***Огляди літератури**, оригінальні дослідження*

DOI 10.11603/1811-2471.2026.v.i1.15703

УДК 061

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GPR133 (ADGRD1) – A POTENTIAL TARGET IN THE TREATMENT OF OSTEOPOROSIS

SUMMARY. **The aim** – to systematise data from reviews and studies devoted to the role of the adhesive G protein receptor GPR133 in the regulation of osteogenesis and its potential as a target for the treatment of osteoporosis.

Material and Methods. A literature search was conducted in the PubMed, Scopus, and Web of Science databases for the period 2014–2025 using combinations of the keywords: "GPR133", "ADGRD1", "adhesion GPCR", "G-protein coupled receptor", "osteogenesis", "osteoporosis". The analysis included 20 sources – systematic reviews, experimental studies, and patent materials that met the study criteria and contained data on the role of GPR133 or related adhesion GPCRs in the regulation of osteogenesis.

Results. Adhesion G-protein-coupled receptors GPR133/ADGRD1 due to the presence of mechanosensitive metabolotropic properties are considered as regulators of bone remodeling. The GPR133/ADGRD1 protein gene has been identified in the tibia, femur, skull, and costal cartilage. The mRNA of this gene has been identified in bone marrow mesenchymal stem cells, primary osteoblasts, osteoclasts, and bone marrow macrophages. The activity of GPR133 depends on both the presence of a ligand and mechanical stress or strain. Receptor activation is realized directly through changes in the tension of the membrane lipid bilayer or through the transmission of mechanical force due to the attachment of the receptor to the cytoskeleton or extracellular matrix. GPR133 deficiency in mice leads to a decrease in trabecular and cortical bone mass, impaired osteoblastogenesis, and compensatory activation of osteoclasts, confirming its key role in maintaining bone homeostasis. Small-molecule GPR133 agonists, such as AP503 and GL64, stimulate osteoblastogenesis, increase bone mass and bone strength, and show synergy with exercise.

Conclusions. GPR133/ADGRD1 is a proven molecular target for osteoporosis therapy: its deficiency reduces bone mass and strength due to osteoblast dysfunction. The use of selective GPR133 agonists opens up new pathogenetical directions for the treatment of osteoporosis, avoiding the potential risks inherent in traditional therapeutic regimens.

KEY WORDS: GPR133; ADGRD1; adhesion GPCR; osteogenesis; osteoblasts; osteoporosis; mechanosensitivity; receptor agonist AP503.

Introduction. The structure of modern morbidity has identified a steady increase in the frequency of osteoporosis, especially in conditions of post-menopausal estrogen deficiency, which is a factor in many changes in the female body [1]. In Ukraine, osteoporosis is a serious social problem: according to the latest data, 31–33 % of women and 23–24 % of men (every third woman and every fourth man) have this disease [2]. According to the International Osteoporosis Foundation for 2021, in Ukraine almost 7 million women in postmenopausal (almost 28%) have osteoporosis or osteopenia [3]. Osteoporosis treatments usually focus on vitamin D and/or calcium, and more specific pharmacological treatments are associated with serious side effects: estrogen therapy in postmenopausal women increases the risk of cancer and thrombosis, and parathyroid hormone therapy provides positive results only for a limited two-year period, after which its catabolic effects become apparent [4,5]. Recently developed sclerostin inhibitors cause vascular calcification, potentially increasing the risk of myocardial infarction (MI) and stroke [6].

To develop new treatments, it is necessary to understand the physiological role and mechanisms of potential targets. One promising target is the G-protein-coupled adhesion receptor GPR133, which plays a key role in the formation and maintenance of bone strength [7]. Understanding the functions of this receptor opens new perspectives for the creation of precise and effective therapeutic strategies that can not only prevent the progression of osteoporosis, but also restore the functional integrity of bone tissue.

The aim of the study was to review the literature and summarize the information over the past ten years regarding the involvement of the GPR133 receptor in osteogenesis and its role as a pharmacological target in the treatment of osteoporosis.

