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Factors Influencing the Development of Osteoarthritis: Evolution and Contemporary Scientific Perspectives (Literature Review)

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Annotation: This article provides a comprehensive overview of the historical origins and current medical perspectives on the risk factors (RFs) contributing to the development of osteoarthritis (OA). OA, which has a polymorphic etiology, is now recognized as a complex multifactorial disease. Key risk factors identified in studies include age, sex, hormonal status, genetic predisposition, acquired biomechanical impairments, excess body weight, trauma, occupational exposure, physical activity, dyslipidemia, and diabetes mellitus—all of which, either independently or collectively, can exacerbate OA development. Special attention is given to modifiable RFs, as their identification and control play a vital role in primary prevention and slowing the chronic progression of OA. The article also thoroughly analyzes the influence of sex hormones—particularly in estrogen-rich conditions—the role of microtrauma in industrial workers, and the mechanical stress related to sports and occupational activity. It is noted that weight gain and increased activity of inflammatory mediators in adipose tissue can raise the risk of osteoarthritis by 2 to 3 times.

Keywords: osteoarthritis, risk factors, sex and age, hormonal imbalance, biomechanical disruption, trauma, occupational load, physical activity, obesity, dyslipidemia, diabetes mellitus, estrogen-related osteoarthritis, microtrauma, metabolic syndrome.

Introduction

Osteoarthritis (OA) occupies a central position among musculoskeletal diseases, particularly in individuals aged 60 years and older, affecting up to 10% of men and 13% of women [1]. Leading experts, based on numerous recent studies, have reached a consensus that OA is a group of distinct (although overlapping) diseases with different etiologies but sharing similar biological, morphological, and clinical outcomes. The pathological process affects all joint tissues, with the hyaline articular cartilage playing a primary role in the early stages of the disease. This cartilage undergoes degenerative-fibrillatory changes, ultimately leading to its complete loss. Simultaneously, or with some delay, remodeling of the bone tissue occurs in the form of subchondral osteosclerosis in the bone plate region, persistent synovitis with edema of the subsynovial space, as well as damage to ligaments, tendons, and entheses. Additionally, joint capsule stretching and inflammation (capsulitis) and periarticular myositis develop, which clinically define the joint syndrome [2, 3].

Risk factors (RFs) for OA have been comprehensively studied in recent years in both scientific and clinical medicine. The term "risk factor" refers to various factors that increase the likelihood of disease onset. These can be internal or environmental in nature [4, 5]. A foundation has now been established for identifying individual or grouped RFs that conditionally or reliably influence the development of OA. This distinction is important from a management perspective—dividing them into modifiable (social, environmental, occupational, behavioral, partially medical-biological, and others — first level) and non-modifiable factors (genetic, phenotypic characteristics of the individual, sex, age, etc. — second level). Of greatest interest to physicians are the modifiable RFs, i.e., those that can be eliminated or mitigated. Awareness of such factors is useful for the primary screening of OA patients during mass population assessments.

A key aspect of OA epidemiology involves risk factors associated with the disease. These include:

1. **Genetic factors**: female sex, defects in type II collagen gene (e.g., Stickler syndrome), mutations in the COL2A1 gene, other inherited disorders of bones and joints, and ethnicity.

2. **Acquired factors**: advanced age, excessive body weight, decreased levels of female sex hormones (e.g., postmenopause), skeletal developmental abnormalities, acquired diseases of bones and joints, surgical interventions on joints (e.g., meniscectomy) and their consequences.
3. **Environmental factors**: excessive joint loading (due to occupational or physical activities), joint injuries—especially repetitive ones, active leisure, or sports activities [1, 6–8].

Risk factors typically exert their effects throughout the pathological process, contributing to OA progression and worsening its prognosis, including the development of comorbid conditions. In patients with clinical manifestations of OA, the prognosis is significantly worse at any level of RF exposure compared to those without OA symptoms.

When assessing OA risk levels, it is important to consider that most RFs are interrelated and can mutually reinforce one another. In practice, physicians often encounter patients whose disease onset results from the simultaneous influence of several RFs. Even if each individual RF has a weak or moderate effect, the overall OA risk may be high due to the cumulative impact of these factors. Therefore, it is necessary to assess each RF individually and all RFs collectively, i.e., determine the cumulative risk using tabulated calculations or computer modeling. Various calculation models and simulations are detailed in specific clinical guidelines [9, 10]. Consequently, risk factor elimination should be an integral part of primary OA prevention and treatment strategies aimed at improving patients' quality of life and mitigating the psychosocial impact of the disease.

