ИЗУЧЕНИЕ ОСТЕОПРОТЕКТИВНОГО ДЕЙСТВИЯ L-АРГИНИНА, L-НОРВАЛИНА И РОЗУВАСТАТИНА НА МОДЕЛИ ГИПОЭСТРОГЕН-ИНДУЦИРОВАННОГО ОСТЕОПОРОЗА У КРЫС

© О.С. Гудырев[1], А.В. Файтельсон[2], М.С. Соболев[2], М.В. Покровский[1], Т.Г. Покровская[1], М.В. Корокин[1], Е.Е. Поветка[1], Э.С. Миллер[1], В.О. Солдатов[1]

ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия (1)
ФГБОУ ВО Курский государственный медицинский университет Минздрава России, Курск, Россия (2)

Воздействие на микроциркуляторное русло костной ткани является одним из перспективных подходов в лечении остеопороза. ***Цель.*** Изучение антиостеопоротических свойств эндотелиопротекторов: L-аргинина, L-норвалина и розувастатина. ***Материалы и методы.*** Исследование остеопротективных свойств L-аргинина, L-норвалина и розувастатина, а также препарата сравнения – стронция ранелата – проведено на 152 самках крыс линии Вистар с использованием модели гипоэстроген-индуцированного остеопороза. Оценку антиостеопоротического и эндотелиопротективного действия препаратов проводили с использованием лазерной допплеровской флоуметрии (ЛДФ) проксимального метафиза бедренной кости, морфометрии костных трабекул, а также расчета коэффициента эндотелиальной дисфункции. ***Результаты.*** При проведении ЛДФ повышение уровня микроциркуляции проксимального метафиза бедренной кости относительно животных с остеопорозом без лечения (61,52±3,74 перфузионных единиц (ПЕ)) было наиболее выражено при применении L-норвалина (115,25±5,36 ПЕ, p<0,001) и розувастатина (106,57±5,22 ПЕ, p<0,001), менее выраженный эффект продемонстрировали L-аргинин (98,10±4,48 ПЕ, p<0,001) и препарат сравнения – стронция ранелат (86,49±4,99 ПЕ). Сходная тенденция наблюдалась при морфометрии костных трабекул: в группе с остеопорозом без лечения диаметр костных трабекул составил 61,68±1,24 мкм, в группе с применением L-норвалина – 91,86±1,18 мкм (p<0,001), в группе с применением L-аргинина – 86,64±1,39 мкм (p<0,001), в группе с применением розувастатина – 85,56±0,86 мкм (p<0,001)и в группе с применением стронция ранелата – 89,08±1,09 мкм. ***Заключение.*** L-аргинин и L-норвалин, а также розувастатин обладают способностью улучшать морфофункциональное состояние костной ткани и могут быть рекомендованы для дальнейшего доклинического изучения.

Ключевые слова: *остеопороз; эндотелиальная дисфункция; L-аргинин; L-норвалин; розувастатин; стронция ранелат; крысы.*

A STUDY OF OSTEOPROTECTIVE EFFECT OF L-ARGININE, L-NORVALINE AND ROSUVASTATIN ON A MODEL OF HYPOESTROGEN-INDUCED OSTEOPOROSIS IN RATS

O.S. Gudyrev[1], A.V. Faitelson[2], M.S. Sobolev[2], M.V. Pokrovskiy[1],
T.G. Pokrovskaya[1], M.V. Korokin[1], E.E. Povetka[1], E.S. Miller[1], V.O. Soldatov[1]

Belgorod State National Research University, Belgorod, Russia (1)
Kursk State Medical University, Kursk, Russia (2)

