



## The Importance of Immunological Factors in the Early Diagnosis of Osteoarthritis in Women

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**Abstract:** Osteoarthritis of the knee joints is a serious disease of the musculoskeletal system, leading to a deterioration in the quality of life and disability. The widespread prevalence of gonarthrosis and the social consequences associated with it have put forward issues of improving the diagnosis and treatment of patients with this pathology in the category of medical, social and economic problems [1].

**Key words:** cartilage, subchondral bone, synovial membrane, ligaments.

The pathological process in osteoarthritis is based on inflammatory and degenerative processes involving articular cartilage, subchondral bone, synovial membrane, ligaments, capsule and periarticular muscles [1-3].

Among large joints, osteoarthritis of the knee joint is most common, which mainly affects women. Features of the trophic articular cartilage suggest that the development of osteoarthritis can contribute to disorders of vascularization in the subchondral zone of the articulating bones and proliferation of cartilage cells. In this regard, studies of the expression of families of vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF) in individuals with initial manifestations of osteoarthritis are of interest. Among the numerous substances that stimulate angiogenesis, members of the VEGF and FGF [4].

Currently, the VEGF family is represented by 6 factors: VEGF-A; VEGF-B; VEGF-C; VEGF-D; VEGF-E and placental growth factor (PLGF — placental growth factor) [5, 6].

Hypoxia is one of the activators of VEGF [7]. In addition, VEGF expression is stimulated by proangiogenic factors, including epidermal growth factor (EGF — epidermal growth factor), the main factor fibroblast growth factor (FGF-2), platelet—derived growth factor (PDGF - platelet-derived growth factor) and interleukin-1 $\beta$  (IL-1 $\beta$ ). Vascular endothelial growth factor type A (VEGF-A) is one of the main mediators in angiogenesis. This cytokine is expressed by endotheliocytes, fibroblasts, osteoblasts, platelets, lymphocytes, polymorphonuclear and smooth muscle cells. The FGF family plays a key role in the regulation of chondrogenesis, osteogenesis, bone and mineral homeostasis during the ontogenesis of the organism [8, 9].

The literature discusses signaling pathways for regulating cartilage homeostasis by fibroblast growth factors such as FGF-2, FGF-18 and FGF-8. Thus, FGF-2 has been found to exhibit catabolic effects in articular chondrocytes, consisting in inhibition of extracellular matrix accumulation, inhibition of proteoglycan synthesis and cell clustering — phenomena characteristic of the development of arthrosis [10].

**The purpose of the study** was to compare and study the relationship between the content of vascular endothelial growth factor and fibroblast growth factor in individuals with initial clinical and radiological manifestations of degeneration of hyaline cartilage of the knee joints and healthy people.

**Material and methods.** There were 30 practically healthy women under observation, their average age was  $49.6 \pm 4.7$  years. The criteria for inclusion in the study were female gender, age from 40 to 60 years, absence of systemic connective tissue diseases, injuries of the musculoskeletal system, acute somatic and chronic diseases in the acute stage, as well as infectious and inflammatory diseases. All the examined persons are divided into two groups: control and main.

The main group consisted of 36 women (average age  $53.1 \pm 4.5$  years), in whom initial manifestations of gonarthrosis were revealed during the survey and X-ray and ultrasound examinations of the knee joints. Thus, 24 people complained of intermittent moderate pain in one of the knee joints after exertion, not accompanied by restriction of movement and does not affect the quality of life, including 12 — a short-term feeling of crunching in the knees, usually in the morning when walking. Initial manifestations of osteoarthritis of the knee joint were found in all 36 subjects examined during instrumental examination (radiography, ultrasound): minimal signs of synovitis, unevenness of articular surfaces, minor manifestations of heterogeneity of cartilage and menisci, single osteophytes on articular surfaces, thinning of cartilage less than 2 about 30 practically healthy women who did not complain and had no clinical and radiological signs of gonarthrosis made up the control group. All subjects gave written informed consent. FGF and VEGF levels were determined in the examined individuals. VEGF-A in the serum of venous blood obtained in the morning, on an empty stomach, from the cubital vein. The serum was stored at  $-20^{\circ}\text{C}$  in the freezer. The study was carried out by enzyme immunoassay using the ANTOS 2020 reader (Austria), as well as enzyme immunoassay kits for the quantitative determination of VEGF: Human VEGF-A Platinum ELISA (cat. BMS277/2) of Bender MedSystems (Austria) and FGF "Human FGF acidic Immunoassay" (cat. no.DF00B) of RD Systems China Co., Ltd (China). Radiography of both knee joints was performed in two standard leads using the Opera Swing digital device (Italy), ultrasound was performed using the Hitachi Aloka ProSound Alpha 10 ultrasound scanner (Japan).