Osteoarthritis is characterized by inflammation with the formation of chondritis, osteitis, chronic synovitis, and other manifestations. It varies in terms of anatomical localization, clinico-morphological signs of the pathological process, and findings from instrumental diagnostic methods. The severity of pathological changes reflects the functional insufficiency of the affected joints. The heterogeneity of the disease becomes evident when evaluating differences in OA localization, primarily based on risk factors and phenotypes. It has been established that the RFs for hip OA and knee OA differ: hip OA does not show sex-based differences, is rarely diagnosed in individuals of Mongoloid race, and is often associated with congenital skeletal abnormalities. Knee OA, on the other hand, is more frequently observed in women of African descent compared to Caucasian women. The development of OA in this region is often preceded by injuries, including sports-related ones. Research has shown that the RFs for patellofemoral joint OA (such as family history and nodal lesions of the hands) differ from those of medial tibiofemoral OA (which are partially linked to obesity, impact loading, and previous knee surgeries).

The current understanding of OA development, including in older adults, is that the disease arises from the interaction of numerous genetic and environmental (including traumatic) factors. Hence, OA is considered to be of multifactorial origin. Identifying risk factors plays a vital role in understanding the causes and pathogenesis of OA, as well as in choosing preventive and therapeutic strategies [11, 12].

Risk factors for OA

Gender and age

Gender and age are the most significant FRs of OA [13]. They are explained by the age-related decrease in the ability to regenerate joint tissues and, as a rule, have a close relationship with other FRs. Degenerative changes in cartilage occur on average in individuals 40-50 years of age in 95% of cases, whereas in individuals over 50 years of age in 100% of cases. However, it is not quite correct to assume that only elderly people suffer from OA, as it affects both middle-aged and young adults. The maximum number of cases of OA is observed at the age of 55-64 years, it affects women more often than men, especially after the age of 50 years. In women, the disease begins 5-10 years earlier than in men [14]. M.G. Astapenko et al. [15] also managed to show that women suffer from this disease 2-4 times more often than men.

However, not all authors were able to confirm this position in their epidemiologic studies. OA of the knee, distal interphalangeal and wrist joints was diagnosed more often in women. Other researchers

note that the most frequent localization in men is knee joints, followed by hip and metacarpophalangeal joints. At the same time, the familial generalized form of OA is significantly more common in women [9, 16-18].

These features suggest the role of endocrine factors in the development of OA. Sex hormones are able to modify metabolic processes in cartilage - in particular, it is after ovariotomy that its degeneration increases [19]. The involvement of sex hormones, especially estrogens in women, is evidenced by the increased incidence of OA during menopause and/or after gynecologic surgeries. Women with an excess of endogenous estrogens are predisposed to a generalized variant of the disease [20].

Estrogens influence pro-inflammatory cytokines and growth factors. Interleukin 1 and tumor necrosis factor α activate pro-inflammatory enzymes that can potentially degrade the cartilage matrix [21]. Estrogens also have a complex effect on insulin-like and transforming growth factors, which are involved in the synthesis and repair of cartilage matrix. High estrogen levels, on the one hand, may increase the risk of OA in premenopause, on the other hand, may slow the progression of the disease in postmenopausal old age, whereas a significant decrease in estrogen levels in postmenopause promotes early onset and rapid progression of OA [9-21]. The role of estrogens is well understood, but the mechanism of their effect on joint tissues remains not completely clear.

In the process of aging, chondrocytes become a target tissue and lose their ability to restore the articular cartilage matrix. It has been shown that the absorption of antioxidants, especially vitamins C, E, and D, is reduced in the elderly. The issue of prophylactic inclusion of these vitamins in the diet of patients with OA is discussed [22].

M.C. Nevitt et al. [23] showed that high systemic bone mineral density (BMD) can provoke narrowing of the articular gap and increase the risk of knee OA, but not radiologic progression of the existing disease. N.G. Kashevarova et al. [24] in a 5-year follow-up of patients with OA revealed that high values of MPC, confirmed by the results of densitometry in the lumbar spine, femoral neck and total hip index, are more often observed at pronounced stages of the disease, and an increase in the same index in the femoral neck and femur as a whole during the same period of observation may indicate the risk of progression of knee OA.

