

**STUDY OF THE EFFECTS OF METFORMIN+ZINC+OMEGA3 COMPLEX IN
EXPERIMENTAL ANIMALS MODELED FOR OSTEOPOROSIS AND
METABOLIC SYNDROME**

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Abstract: In the experiment, the effects of metformin+zinc+omega3 complex were evaluated in male and female rabbits modeled with metabolic syndrome and osteoporosis. In this case, systolic pressure and diastolic pressure were evaluated according to the results of laboratory analyses. Metformin+zinc+omega3 drug can be recommended in practice as a means of pathogenetic treatment of metabolic syndrome and bone destructive changes.

Key words: metabolic syndrome, osteoporosis, metformin+zinc+omega3 complex.

Аннотация: Тажрибада метаболик синдром ва остеопороз моделлаштирилган эркак ва урғочи жинсли қуёнларда метформин+цинк+омега3 комплексини қўллаб, унинг таъсири баҳоланди. Бунда систолик босим ва диастолик босим кўрсаткичлари, лаборатор таҳлиллар натижалари бўйича баҳоланди. Метформин+цинк+омега3 препаратини амалиётда метаболик синдром ва суяк деструктив ўзгаришларни патогенетик даволаш воситасида тавсия қилиш мумкин.

Калит сўзлар: метаболик синдром, остеопороз, метформин+цинк+омега3 комплекси.

Аннотация: В эксперименте оценивали действие комплекса метформин+цинк+омега3 на кроликах-самцах и самках с модельным метаболическим синдромом и остеопорозом. При этом систолическое давление и диастолическое давление оценивали по результатам лабораторных анализов. Препарат метформин+цинк+омега3 может быть рекомендован на практике как средство патогенетического лечения метаболического синдрома и деструктивных изменений костной ткани.

Ключевые слова: метаболический синдром, остеопороз, комплекс метформин+цинк+омега3.

Metabolic syndrome is becoming a medical and public health problem worldwide as its prevalence is increasing year by year. Metabolic syndrome (MS) is an umbrella term for a group of diseases or pathological conditions with a common cause.[Alessi M. C., Juhán-Vague I. PAI-1 and the metabolic syndrome: the links, causes and consequences. Arterioscler Thromb Vasc Biol 2006; 26 (10): 2200–7.]. Metabolic syndrome is a very common clinical condition, affecting on average one in five adults in developed countries.

The main factors in the development of the syndrome are abdominal obesity and insulin resistance. Obesity and metabolic syndrome (MS) are becoming a growing problem for public health and clinical practice due to increasing sedentary lifestyles and excess caloric intake from processed foods high in fat and sugar. There are several definitions of MS, but most of them include conditions such as abdominal obesity, high-density lipoproteins, elevated cholesterol, triglycerides, hypertension, etc. Despite the increasing prevalence of MS, understanding of its pathophysiology and disease correlates is still limited. Obesity manifests as excessive fat accumulation, which not only leads to weight gain, but also causes chronic low-grade inflammation, which induces vascular dysfunction and metabolic abnormalities, ultimately leading to cardiovascular disease and type 2 diabetes. These consequences of obesity are related to excessive expansion and improper remodeling of adipose tissue. Diabetic dyslipidemia is characterized by hypertriglyceridemia, low high-density lipoprotein, postprandial lipemia, small and dense LDL particles, which is the main predisposing factor for various macrovascular complications.

The aim of this study is to study the effects of metformin+zinc+omega3 complex in an experimental rabbit model of metabolic syndrome and osteoporosis.

Modeling the metabolic syndrome

Against the background of metabolic syndrome, physical inactivity, rabbits were prescribed a combined diet with the addition of crystalline cholesterol at a dose of 250 mg/kg mixed with chopped carrots (about 100 g) in the daily diet. Freshly prepared 5% glucose solution is poured into the animal's drinking bowl every day. Every 2 days, insulin was injected subcutaneously from the back of the animals at a dose of 0.1 units/100 g of body weight. MS modeling lasted up to 2 months.

