Osteogenic Effects of GLP-1RA in the presence of LDL and Oxidized LDL

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INTRODUCTION: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an emerging class of medications used in the management of type 2 diabetes and obesity; conditions often linked to poor bone health.[1] Previous studies suggest that GLP-1RAs may also promote bone formation by enhancing osteoblast activity and increasing the expression of osteogenic markers such as osteocalcin and RUNX2.[2,3] While in-vitro studies support an osteogenic role for GLP-1RAs, clinical trials have yielded inconsistent results regarding fracture risk reduction.[1,4,5] One potential explanation is that individual differences in lipid metabolism, particularly LDL and ox-LDL levels, may influence skeletal outcomes.[5,6] GLP-1RAs have been associated with reductions in circulating low-density lipoprotein (LDL) levels,[7] but their impact on oxidized LDL (ox-LDL), a key mediator of impaired bone metabolism and the development of osteoporosis, remains poorly understood. This study aims to determine whether GLP-1RAs can counteract the detrimental effects of LDL and ox-LDL on osteoblasts, to clarify their role in bone health and inform therapeutic strategies for patients with metabolic and skeletal disorders.

METHODS: We conducted an in-vitro study using human osteoblasts (SAOS-2) to evaluate the osteogenic effects of a GLP-1 receptor agonist (GLP-1RA) in the presence of low-density lipoprotein (LDL) and oxidized LDL (ox-LDL). Cells were cultured under eight experimental conditions in either normal (N) or osteogenic differentiating medium (OS): control (no treatment), GLP-1RA alone, GLP-1RA + LDL (50 mg/dL), and GLP-1RA + ox-LDL (50 mg/dL). Osteogenic responses were assessed through real time quantitative PCR (RT-qPCR) at 7 and 14 days for markers of osteogenic differentiation (COL1A1, RUNX-2, OCN), inflammation (IL-6), and lipid metabolism (PPARγ, NKX1-2, LPL). Alkaline phosphatase (ALP) activity was also measured at days 3, 5, and 7, and mineralization was quantified by Alizarin Red staining at 14 and 21 days. Statistical differences between groups were determined by Student's t-test with statistical significance set at $p < 0.05$.

RESULTS SECTION: LDL suppressed ALP activity compared with control, with the greatest reduction at day 3, while ox-LDL resulted in no changes when compared to the control. Addition of GLP1-RA increased ALP at every time point relative to the corresponding lipid condition without GLP1-RA. By day 7, cultures treated with GLP1-RA + LDL, or GLP1-RA + ox-LDL reached the highest ALP values, with no difference with GLP1-RA alone (Figure 1). Figure 2 demonstrates that under growth medium (N), GLP-1RA reduced expression of collagen, type I, alpha 1, a (COL1A1) and Runt-related transcription factor 2 (RUNX-2) compared to control, with no change in lipoprotein lipase (LPL). In the presence of LDL or ox-LDL, GLP-1RA did not further suppress these markers; LDL co-exposure restored RUNX-2 and LPL toward baseline, whereas ox-LDL maintained lower levels. After 7 days of treatment under osteogenic conditions (OS), the control increased COL1A1 and RUNX2 as expected. GLP-1RA alone suppressed COL1A1, reduced RUNX-2, and increased LPL. Co-treatment with GLP-1RA + LDL or GLP-1RA + ox-LDL restored RUNX2, and particularly increased LPL expression beyond GLP-1RA alone and OS control (LDL > ox-LDL), while COL1A1 remained low across all conditions.

DISCUSSION: In growth medium, GLP1-RA lowered COL1A1 and RUNX-2, while in osteogenic medium, GLP1-RA continued to suppress COL1A1, and co-treatment with LDL or ox-LDL enhanced RUNX-2 and strongly increased LPL compared with GLP1-RA alone. These findings suggest that GLP1-RA, particularly in a lipid-rich environment, promotes early osteoblast programming (ALP and RUNX-2) while attenuating type I collagen transcription and engaging lipid metabolism pathways, reflected by higher LPL. Taken together, GLP1-RA improves early osteogenic activity and partially rescues lipid-induced suppression, yet it may transiently reduce collagen gene expression and shift metabolism toward increased lipolysis. This lipid-dependency may help explain the mixed skeletal outcomes reported clinically and highlights the need to account for dyslipidemia when evaluating GLP1-RA effects on bone.

SIGNIFICANCE/CLINICAL RELEVANCE: GLP-1RAs show promise in stimulating osteoblast activity, but inconsistent clinical findings on fracture risk suggest that metabolic factors such as LDL and ox-LDL may limit their bone-protective potential. This study gives new insights on whether GLP-1RA interferes with and LDL and ox-LDL, with the goal of clarifying bone–lipid–drug interactions and informing future strategies for skeletal health in patients with diabetes, obesity, and osteoporosis.

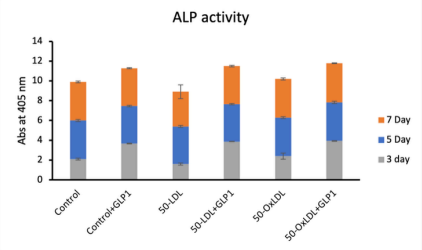

Figure 1. ALP activity level of Saos-2 cells after incubation for 3, 5, and 7 days under osteogenic differentiation medium.

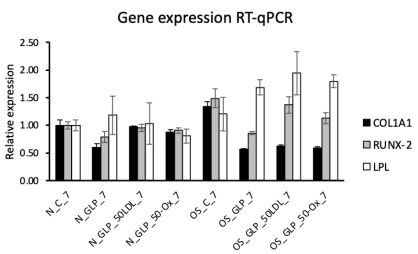

Figure 2. COL1A1, RUNX-2, and LPL transcripts expression of Saos-2 cells after incubation for 7 days under normal (N) and osteogenic differentiation (OS) medium.

REFERENCES:
[1]Al Refaie A, et al. Endocrine. 2025;89(1):30-38. [2]Xie B, et al. Front Pharmacol. 2021;12:697442. [3]Mabilleau G, et al. J Endocrinol. 2018;236(1):R29-R42. [4]Kim HJ, et al. Diabetes Metab Res Rev. 2024;40(6):e3843. [5]Alalwani YJ, et al. BMC Musculoskelet Disord. 2025;26(1):742. [6]Hachuła M, et al. Int J Mol Sci. 2024;25(3):1854. [7]Szekeres Z, Nagy A, et al. Int J Mol Sci. 2024;25(15):8214.