Biomechanical impairment and congenital dysplasias

A number of cohort studies investigating the causes of OA have concluded that the disease develops when biomechanics in the altered joint are disturbed. An established FR of OA is hip dysplasia, when the acetabulum, reduced in size, does not completely cover the femoral head [25, 26]. Incomplete contact between the femoral head and acetabulum can increase the risk of hip OA tenfold, and the terminal stage of the disease can develop within an average of 5 years. The prognosis can be positive in 6-25% of cases depending on the severity of the anomaly, while the negative prognosis is 98-99% [26]. Similarly, the development of dysplasia of the tibial and/or femoral bones that make up the knee joint can provoke the development of OA in it [27].

Varus or valgus deformity of the knee joint often increases the risk of OA development and progression in the most loaded region of the joint [28, 29]. In addition, when leg length difference ≥1 cm occurs, the risk of knee OA is almost 2-fold higher in the shorter limb than in the longer limb [30]. Loss of quadriceps muscle mass may also increase the risk of progression of knee OA [31]. Nevertheless, the disease does not develop in most people when joint biomechanics is disturbed - the development of pathology in the joint is more often determined by systemic factors [26].

Trauma

Trauma as a FR can lead to disruption of joint biomechanics, bone and/or cartilage damage, and secondary OA; the joint becomes more susceptible to further involvement of ligaments and meniscus. Worldwide, 10-12% of all OA cases are post-traumatic in nature. However, microtraumatization is also significant, which patients, as a rule, do not remember or do not know about. It is microtrauma as a cause of OA in workers at industrial enterprises that is beyond doubt. In obese individuals, especially

the elderly, the joints, more often the knee joints, are exposed to constant mechanical impact, including chronic microtrauma [32, 33]. The epidemiologic differences between primary OA and posttraumatic OA are unquestionable. Patients with knee joint trauma have an earlier onset of the disease due to structural and biomechanical changes, it manifests joint syndrome in walking and running more often than primary OA cases [34-36].

Occupational factors and working conditions. Athletic exertion

Occupational OA is usually primary, as it occurs in healthy cartilage under the influence of mechanical loading and subsequent changes in it. It is primarily associated with physical overstrain or heavy manual labor, and is diagnosed in pneumatic hammer and electric saw workers, miners, dockers, textile workers, seamstresses, weavers, knitters, truck drivers, agricultural workers engaged in cotton farming.

Simultaneously with physical labor, other predisposing factors may contribute to the development of OA: hypothermia, increased chronic traumatization of joints, vibration, emotional overstrain, etc. Forced prolonged body posture and stereotyped movements, as well as other mechanical loads, increase the risk of the disease almost 3 times. That is why it is important to create optimal working conditions and organize the workplace to prevent OA [37].

Numerous studies to identify the relationship between regular physical activity and OA in track and field athletes and soccer players have shown that only repeated or severe injuries can be considered as FR in them. No other patterns have been revealed [38]. But some authors believe that the influence of sport on the frequency, localization and severity of OA is not sufficiently proven. It could not be proved that sports, especially professional sports, is a consistent FR of hip OA [39]. However, high-intensity activity during adolescence may contribute to the development of impingement syndrome in the acetabulum of the hip. The only thing that can be said for sure is that athletes in the presence of impingement may develop pain syndrome much earlier than those who have not engaged in excessive physical activity.

S.G. Muthuri et al. conducted a meta-analysis of observational studies and showed that knee trauma, including sports trauma, depending on the degree of severity leads to bone and cartilage remodeling. The knee joint with altered biomechanics becomes more susceptible to repetitive trauma, the risk of OA increases more than 4-fold.

Obesity, dyslipidemia

Excess body weight, especially obesity, has been shown by epidemiologic studies to increase the risk of OA and contribute to more rapid degeneration of articular cartilage, which bears the main load. Joints in obese patients are more susceptible to mechanical stress. These patients often have impaired glucose tolerance and elevated lipid levels, which are considered as possible FRs of OA [4].

