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ФЕТУИН-А И ВТОРИЧНЫЙ ОСТЕОПОРОЗ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

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Цель. Изучить уровень фетуина-А (ФА), минеральную плотность костной ткани (МПКТ) и отдельные маркеры костного ремоделирования у больных ревматоидным артритом (РА). ***Материалы и методы.*** Было исследовано 110 больных РА и 30 условно здоровых лиц. В обеих группах определялся уровень ФА и МПКТ. В группе больных РА определяли уровни С-телопептида коллагена I типа, N-терминального пропептида проколлагена I, 25-гидроксиколекальциферола, общей щелочной фосфатазы, общего кальция крови. ***Результаты.*** Средняя сывороточная концентрация ФА в крови больных РА составила 765,67±120,66 мкг/мл, что ниже показателей доноров – 812,95±76,21 мкг/мл (p=0,0437). В группе больных РА средний уровень ФА при наличии остеопороза (n=52) составил 733,65±135,84 мкг/мл, а в группе без остеопороза – 794,37±97,7 мкг/мл (p=0,0044). Также уровень ФА был снижен у пациентов с остеопоретическими переломами (n=24) и составил 694,79±110,47 мкг/мл, против 785,45±116,43 мкг/мл для пациентов без остеопоретических переломов (n=86; p=0,00091). Выявлена положительная корреляционная взаимосвязь между уровнем ФА и МПКТ L1-L4 (r=0,194; p=0,042), шейки бедра (r=0,328; p<0,0001) и проксимальным отделом бедра (r=0,293; p=0,002), уровнем 25-гидроксиколекальциферола (r=0,259; p=0,006) и отрицательная – с С-телопептидом коллагена 1 типа (r=-0,203; p=0,033). ***Выводы.*** Для больных РА с пониженным уровнем ФА характерна бóльшая частота выявления остеопороза и остеопоретических переломов, меньшая – МПКТ по L1-L4, шейке бедра и проксимальному отделу бедренной кости, Также, пониженный уровень ФА ассоциирован с меньшим уровнем 25-гидроксиколекальциферола и большим – С-телопептида коллагена 1 типа, что позволяет предположить наличие остеопротективной функции у данного гликопротеина

Ключевые слова: *фетуин-А; остеопороз; костный обмен; минеральная плотность костной ткани; ревматоидный артрит.*

FETUIN-A AND SECONDARY OSTEOPOROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Aim. To study the level of fetuin-A (FA), bone mineral density (BMD) and certain markers of bone remodeling in patients with rheumatoid arthritis (RA). ***Materials and Methods***. 110 Patients with RA and 30 conventionally healthy patients were examined. In both groups the levels of FA and BMD were determined. In the group of patients with RA the levels of C-telopeptide of

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type I collagen, N-terminal propeptide of procollagen I, 25-hydroxy-cholecalciferol, total alkaline phosphatase, total calcium of blood were determined. ***Results.*** The mean concentration of FA in blood serum of patients with RA was 765.67±120.66 μg/mL, which was below the respective parameter in donors – 812.95±76.21 μg/mL (p=0.0437). In the group of patients with RA with osteoporosis (n=52) the mean level of FA was 733.65±135.84 μg/mL, and in the group without osteoporosis – 794.37±97.7 μg/mL (p=0.0044). The level of FA was also reduced in patients with osteoporotic fractures (n=24) – 694.79±110.47 μg/mL against 785.45±116.43 μg/mL in patients without osteoporotic fractures (n=86; p=0.00091). A positive correlation relationship was found between the level of FA and BMD of L1-L4 (r=0.194; p=0.042), femoral neck (r=0.328; p<0.0001) and proximal femur (r=0.293; p=0.002), and the level of 25-hydroxy-cholecalciferol (r=0.259; p=0.006), and the negative correlation relationship – with C-telopeptide of type I collagen (r=-0.203; p=0.033). ***Conclusions***. Patients with RA with reduced FA level were characterized by a higher detection rate of osteoporosis and of osteoporotic fractures, and by a lower BMD of L2-L4, femoral bone and proximal femur. Besides, a lower level of FA was associated with a lower level of 25-hydroxy-cholecalciferol and with a higher level of C-telopeptide of type I collagen which permits to suggest existence of osteoprotective function in this glycoprotein.