Modeling of bone and cartilage destruction

Modeling of bone tissue destruction in rabbits was performed by intramuscular injection of dexamethasone solution at a dose of 1,675 mg/kg once a day for 2 weeks.

Modeling the metabolic syndrome associated with osteoporosis Cholesterol was added to the standard daily diet of the animals at a dose of 250 mg/kg body weight and 5% sucrose solution was used instead of water for 8 weeks, and insulin was injected subcutaneously from the back of the animals at a dose of 0.1 units per 100 g body weight every 2 days. In order to increase the development of hypercholesterolemia, hyperglycemia and reduce bone mineral density, animals were injected intramuscularly with dexamethasone at a dose of 0.1 mg/kg.

Blood pressure monitoring

Blood pressure in rabbits was measured non-invasively using Little Doctor 2 blood pressure monitor, using Neo#2 series veterinary cuffs for cats and rabbits (China) at every 7-day follow-up.



Materials and methods:

Experimental studies were conducted on 36 male and female rabbits weighing 2000-2600 g, aged (10-14) months. The animals were kept in standard vivarium conditions with a natural 12-hour light-dark cycle and an air temperature of 20 ± 20 0. Each group included 6 male and 6 female rabbits as follows:

1. Control group - 6 male rabbits modeled metabolic syndrome (№1-6).
2. The second group of metabolic syndrome modeled (№7-12) 6 male rabbits received metformin at a dose of 120 mg/kg orally for 35 days.

3. The third group modeled metabolic syndrome (№13-18) 6 male rabbits + metformin+zinc+omega3 complex received orally for 35 days.

4. The fourth control group modeled metabolic syndrome (№19-24) 6 female rabbits.

5. The fifth group of modeled metabolic syndrome (№25-30) 6 female rabbits received metformin at a dose of 120 mg/kg orally for 35 days.

6. Sixth group of modeled metabolic syndrome (№31-36) 6 female rabbits received + metformin+zinc+omega 3 complex orally for 35 days.

24 hours after the last drug administration, systolic and diastolic blood pressure were determined in all groups of animals, and the results of biochemical blood tests were studied. All experiments were conducted in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes (Strasbourg 1986). The results obtained from the study were statistically processed using the Biostat 2009 software package, and the data were presented as the mean (M) and the error of the mean (μ). A difference at the 95% and higher probability level ($p < 0.05$) was considered as a statistically significant change.

Results of the experimental protocol

The results of systolic and diastolic blood pressure after treatment with metformin and metformin+zinc+omega3 complex in male and female rabbits modeled with osteoporosis and metabolic syndrome were presented in tables.

Table 1. Systolic and diastolic blood pressure values in male rabbits (№7-12) with

№	Day 1		Day 15		Day 35	
	SB	DB	SB	DB	SB	DB
1	170	68	124	56	105	48
2	168	65	120	53	105	49
3	168	71	119	51	100	48
4	165	61	118	52	105	46
5	166	67	121	49	96	45
6	173	69	118	50	96	45
M± m	168,3±1,2	66,8±1,4	120,0±0,9	51,8±1,0	101,2±1,8	46,8±0,7

osteoporosis and metabolic syndrome modeled.

Table 1 shows the systolic (101.2 ± 1.8) and diastolic (46.8 ± 0.7) blood pressure values after metformin treatment in osteoporosis and metabolic syndrome modeled male rabbits. The results showed that by the last days of the treatment, the blood pressure was close to the norm, that is, it decreased to 60-65 mm Hg compared to the untreated group.

Table 2. Systolic and diastolic blood pressure values in male rabbits (№13-18) with osteoporosis and metabolic syndrome modeled.

№	Day 1		Day 15		Day 1	
	SB	DB	SB	DB	SB	DB
1	169	67	120	57	90	42
2	165	65	123	55	90	41
3	166	70	117	53	90	40
4	165	68	119	49	91	40
5	164	66	125	50	92	41
6	170	68	117	50	90	40
M± m	166,5±1,0	67,3±0,7	120,2±1,3	52,3±1,3	90,5±0,3	40,7±0,3

Table 2 shows the systolic (90.5 ± 0.3) and diastolic (40.7 ± 0.3) blood pressure values after treatment with metformin+zinc+omega3 complex in male rabbits modeled with osteoporosis and metabolic syndrome. The results showed that blood pressure decreased by 8-10 mm Hg on the last days of treatment compared to the group treated with metformin.

