

## PATHOLOGY OF LOWER EXTREMITY VEINS IN OSTEOARTHRITIS OF KNEE JOINTS

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### ABSTRACT

Based on a thorough clinical and instrumental study, establish a possible association between osteoarthritis (OA) of the knee joints (KJ) and lower extremity vein pathology (LVC). A case-control study was conducted including women 45-65 years old. The main group included 75 women with OA KJ and the control group included 40 women without OA KJ. Patients of both groups underwent evaluation of complaints and targeted objective examination to detect joint diseases and chronic VNS diseases, X-ray examination of the KJ, and duplex scanning of the VNS. Varicose vein disease (VWD) of the lower extremities (42% vs 23%;  $p=0.016$ ) and signs of chronic venous insufficiency (29% vs 11%;  $p=0.04$ ) were diagnosed more frequently in female patients with OA KJ than in the control group. Duplex scanning of NK revealed a generalized lesion of VNK (bilateral lesion of great saphenous vein and small vein valves, severe degree of valve insufficiency), which was revealed in 52% of patients in this group versus 20% of the control group ( $p=0,0005$ ). After correction for body mass index, differences in the incidence of CH between the groups remained clinically and statistically significant (odds ratio 2.8 at 96% confidence interval from 1.2 to 6.8;  $p=0.037$ ). In female patients with OA KC aged 45-65 years with VB NK, signs of chronic venous insufficiency develop more frequently than in their healthy female peers. Although obesity is a risk factor for both diseases, there is an independent association between OA KJ and CHF.

**Keywords:** osteoarthritis, varicose veins of the lower extremities.

### INTRODUCTION

Osteoarthritis (OA) is a multifactorial disease whose multifaceted pathogenesis is obvious. At the same time, there is still interest in studying the role of vascular disorders in the development and progression of OA of large joints. Acad. V.A. Nasonova pointed

out that venous disorders are noted in 50% of patients with OA. Other researchers also quote high figures: lower limb venous diseases (LVC) were registered in 53.3% of patients with oligo- or polyosteoarthritis, of them 73.2% had varicosity of the lower limbs (VB), 27.6% - postthrombotic syndrome. The opposite situation was also described, when knee joint OA (KA) was detected in 68% of patients with VB NK. Meanwhile, the frequent combination of such two common diseases as OA KJ and IKD does not necessarily reflect the presence of their pathogenetic relationship, but may be a simple coincidence, since both diseases frequently occur in the population. Moreover, the commonness of such risk factors (FR) as female sex, age, excessive body weight and heredity may play a certain role in the simultaneous development of these diseases in a patient. At the same time, connective tissue dysplasia is also a common PR for the development of gonarthrosis (GA) and HF. We should also emphasize that the above studies demonstrating associations between HA and vein pathology mainly described case series and did not include control groups; they used different criteria for HF diagnosis (clinical or clinical-instrumental). Consequently, according to their results, the association cannot be considered proven. This defined the purpose of our study: to establish a possible association between KJ OA and IBD pathology.

Women aged 45 to 65 years were selected for the case-control study. Seventy-five female patients with OA KJ were included in the main group with rheumatologist's appointment. Diagnosis was made according to the clinical, laboratory and radiological diagnostic criteria of the American College of Rheumatologists (ACR) 1986. The control group included women without complaints of KJ pain and other clinical and radiological signs of OA KJ. An information campaign was conducted to recruit this group. Invitations for women to participate in the study with a thorough examination of the KJ were distributed to schools, kindergartens, stores, a streetcar and trolleybus company adjacent to the hospital, a neighboring factory, as well as to outpatient appointments of doctors of other specialties (gastroenterologists, mammologists, doctors of the occupational disease center, therapists). All in all 57 women applied by invitations, 10 of them were over 65 years old. Three of them had clinical signs of coxarthrosis and the other 3 - clinical manifestations of radiculopathy against the background of lumbosacral spine pathology, which were the exclusion criterion. Thus, 55 women were included in the control group. Inclusion criteria for the main group: female sex; age 45-65 years inclusive; presence of KJA according to clinical, laboratory and radiological criteria of ACR 1986.