Keywords: *fetuin-A; osteoporosis; bone metabolism; bone mineral density; rheumatoid arthritis.*

Osteoporosis and osteoporotic fractures are one of central problems in modern medicine. Osteoporosis is one of most common non-infectious diseases which makes a significant contribution into disability and mortality of individuals above fifty [1]. Risks for osteoporotic fractures of hip, spine and forearm in individuals above 50 make 40% in women and 13% of men of the overall population [2].

Secondary osteoporosis considerably impairs the quality of life of patients with rheumatoid arthritis (RA). It was found that development of secondary osteoporosis in RA is promoted by both traditional risk factors (female gender, smoking, age, low body mass index, low bone mineral density, deficit of vitamin D, etc.) and also by the risk factors inherent to the pathogenesis of RA (increased level of pro-inflammatory cytokines, high activity of the disease, functional insufficiency of joints with reduction of physical activity, hormonal disorders, reduction of renal clearance, increase in the concentration of homocysteine in blood plasma, etc.) [3]. According to the data of Research Institute of Rheumatology of Russian Academy of Medical Sciences, analysis of densitometry protocols of 1923 patients with RA (88% of women and 12% of men) showed reduction of parameters of BMD below the norm in more than half of the examined patients, and in 29% of patients osteoporosis was detected in at least one of the examined zones (L1-L4, femoral neck, distal forearm of the non-dominant arm) [4]. By the literature data, risk for deformations and fractures of vertebral bodies in patients with RA is 2 times and the incidence of osteoporotic fractures of proximal femur is 1.5-2 times that in the population [5].

One of important proteins of bone matrix is fetuin-A (FA). It is a non-collagen glycoprotein synthetized by the liver and possessing a wide spectrum of biological functions [6]. The main mechanism of the effect of FA on the bone metabolism consists in its ability to bind calcium and the members of the super family of TGF-β (transforming growth factor β) [7]. The latter play a key role in development of bone tissue and in bone remodeling. Biological effects of different isoforms of TGF-β are realized through their interaction with one of specific receptors – TβRI or TβRII [8].

Adequate osteogenesis is based on the intricate balance between the levels of FA and

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TGF-β. It is proved that the optimal concentration of TGF-β is necessary for differentiation of bone tissue, and its high concentration inhibits mineralization [9]. A FA molecule competitively binds and blocks TGF-β and bone morphogenetic protein (BMP) due to the existence of the site identical to TβRII [7].

The interrelation between FA and inflammatory processes is studied by many authors and remains contradictory. Thus, M. Daveau, et al. found out that FA may be referred to negative acute phase proteins, since its synthesis decreases under influence of pro-inflammatory cytokines [10]. On the other hand, A. Tuttolomondo, et al. noted that FA may also be a positive acute phase protein, since its level positively correlates with the level of *high-mobility group box-1* (HMGB-1) in ischemic stroke [11]. In turn, K.M. Dziegielewska, et al. noted that FA is capable of blocking production of IL-1 by macrophages through stabilization of their membrane [12]. There also exist some works devoted to study of the level of FA in RA. The majority of works emphasize the negative correlation between the level of FA and activity of the disease [13-15]. Thus, of interest is a study of the interrelation of the level of FA and secondary osteoporosis in patients with RA.

The *aim* of work – to study the level of fetuin-A, bone mineral density and some markers of bone remodeling in patients with rheumatoid arthritis.

Materials and Methods

The study included 110 patients with RA verified on the basis of ACR/EULAR 2010 criteria, and 30 conventionally healthy individuals.

The level of FA (ELISA BioVendor, Czech Republic) and bone mineral density (Lunar DPX-NT GE) were determined in both groups. The level of 25-hydroxycholecalciferol, C-telopeptide of type I collagen, N-terminal propeptide of procollagen I, total blood calcium and total alkaline phosphatase were measured in the group of patients with RA.

Diagnosis of osteoporosis was made on the basis of WHO criteria (for women above 50 in the post- menopausal period), Russian Clinical Recommendations for osteoporosis (for women with intake of glucocorticoids in history) and Recommendations of the International Society of Clinical Densitometry (for women in pre-menopausal period). All patients signed Informed consent for examination and processing of individual data.

Statistical processing of the data of clinical examination was carried out using program packages Statistica 10.0 Stat Soft Inc., USA). Analysis of the grouping criteria was conducted using ANOVA-tests. Determination of statistical significance of differences from the control group – post-hoc analysis. Interrelation of quantitative parameters – correlation analysis. Results were considered statistically significant at $p<0.05$.