Statistical processing of the results of the study was performed using the AtteStat data analysis program (version 12.0.5) for Excel. Checking the variation series for normality the distributions were carried out with the calculation of the criterion Shapiro — Wilk. Due to the lack of normality of the distribution, statistical processing of the variation series was carried out using the nonparametric Mann—Whitney method with the determination of the median (Me), the 25% and 75% quartiles, and the calculation of the Mann—Whitney criterion. Functional relationships between the studied parameters were evaluated using Spearman correlation analysis. Differences were considered significant at  $p < 0.05$ .

**Results.** The conducted studies have shown that there is no statistically significant difference in the content of FGF and VEGF-A between the control and main groups (Table).

**The content of FGF and VEGF-A in the blood serum of women with initial manifestations of arthrosis of the knee joint and women of the control group**

Investigated growth factors Me (25%; 75%)	Control Group	Comparison Group	p
FGF	28,4 (24,9; 34,0) n=12	34,0 (26,3; 35,4) n=21	0,227
VEGF-A	202,1 (104,2; 282,6) n=24	205,1 (161,7; 386,6) n=27	0,177

Pr i m e h a n i e : FGF —fibroblast growth factor, VEGF-A — vascular endothelial growth factor.

Interpretation of the results of the performed correlation analysis using the Cheddock scale allowed us to establish that in the control group there is a positive medium-strength relationship between the content of acid FGF and VEGF-A ( $r=+0.52$ ;  $p=0.09$ ), while in the main group this weak relationship is negative ( $r=-$

0.43;  $p=0.037$ ).

Discussion. A clinical examination of the persons under observation showed that 16 women had complaints related to knee pathology joints, but not affecting their lifestyle and its quality. Moreover, all these subjects believed that they did not have any disorders on the part of the musculoskeletal system. X-ray and ultrasound diagnostic procedures revealed the initial signs of osteoarthritis of the knee joint not only in those who noted the presence of subjective sensations associated with degenerative changes in joint structures, but also in 11 women who had no complaints.

These results coincide with the data of an epidemiological study conducted in the UK at the beginning of this century: in the absence of clinical symptoms of the disease, 17% of the examined women aged 45-65 years had X-ray signs of arthrosis [12]. At the same time, it should be borne in mind that conservative treatment is provided effective only in stages I–II of osteoarthritis [13]. The importance of preclinical diagnosis of the disease dictates the need to search for additional methods for detecting initial changes in hyaline cartilage, including biochemical ones. The conducted study on the content of VEGF and FGF growth factors, which are directly related to both angiogenesis and tissue proliferation in women with primary signs of gonarthrosis in the absence of clinical manifestations of the disease, did not encourage the use of these cytokines as early markers of degenerative lesions of the knee joints, since no intergroup difference between them was revealed concentrations. However, the analysis of correlations between these two germinal factors allows us to make an assumption about the development of competitive relationships between them during the degenerative process.

On the other hand, optimal blood circulation in the knee joint area is a condition for the normal formation of synovial fluid, which also serves as a nutrient medium for articular cartilage. In individuals with initial manifestations of degeneration of knee joint tissues, the correlative method of studying the relationship between VEGF-A and FGF revealed an inverse relationship between them, which, quite likely, may reflect the primary changes that develop at the local metabolic level in the process of degeneration of hyaline cartilage and other soft tissues of the joint.

### Conclusions:

1. The onset of osteoarthritis of the knee joint may be asymptomatic in the presence of radiological and ultrasound signs of the initial stages of the disease.
2. FGF and VEGF levels at the initial stages of knee osteoarthritis correspond to reference values, which excludes their use as early markers of gonarthrosis. In at the same time, a change in the correlation relationship between them from positive to negative in the norm at the onset of the pathological process

should be considered as a sign of a violation of local regulation of blood circulation and, accordingly, trophic articular cartilage.

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