Inclusion criteria for the control group: female sex; age 45-65 years inclusive; no complaints of KJA pain in the present and in the past. Exclusion criteria: indications of severe NK trauma; history of NK joint surgery; previous inflammatory joint diseases; clinical signs of hip joint OA; spinal diseases accompanied by signs of radiculopathy; neuropathic pain in NK; history of deep VNK thrombosis; congenital anomalies of VNK. The presence of clinical manifestations of OA of the hip joints excluded participation in the study, while OA of the joints of the hands and feet was not an exclusion criterion. Thus, patients with possible secondary OA of the KJ were excluded from the main group, and women with diseases that could complicate the assessment of clinical manifestations of OA of the KJ and IU were excluded from both groups.

## METHODOLOGY

Patients in both groups underwent clinical examination, which included targeted collection of complaints and objective examination of the musculoskeletal system (OA symptoms) and VNA, as well as KJ radiography in two projections with assessment according to Kellgren and Lawrence (1957). Radiological examination of the KJ was not performed in 7 patients of the main group, but these cases fully corresponded to the clinical and laboratory diagnostic criteria of OA. The severity of OA was assessed by the Lequesne index (M. Lequesne). Patients were asked about the presence of complaints characteristic for venous disease as well as about possible factors of VD development: high body mass index (BMI), heredity, heavy physical labor with weight lifting more than 15 kg per shift, walking more than 3.5 km per shift, long sitting position, professional practice of heavy sports, long-term wearing high-heel shoes, having more than 3 pregnancies, constipation, taking hormonal replacement therapy. Objective examination was performed to detect visible manifestations of VNK diseases, such as telangiectasia (dilated intradermal veins less than 1 mm in diameter), reticular dilated veins (tortuous subcutaneous veins 1-3 mm in diameter), varicose veins (subcutaneous dilated veins greater than 3 mm in diameter when standing), limb edema, skin changes (hyperpigmentation of the lower third of the tibia and/or varicose eczema) and subcutaneous tissue (lipodermatosclerosis and/or white skin atrophy), healed or open venous trophic ulcers. In addition, ultrasound scanning (duplex scanning) of VNS on SonoSCAPE S50 machine was performed in both groups of patients. Venous diameter was measured in B-mode, refluxes were determined in pulse-wave Doppler and color Doppler mapping. The

examination was performed according to standard technique in the supine and standing positions with the use of functional tests (Valsalva test, compression tests). We assessed patency of deep veins, the presence of refluxes in the valves of sapheno-femoral and sapheno-popliteal arteries, valves of great saphenous vein (GPV), small saphenous vein (LSV), perforating veins on both legs. The physician who performed the study was unaware of the patient's membership in one group or another. The severity of refluxes was assessed using the Zontsich and Baldt (2003) classification. The classification identifies degrees of valve insufficiency depending on the extent of reflux. Thus, there are IV degrees of valve insufficiency in the BPV: I degree - reflux is registered only in the proximal femur, II degree - reflux is registered to the distal femur, III degree - reflux extends to the proximal tibia, IV degree - reflux is registered throughout the BPV. There are 3 degrees of valve insufficiency in the MVC: I degree - reflux only within the first MVC valve, II degree - reflux up to the middle of the tibia, III degree - reflux throughout the MVC. Perforating veins were evaluated for reflux only. Thus, 6 veins were examined: BPV, MPV, perforating veins on both legs in order to analyze the valve apparatus condition. Venous pathology was assessed according to CEAP international classification. Statistical processing of the obtained data was performed using Statistica 6. Quantitative signs in the main and control groups were compared under the condition of normal distribution using Student's test. Quantitative variables whose distribution did not obey the law of normal distribution were evaluated using the Mann-Whitney test. Qualitative binary variables were compared using Fisher's two-sided exact test. The degree of correlation between qualitative variables was studied using Spearman's coefficient. Multivariate logistic regression analysis was used to study the relationship between OA and IBD, taking into account the influence of BMI; the degree of association was expressed as odds ratio (OR). Results were presented as median (lower quartile; upper quartile),  $M \pm m$ , or absolute numbers (% of the total). Differences at  $p < 0.05$  were considered statistically significant.

