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RESEARCH ARTICLE

Features of bone destruction in rabbits with experimental metabolic syndrome

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Abstract

There is now evidence that abdominal obesity and metabolic syndrome in general, are associated with a decrease in bone mineral density, which in turn leads to an increased risk of fractures. A high incidence of osteoporosis and vertebral fractures in patients with MS has been proven. Thus, MS can be considered a new risk factor for osteoporosis. We studied biochemical parameters in rabbits with experimental metabolic syndrome, accompanied by bone destruction, as well as in models of metabolic syndrome (MS) and osteoporosis. The level of glucose and c-peptide indicates the development of insulin resistance in animals with MS and MS, accompanied by bone destruction. It has been shown that with metabolic syndrome associated with bone destruction, rabbits exhibit more profound disorders of lipid metabolism than with MS, the level of which differs slightly from each other. The study of bone remodeling indicators in a model of MS accompanied by bone destruction showed individual and gender differences in the content of bone remodeling markers in blood serum. It has been shown that in most experimental animals, there is a decrease in osteocalcin, which is a marker of osteosynthesis, and an increase in the level of type I collagen C-telopeptide, which indicates increased destruction of bone collagen. Moreover, the level of bone destruction was more pronounced in males than in females. A study of cartilage tissue degradation biomarkers showed that the change level in COMP and hyaluronic acid was higher in females than in males, and the deviation of aggrecan levels from the reference value was higher in males. From our results, we can conclude that bone tissue damage predominated in male rabbits with MS, while in females, the degree of cartilage tissue damage was higher.

Keywords: Metabolic syndrome, osteochondral destruction, rabbits.

Introduction

There is now evidence that abdominal obesity and metabolic syndrome in general, are associated with a decrease in bone mineral density, which in turn leads to an increased risk of fractures. A high incidence of osteoporosis and vertebral fractures in patients with MS has been proven (Schmidt Georg, 2020). Thus, MS can be considered a new risk factor for osteoporosis.

According to foreign publications, 70% of patients who have suffered an osteoporotic hip fracture have the pathology of the cardiovascular system (Diamond T, Thornley S, Sekel R. and Smerdely P 1997).

It should be emphasized that a number of authors classify loss of bone mineral density (BMD) as a predictor of CVD, namely lesions of the coronary arteries (Marcovitz P. A. and *et al*., 2005). This is explained by a certain similarity in the pathogenesis of osteoporosis and atherosclerosis, in which damaged monocytic cells in one case, differentiate in the vascular wall into macrophage-like "foam" cells, in the other into osteoclasts. In addition, bone and vascular tissues have a number of other common morphological and molecular properties. Vascular calcification is represented by the same elements as bone tissue: calcium salts, phosphates associated with hydroxyapatite, osteopontin, bone morphogenic protein, matrix Gla protein, type 1 collagen, osteonectin, osteocalcin, etc. (Tintut Y, Demer LL. 2001, V.B. Simonenko, A.Yu. Ekimovskikh, I.V. Dolbin 2013). A number of studies have noted the commonality of the pathogenesis of hypertension and osteoporosis. In particular, the activity of the renin-

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angiotensin-aldosterone system (RAAS), on the one hand, due to its influence on local blood flow and blood supply to bones, causes vasoconstriction of the microvasculature, and on the other, has a direct effect on the production of angiotensin II. The latter is a growth factor that directly stimulates the proliferation of osteoclasts and increases the level of endothelin-1, the content of which, upon activation of the RAAS, increases not only in the endothelium but also in osteoclasts. These data are confirmed in the clinic by the osteoprotective effect of angiotensin-converting enzyme inhibitors. By suppressing the activity of angiotensin II, these drugs promote less resorption of osteoclasts in bone tissue, reducing its loss of BMD.

In women with osteoporosis, an increase in the average daily values of SBP, DBP and average pressure in the aorta was detected. A direct correlation has been identified between parameters of central pressure, arterial stiffness and a history of fractures, their number, as well as indicators of the absolute ten-year risk of osteoporotic fractures and hip fractures (Tsarenok S.Yu., Gorbunov V.V., Aksenova T. A. 2017). Osteoporosis is considered one of the risk factors for cardiovascular events and a component of the cardiovascular continuum in women (Chazova I.E., Smetnik V.P., Balan V.E., *et al*. 2008).