Effect on the microcirculatory bed of the bony tissue is one of promising approaches to treatment of osteoporosis. ***Aim.*** To study anti-osteoporotic properties of endothelioprotectors: L-arginine, L-norvaline and rosuvastatin. ***Materials and Methods***. Osteoprotective properties of L-arginine, L-norvaline and rosuvastatin, and also of a reference drug– strontium ranelate – were studied on 152 female rats of Wistar line using a model of hypoestrogen-induced osteoporosis. Anti-osteoporotic and endothelioprotective effect of the drugs were evaluated by laser dopplerflowmetry (LDF) of the proximal metaphysis of the femoral bone, morphometry of trabeculae of bone, and also by calculation of the coefficient of endothelial dysfunction. ***Results.*** LDF showed that maximal increase in microcirculation of the proximal metaphysis of the femoral bone, in comparison with animals with untreated osteoporosis (61.52 ± 3.74 perfusion units, PU) was achieved with L-norvaline (115.25 ± 5.36 PU, $p<0.001$) and rosuvastatin (106.57 ± 5.22 PU, $p<0.001$), less expressed effect was demonstrated by L-arginine (98.10 ± 4.48 PU, $p<0.001$) and a reference drug – strontium ranelate (86.49 ± 4.99 PU). A similar tendency was observed in morphometry of trabeculae of bone: in the group with untreated osteoporosis the diameter of trabeculae was 61.68 ± 1.24 μm, in the group with use fL-norvaline – 91.86 ± 1.8 μm ($p<0.001$), in the group with use of L-arginine – 86.64 ± 1.39 μm ($p<0.001$) and in the group with use of strontium ranelate – 89.08 ± 1.09 μm. ***Conclusion.*** L-arginine and L-norvaline and also rosuvastatin possess the property of improving a morphofunctional condition of bone tissue and may be recommended for further preclinical study.

Keywords: osteoporosis; endothelial dysfunction; L-arginine; L-norvaline; rosuvastatin; strontium ranelate; rats.

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A cause of development of osteoporosis is derangement of the main processes of osteogenesis – resorption and formation of bone tissue. Frustration of the regional blood supply of the bone results in reduction of the quantity of osteoblasts and in inhibition of their activity, with simultaneous activation of the activity of osteoclasts [1,2]. Therefore, blood supply plays a key role in the processes of remodeling and reparative regeneration of bone tissue. Endothelial dysfunction and endothelium-associated pathologies are usually the main cause of impairment of microcirculatory blood flow in the bone tissue which, in turn, deranges osteogenesis, thus leading to osteoporosis [3].

A principally new approach based on connection of the endothelial dysfunction with osteoporosis, consists in use of preparations that improve the function of the endothelium, with the aim of increasing density of the bone tissue [4]. This approach opens a possibility for application of inhibitors of 3-hydroxy-3-methylglutaryl-coenzymeA reductase (HMG-CoA-reductase), and also of L-arginine and L-norvaline as osteoprotective drugs [5].

L-arginine and L-norvaline are amino acids that facilitate increased production of nitric oxide (NO) by NO-synthase endothelial enzyme [6,7]. Inhibitors of HMG-CoA-reductase (statins), besides producing a hypo-

lipidemic effect, also possess endothelio-protective activity [8]. Inhibiting synthesis of mevalonic acid, statins prevent synthesis of isoprenoid intermediates of farnesyl pyrophosphate and of geranylgeranyl pyrophosphate required for activation of some heterotrimeric G-proteins including *Ras* and *Rho* [9,10]. These proteins control proliferation, differentiation of cells, apoptosis and the structure of cytoskeleton [11,12]. Excessive activity of *Ras* and *Rho* leads to reduction of synthesis of *eNOS*, to synthesis of proinflammatory cytokines, to increase in the permeability of the vessel wall and in the amount of foam cells [13,14].

The described properties positively influence the condition of the intrabone microcirculation, and thus indirectly improve trophism of the bone tissue including a positive effect onosteoregeneration. In this connection, there exist important theoretical premises for studying anti-osteoporotic effect of the given drugs.

The *aim* of work was to study anti-osteoporotic properties of endothelioprotectors: L-arginine, L-norvaline and rosuvastatin.

