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Microbiological factors in osteoarthritis

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Abstract

Introduction Osteoarthritis (OA) is a common polyetiological disease of the musculoskeletal system, leading to disability. The condition can prevent a person from work, affect mental health, increasing mortality and affecting health care resources around the world as a current and future disease burden. OA had been considered an aseptic disease in the past and now the microbiological factor is viewed as one of the significant etiological aspects of the condition.

The **objective** was to summarize the literature data on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

Material and methods The original literature search (2010 to 2023) was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org). Literature searches included both Russian and English studies reporting the effect of microbiological factors on the development of arthropathy.

Results and discussion New, more advanced microbiological diagnostic methods have been used. There has been evidence of a variety of microorganisms including pathogenic and opportunistic pathogens in the absence of clinical and radiological signs of arthritis. This changes ideas about the etiology and pathogenesis of degenerative processes in the articular cartilage and necessitates a revision of treatment protocols for some joint diseases. Multicenter comprehensive studies of the microbiome of joint formations, blood and intestines are needed.

Conclusions The presence of pathogenic microflora in the joint structures is evident in a significant number of observations. There is evidence of a local infectious process in the local cellular elements of osteochondral tissue in patients with previously diagnosed aseptic osteoarthritis. Intestinal microbiomes and the urogenital tract are most common sources of infection. A local influence of the immunodeficiency virus on the development of osteonecrotic processes in joint formations can be suggested in HIV patients.

Keywords: osteoarthritis, microbiome, osteonecrosis, HIV, aseptic necrosis

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INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal condition affecting millions of people. OA has considerable impact on quality of life and is a significant cause of disability imposing a significant burden on healthcare systems worldwide. According to the World Health Organization, about 10 % of the global population suffer from OA affecting approximately 830 million people [1]. OA is characterized by pathological changes in the joint structure causing pain [2], disability [3], can prevent a person from work [4], affect mental health [5] increasing mortality [6]. OA can affect any joint but is most common in the knees, hips and small joints in the hands [7]. According to reports from the Russian Ministry of Health, prevalent cases of OA increased Russia by 3.7 % over 5 years (from 2013 to 2017) affecting more than 4.3 million people [8]. However, these data cannot be considered accurate since they include identified and registered cases of the disease. The results of a large-scale Russian epidemiological study indicate to the knee and hip OA being detected in 13 % of the adult population. The true number of OA cases in the Russian Federation may reach 14–16 million people [9]. The unrecognized pandemic of OA is the leading cause of disability in the United States, with rates higher than the other four leading causes of disability combined [10]. OA accounts for approximately 23 % of the general population in the United States, representing approximately half of people aged 65 years and older [11]. It is the third fastest growing chronic disease associated with disability worldwide [12, 13]. Recent estimates place the cost of OA treatment in the United States at $128 billion, representing nearly 1 % of the gross domestic product [14], and the incidence of severe OA requiring joint replacement is increasing due to obesity and aging [15]. The incidence of OA has approximately doubled in the post-industrial era due to demographic factors and body mass index, a fact that remains to be fully explained [16]. Despite the significant economic component, there is no fully effective conservative treatment of OA [17].

It is generally accepted that the pathogenesis of OA involves the interaction of three main factors: genetic predisposition, aging and environment [18]. Genetic heritability, for knee OA in particular, is relatively low, less than 50 % [19]. Significant research efforts are aimed at identifying non-genetic risk factors in the pathogenesis of the condition.

The prevalence of OA increases with age, in people aged >65 years, in particular. It is estimated that more than 30 % of people aged 65 to 74 suffer from OA, with the number rising to 65 % in people over 75 [1]. The incidence of osteonecrotic processes in the joints is 2.5–100 times higher in HIV patients than in the general population [20, 21].

OA remains a naturally progressive disease that requires radical treatment in the terminal stage in the form of total joint replacement. Arthroplasty can be associated with loosening of the implant and periprosthetic joint infection [22, 23].

Alternative treatments of OA are limited in the effectiveness and can be associated with adverse effects. Non-surgical treatments include non-pharmacological and medicinal methods. Non-drug methods include physiotherapy and exercise therapy, diet and weight control. There is a wide range of medications used for the treatment of this pathology. These are non-steroidal anti-inflammatory drugs, corticosteroids, structure-modifying drugs based on glucosamine and chondroitin, hyaluronic acid. Relatively new biological and immunological methods of treating OA include the use of stem cells to restore cartilage, introduction of genetically modified cells,the use of inhibitors of inflammatory

cytokines and monoclonal antibodies [24]. These methods are not etiological and are aimed at suppressing the inflammatory process and its consequences in the form of degeneration of hyaline cartilage [25]. Primarily, the treatment methods were developed with an absolute interpretation of the disease as an aseptic process. However, the improvement of microbiological diagnostic methods has led to the emergence of data on the presence of microbiological and viral agents in previously considered aseptic joint. These data allow us to take a new look at the mechanism of joint destruction that is irreversible in OA.