Material and Methods. A search was conducted in the PubMed, Scopus, and Web of Science databases among publications mainly in the last 5 years (2020–2025) using the keywords: "G-protein", "osteoporosis", "G-protein coupled receptor", "GPR133". The review includs 20 systematic reviews, experimental studies, and patents that met the criteria: the presence of an assessment of the impact of G-protein-coupled receptors on osteogenesis.

Results and Discussion. G-protein-coupled receptors (GPCRs) have traditionally been considered

ligand-dependent. However, they have recently attracted considerable attention as mechanosensitive metabotropic receptors. Due to their mechanoreception capacity, the adhesion-type G-protein-coupled receptor (aGPCR) family, namely GPR133, is considered a central link between mechanical signals and the biochemical response of the cell [8,9].

According to research results, GPR133/ADGRD1, expressed in osteoblasts, is associated with changes in bone mineral density (BMD) in humans, and its activity depends on both the presence of a ligand (PTK7) and mechanical stimuli – tension or stretching [7].

Although ionotropic receptors have traditionally been considered the main mechanosensors, recent studies have shown that individual GPCRs can also respond to mechanical stimuli, demonstrating the ability to be activated by physical forces, and not only by binding to a chemical ligand [10].

Mechanical reception of GPCRs occurs through two main types of stimuli: shear stress and cell swelling or stretching [11]. Receptor activation occurs through two key mechanisms: either directly through changes in the tension of the membrane lipid bilayer ("lipid force"), or through the transmission of mechanical force through the attachment of the receptor to the cytoskeleton or extracellular matrix ("tethering force"). Both concepts, previously proposed for ion channels, explain how external mechanical signals are translated into conformational changes and functional activation of GPCRs. In many cases, it is the mechanical force transmitted through these protein-protein associations that is the key factor in receptor activation and triggering its mechanosensory and signaling functions [12].

Activation of aGPCRs occurs according to the "tethered agonism" model, which explains their mechanosensitivity. It is the intramolecular binding of the "tethered agonist" to the 7TM domain that transmits the initial extracellular signal to the cell. [13] Autoproteolysis in the GPS motif generates a short Stachel peptide at the beginning of the C-terminal fragment (CTF), which is at rest hidden in the GAIN domain due to a stable complex with the N-terminal fragment (NTF). Mechanical stress on the membrane – shear, tension or stretching – leads to displacement of the NTF-CTF complex, exposure of the Stachel peptide and its interaction with the 7TM domain of the receptor. This process causes conformational changes and triggers G-protein-mediated intracellular signaling. Experimental data show that signaling can also be activated in the form of CTF alone or upon addition of free Stachel peptide, highlighting the key role of protein-protein interactions in the transmission of mechanical stimulus [14].

GPR133 (also known as ADGRD1) has been identified as a potential genetic factor affecting bone mineral density in humans, and its genetic variants have been associated with differences in human height. In addition to vertebrae, the GPR133/ADGRD1 protein gene has been detected in the tibia and femur, skull, and costal cartilage of 23-week-old wild-type mice, suggesting a role for GPR133/ADGRD1 in maintaining bone homeostasis.

The expression level of GPR133/ADGRD1 in different cell types was quantified. The mRNA of this gene was detected in bone marrow mesenchymal stem cells (BM-MSC – Bone Marrow–Derived Mesenchymal Stem Cells), in primary osteoblasts derived from BM-MSC, and in the MC3T3 cell line (Mouse Calvaria Clone 3, Subclone E1)–both in undifferentiated and differentiated forms. In addition, expression was observed in primary bone marrow macrophages (BMM) and osteoclasts. In contrast, the MLO-Y4 (osteocyte-like) and RAW 264.7 (osteoclast-like) cell lines showed very low levels of GPR133/ADGRD1 mRNA [15].

