DOI: https://doi.org/10.17816/RCF623110

Pharmacological correction of experimentally induced osteoporosis complicated by type 2 diabetes mellitus

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ABSTRACT

BACKGROUND: Osteoporosis remains one of the most important medical problems worldwide with significant economic consequences. The development of new drugs based on unique biologically active compounds can contribute significantly to osteoporosis management.

AIM: To evaluate the osteogenesis processes by evaluating bone-remodeling markers in the blood serum during the treatment of experimental osteoporosis complicated by type 2 diabetes mellitus.

MATERIALS AND METHODS: The study was performed on an experimental model of osteoporosis, followed by the induction of type 2 diabetes mellitus, using biochemical methods to analyze markers of osteoporosis in the blood serum.

RESULTS: The results of the analysis of bone remodeling markers revealed that the antiosteoporotic activity of a composite preparation based on succinic acid salts is dependent on glucose metabolism disorders such as diabetes mellitus. The high efficacy of the new drug in monotherapy and combination with vitamin D_3 in the activation of osteogenesis in experimental osteoporosis was balanced by impaired metabolic processes in type 2 diabetes mellitus.

CONCLUSIONS: The results indicate the dependence of the pharmacological effectiveness of the antiosteoporosis agent on metabolic disorders, such as type 2 diabetes mellitus, in female rats with experimental osteoporosis.

Keywords: osteoporosis; experimental model; markers of osteogenesis; bone tissue remodeling; antiosteoporosis agent; diabetes mellitus type 2.

To cite this article

Bairamov AA, Mamina NSh, Karonova TL, Simanenkova AV, Kozhurin MV, Kosyakova GP, Shabanov PD. Pharmacological correction of experimentally induced osteoporosis complicated by type 2 diabetes mellitus. *Reviews on Clinical Pharmacology and Drug Therapy.* 2024;22(1):75–80. DOI: https://doi.org/10.17816/RCF623110

Received: 08.10.2023 **Accepted:** 28.02.2024 **Published:** 29.03.2024

УДК 612.8, 616
DOI: https://doi.org/10.17816/RCF623110

Фармакологическая коррекция экспериментально индуцированного остеопороза, осложненного сахарным диабетом 2-го типа

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АННОТАЦИЯ

Актуальность. Остеопороз остается одной из важнейших медицинских проблем в мире со значительными экономическими последствиями. Разработка новых препаратов на основе уникальных биологически активных соединений может стать значимым вкладом в решение проблемы остеопороза.

Цель — оценка процессов остеогенеза по данным оценки маркеров костного ремоделирования в сыворотке крови на этапах терапии экспериментального остеопороза, осложненного диабетом 2-го типа.

Материалы и методы. Исследование выполнено на экспериментальной модели остеопороза, с последующей индукцией диабета 2-го типа, с применением биохимических методов анализа маркеров остеопороза в сыворотке крови.

Результаты. По результатам исследования содержания маркеров костного ремоделирования показана зависимость антиостеопорозной активности композитного препарата на основе солей янтарной кислоты от нарушения обмена глюкозы при сахарном диабете. Высокая эффективность нового препарата при монотерапии и в комбинации с витамином D_3 в активации процессов остеогенеза при экспериментальном остеопорозе была нивелирована нарушением обменных процессов, индукцией диабета 2-го типа.

Заключение. Показана зависимость фармакологической эффективности антиостеопорозного средства на модели остеопороза у самок крыс от нарушений обменных процессов в виде сахарного диабета 2-го типа.

Ключевые слова: остеопороз; экспериментальная модель; костное ремоделирование; маркеры остеогенеза; антиостеопорозное средство; сахарный диабет 2-го типа.

Как цитировать

Байрамов А.А., Мамина Н.Ш., Каронова Т.Л., Симаненкова А.В., Кожурин М.В., Косякова Г.П., Шабанов П.Д. Фармакологическая коррекция экспериментально индуцированного остеопороза, осложненного сахарным диабетом 2-го типа // Обзоры по клинической фармакологии и лекарственной терапии. 2024. Т. 22. № 1. С. 75–80. DOI: https://doi.org/10.17816/RCF623110

Рукопись получена: 08.10.2023 **Рукопись одобрена:** 28.02.2024 **Опубликована:** 29.03.2024

BACKGROUND

According to the Research Institute of Rheumatology of the Russian Academy of Sciences, 14 million people (10% of the country's population) are diagnosed with osteoporosis (OP), and 20 million people are diagnosed with osteopenia in Russia. Thus, 34 million Russian residents country have a real risk of OP fractures [1, 2]. OP is a chronic, progressive metabolic disease of the skeleton characterized by a decrease in bone mineral and organic density and impaired microarchitectonics. This leads to an increased risk of fractures [3, 4].