## RESULTS

The study group included 75 patients with OA KJ and the control group included 40 women with undiagnosed HA. The two groups did not differ in age ( $53.3 \pm 5.34$  and  $52.2 \pm 5.3$  years, respectively;  $p = 0.84$ ), number of postmenopausal women (80 and 70%;  $p = 0.29$ ), and duration of menopause: median was 6 (3; 12) years in the main group and 5 (2; 7) years in the control group;  $p = 0.555$ . The BMI of patients with OA KJ



( $33.5 \pm 6.7$  kg/m<sup>2</sup>) was higher than that of the control group ( $25.9 \pm 3.8$  kg/m<sup>2</sup>;  $p=0.00001$ ), and there were almost 5 times as many obese patients in the main group as in the control: 49 (65%) versus 7 (17%;  $p=0.000$ ). The mean age of HA symptom onset in the study group was  $53.3 \pm 5.34$  years, median duration of disease by the time of study inclusion was 3 (2; 7) years. The frequency of OA exacerbations was  $5.5 \pm 5$  times per year, with a median Leiken severity index of 7 (3; 12) points, corresponding to a pronounced degree of GA severity. Stage I was detected in 51%, Stage II in 42%, and Stage III of AA in 5.5% of the CW radiographs. A small number of women in the control group revealed clinical symptoms of knee joint affection that could be interpreted as symptoms of HA (crunch and crepitation in 37%, instability or sudden feeling of loss of support in a limb in 10.5%, suspected slight synovitis in 4.5%, painfulness on palpation of joint fissure in 5%), without revealing a complete set of AA diagnostic criteria by the ACR classification. X-ray examination of the KJ revealed signs of OA in 59% of the patients in this group and in 11% of the patients in the second radiological stage without clinical symptoms. Bouchard or Heberden's nodules (22% in the main group;  $p>0.04$ ) and valgus deformity of the first toe (27% vs. 32% in the main group;  $p>0.055$ ) were detected in 22.5% of control group patients. Vein clinical examination data (complaints and objective examination). A comparative analysis of complaints and physical vein findings according to CEAP classification in the two groups is shown in Table 1. Among the complaints characteristic of CVD, only sensation of swelling of ankles and shins was statistically significantly more frequent in patients with OA KJ than in the control group (75 and 55%, respectively;  $p=0.0001$ ). At the same time, these complaints were not accompanied by objective signs of limb edema. There were no differences in the frequency of other complaints, but a combination of complaints characteristic of CPV (5 and more) was observed more frequently in patients with OA KC than in the control group. On objective examination, varicose-expanded subcutaneous VNKJ were detected 2 times more frequently in women with OA KJ (CEAR clinical class C2;  $p=0.0155$ ). Trophic changes of the shins in the form of hyperpigmentation or lipodermatosclerosis (clinical grade C4) were present only in women with OA KJ ( $p=0.047$ ). At the same time, minimal visible manifestations of CVD (telangiectasia and reticular veins) were even more frequent in the control group patients ( $p=0.055$ ). In general, signs of chronic venous insufficiency - CVI (clinical classes C3-C6) were revealed more frequently in patients with HA than in controls (29% vs 13%,  $p=0,04$ ). Moreover, according to the history, the first symptoms of CHD (detection of varicose veins by a patient

or a doctor) in the main group were determined several years earlier (mean age  $36.78 \pm 10.9$  years vs.  $43.4 \pm 11.8$  years in the control group), though statistically insignificantly ( $p=0.08$ ). It should be noted that in the group of patients with HA, the debut of UA preceded the onset of the first symptoms of OA KJ ( $52.2 \pm 5.4$  years) by an average of 14 years. Table 1. Complaints and clinical signs of CVD NK in women with OA KJ compared to the control group Note. CVD - chronic vein diseases; CEAP - international classification of chronic vein diseases: C - clinic, E - etiology, A - anatomy, P - pathogenesis. IVC ultrasound scanning was performed in 54 women of the study group and 48 women of the control group (Table 2). Venous abnormalities were detected equally frequently in women of both groups ( $p=0.2$ ). Clinically significant congenital anomalies (phlebodysplasia) that could lead to secondary varicose veins were not detected in either group by anamnesis or angioscanning. Failure of the BPV and MPV valves was a rather frequent finding in both studied groups; however, valve involvement in two legs at once was found almost twice as often in the group with OA KJ than in the control group. It is also important that perforating vein valve insufficiency was registered more frequently in patients with OA KJ. Generalized process, which we defined as valve failure in 4 of 6 veins examined, was detected in 54% of the study group versus 23% of the control group ( $p=0.0004$ ). Table 2. Results of VVC ultrasound scan When studying the state of vein valves, it is important to assess the degree of valve incompetence. Maximum refluxes (throughout the vein) were significantly more frequent in the OA group. Thus, grade IV refluxes on BPV occurred in 21% of women in the study group and only 3% in the control group ( $p=0.003$ ). Grade III refluxes on the MBV were detected 2.4 times more frequently in patients of the OA group than in the control group ( $p=0.02$ ). Both in the study and the control groups, the complaints considered to be characteristic for VVC lesions (pain, cramps, edema, etc) did not correlate with the objective examination data or angioscan findings ( $p>0.05$ ), which confirms their low specificity. However, there was a statistically significant correlation of moderate strength between the symptoms detected by the objective examination of VVC and angioscan findings in both the main ( $r=0.65$ ;  $p=0.000000$ ) and control ( $r=0.4$ ;  $p=0.005$ ) groups. Localization of detected vein changes in patients with GA did not correlate with the side of KJ lesion. Overall, on the basis of objective clinical examination and ultrasound scanning, VVC (C2) was detected in 44% of examined women with VA and in 23% of the control group ( $p=0,015$ ), CVD - respectively in 29 and 12% ( $p=0,03$ ). Analysis showed that women with IBN (C2) were 2.6 times more likely to have