In recent years, data have emerged on the unequal contribution of metabolic disorders to the formation of metabolic syndrome (MS) in men and women. Thus, Dallongeville J. *et al*. found that in women, increased weight, waist circumference, and high-density lipoprotein (HDL) levels make a greater contribution to the formation of MS; in men, systolic and diastolic blood pressure and Apolipoprotein B make a greater contribution to metabolic syndrome (Dallongeville J., Cottel D., Arveiler D. *et al*. 2004). These data support the concept of the need for different diagnostic criteria for metabolic syndrome in men and women.

It has been shown that arterial hypertension (AH) is often one of the first clinical manifestations of MS. The pathogenesis of hypertension in MS is based on insulin resistance and the compensatory hyperinsulinemia caused by it in combination with concomitant metabolic disorders Shilov A.M., Chubarov M.V., Melnik M.V., Rybkina T.E. 2003). With insulin resistance, the level of plasma insulin increases, which is not only a direct vasodilation agent but also leads to an increase in the level of catecholamine due to activation of the sympathoadrenal system, increasing cardiac output. Insulin stimulates tissue growth factors, increasing the proliferation of fibroblasts and vascular smooth muscle cells, and increases collagen synthesis in atherosclerotic plaques, narrowing their lumen.

To study biochemical parameters in rabbits with experimental metabolic syndrome and to accompany by bone destruction, as well as in models of metabolic syndrome (MS) and osteoporosis.

Materials and Methods

Experimental studies were carried out on 30 male and female rabbits weighing 2.0-2.5 kg. The animals were kept in standard vivarium conditions with a natural 12-hour light-and-dark cycle at an air temperature of 20±20C. The experiments were carried out in accordance with the rules adopted by the "International Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes" (Strasbourg, 1986).

Metabolic syndrome modeling

Metabolic syndrome was induced in rabbits on a combination diet with the addition of crystalline cholesterol to the daily diet at a dose of 250 mg/kg body weight mixed with grated carrots (approximately 100 g) against a background of physical inactivity. A freshly prepared 5% sucrose solution was poured into the animals' drinking bowl every day. Every 2 days, insulin was injected subcutaneously into the animals from the back at a dose of 0.1 units/100 g body weight. For modeling, mature male rabbits weighing at least 2000 are taken. MS modeling lasts up to 2 months.

Osteoporosis modeling

Estimates of osteoporosis in rabbits was performed by administering dexamethasone at a rate of 1.675 mg/kg intramuscularly once a day for 2 weeks.

Modeling 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 a 5% sucrose solution was used instead of water for 8 weeks, while every 2 days, insulin was injected subcutaneously from the back of the animals at a dose of 0.1 unit/100 g body weight, and the animals were kept under conditions of physical inactivity; to enhance the development of hypercholesterolemia, hyperglycemia and reduce bone mineral density, the animals were intramuscularly injected with dexamethasone at a dose of 0.1 mg/kg.

Blood sampling for biochemical analysis

The rabbit is fixed in its natural position using special boxes to obtain blood from the marginal ear vein. The most suitable place for a puncture is the lateral edge of the ear. Here, the vein is firmly fixed to the surrounding tissues. At the puncture site, the fur is cut off with scissors, and the skin is wiped with alcohol ether. Immediately before taking blood, additional arterial hyperemia of the ear is caused by heating it with an electric lamp or rubbing it with a cotton swab soaked in xylene. The base of the ear is slightly pinched. The marginal vein is cut with a blade closer to the tip of the ear or pierced with a needle. The escaping blood is collected into prepared capillaries or tubes. After blood collection, the tube is placed in a thermostat for 30 minutes at 37°C to form a blood clot. Carefully separate the formed

Table 1: Indicators of carbohydrate metabolism in rabbits of the studied groups (n = 5)

