western blotting revealed higher Collagen I and osteocalcin protein levels after 1–10 nM Dex, with densitometric analysis showing roughly 2–3-fold increases in Collagen I and osteocalcin at 10 nM (Figure 6C–E). In 7F2 cells, Dex had little effect on Collagen I mRNA but markedly increased osteocalcin transcripts, with ~10–15-fold induction at 10 nM (Figure 6F,G). At the protein level, both Collagen I and osteocalcin were elevated following low-dose Dex, and densitometry confirmed a significant rise in Collagen I at 10 nM (Figure 6H–J). Together, these data indicate that low-dose Dex promotes an osteogenic shift in matrix production, particularly by boosting Collagen I and osteocalcin expression.

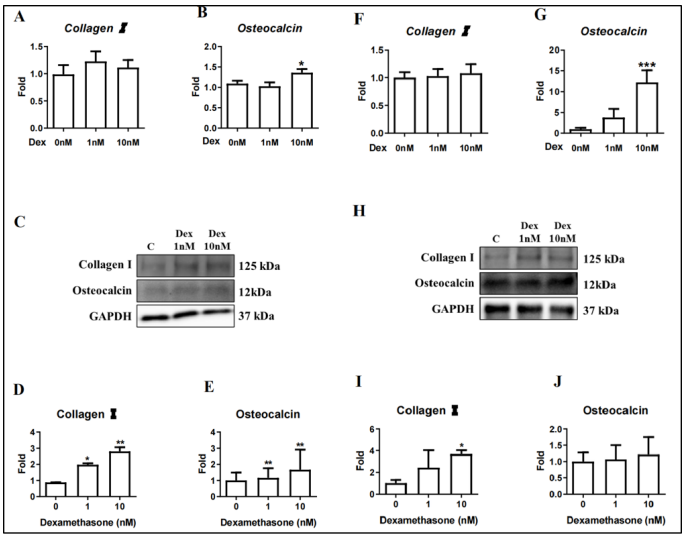

Figure 6: Low-dose dexamethasone promotes osteogenic effector expression in osteoblasts.

(A, B) hFOB1.19 cells were treated with Dex (0, 1, or 10 nM) for 48 h. Collagen I and osteocalcin mRNA levels were quantified by qPCR and expressed as fold-change relative to vehicle-treated controls. Dex at 10 nM significantly increased osteocalcin transcripts, with a trend toward higher Collagen I.
(C) Representative Western blots showing Collagen I and osteocalcin protein expression in hFOB1.19 cells after treatment with 1 or 10 nM Dex; GAPDH served as a loading control.
(D, E) Densitometric analysis of Collagen I and osteocalcin protein levels in hFOB1.19 cells, normalised to GAPDH and expressed as fold-change vs. control, demonstrating ~2–3-fold induction at 10 nM Dex.
(F, G) 7F2 cells treated with Dex (0, 1, or 10 nM) for 48 h showed minimal changes in Collagen I mRNA but a robust, dose-dependent increase in osteocalcin transcripts, particularly at 10 nM.
(H) Representative Western blots of Collagen I, osteocalcin, and GAPDH in 7F2 cells following Dex treatment.
(I, J) Densitometric quantification of Collagen I and osteocalcin protein levels in 7F2 cells, normalized to GAPDH. Low-dose Dex significantly increased Collagen I at 10 nM, with a consistent upward trend in osteocalcin. Data are presented as mean ± SEM; one-way ANOVA with Bonferroni post-hoc test (*p < 0.05, **p < 0.01, ***p < 0.001 vs. 0 nM Dex).

Vitamin D_3 promoted time-dependent matrix mineralization in both osteoblast models. In hFOB1.19 cells, Alizarin Red S staining revealed few mineralized nodules at day 7 under osteogenic conditions without Vitamin D_3, with a gradual increase in staining intensity by days 14 and 21 (Figure 7A). Supplementation with 10 or 100 nM Vitamin D_3 accelerated this process: mineralized foci appeared earlier and became denser at days 14 and 21 compared with vehicle, before plateauing or slightly declining by day 28. A similar pattern was observed in 7F2 cells (Figure 7B), in which Vitamin D_3 enhanced the extent and density of mineral deposition across the 7–28-day time course. These findings confirm Vitamin D_3 as a positive control for osteoblast mineralization in our culture system.