Constitutive and osteoblast-specific knockout of GPR133/ADGRD1 in mice results in reduced cortical bone mass and trabecularization in the hip and vertebrae, hallmarks of osteoporosis. This osteopenic phenotype in receptor-deficient mice is caused by impaired osteoblast function, which in turn promotes increased osteoclast activity. At the molecular level, GPR133/ADGRD1 regulates osteoblast function and differentiation through a combined activation mechanism involving interaction with its endogenous ligand, protein tyrosine kinase 7 (PTK7), and mechanical forces [15]. It has been shown that GPR133 activation in bone tissue occurs both through interactions between neighboring bone cells and through mechanical loading. This activation triggers a signal that enhances osteoblast activity while simultaneously inhibiting osteoclasts. The result is increased bone mass [16].

A GPR133/ADGRD1 receptor agonist, AP503, induces osteoblastogenesis in vitro and in vivo. AP503 activates the Gs pathway, increases cAMP levels in osteoblasts, which leads to the activation of β-catenin signaling [17]. Subsequently, activation of the cAMP/PKA/CREB signaling pathway promotes osteogenic differentiation of mesenchymal stem cells. AP503 significantly increased markers of bone formation and increased bone volume, trabeculae number, and cortical thickness when was administered to wild-type and heterozygous knockout mice. In addition, the bones withstood greater maximal loads than those with partial or complete GPR133/ADGRD1 knockouts, both constitutively and osteoblast-specifically. The compound was particularly effective in a mouse model of ovariectomized postmenopausal

osteoporosis, where it significantly restored bone parameters to normal levels. Interestingly, the combination of AP503 and exercise positively affected all parameters, suggesting a synergistic effect [18]. A small molecule, GL64, has also been identified as a selective agonist of ADGRD1. GL64 has low selectivity for the isoforms ADGRD2, ADGRG5, ADGRG6, CELSR1, CELSR2, CELSR3, and ADGRG4. GL64 activates ADGRD1 by mimicking the satchel sequence (an internal peptide of adhesive GPCRs that is activated by mechanical shearing of the N-terminal and triggers G-protein signaling) [13]. GL64 regulates osteoclast maturation through the cAMP-PKA-NFATC1 pathway. GL64 effectively inhibits osteoclastogenesis and prevents bone loss both in vitro and in vivo. GL64 is useful in the study of osteoclast-related diseases, but so far this substance has only been used for laboratory use [19].

A new low-molecular-weight compound that exhibits high agonist activity towards the GPR133 receptor (ADGRD1) was patented in 2024. The compound is considered a promising candidate for the development of drugs aimed at the treatment or prevention of diseases associated with reduced bone strength and other related pathological conditions [20].

Conclusions. Analysis of current data confirms that the G-protein-coupled receptor GPR133/ADGRD1 is a critical molecular target in the treatment of osteoporosis: its deficiency leads to reduced bone mass, impaired bone structure, and reduced mechanical strength due to osteoblast dysfunction. The development of new selective GPR133 agonists, in particular AP503 and the compound GL64, confirms the therapeutic potential of the receptor and opens the possibility of creating a tool for more delicate regulation of osteogenesis, avoiding the potential risks characteristic of traditional osteoporosis treatment regimens. The recently issued patent of 2024, dedicated to new small molecule GPR133 agonists, indicates the high intensity of research in this direction, and therefore the continued relevance of this issue.

Sources of funding. Self-financing by the authors.

Contribution of the authors:

S. S. Tkachenko – development of the research idea, analysis and interpretation of data, processing of guiding documents, generalization of conclusions, writing of the article.

O. H. Rodynskyi – development of the research idea, processing of guiding documents, generalization of conclusions

M. M. Portnyaga – development of the research idea and publication, literature review, analysis and interpretation of data, generalization of conclusions, writing of the article.

Conflict of interest. There is no conflict of interest.

REFERENSES

1. Mykhailovska NS, Stetsiuk IO, Manuilov SM, Mykhailovskyi YaM, Lisova OO, Shershnova OV. Osteoporosis in postmenopausal women: pathogenetic relationships with coronary heart disease and obesity (literature review). Pathologia. 2025;22(2):159-67. DOI: 10.14739/2310-1237.2025.2.332421.