Group	*Observation days*			
	15	*30*	*45*	*60*
Metabolic syndrome (M ± m)				
Males	8,82	9,45	10,48	11,03
GI level	0,14	0,18	0,22	0,12
M	+92	+111	+136	+133
M	438,86	433,29	444,40	505,50
Change in GL level compared to control, %	35,91	12,17	11,11	30,32
c-peptide level	+37	+35	+38	+57
M	8,68	9,52	10,43	10,40
M	0,22	0,27	0,32	0,18
Change in c-peptide level compared to control, %	+89	+104	+124	+113
Females	449,96	449,95	483,28	483,28
GI level	33,05	7,46	23,95	39,20
M	+40	+40	+50	+50
Metabolic syndrome + osteoporosis (M±m)				
Males	10,22	11,18	12,12	13,37
GI level	0,06	0,14	0,16	0,14
M	+123	+150	+156	+183
M	562,45	550,72	550,46	555,96
Change in GL level compared to control,%	12,86	20,53	11,27	11,00
c-peptide level	+75	+71	+71	+73
M	10,98	11,90	13,20	15,08
M	0,16	0,08	0,11	0,12
Change in c-peptide level compared to control, %	+139	+156	+184	+209
Females	617,06	619,73	624,94	626,63
GI level	4,22	5,01	3,09	3,32
M	+92	+93	+95	+95
Osteoporosis (M±m)				
Males	10,17	10,37	10,58	10,78
GI level	0,20	0,20	0,25	0,25
M	+122	+132	+124	+128
M	455,5	449,955	400,96	399,96
Change in GL level compared to control, %	55,54	52,87	24,63	24,34
c-peptide level	+42	+40	+25	+25
M	9,68	9,98	10,18	10,13
M	0,12	0,11	0,15	0,13
Change in c-peptide level compared to control, %	+110	+115	+119	+108
Females	372,185	372,185	366,63	349,965
GI level	13,37821	10,24291	8,605769	20,63591
M	+16	+16	+14	+9
Control (M±m)				
Males	4,58	4,47	4,73	4,73
GI level	0,16	0,13	0,15	0,18
M	320,74	320,69	320,73	320,74
M	0,008	0,047	0,011	0,013
c-peptide level	4,60	4,65	4,65	4,87
M	0,17	0,13	0,13	0,22
M	320,72	320,73	320,73	320,72
Females	0,010	0,008	0,008	0,008

blood clot from the walls. The sample is centrifuged at 1500 to 2000 rpm (189–335 g). After centrifugation, carefully, without capturing the sediment, remove the supernatant liquid - blood serum.

Determination of serum glucose and cholesterol levels

Sugar and cholesterol levels were determined in serum using an enzymatic colorimetric test produced by Langdorpsesteenweg, Langdorp-Belgium on a biochemical analyzer Basic SECOMAM, Anova Analytics company (France), following the manufacturer's instructions, at a wavelength of 505 nm and a temperature of 37°C, a 1-cm cuvette.

Determination of serum levels of bone remodeling markers

The levels of osteocalcin, type I collagen C-telopeptide, cartilage oligomeric matrix protein (COMP), hyaluronic acid and aggrecan were determined by ELISA using kits from Cloud-Clone Corporation on a HumaRider HS ELISA analyzer, following the manufacturer's instructions.

Results

We used male and female rabbits to study the main factors that contribute to the development or are markers of MS in a model of MS associated with bone destruction. The data obtained indicate a certain contribution of manifestations of bone destruction to clinical markers of MS, while the influence of these factors on the physical condition of males and females differed.

The level of changes in the metabolic parameters of rabbits with MS also had certain differences in males and females (Table 1). In rabbits with MS, the blood glucose level on the 60th day of observation increased by 133% (males) and 113% (females) compared to the control, and the c-peptide level increased by 57 and 50%, respectively. In the model of MS, accompanied by bone destruction, more severe disorders of carbohydrate metabolism were observed in animals than in MS. Thus, if in males the increase in glucose levels was 183%, then in females it was 209%, and the increase in c-peptide levels was 73 and 95%, respectively. With bone destruction, the glucose level in males increased by 122 to 128%, and in females by 108%.

Table 2: Indicators of lipid metabolism in rabbits of the studied groups (n = 5)