Materials and Methods

The study was conducted in compliance with the requirements of Cruelty to Animals Act of RF of 24.06.1998, of Rules of laboratory practice in preclinical studies in RF (GOST 3 51000.3-96 and GOST P 53434-2009), Directive of European Community (86/609 EU), rules of International recommendations of European Convention for the protection of vertebrate animals used in experimental and other scientific purposes and Rules of laboratory practice adopted in RF (Order of HM RF №708 of 29.08.2010).

Experiments were conducted on 152 female white rats of Wistar line of 250±50 g mass. To model experimental osteoporosis, the rats were narcotized by intraperitoneal introduction of chloral hydrate solution at a dose of 300 mg/kg, and were conducted an operation of bilateral ovariectomy. Development of osteoporosis and anti-osteoporotic action of the studied preparations were ascertained in eight weeks (on the 57th day) after ovariectomy by evaluation of the regional microcirculation, using vascular tests and histomorphometric examination.

The level of microcirculation was evaluated in the spongy bone tissue of the proximal metaphysis of the right femoral bone. The data of microcirculation in the bone were obtained using equipment of BIOPAC Systems (USA): polygraph MP 100-150 with laser Doppler flowmetry module LDF 100C and sensor TSD 144. Results of laser LDF were recorded using Acq Knowledge program 3.8-4.2 version, microcirculation was measured in perfusion units (PU).

Hypoestrogen-induced dysfunction was assessed after measurement of the level of intrabone microcirculation, for which vascular tests were conducted for endothelium-dependent (acetylcholine intravenously 40 μg/kg) and non-endothelium-dependent (sodium nitroprusside intravenously 30 μg/kg) vasodilatation. Using the results of vascular tests, the coefficient of endothelial dysfunction (CED) was calculated as the ratio of the area of the triangle above the curve of recovery of microcirculation in response to introduction of nitroprusside to the area of the triangle above the curve of recovery of microcirculation in response to introduction of acetylcholine.

To confirm development of osteoporosis and to assess effectiveness of the studied preparations, morphological examination of the proximal metaphysis of femoral bones was conducted for which the microscopic glasses with histological preparations were examined in light microscopy. Histomorphometry of the bone tissue was performed using previously calibrated Image J program of 1.39-1.43 versions where the width of bone trabeculae was measured and expressed in micrometers.

The studied preparations were introduced intragastrically daily once a day for eight weeks after ovariectomy in the form of suspension in 1% starch paste: L-arginine – at a dose of 200 mg/kg, L-norvaline – at a dose of 10 mg/kg, rosuvastatin – at a dose of 0.86 mg/kg. A reference drug was an effective preparation for prophylaxis and correction of osteoporotic disorders – strontium ranelate –

given at a dose of 171 mg/kg. Animals with experimental osteoporosis intragastrically received 1% starch paste as placebo. A control group included falsely operated animals (a false operation of ovariectomy without removal of ovaries) who also received 1% starch paste intragastrically within eight weeks as placebo.

The experimental data obtained in the work, were analyzed using descriptive statistics (Microsoft Excel analysis package). The mean values (M) and error of mean (m) of the group parameters were determined. Analysis of statistically significant differences in comparison between groups was conducted using 2-sample t-test with different dispersions. For analysis of a large number of comparisons Student's t-test was used with Newman-Keuls correction.

Results and Discussion

On the 57th day after bilateral ovariectomy the level of microcirculation was evaluated in the proximal metaphysis of the right femoral bone. Examination of blood supply of the bone tissue of rats revealed a lower level of microcirculation in the bone tissue of the hip in rats with osteoporosis (n=30) – 61.52 ± 3.74 PU as compared to the control animals (n=42) – 100.51 ± 4.41 PU (p<0.001).

After measurement of microcirculation in the bone tissue of the hip, functional vascular tests of endothelium-dependent and non-endothelium dependent vasodilatation were conducted, and CED was calculated for microcirculatory bed of the proximal metaphysis of the femoral bone in rats. Thus, in the group of control animals CED=1.30 ± 0.19 was recorded, and in the group of rats with experimental osteoporosis –2.38 ± 0.23 (p=0.002), which evidences development of endothelial dysfunction in animals with osteoporosis.