Overweight is the most frequent and assessable FR of knee OA in both men and women. The risk of OA development in overweight individuals is on average 2 times higher than in people with normal weight, and in men - 2.5 times, in women - 1.9 times. Knee joints are more often affected in obesity [4]. D.T. Felson et al. showed that an increase in body weight or keeping it at a high level increases the frequency of knee OA (about 25-35%), while a decrease in body weight can reduce the severity of the joint syndrome.

To determine the degree of obesity, it is recommended to use the waist-to-hip ratio. Abdominal fold thickness has not lost its importance, but body mass index (BMI) is more important in practical terms. If it is less than 25 kg/m2, the body mass is considered normal, with a BMI of 25-29 kg/m2 - excessive, with a BMI of 30-34 kg/m2diagnose obesity, and with a BMI of more than 35 kg/m2 - pronounced obesity. In severe obesity, knee OA was diagnosed in 65% of patients.

Hereditary predisposition

Hereditary predisposition plays a role in the development of OA, but its influence is ambiguous in different localizations of OA. A number of studies have already noted that hereditary predisposition

underlies generalized OA. In particular, the association of nodular OA with HLA A1 and HLA D8 haplotypes and with one of the antitrypsin genes has been shown.

Familial forms, such as OA with Stickler syndrome, are characterized by autosomal dominant inheritance, as are chondrodysplasias and pyrophosphate arthropathy with onset at an early age, mostly before 20 years of age. Linkage analysis has been used to show co-inheritance of this familial form of the disease and an allele of the procollagen gene (COL2A1) located on chromosome 12, on which a single mutation at position 519 in the first chain of collagen was found, present in all members of families with OA and not detected in any healthy patient [5].

Whole-genome association studies have identified 11 loci associated with OA. The magnitude of their influence is small (odds ratio 1.11-1.21) and is consistent with data from other similar studies. Single nucleotide polymorphisms have been associated with several known FRs, including hip volume, BMI, and BMD [51]. Examination of polymorphic markers of genes encoding type II collagen, cartilage matrix protein and binding protein did not support the assumption that they are related to OA susceptibility loci. On this basis, it was concluded that OA is a heterogeneous disease and may be associated with alterations in other genes [50]. Genomics alone is unlikely to reliably identify individuals who will develop the disease, but it may allow a different perspective on the pathogenesis of different forms of OA given the current understanding of its phenotypes.

Social factors

A comparative analysis of the level of education and living conditions of patients with OA in the 20th century did not reveal a reliable influence of social status on the frequency of OA, but, according to other authors, patients with this pathology were more numerous among those with a low level of education. However, this may be due to the nature of labor, which was predominantly physical [9].

Conclusion

During the last years, the number of publications dealing with all aspects of OA has increased, which has helped to clarify data on its prevalence. The identification of FRs plays a central role in understanding the causes of OA and selecting targets for its prevention and treatment. Analysis of numerous clinical, epidemiological and therapeutic studies of OA in different populations has shown that FRs, clinic and treatment differ depending on the localization of OA, its phenotype and the stage of the pathological process.

Age is the most significant FR, as the prevalence of OA of all localizations increases with its increase. Another important FR is excessive body weight, which increases the load on the supporting joints, especially the knee joints. Obese individuals are diagnosed with higher BMD, which is considered an additional FR. Reducing body weight can not only stop OA, especially of the knee joints, but also prevent it.

Elevated estrogen levels in women have different biological effects depending on the timing of menopause and the stage of OA. High estrogen levels may increase the risk of OA in premenopausal women, whereas estrogen deficiency in postmenopausal women leads to disease progression.

The genetic basis of OA has been known for many years due to the results of family studies. Structural defects in collagen or metabolic changes in cartilage and periarticular tissue may be associated with the disease phenotype. A state-of-the-art study of specific gene mutations in OA will help to more fully visualize the etiology and pathogenesis of the disease.

The main biomechanical FRs identified for knee OA are tendon instability, obesity, repetitive pushing, and previous meniscus surgery. The development of hip OA is the result of congruence disorder of the articular surfaces due to asymptomatic dysplasia, Perthes disease, congenital hip dislocation, etc. not diagnosed in childhood and adolescence. In this regard, the described mechanism of femora-acetabular impingement (conflict) as a syndrome (traumatic impact of the femoral head and the edge of the acetabulum) is considered the main cause of hip OA development. Identification of the causes,

including FR, is central to understanding OA as a multifactorial disease and also helps in its treatment and prevention.

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