Results and Discussion

The mean level of fetuin-A in patients with RA was 765.67±120.66 μg/mL, which was reliably lower than respective parameter of donors – 812.95±76.21 μg/mL ($p=0.0437$). According to the criteria of Kolmogorov-Simonov, FA values in the groups of patients with RA and of conventionally healthy individuals obeyed normal distribution ($d=0.083$; $p>0.2$ and $d=0,153$; $p>0.2$ respectively).

Osteoporosis was identified in 52 patients (47.2%) with RA. The analysis of differences of the mean level of FA in the groups of patients with osteoporosis, without osteoporosis, and of conventionally healthy individuals is given in Table 1.

According to the obtained data, FA level in blood serum of patients with RA complicated with osteoporosis was reliably lower than in groups without osteoporosis and in conventionally healthy individuals. Besides, the mean level of FA in the group of patients with osteoporotic fractures (n=24) was 694.79±110.47 μg/mL which is lower than in

Table 1

Analysis of Differences of Mean Values of Fetuin-A in Studied Groups

Group	Fetuin-A Level (mean ± standard deviation)	p
With osteoporosis (n=52)	733.65±135.84	p=0.0044[1] and p=0.002[2]
Without osteoporosis (n=58)	794.37±97.77	p=0.0044[1] and p=0.453[3]
Conventionally healthy individuals (n=30)	812.95±76.21	p=0.453[3] and p=0.002[2]

Note: 1 – statistical significance of differences between patients with and without osteoporosis; 2 – statistical significance of differences between patients with osteoporosis and conventionally healthy individuals; 3 – statistical significance of differences between patients without osteoporosis and conventionally healthy individuals.

the group without fractures (n=86) – 785.45±116.43 μg/mL (p=0.00091).

Thus, decreased FA level in the blood serum of patients with RA may indicate the existence of osteoporosis and an increased risk of osteoporotic fractures.

To determine the interrelation between bone mineral density (BMD) and FA level, correlation analysis of selected parameters in the group of patients with RA was conducted. The results are presented in Table 2.

Table 2

Correlation Interrelation of FA Level and Bone Mineral Density in Patients with Rheumatoid Arthritis

Parameter	Correlation Degree, r	p
BMD of L1-L4	0.1943	p=0.042
BMD of femoral neck	0.328	p<0.0001
BMD of proximal femur	0.293	p=0.002

As it follows from Table 2, a statistically significant positive correlation with all parameters was found. Reduction of FA level was accompanied by loss of BMD in the studied group of patients. It should be noted that in division of patients to groups with and without osteoporosis, a reliable moderate positive correlation with FA was found only in one parameter – femoral neck (r=0.3356; p=0.015). *Thus, alteration of BMD may be associated with the dynamics of FA level in blood serum of patients with RA.*

Analysis of interrelation of FA level with parameters of the bone metabolism in the group of patients with RA is given in Table 3.

Table 3

Interrelation of Fetuin-A Level and Parameters of Bone Metabolism

Parameters of Bone Metabolism and 25(OH) Vitamin D of Serum	Correlation Degree, r	p
25(OH) vitamin D, nmol/L	0.259	p=0.006
C-telopeptide of type I collagen, ng/mL	-0.203	p=0.033
P1NP, pg/mL	-0.054	p=0.573
Total blood calcium, mol/L	0.273	p=0.777
Total alkaline phosphatase, Un/L	0.003	p=0.975

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According to the presented data (Table 3), a positive correlation dependence was found between FA and the level of 25(OH)VitD, and a negative correlation dependence – with C-telopeptide of type I collagen which permits to suggest existence of *osteoprotective properties in the given glycoprotein.*

Conclusion

Patients with rheumatoid arthritis with a reduced level of fetuin-A are characterized by a high incidence of osteoporosis and osteoporotic fractures, lower bone mineral density in L1-L4, femoral neck and proximal femur.

Besides, decreased level of FA is associated with the lower level of 25-hydroxycholecalciferol and with the higher level of C-telopeptide of type I collagen.

In result, it is reasonable to propose creation of medical drugs on the basis of fetuin-A molecule that can facilitate prevention and/or treatment of secondary osteoporosis.

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Дополнительная информация [Additional Info]

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