Table 3. Systolic and diastolic pressure indicators in female rabbits (N 25-30) with osteoporosis and metabolic syndrome modeled.

№	Day 1		Day 15		Day 35	
	SB	DB	SB	DB	SB	DB
1	169	65	125	55	100	48
2	171	65	120	54	102	48
3	168	71	119	51	98	49
4	166	61	119	50	96	45
5	165	67	120	50	98	48
6	170	69	119	53	95	45
M± m	168,2±0,9	66,3±1,4	120,3±1,0	52,2±0,9	98,2±1,0	47,2±0,7

Table 3 shows the systolic (98.2 ± 1.0) and diastolic (47.2 ± 0.7) blood pressure values after metformin treatment in female rabbits with osteoporosis and metabolic syndrome

models. The results showed that by the last days of the treatment, the blood pressure was close to the norm, that is, it decreased to 55-65 mm Hg compared to the untreated group.

Table 4. Systolic and diastolic pressure indicators in female rabbits (N 31-36) with

№	Day 1		Day 15		Day 35	
	SB	DB	SB	DB	SB	DB
1	170	66	121	55	90	40
2	165	65	121	55	91	41
3	166	69	118	50	90	40
4	164	65	118	51	98	41
5	165	64	120	51	95	42
6	171	68	119	51	90	43
M ± m	166,8±1,2	66,2±0,8	119,5±0,6	52,2±0,9	92,3±1,4	41,2±0,5

osteoporosis and metabolic syndrome modeled.