For further morphological examinations, bone biomaterial was taken. Histological cuts of proximal parts of femoral bones of the animals were subjected to microscopy and histomorphometry. Osteoporotic alterations in bones of the skeleton were histologically confirmed in all the rats in eight weeks after ovariectomy. In microscopy, pathological alterations were found in the spongy tissue of hip of rats with experimental osteoporosis. Thinning of the reticulated tissue of the trabeculae of bones and also thinning and perforation of bone lamellae were found. In some histological preparations microfractures of trabeculae were determined.

Reduction of the mean width of the trabeculae in the spongy tissue of proximal metaphysis of the femoral bone was detected. Thus, the mean width of trabeculae of bones in this localization in rats with osteoporosis was 61.68 ± 1.24 μm which is less than that in control animals – 97.69 ± 1.02 μm (p<0.001).

So, endothelial dysfunction including that in the microcirculatory bed of the bone tissue, developing in female rats as a result of ovariectomy, leads to a marked impairment of the regional blood flow which, in turn, unbalances the bone remodeling processes and promotes osteoporotic alterations in the bone tissue.

It was found that the studied preparations, as well as the reference drug – strontium renelate – prevented reduction of the regional blood flow in the bone tissue of the hip of rats with osteoporosis (Figure 1).

Results of LDF in the group of rats who received L-arginine (n=20) reliably exceeded those in the group of rats with osteoporosis without treatment (p<0.001) and did not show any statistically significant differences from the parameters of the groups receiving reference drug (p=0.091, n=20) and of control groups (p=0.736).

Results of LDF in the rats who received L-norvaline (n=20), were also higher than in the group of rats with osteoporosis without treatment (p<0.001) and of animals given strontium renelate (p<0.001), but did not show any statistically significant differences from the control group (p=0.051).