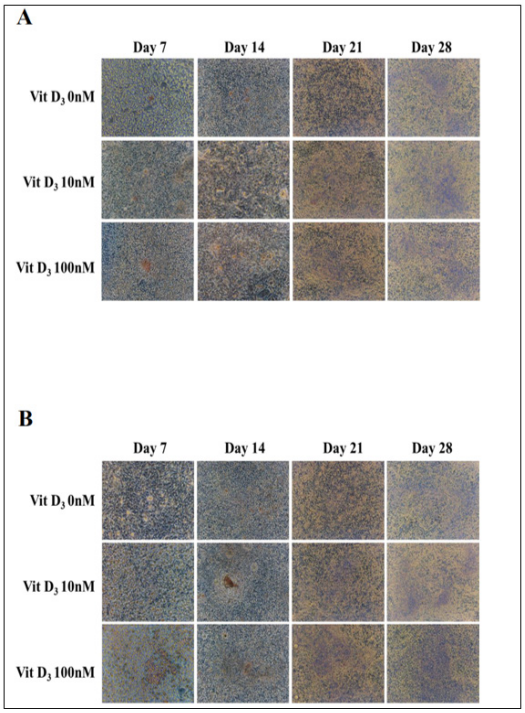

Figure 7: Vitamin D_3 enhances time-dependent matrix mineralization in hFOB1.19 and 7F2 osteoblasts.
(A) hFOB1.19 and (B) 7F2 cells were cultured under osteogenic

conditions (β-glycerophosphate + ascorbate) and treated with 0, 10, or 100 nM Vitamin D_3 for 7–28 days. At the indicated time points, cultures were fixed and stained with Alizarin Red S to visualise calcium deposition. Representative phase-contrast images (40×) show progressive mineral nodule formation over time, with more extensive and earlier mineralisation in Vitamin D_3-treated cultures compared with vehicle.

Consistent with its pro-proliferative and osteogenic effects, low-dose Dex also enhanced matrix mineralization over time. In hFOB1.19 cells cultured under osteogenic conditions, Alizarin Red S staining showed only sparse mineralized nodules at day 7 in the absence of Dex, with gradual accumulation by days 14–21 (Figure 8A). Treatment with 1 or 10 nM Dex led to earlier and more intense mineral deposition, with prominent Alizarin-positive areas already visible at day 14 and dense, confluent mineralized regions at day 21 compared with controls. By day 28, mineralization in all groups approached a plateau. A similar time-dependent pattern was observed in 7F2 cells (Figure 8B): low-dose Dex (1–10 nM) accelerated the appearance and increased the density of mineralized nodules relative to Dex-free cultures. Together with the Vitamin D_3 data, these findings indicate that low-dose Dex is sufficient to drive functional mineralization in both osteoblast models. Together, these findings demonstrate that low-dose Dex not only drives osteoblast proliferation and osteogenic gene expression but also translates into increased matrix mineralization over time.