Group	*Males*				*Females*			
Observation days	15	30	45	60	15	30	45	60
Metabolic syndrome (M±m)								
HL	4,93	6,62	7,50	9,27	5,35	7,27	8,27	9,82
M	0,13	0,12	0,10	0,19	0,12	0,11	0,22	0,15
M	4,93	6,3	6,0	7,4	5,2	6,7	6,9	7,67
Increase in CL level compared to control, x times	1,92	2,01	2,21	3,13	2,00	2,13	2,38	3,24
TG	0,03	0,04	0,04	0,06	0,02	0,03	0,04	0,06
M	31	34	84	100	38	42	59	100
M	47,13	46,88	46,62	46,35	44,68	44,37	44,03	43,73
Increase in TG level compared to control, %	0,31	0,30	0,31	0,26	0,18	0,15	0,13	0,13
HDL	-23	-24	-25	-25	-31	-32	-33	-34
M	132,02	182,52	254,67	306,77	129,08	209,27	284,30	354,88
M	6,33	11,57	17,12	2,80	1,99	4,43	12,28	19,08
Change in HDL level compared to control,%	+17	+61	+125	+171	+14	+85	+151	+214
Metabolic syndrome + osteoporosis (M±m)								
HL	5,81	8,35	9,36	11,80	7,02	8,80	10,02	12,85
M	0,25	0,24	0,18	0,37	0,15	0,15	0,13	0,19
M	5,8	7,95	7,8	9,44	7,0	8,0	8,35	10,0
Increase in CL level compared to control, x times	1,97	2,17	2,94	3,41	2,07	2,41	3,27	3,59
TG, mmol/l	0,01	0,02	0,02	0,03	0,01	0,02	0,03	0,02
M	35	49	100	133	43	60	118	139
M	36,47	36,35	35,97	35,73	34,43	34,23	33,90	33,37
Increase in TG level compared to control, %	0,20	0,14	0,19	0,17	0,09	0,05	0,06	0,12
HDL	-59	-60	-61	-63	-70	-71	-73	-75
M	134,70	224,28	317,73	416,45	141,32	229,20	340,57	442,07
M	2,00	2,74	3,19	3,60	2,57	2,28	2,90	2,66
Change in HDL level compared to control,%	+19	+98	+181	+268	+25	+102	+200	+291
Osteoporosis (M+m)								
HL	2,68	4,05	5,12	6,12	3,16	4,55	5,88	7,045
M	0,12	0,12	0,15	0,14	0,10	0,19	0,06	0,11
M	2,68	3,86	4,3	4,9	3,13	4,17	4,9	5,5
Increase in CL level compared to control, x times	1,66	1,81	2,04	2,66	1,78	1,95	2,21	2,95
TG	0,02	0,03	0,02	0,05	0,02	0,02	0,01	0,10
M	14	21	34	72	23	34	52	103
M	51,98	51,82	51,45	51,15	51,15	50,82	50,50	50,30
Increase in TG level compared to control, %	0,18	0,14	0,16	0,16	0,08	0,10	0,13	0,12
HDL	- 12	-12	-13	-14	-11	-12	-13	-13
M	123,18	164,98	223,57	292,42	125,40	179,25	209,28	275,73
M	0,85	2,29	1,17	1,65	1,14	2,10	1,93	2,84

Change in HDL level compared to control,%	+9	+50	+100	+264	+9	+159	+189	+252
Control (M±m)								
HL	1,0	1,05	1,20	1,25	1,01	1,09	1,20	1,28
M	0,03	0,03	0,02	0,02	0,02	0,03	0,03	0,02
M	1,46	1,50	1,52	1,55	1,45	1,50	1,55	1,59
TG	0,01	0,02	0,02	0,02	0,01	0,01	0,01	0,01
M	58,17	56,90	55,62	54,45	58,52	56,88	56,42	55,88
M	0,16	0,33	0,38	0,47	0,17	0,19	0,15	0,14
HDL	112,98	109,80	109,82	110,53	113,13	112,13	110,68	109,22
M	1,31	2,08	1,85	1,95	2,10	1,73	1,25	1,78

The level of c-peptide increased in males by 25%, while it remained virtually unchanged (9%) in females. All indicators were calculated in comparison with the control. In type 2 diabetes, high c-peptide values indicate insulin resistance. Thus, we can conclude that IR develops in animals with MS and MS, accompanied by bone destruction.

The general trend of lipid metabolism disorders demonstrates an increase in blood cholesterol, triglycerides, LDL and a decrease in HDL (Table 2). At the same time, in male and female rabbits with MS, the cholesterol content increased by 7.4 and 7.7 times compared to the control, the level of triglycerides - by two times in both groups, LDL - by 1.7 and 2.14 times, and the level HDL is reduced by 24 and 34%, respectively. In metabolic syndrome associated with bone destruction, male and female rabbits exhibit more profound disturbances in lipid metabolism, the level of which differs slightly from each other. Thus, cholesterol levels increase by about 10 times compared to the control, triglycerides by 33-39 times, LDL by 2.7 to 2.9 times, HDL levels decrease by 63% in males and 75% in females. In the model of bone destruction, serious disturbances in lipid metabolism were also observed, however, less pronounced than in the two previous models: an increase in cholesterol in males and females by 5-5.5 times, triglycerides by 72 and 103%, LDL by 2.5 -2.6 times, HDL drop by 13-14%.