The development of new drugs based on unique biologically active compounds involved in the activation of metabolism and bone tissue remodeling may significantly contribute to preventing OP. Succinates, based on natural conformers of succinic acid, are the strongest modulators of orphan and succinate receptors SUCNR1, K^+channels of L-type, activate Ca^{2+} accumulation inside the cells, and activate the limiting step in cholesterol metabolism (entry into the mitochondria and subsequent biotransformation into active steroid forms) [5, 6]. In an experimental study, the preparation containing bone macronutrients such as succinic acid salts increased the mineral and organic density of the femur and increased the synthesis of estrogens and androgens in cases of hormonal deficiency [7–9].

The efficacy of anti-OP therapy is contingent upon the presence of comorbidities, including type 2 diabetes mellitus (DM2) and its associated complications, which can precipitate metabolic disturbances in the bone tissue [10]. Nevertheless, DM is an independent risk factor for fractures [11].

Thus, *this study aimed* to investigate the pharmacological efficacy of a new drug in an experimental model of OP in combination with a DM2 model in female rats according to the study of bone remodeling markers in the serum.

MATERIALS AND METHODS

In the experimental study, 25 sexually mature female Wistar rats were used, in which an experimental OP model was created in accordance with the objective of the study.

The method of establishing an experimental OP model and its validation have been described previously [12–14]. Briefly, bilateral ovaries were removed surgically in female rats, followed by twice-daily administration of prednisolone at a dose of 25 mg per kg of rat body weight. Healthy female Wistar rats aged 4–6 months and weighing 240–260 g were used for the experiment. Bilateral ovarioectomy was performed according to the recommendations of the Bunoc manual (1968). Animals were anesthetized with ether and restrained in the prone position on the operating table. The surgical field on the back was clipped and prepped with alcohol and dilute alcoholic iodine solution. A longitudinal incision of 1.5–2 cm was made with a scalpel along the midline of the back. A puncture was made in the posterior part of the abdominal cavity by moving the incision alternately to the left and right. After finding the right or left uterine horn, the ovary was removed by puncture and cut off from the uterine horn by electrocautery. The second ovary was removed in the same manner. Before suturing, peritoneal puncture and dorsal incision were treated with streptocide. Three weeks after surgery, female rats were injected intraperitoneally with prednisolone at a dose of 25 mg/kg. The second injection was given 15 days apart.

Nicotinamide solution at a dose of 230 mg/kg was administered intraperitoneally to model DM 4 weeks after the initiation of high-fat diet maintenance and 2 weeks after ovarioectomy. This technique has been described in detail in several studies [15–17]. On days 2 and 3, venous blood glucose was measured at a random time point. DM was diagnosed when the blood glucose was ⩾11.1 mmol/L in two measurements on different days. During the test, blood glucose was measured at baseline, after which a 40% glucose solution was administered orally at a dose of 3 g/kg via a gastric tube. Blood glucose was measured again at 15, 30, 60, and 120 min of the test. DM was diagnosed when the blood glucose was ⩾11.1 mmol/L at any time point [18].

After OP and DM modeling, the following groups were randomly formed: DM2 group (females with DM2, no OP, and no therapy, $n = 6$), OP group (post-OP females with MD without therapy, $n = 5$), and OP-DM2+X3+D_3 group (with OP and DM2, receiving drug X3 and vitamin D_3, $n = 6$).

Drug administration and observation of animals continued for another 6 weeks, and the total study duration was 12 weeks. At the end of the experiment, blood was collected to determine phosphorus–calcium metabolism parameters and markers of bone remodeling such as osteocalcin (OK), sclerostin, osteoprotegerin (OPG), fibroblast growth factor 23 (FGF23), and nuclear factor kappa-β activator ligand (RANKL) by enzyme-linked immunosorbent assay.

The study focused on a new composite preparation based on succinic acid salts as a drug for the treatment and prevention of OP (hereinafter, preparation X3, patent for invention RU2582973C1, Mioran NPF) [19]. The study was conducted within the framework of preclinical studies required for the registration of the product and aimed at determining the properties of the test object at multiple oral administrations in a fixed dose (62.5 mg/kg, compound without drug base). The study was conducted in accordance with GLP laboratory research standards at the Center for Preclinical and Translational

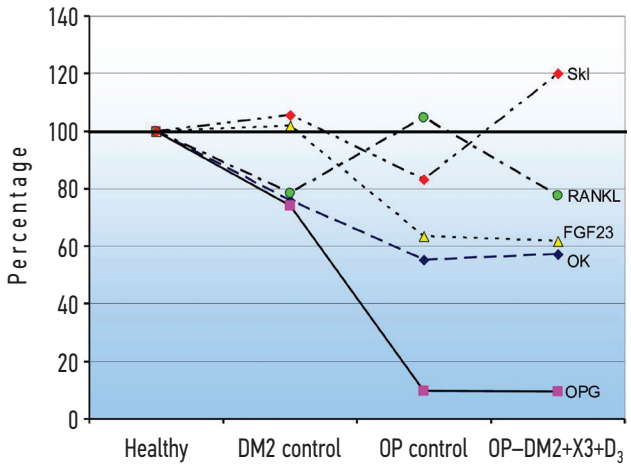

Figure. Dynamics of osteoporosis markers in the blood serum of female rats with experimental osteoporosis complicated by type 2 diabetes mellitus during pharmacotherapy with X3 and vitamin D_3 drugs. Data from intact rats are taken as 100%. FGF23, fibroblast growth factor-23; OP–DM2+X3+D3, group with osteoporosis and type 2 diabetes mellitus, receiving drug X3 and vitamin D_3; Skl, sklerostin; OK, osteocalcin; OPG, osteoprotegerin; RANKL, ligand of the nuclear factor kappa-β activator