2. Povoroznyuk V, Grygorieva N, Johansson H, et al. FRAX-Based Intervention Thresholds for Osteoporosis Treatment in Ukraine. J Osteoporos. 2021;2021:2043479. DOI: 10.1155/2021/2043479

3. Egudina ED. Osteoporoz: osnovy diahnostyky ta profilaktyky [Osteoporosis: basics of diagnosis and prevention]. Zdorov'ia Ukrainy. Kardiolohiia, revmatolohiia, kardiokhirurhiia. 2025;98(1):31-3. Ukrainian. Available from: https://health-ua.com/revmatologia/79724-osteoporoz-osnovi-diagnostiki-ta-profilaktiki

4. Khajuria DK, Razdan R, Mahapatra DR. Drugs for the management of osteoporosis: a review. Rev Bras Reumatol. 2011;51(4):365-71,379-82. Available from: https://pubmed.ncbi.nlm.nih.gov/21779712

5. McGreevy C, Williams D. Safety of drugs used in the treatment of osteoporosis. Ther Adv Drug Saf. 2011;2(4):159-72. DOI: 10.1177/2042098611411012

6. Chiu SH, Wu WT, Yao TK, Peng CH, Yeh KT. Sclerostin and cardiovascular risk: evaluating the cardiovascular safety of romosozumab in osteoporosis treatment. Biomedicines. 2024;12(12):2880. DOI: 10.3390/biomedicines12122880

7. Lehmann J, Lin H, Zhang Z, Wiermann M, Ricken AM, Brinkmann F, та ін. The mechanosensitive adhesion G protein-coupled receptor 133 (GPR133/ADGRD1) enhances bone formation. Signal Transduct Target Ther. 2025;10(1):199. DOI: 10.1038/s41392-025-02291-y

8. Sun S, Wang W. Mechanosensitive adhesion G protein-coupled receptors: insights from health and disease. Genes Dis. 2024;12(3):101267. DOI: 10.1016/j.gendis.2024.101267

9. Lin HH, Ng KF, Chen TC, Tseng WY. Ligands and beyond: mechanosensitive adhesion GPCRs. Pharmaceuticals. 2022;15(2):219. DOI: 10.3390/ph15020219

10. Marullo S, Doly S, Saha K, Enslen H, Scott MGH, Coureuil M. Mechanical GPCR activation by traction forces exerted on receptor N-glycans. ACS Pharmacol Transl Sci. 2020;3(2):171-8. DOI: 10.1021/acsptsci.9b00106

11. Kim H, Baek I-Y, Seong J. Genetically encoded fluorescent biosensors for GPCR research. Front Cell Dev

Biol. 2022;10:1007893. DOI: 10.3389/fcell.2022.1007893

12. Wilde C, Mitgau J, Suchý T, Schöneberg T, Liebscher I. Translating the force–mechano-sensing GPCRs. Am J Physiol Cell Physiol. 2022;322(6):C1047-60. DOI: 10.1152/ajpcell.00465.2021

13. Jones DTD, Dates AN, Rawson SD, та ін. Tethered agonist activated ADGRF1 structure and signalling analysis reveal basis for G protein coupling. Nat Commun. 2023;14:2490. DOI: 10.1038/s41467-023-38083-7

14. Lala T, Hall RA. Adhesion G protein-coupled receptors: structure, signaling, physiology, and pathophysiology. Physiol Rev. 2022;102(4):1587-624. DOI: 10.1152/physrev.00027.2021

15. The newly found bone switch that could stop osteoporosis. SciTechDaily [Internet]. 2025 [cited 2025 Nov 19]. Available from: https://scitechdaily.com/tag/osteoporosis

16. Yang Z, Ping YQ, Wang MW, Zhang C, Zhou SH, Xi YT, et al. Identification, structure, and agonist design of an androgen membrane receptor. Cell. 2025;188(6):1589-604.e24. DOI: 10.1016/j.cell.2025.01.006