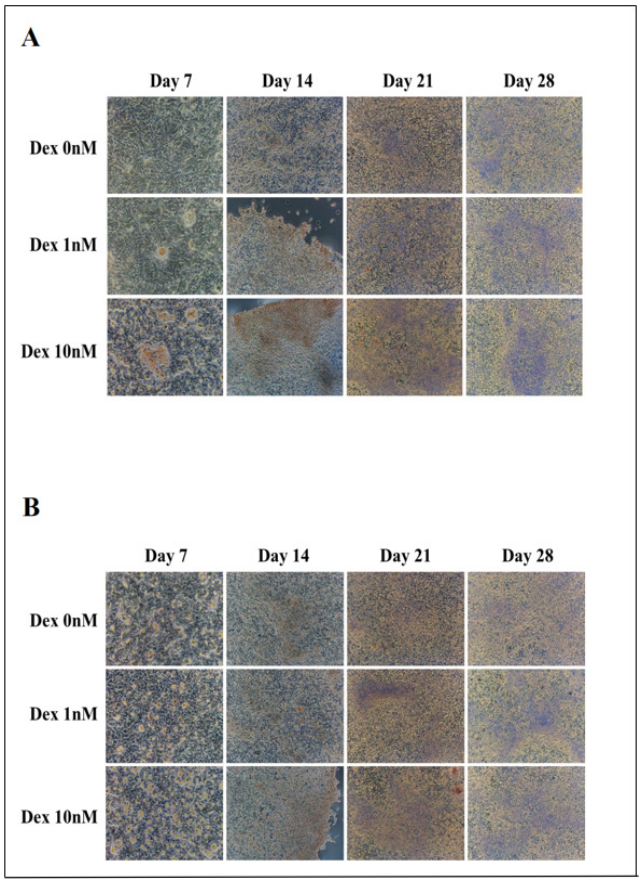

Figure 8: Low-dose dexamethasone accelerates matrix mineralization in hFOB1.19 and 7F2 osteoblasts. (A) hFOB1.19 and (B) 7F2 cells were cultured under osteogenic conditions (β-glycerophosphate + ascorbate) and treated with dexamethasone (Dex; 0, 1, or 10 nM) for 7–28 days. At the indicated time points, cultures were fixed and stained with Alizarin Red S to visualize calcium deposition. Representative phase-contrast images (40×) demonstrate progressive mineral nodule formation over time, with earlier onset and greater density of Alizarin-positive areas in Dex-treated cultures compared with Dex-free controls.

Discussion

This study demonstrates that clinically relevant low-dose Dex can reprogramme osteoblasts toward an anabolic phenotype by expanding cell viability, promoting proliferation, rewiring VDR/GR signalling, and upregulating IGF-1R, culminating in enhanced matrix mineralisation. These observations offer a mechanistic counterpoint to the conventional view of glucocorticoids as purely deleterious for bone and suggest that dose and context critically determine their skeletal effects [18].

Traditional models of HOD emphasise diminished hepatic IGF-1 synthesis and reduced circulating IGF-1 as primary drivers of impaired bone formation [2-8]. Our data refine this paradigm by highlighting osteoblast IGF-1R abundance as an additional determinant of effective IGF-1 signalling. In these *in vitro* osteoblast models (which do not fully recapitulate the endocrine milieu of chronic liver disease), low-dose Dex increased IGF-1R expression without exogenous IGF-1, suggesting that osteoblasts can "prepare" their receptor machinery to extract maximal signalling from a limited hormone pool. In this framework, HOD reflects not only a failure of hormone supply but also a potential failure of receptor preparedness at the cellular level [1-4].

The observed modulation of VDR and GR, including changes in the p-GR/GR ratio, points to complex cross-talk between glucocorticoid and vitamin D pathways in osteoblasts [19-22]. Rather than uniformly suppressing bone formation, low-dose Dex appears to act as a signal that, in the right concentration range and osteogenic environment, enhances proliferation and primes osteogenic gene expression. This aligns with reports that vitamin D_3 analogues and BMPs can synergistically promote osteoblast differentiation and matrix production [19-22], and it suggests that timing and dosing of Dex relative to vitamin D_3 may be critical for achieving net anabolic effects.

For patients with HOD undergoing fracture fixation or orthopaedic surgery, these findings suggest a testable perioperative strategy. Although we did not directly test combinatorial Dex plus vitamin D_3 regimens in this study, our data provide a mechanistic rationale to evaluate such pairing in translational models and perioperative protocols. Vitamin D_3 repletion, already recommended in many chronically ill populations to support bone health [13-17], could be paired with a short-course, carefully titrated low-dose Dex regimen designed to transiently increase osteoblast IGF-1R abundance and osteogenic capacity. Such an approach may synergise with early mobilisation and mechanical loading to improve fracture

healing, implant integration, and functional recovery in cirrhotic or hepatopathic patients [1,4,16,17]. Importantly, the Dex doses identified here are substantially lower than those associated with classical glucocorticoid-induced osteoporosis, offering a potential therapeutic window between toxicity and benefit [18].

This study is limited by its in vitro design and reliance on two osteoblast models. We did not directly test the effects of low-dose Dex on fracture healing or bone strength *in vivo*, nor did we perform rescue experiments in animal models of HOD to link IGF-1R upregulation causally to improved skeletal outcomes. In addition, we did not systematically explore the interaction between exogenous IGF-1 and Dex-induced IGF-1R upregulation. Future work should extend these findings to in vivo models of HOD, incorporate IGF-1 supplementation or blockade, and assess biomechanical properties of bone healing under clinically relevant perioperative regimens.

Conclusion

Low-dose Dex expands osteoblasts' anabolic capacity by upregulating IGF-1R, increasing proliferation and osteogenic gene expression, and enhancing matrix mineralisation. In the context of hepatic osteodystrophy, where endocrine IGF-1 is reduced and conventional vitamin D_3 supplementation is often insufficient, a carefully titrated short-course Dex regimen—paired with vitamin D_3—merits clinical evaluation as an adjunct to improve skeletal outcomes while avoiding glucocorticoid-induced osteoporosis [1-4,13-20].

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