The study of bone remodeling indicators in a model of MS accompanied by bone destruction showed individual and gender differences in the content of bone remodeling markers in blood serum. Measurements were carried out on the 45th day of the experiment.

In male and female rabbits with MS accompanied by bone destruction, changes in the levels of bone remodeling showed a similar trend. Osteocalcin (OC) levels were below (60%) or within (40%) the reference value. The type I collagen c-telopeptide level in 60% of animals was higher, and in 40% it was within the reference value. Oligomeric cartilage matrix protein (COMP) was within the reference value in 80% of males and 60% of females. Hyaluronic acid was above (60%) or within the reference value, and aggrecan (AGC) was below (60%), above or within the reference value (40%) (Table 3).

However, the degree of change in the levels of bone turnover markers in males and females was different. Thus, the OS level in males was 1.54 to 20 times lower than the reference value; in females, it was 1.2 to 2.2 times lower. The type I collagen c-telopeptide level in male rabbits decreased by 2.44 to 537 times or increased by 1.3 to 2.48 times, and in females, it increased by 1.86 to 3.2 times relative to the reference value.

One of the most specific markers of bone formation is the non-collagenous protein osteocalcin (OC) (Brown J. P. 1984). Osteocalcin, produced by osteoblasts and odontoblasts (Garnero P. 1996, P. Garnero, E.Sornay-Rendu, B.Claustrat, P. D. Delmas 2000), has calcium-binding ability and interacts with hydroxyapatite, is involved in bone mineralization.

Primary osteoporosis's OC level is either within normal limits or slightly increased. High osteocalcin levels indicate a significant level of bone turnover and an increased risk of osteoporotic fractures in the postmenopausal period. Most osteocalcin is bound to hydroxyapatite, and only about 10% of the intact form circulates in the blood. In the bloodstream, OA is degraded into polypeptide fragments: N-terminal, MID, N-MID, C-terminal, MID-C. The N-terminal and N-MID fragments are of diagnostic importance (L.B. Drygina, I.V. Trofimova, O.A. Sablin, I.D. Nikiforova 2011).

Serum osteocalcin is used in clinical diagnosis as a marker of bone formation (Ivaska KK. 2005). The advantage of its use as an indicator of bone formation is its tissue specificity and relatively low variability (Jagtap VR, Ganu JV, Nagane NS. 2010).

Genetic studies in mouse models have shown that OC in decarboxylated form has effects on pancreatic β-cells to increase insulin production, and in peripheral tissues, its effects increase glucose utilization through increased insulin sensitivity and reduce visceral fat. When affecting the pancreas, osteocalcin acts through the GPCR6A receptor, as a result of whose activation the cAMP-related signaling pathway is triggered (Grebennikova T.A., Belaya Zh.E., Tsoriev T.T., Rozhinskaya L.Ya., Melnichenko G.A. 2015).

Thus, in MS with bone destruction, low levels of OC may enhance the manifestations of MS at the hormonal level, increasing insulin resistance.

Table 3: Level of bone metabolism markers in rabbits compared with reference values (n = 5)

Indicators, ng/mL				
Osteocalcin (OC)	*Type I collagen C-telopeptide*	*Cartilage oligomeric matrix protein (COMP)*	*Hyaluronic acid*	*Aggrecan (AGC)*
Males				
1,3	1,062	0,846	11,0	0,01
0,7	0,701	1777	630,0	33
0,1	1,331	0,075	1237	0,144
5,8	0,220	0,220	975,0	83
2,2	0,001	947	51,0	0,794
Females				
10,0	0,352	1396	1396	0,373
31,1	0,998	666	818	98
0,9	1,735	2174	1954	21
26,3	0,110	0,641	0,011	0,463
1,1	1,004	1062	220	288
Reference value				
2,0 - 22,0	< 0,537	<1000	4,94-400	0,625-40

Our results are supported by clinical data obtained by studying the relationship of bone turnover markers with bone mineral density, metabolic parameters and body composition in postmenopausal women with type 2 diabetes. In these patients, the concentrations of osteocalcin and osteoprotegerin were significantly reduced compared to controls (Klimontov V.V., Fazullina O.N., Lykov A.P., Konenkov V.I. 2016).