Рисунок. Динамика маркеров остеопороза в сыворотке крови самок крыс с экспериментальным остеопорозом (ОП), осложненным сахарным диабетом 2-го типа (СД2) при фармакотерапии препаратами X3 и витамином D_3. Данные интактных крыс приняты за 100 %. ОП–СД2+X3+D_3 — группа с остеопорозом и сахарным диабетом 2-го типа, получавшая препарат X3 и витамин D_3; Skl — склеростин; OK — остеокальцин, OPG — остеопротегерин; FGF23 — фактор роста фибробластов-23; RANKL — лиганд активатора ядерного фактора каппа-β

Research of the V.A. Almazov National Medical Center of the Russian Ministry of Health.

RESULTS

As described in the methodology, experimental animals had a combined pathology of OP and DM2 to determine the effectiveness of anti-OP therapy in carbohydrate metabolism disorders.

In the OP-DM2+X3+D_3 group, the anti-OP therapy at a dose of 62.5 mg, enhanced by the addition of vitamin D_3 at a dose of 500 IU per kg of rat weight to the treatment regimen, had no significant effect on the correction of experimental OP. Thus, of all bone remodeling markers, only RANKL showed a significant decrease in its level, suggesting a decrease in osteoclast activity. Correspondingly, the level of Skl, another marker of osteoclastogenesis, normalized and increased compared with the healthy group. The main indicators of osteoblastogenesis (OK, OPG, and FGF23) remained indifferent to the performed pharmacotherapy with X3 and D_3 drugs (figure).

In summary, carbohydrate metabolism disorders may be an inhibitory factor in the treatment of experimentally induced OP. Careful selection of drug therapy for DM2 is a prerequisite for its treatment to normalize calcium–phosphorus metabolism, level the bone remodeling markers in the blood serum, and restore bone tissue microarchitecture during anti-OP therapy.

In an earlier pilot study, achieving effective OP therapy in a comorbid condition is not easy. The use of modern antihyperglycemic drugs, which proved to be effective in both the low-selective inhibitor of sodium-glucose cotransporter 2 (SGLT2) canagliflozin and the glucagon-like peptide-1 receptor agonist liraglutide, did not significantly affect the phosphorus–calcium metabolism parameters and the concentration of sclerostin and osteocalcin [17]. However, the use of canagliflozin SGLT2 was associated with a decrease in the number of bone bars in the epiphyseal region of the femur.

Thus, the administration of the anti-OP drug X3 as a single intervention and in combination with vitamin D_3 leads to a significant increase in the concentration of bone remodeling markers in the serum, indicating an increase in osteogenesis and osteoblastogenesis. Impaired carbohydrate metabolism in DM2 makes the current therapy of experimentally induced OP ineffective.

CONCLUSIONS

The developed preparation X3, when tested on the experimental model of postmenopausal OP, demonstrated high efficiency because of the increase in bioavailability and assimilation of macro- and microelements from the composition of the preparation by bone tissue [9, 14, 20]. The bioavailability of the drug components was enhanced by the use of salts of natural conformers of succinic acid in the preparation and the ligand–receptor interaction of succinate with the SUCNR1 receptor [5, 7, 8]. The activation of the SUCNR/SUCNR1 system is associated with increased bone tissue metabolism, enhanced osteogenesis, and osteoblastogenesis. Consequently, impaired carbohydrate metabolism, as exemplified by DM2, impairs osteoblastogenesis and reduces the pharmacological efficacy of X3.

The administration of anti-OP drug X3 in combination with vitamin D_3 to female rats with OP resulted in the normalization of bone remodeling markers in the serum. The disturbance of carbohydrate metabolism in the combined pathology of OP and DM2 renders the anti-OP therapy ineffective, indicating the necessity of preliminary correction of DM2 with hypoglycemic drugs.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. The contribution of each author: A.A. Bairamov, N.Sh. Mamina, T.L. Karonova, A.V. Simanenkova, M.V. Kozhurin, G.P. Kosyakova — manuscript drafting, writing and pilot data analyses; A.A. Bairamov, P.D. Shabanov — paper reconceptualization and general concept discussion.

Funding source. The work was supported by the Committee for Science and Higher Education of St. Petersburg (grant No. 13-ZDR of 2023).

Competing interests. The authors declare that they have no competing interests.

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