The **objective** was to summarize the literature data on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

MATERIAL AND METHODS

The original literature search (2010 to 2023) was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org). Literature searches included both Russian and English studies reporting the effect of microbiological factors on the development of arthropathy. 53 full-text articles were selected based on keywords and abstracts. The choice was determined by the relevance of data on the results of studies on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection. Based on keywords and abstracts 53 full-text articles were selected. The choice was determined by the relevance of data on the results of studies on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

RESULTS AND DISCUSSION

Treatment of chronic joint diseases with degeneration of the articular cartilage can be associated with failures. With the use of new techniques and drugs for conservative treatment and sparing surgical technologies we still observe the inevitable progression of the pathological process. Radical functional restoration can be achieved with total joint replacement that can be associated with risks and disadvantages. In our opinion, failures of organ-preserving treatments of OA are associated with erroneous ideas about the etiology and pathogenesis of the disease, including underestimation of the microbiological factor. OA is defined as a degenerative-dystrophic disease in the Russian-language literature with primary damage to cartilage, there is an inflammatory component with the activation of pro-inflammatory cytokines in all tissues of the synovial joint and characteristic tissue reactions [26, 27]. More advanced microbiological methods indicate the presence of a variety of microorganisms, including pathogenic and opportunistic pathogens, in joint formations in the absence of clinical and radiological signs of OA. This changes ideas about the etiology and pathogenesis of degenerative processes in articular cartilage and necessitates a revision of treatment protocols for joint diseases.

A role of microorganisms can be suggested in the development of OA. Mycoplasmas were among the first microorganisms isolated from animal and human joints. The role of mycoplasmas in the development of synovitis in rheumatological and orthopedic patients was reported at the end of the last century. Mycoplasmas were isolated from arthritic joints of many animals [28]. Some patients with serologically confirmed *M. pneumoniae* developed arthritis [29, 30, 31], and four-year peaks in the incidence of *M. pneumoniae* in Canada showed a significant epidemiological association with new cases of juvenile chronic arthritis [32]. *M. pneumoniae* and *M. salivarium* were isolated from the joints of patients with hypogammaglobulinemia [33, 34, 35]. Although this

microorganism is not usually considered pathogenic, it was reported as causing inflammatory changes in the joint [36]. *M. pneumoniae* and *M. salivarium* were also found in the synovial fluid of 24 of 33 patients with temporomandibular pathology [37].

Rozin, a rheumatologist from the Rambam Medical Center, reported the infectious nature of arthropathy and the successful use of the antibacterial drug co-trimoxazole (sulfometaxazole/trimethoprim) in the treatment of OA. Based on his study and analysis of global experience, he concluded that degenerative diseases of the joints and spine may be associated with infection [38].

The expanded range of microorganisms isolated from joints were reported. Stirling et al. detected Propionibacterium acnes in degenerative intervertebral discs in sciatica patients [39].

In 2016, Belarusian scientists explored 90 patients using polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) "to identify etiologically significant microorganisms and antibodies in the biological material of patients with AVN of the femoral head of non-traumatic origin."Articular synovial fluid, removed femoral head and joint capsule during arthroplasty were examined. PCR of 59 synovial samples demonstrated DNA of the Epstein-Barr virus detected in 15.3 %, DNA of herpes simplex virus (HSV) types 1 and 2 in 5.1 %, DNA of cytomegalovirus infection (CMV) in 3.4 %, *C. trachomatis* DNA in 5.1 % of samples. *Mycoplasma hominis* DNA was detected in 3.4 % of samples. CMV DNA was detected in the synovium of 1 of 51 (2.0 %) patients and the presence of a *C. trachomatis* plasmid DNA fragment in 1 (2.0 %) patient. Epstein-Barr virus DNA was detected in 9 (17.7 %) samples. *M. genitalium* DNA and *U. urealyticum/parvum* DNA were detected in 2.0 %. *C. trachomatis* DNA was detected in the cartilage of the hip joint in 2 out of 53 (3.8 %) cases. HSV type 1 and 2 DNA was detected in 1 case (1.9 %). Epstein-Barr virus DNA was detected in 4 cases (7.6 %). *Ureaplasma urealyticum/parvum* DNA was detected in 1 case (1.9 %). Several intracellular microorganisms were isolated in 26 of 90 (28.9 %) patients with AVN of the femoral head of non-traumatic origin with aseptic necrosis established microbiologically. Markers of the herpes and chlamydial infection were determined in 22.2 % and 14.4 %, respectively. The authors concluded about possible dissemination of pathogens from primary urogenital foci of infection and their role in the development and progression of AVN of the femoral head [40].