Type I collagen C-telopeptide (β-CrossLaps) enters the bloodstream when type I collagen is degraded in osteoclasts. Type I collagen is a protein that makes up more than 90% of the organic bone matrix and consists of three peptide chains. The C-telopeptide of type I collagen is a fragment of the α chain. An increase in blood β-CrossLaps is associated with a decrease in bone mineral density in Crohn's disease and osteoporosis and with the severity of bone damage in rheumatoid arthritis (Nurullina G.M., Akhmadullina G.I. 2018).

Thus, our studies have shown that in most experimental animals with MS associated with bone destruction, there is a decrease in osteocalcin, which is a marker of osteosynthesis, and an increase in the level of type I collagen C-telopeptide, which indicates increased destruction of bone collagen. Moreover, the level of bone destruction was more pronounced in males than in females.

A study of cartilage tissue degradation biomarkers showed that the level of COMT in males was within the reference values, and only in 20% of animals was increased by 1.7 times; in females, the level of COMT increased by 1.4 to 2.17 times. The level of hyaluronic acid in males was within the reference value or increased by 1.57 to 2.44 times, in females, it was increased by 2.4 to 4.88 times. And in 20% it was decreased by 449 times. The level of aggrecan in males was reduced by 4.34 to 62.5 times or increased by 1.27 to 2.07 times, in females, it was reduced by 1.35-1.67 times or increased by 2.45-7.2 times relative to reference values.

Cartilage oligomeric matrix protein (COMP) is a specific non-collagenous protein of the extracellular matrix of connective tissue, localized mainly in cartilage, ligaments and tendons. For the first time, COMP was discovered in the blood serum and synovial fluid of patients with rheumatoid arthritis (RA), a chronic systemic disease accompanied by damage not only to joint structures but also to internal organs. According to research, COMP has established itself as a diagnostic and prognostic indicator of disease severity and treatment effectiveness (Belova Yu., Gladilin G. 2017). Hyaluronic acid is a natural component of synovial fluid; it reduces the friction of articular surfaces and provides a number of protective and regulatory effects (Otvetchikova D.I., Ryabkov E.N. 2022).

Aggrecan is a large proteoglycan, one of the most important components of the matrix. Its function is to counteract mechanical stress and provide the osmotic pressure necessary for the normal functioning of cells and tissues. Aggrecan, as a structural proteoglycan, plays an important role in cell-cell and cell-matrix interactions due to its ability to bind to hyaluronic acid and collagen (C. Kiani, L. Chen, Y.J. Wu *et al*. 2002). Degradation of aggrecan in articular cartilage, both with age and in osteoarthritis, is carried out by matrix metalloproteinases and aggrekinase, which leads to disruption of its organization and functioning (Grandfather N.V. Aggrekan 2012).

Analysis of data obtained from experimental animals showed that the changes in COMP and hyaluronic acid were higher in females than in males. The deviation of aggrecan levels from the reference value was higher in males.

Thus, in male and female rabbits with MS accompanied by osteochondral destruction, the level of changes in markers of bone remodeling compared to reference values was different. It has been shown that in most experimental animals, there is a decrease in osteocalcin, which is a marker of osteosynthesis, and an increase in the level of type I collagen C-telopeptide, which indicates increased destruction of bone collagen. Moreover, the level of bone destruction was more pronounced in males than in females. A study of cartilage tissue degradation biomarkers showed that the change level in COMP and hyaluronic acid was higher in females than in males, and the deviation of aggrecan levels from the reference value was higher in males.

From our results we can conclude that in male rabbits with MS, bone tissue damage predominated, while in females, the degree of cartilage tissue damage was higher.

Discussion

Osteoporosis is considered as one of the risk factors for cardiovascular events and a component of the cardiovascular continuum in women (Tsarenok S.Yu., Gorbunov V.V., Aksenova T.A. 2017).

In recent years, data have emerged on the unequal contribution of metabolic disorders to the formation of metabolic syndrome (MS) in men and women. Thus, Dallongeville J. *et al*. found that in women, increased weight, waist circumference, and high-density lipoprotein (HDL) levels make a greater contribution to the formation of MS; in men, systolic and diastolic blood pressure and apolipoprotein B make a greater contribution to metabolic syndrome.