Results of LDF in the group of rats who received rosuvastatin (n=20), were also higher than both in the group of rats with osteoporosis without treatment (p<0.001), and in the group receiving the reference drug (p=0.008), and were also comparable with the parameters of control animals (p=0.412).
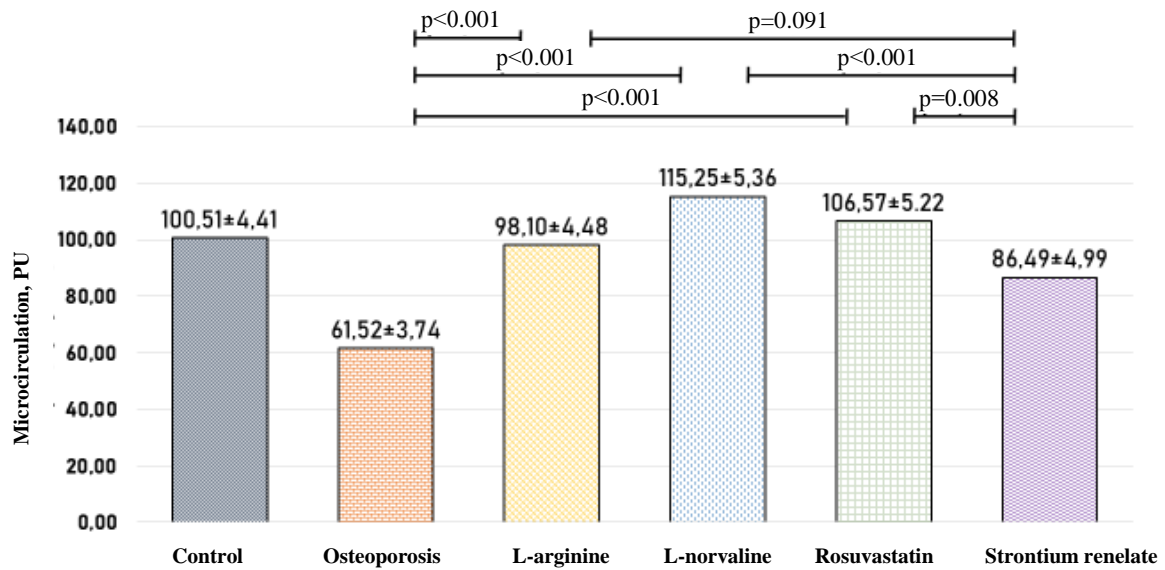
Fig. 1. Results of the influence of L-arginine, L-norvaline, rosuvastatin
and strontium renelate on the blood supply of the proximal metaphysis of femoral bone
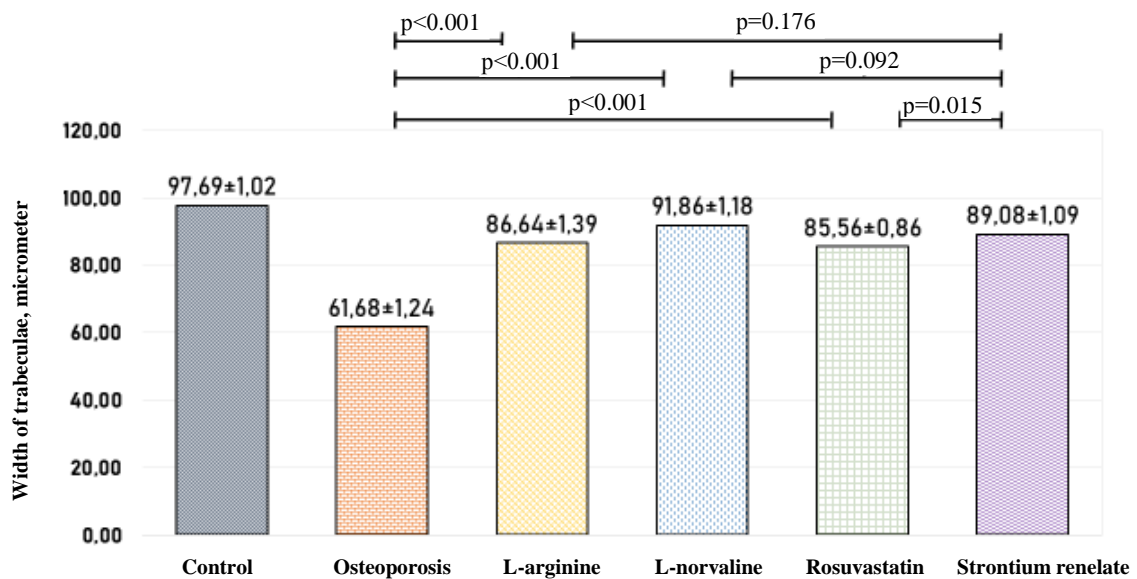in 8 weeks after bilateral ovariectomy

Fig. 2. Results of influence of L-arginine, L-norvaline, rosuvastatin
and strontium renelate on the average width of trabeculae of proximal metaphysis
of femoral bone in 8 weeks after bilateral ovariectomy

Here, all the studied preparations showed endothelioprotective activity reliably preventing increase in the coefficient of endothelial dysfunction. CED of rats receiving L-arginine, was 1.34±0.21 (p=0.012), of those receiving L-norvaline – 1.37±0.10 (p=0.003), and rosuvastatin – 1.35±0.12 (p=0.017).The reference drug – strontium renelate – did not show a reliable endothelioprotective activity with CDF=2.14±0.11 (p=0.532).

In microscopy of cuts of femoral bones of rats given treatment, the structure of the bone tissue of the proximal metaphysis of femoral bone was preserved. Morphometric examinations showed prevention of reduction of the average width of trabeculae in the proximal metaphysis of the hip of laboratory animals under influence of all the studied preparations as well as of the reference drug (Figure 2). Among the studied preparations, L-nor-valine possessed the highest anti-osteoporotic activity.