The human microbiome, including the microbiota of joints has been explored in recent years, with the advent of more advanced methods. In 2020, a group of researchers examined composition of the microbiota in the knee and hip joints in OA patients in comparison with healthy patients. *Micrococcaceae* family, *Exiguobacterium* were common microorganisms isolated from the knee joint. *Rhodocyclaceae* and *Proteobacteria* were predominant bacterial families in the hip joint. Microorganisms isolated from different joints were genetically distant from each other [41].

Composition and diversity of the gut microbiome were examined in OA patients. Bacterial diversity (alpha diversity) was reported in OA patients, and some authors reported an increase in microbial burden associated with OA. In 2019, Boer et al. reported the fecal microbiome examined in a large series of 1427 patients with knee OA and a control group of healthy patients [42]. Bacterial markers (class *Bacilli*, order *Lactobacillales*, family *Streptococcaceae*, genus *Streptococcus*) associated with pain and effusion in the knee joint were identified in OA patients with MRI [43]. Changes in the microbiome are closely associated with OA and individual OA risk factors. Interventions targeting the microbiome have been shown to potentially prevent or slow the progression of OA [44].

In 2018, Chen et al. reported a comparative analysis of the oropharyngeal microflora in 155 healthy patients, 110 patients with rheumatoid arthritis and 67 patients with knee OA, identified using 16S rRNA gene sequencing. OA patients showed increased bacterial diversity compared to controls, including *Firmicutes*, *Streptococcus*, *Actinomyces*, *Ruminococcus*, *Bifdobacterium* [45].

Using next-generation sequencing (NGS) Torchia et al isolated at least one microorganism from the affected knee in 12 of 40 patients (30 %) undergoing primary total arthroplasty. Forty-eight unique microorganisms were identified in the patients including four fungi (*Cladosporium herbarum*, *Alternaria alternata*, *Filobasidium magnum*, *Naganishia friedmannii*). *E. coli* was a common organism identified in seven patients from 10 separate samples) [46]. The authors suggest that the greatest danger is not, but the native microbiome poses more threat than pathogenic microbes. The role of the microbiome as an etiological factor in the development of OA was supported by other authors.

Researchers from the USA showed that a microbiome is present in the synovial membranes and illustrated its role in the progression of OA. Synovial RNA sequencing from an OA patient was compared to a library of microbial reference genomes to identify microbial reads indicative of microbial abundance. With contamination adjusted, the authors identified 43 microbes that differed in abundance between the OA group and healthy samples. The authors emphasized that the isolated microbes were part of the gut microbiome. Legitimate individual bacterial sequences were identified using high-throughput RNA sequencing, and the microbial mass was significantly higher in OA compared with normal, although all biopsies were obtained from the same medical institution [47]. The mechanism of infection of the joint cavity suggested impaired intestinal barrier function, leading to microbial translocation. A pathogenic bacteria migrated from the intestine into the synovium in OA patients may contribute to the pathogenesis of OA [48, 49, 50]. In contrast to the initial belief that joints are sterile, increasing evidence indicates the presence of a synovial fluid and synovial tissue microbiome [51, 52].

Goswami et al. performed a multicenter review with a high level of evidence and reported the presence of microflora in the form of pathogenic and opportunistic bacteria in the cavity of large joints in patients with arthrosis after intra-articular injections and administration of sodium hyaluronate and corticosteroids using the 16S-rRNA sequencing method [53]. The results of the study confirm that previous intra-articular injection and nosocomial flora can influence the microbial composition of the joint.

Patients with HIV infection constitute a special cohort of orthopedic patients. The influence of microorganisms on the etiology and pathogenesis of OA in the cohort of patients was reported by several authors. Back in 1987, Withrington et al. isolated HIV from the synovial fluid of a patient with HIV-associated oligoarthritis and suggested "a direct inflammatory effect of the immunodeficiency virus on the osteoarticular system" [54]. Lamers et al. reported the presence of HIV DNA in pathological tissues obtained at autopsy [55]. The p24 antigen detected in the synovial fluid of affected joints can be higher than in blood, HIV DNA and tuboreticular inclusions [55, 56], which may be indicative of a viral etiology of the inflammatory process. In 2018, French scientists experimentally proved the role of osteoclasts as a reservoir of the HIV virus, and *in vivo* demonstrated "the direct destructive effect of HIV-1 on the structure and function of osteoclasts" [57]. Russian researchers from the National Medical Research Center FPI discovered RNA of the immunodeficiency virus in bone biopsies from the femoral head with a previously established diagnosis of avascular necrosis [58].

CONCLUSION

There is evidence of pathogenic microflora in the joints in significant number of observations; there is evidence of a local infectious process in the local cellular elements of osteochondral tissue in patients with previously diagnosed aseptic OA. The intestinal microbiome and the urogenital tract are common sources of infection. Multicenter comprehensive studies of the microbiome of joint formations, blood and intestines are needed. A local effect of the immunodeficiency virus on osteonecrotic processes in the joint can be suggested in HIV patients.

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