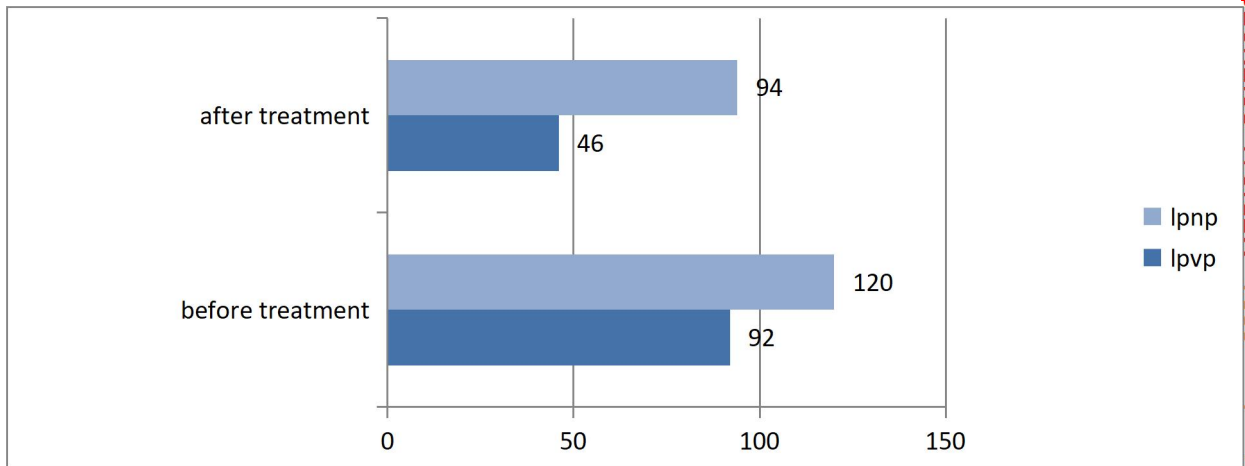
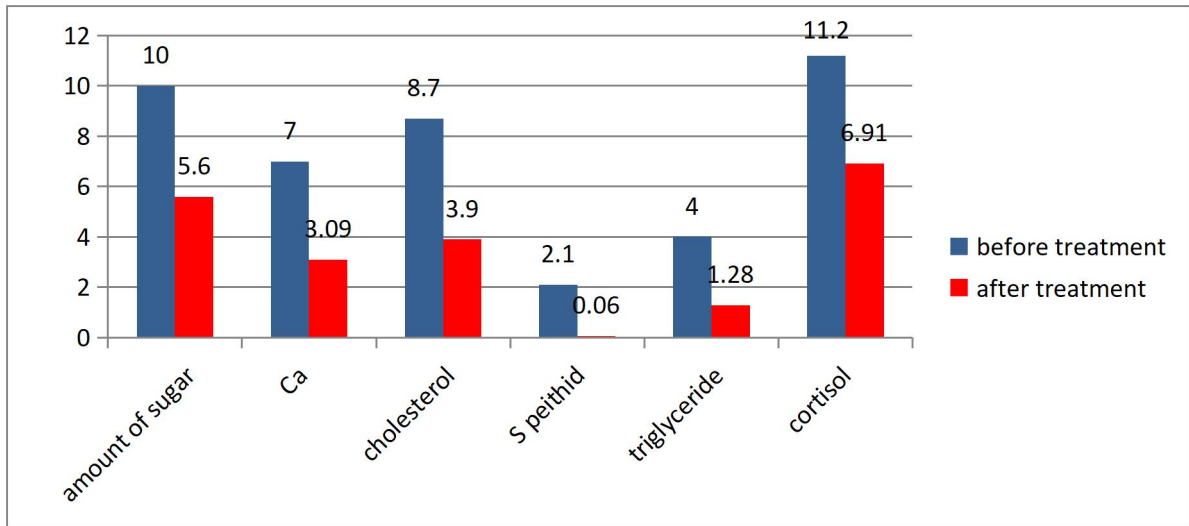
Table 4 shows the systolic (92.3±1.4) and diastolic (41.2±0.5) blood pressure values after treatment with metformin+zinc+omega 3 complex in female rabbits with osteoporosis and metabolic syndrome, compared with the metformin-treated group. were compared and the results were studied. On the last days of treatment, it was found that blood pressure decreased by 6-8 mmHg compared to the group treated with metformin. The results confirmed that the use of metformin+zinc+omega3 significantly reduced total cholesterol, triglycerides, low-density lipoproteins, and Castelli's atherogenic risk N index, and increased high-density lipoprotein levels, but had no effect on very low-density lipoproteins. The study showed that the changes in the metabolic syndrome and osteoporosis modeled group were significantly increased and closer to normal in those treated with metformin+zinc+omega3 compared to the metformin group.

Results of blood biochemical parameters after treatment in male rabbits modeled with osteoporosis and metabolic syndrome