concurrent CVA than women without IBN (OR 2.8 at 96% confidence interval, CI 1.95 to 3.5;  $p=0.023$ ). In the presence of CVI (C3-C6), the risk of GA was also high (OR 2.8 with 96% CI 1.94 to 3.87;  $p=0.04$ ). Although age is a FR for the development of HF, our study did not obtain a correlation between age and the presence of HF in either the main ( $r=-0.0045$ ;  $p=0.96$ ) or control ( $r=0.10$ ;  $p=0.46$ ) groups. Given the imbalance between the main and control groups in terms of BMI, and because obesity was an established FR for the development of both OA and CHD, we performed a multivariate logistic regression analysis in which differences in the frequency of CHD between comparison groups were corrected for the patients' BMI. After correction for BMI, the differences in the incidence of CHD between the groups remained clinically and statistically significant: OR 2.6 with a 96% CI of 1.11 to 6.77;  $p=0.0366$ ). In other words, patients with OA KJ had a 2.8-fold greater chance of developing VB NK than the control group. Consistently, high BMI proper was strongly associated with the diagnosis of OA KJ: for each additional 1 kg/m<sup>2</sup>, the odds that a patient would have OA KJ increased 1.2-fold on average: OR 1.25 with a 96% CI of 1.3 to 1.45;  $p<0.001$ ).

## DISCUSSION

In recent years, there have been many publications indicating the possibility of different phenotypes of OA, which have their own clinical, morphological, metabolic features and, possibly, genetic basis. One of such subtypes of OA KJ may be a variant associated with VB NK and CVI. Interest in the issues of venous vascular involvement in the pathogenesis of OA of the NK joints has been manifested since the middle of the last century. Thus, a number of authors used intraosseous phlebography to study venous outflow from the femoral head and neck in patients with hip joint OA and from the epiphysis and metaphysis of the distal femur in patients with OA KJ. Russian scientists continue to work in this direction. Nagibin R.M. and Kozlova O.G. measured the postocclusive pressure in the posterior tibial vein (PTBV) by ultrasound Dopplerography and found that in patients with OA KC without clinical signs of VB NC, the pressure in the PTBV was 26.6% higher than in the population by 68.8%, and in patients with OA KC combined with PTB NC by 68.8%. The same authors demonstrated a positive correlation between the postocclusive pressure in the VBBV and BMI in patients with OA KJ, and also showed that the level of postocclusive pressure in the VBBV in radiological stage III of OA KJ was 22% higher than in stage II of OA KJ. In another series of works, the Russian scientists using