Conclusion

The endothelial monolayer of intrabone vessels plays the central regulatory role and possesses a considerable metabolic activity. Endothelial functions include regulation of leukocyte adhesion, of the level of microcirculation, aggregate condition of blood, anatomy of the vascular bed of the bone tissue,

activity of osteoclasts and osteoblasts [15].

It was shown in the given study that L-arginine and L-norvaline amino acids, and also inhibitor of HMG-CoA reductase – rosuvastatin, possess the ability to improve morphofunctional condition of bone tissue and to increase the level of microcirculation in the proximal metaphysis of the femoral bone. The obtained data permit to recommend the given preparations for further clinical study as drugs possessing an evident anti-osteoporotic activity. In particular, experimental verification of the influence of these preparations on the course of other models of osteoporosis (diabetic, glucocorticoid-induced) is required, as well as identification of the biochemical markers of endothelial dysfunction and of osteoporosis, and of the link between anti-osteoporotic activity and the mode of introduction of the drug.

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Информация об авторах [Authors Info]

*Гудырев Олег Сергеевич – к.м.н., доцент, доцент кафедры фармакологии и клинической фармакологии, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Oleg S. Gudyrev** – MD, PhD, Associate Professor, Associate Professor of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 5936-4774, ORCID ID: 0000-0003-0097-000X, Researcher ID: N-5527-2016. E-mail: gudyrev@bsu.edu.ru

Файтельсон Александр Владимирович – д.м.н., доцент, профессор кафедры травматологии и ортопедии, ФГБОУ ВО Курский государственный медицинский университет Минздрава России, Курск, Россия. [**Aleksandr V. Faitelson** – MD, PhD, Associate Professor, Professor of the Department of Traumatology and Orthopedics, Kursk State Medical University, Kursk, Russia.]
SPIN: 7389-8181, ORCID ID: 0000-0003-3759-6373, Researcher ID: A-9809-2017.

Соболев Михаил Сергеевич – аспирант кафедры травматологии и ортопедии, ФГБОУ ВО Курский государственный медицинский университет Минздрава России, Курск, Россия. [**Mikhail S. Sobolev** – PhD-Student of the Department of Traumatology and Orthopedics, Kursk State Medical University, Kursk, Russia.]
SPIN: 2987-3470, ORCID ID: 0000-0001-7839-2049, Researcher ID: A-9473-2019.

Покровский Михаил Владимирович – д.м.н., профессор, заведующий кафедры фармакологии и клинической фармакологии, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Mikhail V. Pokrovskiy** – MD, PhD, Professor, Head of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 9201-3580, ORCID ID: 0000-0002-1493-3376, Researcher ID: A-4427-2017.

Покровская Татьяна Григорьевна – д.м.н., профессор, профессор кафедры фармакологии и клинической фармакологии, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Tat'yana G. Pokrovskaya** – MD, PhD, Professor, Professor of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 8338-0100, ORCID ID: 0000-0001-6802-5368, Researcher ID: A-5281-2017.

Корокин Михаил Викторович – д.м.н., профессор, профессор кафедры фармакологии и клинической фармакологии, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Mikhail V. Korokin** – MD, PhD, Professor, Professor of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 8385-3508, ORCID ID: 0000-0001-5402-0697, Researcher ID: A-6652-2017.

Поветка Елена Евгеньевна – студент, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Elena E. Povetka** – Student, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 3609-4411, ORCID ID: 0000-0003-4517-1041, Researcher ID: A-8035-2019.

Миллер Эдуард Сергеевич – студент, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Eduard S. Miller** – Student, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 8028-5617, ORCID ID: 0000-0001-7982-7518, Researcher ID: A-7578-2019.

Солдатов Владислав Олегович – ассистент кафедры фармакологии и клинической фармакологии, ФГАОУ ВО Белгородский государственный национальный исследовательский университет, Белгород, Россия. [**Vladislav O. Soldatov** – Assistant of the Department of Pharmacology and Clinical Pharmacology, Belgorod State National Research University, Belgorod, Russia.]
SPIN: 8763-8217, ORCID ID: 0000-0001-9706-0699, Researcher ID: A-7292-2019.