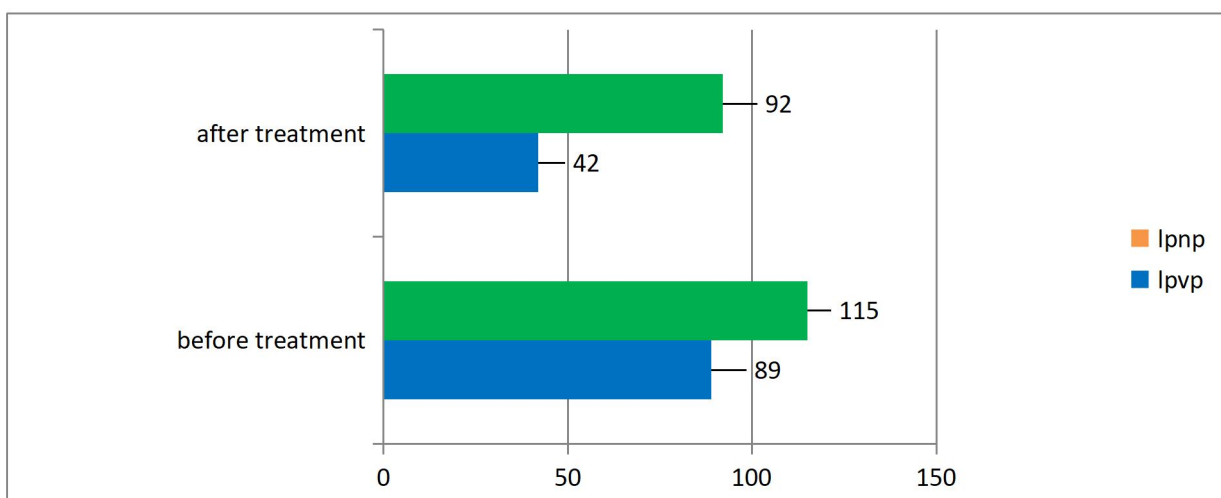
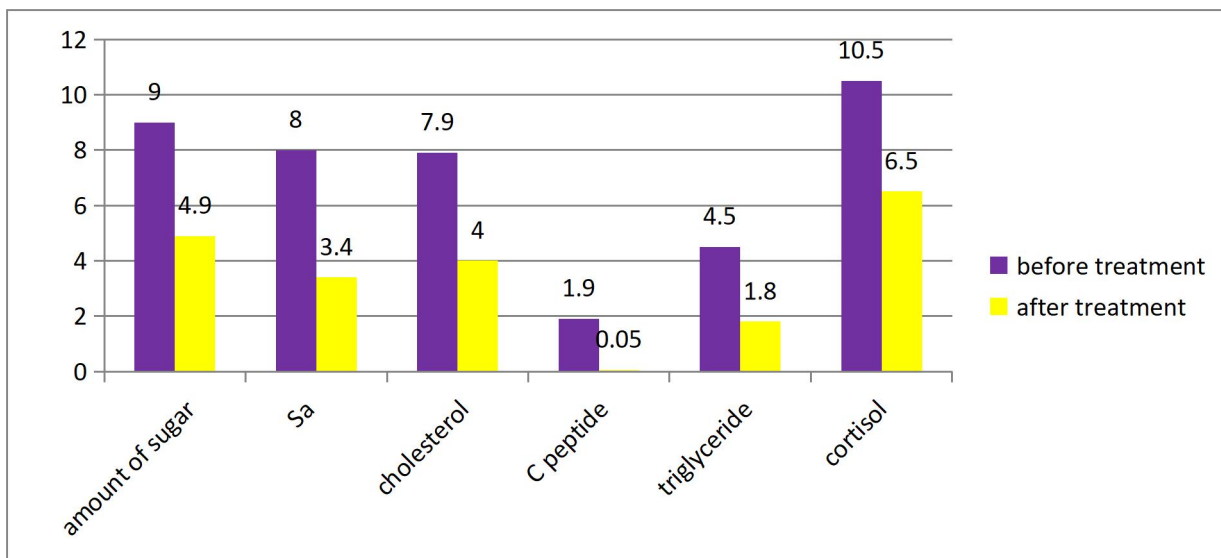
In the study of blood composition, serum C-peptide, glucose, triglycerides, cholesterol, and high-density lipoproteins were examined after treatment. Blood from the capillaries was collected in pre-prepared tubes. After blood collection, the tube was placed in a thermostat for 30 min at 37°C to induce blood clotting. The resulting serum is carefully separated from the walls. The sample was centrifuged at 1500 - 2000 rpm (189 - 335 g). After centrifugation, the liquid, serum, was carefully collected without catching the precipitate. The study of biochemical parameters of blood serum was carried out on a semi-automatic biochemical

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analyzer of the HUMAN (Germany) company, following the manufacturer's instructions, using appropriate open-type test kits.



Results of blood biochemical parameters after treatment in female rabbits modeled with osteoporosis and metabolic syndrome



The analysis of the last results from the treatment showed that in male and female rabbits with metabolic syndrome and osteoporosis, blood biochemical parameters were almost identical to those of healthy rabbits.

Summary

1. After treatment with metformin and metformin+zinc+omega3 complex in male and female rabbits with osteoporosis and metabolic syndrome, systolic and diastolic blood pressure indicators were studied. Compared to the group treated with metformin, the indicators of the group treated with metformin+zinc+omega3 complex did not differ from those of the healthy group. .

2. The results confirmed that the use of metformin+zinc+omega3 significantly reduced total cholesterol, triglycerides, low-density lipoproteins, and Castelli's atherogenic risk N index and increased high-density lipoproteins.

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