rheovasography (RVG) showed an increase in peripheral resistance and reduction of venous outflow in the KJ area in patients with KJ OA of the II-III radiological stage compared to healthy volunteers, with no differences in RVG values at the level of the shins. However, the clinical significance of these instrumental findings remains unclear. It is unknown what role common FRs of these two diseases, such as high BMI, may play in the revealed changes. We aimed to compare clinical and instrumental characteristics of vein pathology in 45-65 year old women with HA with those without signs of HA. For this purpose, we selected patients with a verified diagnosis of OA and women without clinical and instrumental signs of HA into a control group, equating the groups by age, since both OA and HA are age-related diseases. The diagnosis of VB was made according to the International Classification of CVD (CEAR). We used exclusion criteria to exclude women with diseases that can affect the intensity of pain or limitation of movements in the KJ (irradiation of pain in the KJ in hip OA, radicular syndrome in spinal pathology, posttraumatic pain, etc.) from the study. By excluding patients with neuropathic pain in NK of different nature, we tried to identify venous complaints as accurately as possible, despite their low specificity. In addition, we used modern instrumental methods to diagnose venous diseases. Russian clinical guidelines on the diagnosis and treatment of CVD emphasize that "ultrasound angioscans (duplex scanning) is the main diagnostic method in the examination of patients with CVD. Our study confirmed that the so-called venous complaints are rather nonspecific, occur frequently and do not coincide with the data of objective clinical and instrumental examination. Thus, the Russian DEVA study of 3788 women showed that 79.5% of participants complained of calf pain by the end of the day and 65.5% noticed swelling of the lower legs, whereas VBDC was revealed only in 21.5%. In addition, the assessment of subjective venous symptoms is difficult due to the possible ambiguous interpretation of the same terms by different patients and even doctors. However, a careful analysis of "venous" complaints revealed a certain regularity: patients with HA more often had a combination of them. More importantly, upon objective examination, we diagnosed VB NK (CEAP class C2) and, in general, signs of CVI (classes C3-C6) more frequently in women with OA KJ than in the control group, while trophic changes of the skin or subcutaneous tissue of the shins (class C4) were detected only in patients with OA KJ. In our opinion, the most interesting are the data of instrumental examination, since it is not only a more objective method, but was also performed by a disinterested person, who did not know the patient's diagnosis. Duplex scanning showed that patients with



OA KJ, in comparison with the control group, more often revealed valve insufficiency of BPV or MPV in both legs at once, perforating veins insufficiency, valve lesion of several veins at once, as well as registered more severe degree of valve insufficiency in BPV and MPV. Thus, despite the fact that superficial and perforating vein valve failures were rather frequent in both examined groups, not only a significant accumulation of pathological manifestations, but also a more generalized and severe nature of vein lesions was observed in female patients with OA. We obtained no correlation between age and the presence of VD in either the main or the control groups, which may be due to the narrow age range of the examined groups. However, the role of obesity in the identified association remained an open question. It is well known to be a factor of both diseases, and the number of obese women in our sample of patients with OA was significantly higher than in the controls. However, multivariate logistic analysis demonstrated that after correction for BMI, the differences between the groups for the presence of UA remained statistically significant. Thus, the clinical diagnosis of UA was independently associated with the diagnosis of OA KJ. The odds of having UA in a woman diagnosed with OA KJ were almost 3.5 times higher than in a female peer from a control group without OA. The retrospective analysis of our group showed that in women with OA KC the obvious signs of UA (according to the patient's observation or the doctor's opinion) long preceded the first signs of OA. The data comparable with ours were obtained by the domestic researchers who, studying connective tissue dysplasia, considered VB NK as one of the dysplasia manifestations, and got its association exactly with HA, but not with OA of other localizations. In our study, correction by BMI did not eliminate the association between the studied diseases. This may indicate that OA KJ and HF, apart from obesity, have other common FRs, in particular the mentioned connective tissue dysplasia. It is known that joint hypermobility, which is characteristic of this pathology, is a FR of OA development. The connection of vein pathology with OA KJ finds its basis in the modern views on the pathogenesis of OA. It has been proved that in OA the subchondral bone is damaged. It is assumed that at the initial stages of OA there is a decrease in subchondral bone mineral density, and then bone formation processes begin to prevail, often leading to an increase in bone mineral density (BMD), although a number of authors claim that OA progression is not accompanied by an increase in subchondral BMD. Nevertheless, it is obvious that the processes of remodeling occur in the subchondral bone, and this is one of the leading links in the pathogenesis of OA. It is not excluded that venous stasis in the NC, leading to intraosseous hypertension of

the subchondral bone with further triggering of the processes of its "incomplete" remodeling, may play a certain role in this. Such hypothesis was formulated by D. Findlay in 2007.

## CONCLUSION

Thus, the study demonstrated an association between OA KJ and chronic VIC pathology. In patients with OA KJ VB, CVN and trophic skin changes were significantly more frequent than in the control group, and angioscans revealed more severe and generalized vein pathology. Further studies, including prospective ones, are required to confirm these findings and to understand the extent to which venous pathology aggravates the course of the pathological process in the joints.

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