There is evidence in the literature of a pathogenetic connection between lipid metabolism disorders, osteoporosis and atherosclerosis associated with the action of oxidized low-density lipoproteins, which are highly atherogenic (Ragino Yu.I., Nikitin Yu.P. 2006). In postmenopausal women, low-density lipoprotein (LDL) cholesterol levels were significantly inversely associated with BMD, leading the authors to suggest that lipids and bone tissue "share common factors linking osteoporosis and atherosclerosis" (Yamaguchi T, Sugimoto T, Yano S, *et al*. 2002).

Abdominal obesity (AO) is not always an early component of MS; the sequence of appearance of hypertension, carbohydrate metabolism disorders (CDM), and dyslipidemia is also different. According to a population-based study by Taiwanese scientists, lipid disorders appear earlier than all components of MS in both sexes (Hwang L.C., Bai C.H., Chen C.J., Chien K.L. 2007). Other Taiwanese researchers have established gender differences in the sequence of development of MS: in women in adolescence, abdominal obesity appears, a decrease in HDL, on average - hypertension and an increase in triglycerides (TG), and later type 2 diabetes; in boys, MS debuts with AO, an increase in TG and a decrease HDL, hypertension appears in middle age, and later type 2 diabetes (Tsay Y.C., Chen C.H., Pan W.H. 2016).

The data we obtained are confirmed by the literature. Thus, it has been shown that rheumatoid arthritis in women is characterized by a more severe course of the pathological process (Gonchar G. A. 2013). Primary osteoporosis is also known to be more common in women than men (Biryukova E.V., Shinkin M.V. 2021).

All these data indicate the need for different diagnostic criteria and pharmacotherapy for metabolic syndrome and osteoporosis in men and women in the clinic.

Conclusion

In the model of MS, accompanied by bone destruction, more severe disorders of carbohydrate metabolism were observed in animals than in MS. Thus, if in males the increase in glucose levels was 183%, then in females it was 209%, and the increase in c-peptide levels was 73 and 95%, respectively. With bone destruction, the glucose level in males increased by 122 to 128%, and in females by 108%. The level of c-peptide increased in males by 25%, while it remained virtually unchanged (9%) in females. Thus, we can conclude that IR develops in animals with MS and MS, accompanied by bone destruction.

It has been shown that with metabolic syndrome associated with bone destruction, rabbits exhibit more profound disorders of lipid metabolism than with MS, the level of which differs slightly from each other. Thus, cholesterol levels increase by about 10 times compared to the control, triglycerides by 33 to 39 times, LDL by 2.7 to 2.9 times, HDL levels decrease by 63% in males and 75% in females. In the model of bone destruction, serious disturbances in lipid metabolism were also observed, however, less pronounced than in the models of MS and MS accompanied by bone destruction: an increase in cholesterol in males and females by 5 to 5.5 times, triglycerides by 72 and 103%, LDL – 2.5 to 2.6 times, HDL drop by 13 to 14%.

The study of bone remodeling indicators in a model of MS accompanied by bone destruction showed individual and gender differences in the content of bone remodeling markers in the blood serum. In male and female rabbits with MS accompanied by bone destruction, changes in the levels of bone remodeling showed a similar trend. Osteocalcin (OC) levels were below (60%) or within (40%) the reference value. The type I collagen c-telopeptide level in 60% of animals was higher; in 40%, it was within the reference value. Oligomeric cartilage matrix protein (COMP) was within the reference value in 80% of males and 60% of females. Hyaluronic acid was above (60%) or within the reference value, and aggrecan (AGC) was below (60%), above or within the reference value (40%).

In male and female rabbits with MS, accompanied by osteochondral destruction, the level of changes in

markers of bone remodeling compared to reference values turned out to be different. It has been shown that in most experimental animals, there is a decrease in osteocalcin, which is a marker of osteosynthesis, and an increase in the level of type I collagen C-telopeptide, which indicates increased destruction of bone collagen. Moreover, the level of bone destruction was more pronounced in males than in females. A study of cartilage tissue degradation biomarkers showed that the change level in COMP and hyaluronic acid was higher in females than in males, and the deviation of aggrecan levels from the reference value was higher in males. From our results, we can conclude that bone tissue damage predominated in male rabbits with MS, while in females, the degree of cartilage tissue damage was higher.

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