17. Yu W, Chen FC, Xu WN, Ding SL, Chen PB, Yang L, et al. Inhibition of Y1 receptor promotes osteogenesis in bone marrow stromal cells via cAMP/PKA/CREB pathway. Front Endocrinol (Lausanne). 2020;11:583105. DOI: 10.3389/fendo.2020.583105

18. He L, Zhang Q, You Y, Sun P, Xu Z, Li R, et al. Exogenous activation of the adhesion GPCR ADGRD1/GPR133 protects against bone loss by negatively regulating osteoclastogenesis. Sci Adv. 2025;11(28):eads3829. DOI: 10.1126/sciadv.ads3829

19. Sharma S, Findlay GM, Bandukwala HS, Oberdoerffer S, Baust B, Li Z, et al. Dephosphorylation of the nuclear factor of activated T cells (NFAT) transcription factor is regulated by an RNA-protein scaffold complex. Proc Natl Acad Sci U S A. 2011;108(28):11381-6. DOI: 10.1073/pnas.1019711108

20. Method for activating adhesion G protein-coupled receptor 133 (GPR133/ADGRD1) [patent]. CN118146176B, China; submission 08 Mar 2024; publication 15 Nov 2024. Available from: https://patents.google.com/patent/CN118146176B/en

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GPR133 (ADGRD1) – ПОТЕНЦІЙНА МІШЕНЬ ДЛЯ ЛІКУВАННЯ ОСТЕОПОРОЗУ

РЕЗЮМЕ. Мета – систематизувати дані оглядів і досліджень, що присвячені ролі адгезійного G-білкового рецептора GPR133 у регуляції остеогенезу та його потенціалу в лікуванні остеопорозу.

Матеріал і методи. Пошук у базах даних PubMed, Scopus та Web of Science у межах періоду 2014–2025 рр. із використанням комбінацій ключових слів: “GPR133”, “ADGRD1”, “adhesion GPCR”, “G-protein coupled receptor”, “osteogenesis”, “osteoporosis”. До аналізу включено 20 джерел – систематичні огляди, експериментальні дослідження та патентні матеріали, що відповідали критеріям дослідження та містили дані щодо ролі GPR133 або споріднених адгезійних GPCR у регуляції остеогенезу.

Результати. Адгезійні G-білок-зв’язані рецептори GPR133/ADGRD1 через наявність властивостей механочутливих метаболотропних рецепторів розглядаються в якості регуляторів кісткового ремоделювання. Ген білка GPR133/ADGRD1 було виявлено у гомілковій та стегновій кістках, черепі й реберному хрящі. мРНК цього гена виявили у мезенхімальних стовбурових клітинах кісткового мозку, первинних остеобластах, остеокластах та макрофагах кісткового мозку. Активність GPR133, що експресується в остеобластах та асоційований із зміною мінеральної щільності кісток, залежить як від наявності ліганду, так і від механічної напруги чи розтягування. Активація рецепторів реалізується безпосередньо через зміни натягу ліпідного бішару мембрани або через передачу механічної сили за рахунок прикріплення рецептора до цитоскелета чи позаклітинного матриксу. Дефіцит GPR133 у мишей призводить до зниження трабекулярної та кортикальної кісткової маси, порушення остеобластогенезу та компенсаторної активації остеокластів, що підтверджує його ключову роль у підтриманні кісткового гомеостазу. Низькомолекулярні агоністи GPR133, такі як AP503 та GL64, стимулюють остеобластогенез, підвищують кісткову масу й міцність кістки, а також проявляють синергізм із фізичними навантаженнями.

Висновки. GPR133/ADGRD1 є доведеною молекулярною мішенню для терапії остеопорозу: його дефіцит знижує кісткову масу та міцність через дисфункцію остеобластів. Застосування селективних агоністів GPR133 відкриває нові патогенетично спрямовані напрямки лікування остеопорозу, уникаючи потенційних ризиків, характерних для традиційних терапевтичних схем.

КЛЮЧОВІ СЛОВА: GPR133; ADGRD1; адгезійний GPCR; остеогенез; остеобласти; остеопороз; механочутливість; агоніст рецептора AP503.

Отримано 25.11.2025

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