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Osteoarthritis of the hip: An overview

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Abstract

Osteoarthritis, as the most common form of arthritis, affects predominantly middle-aged and elderly population worldwide. This chronic, degenerative, progressive and multifactorial joint disease can affect different joints in the body. One of the most commonly affected joints with osteoarthritis is the hip joint. Hip osteoarthritis is characterized by the presence of pain, stiffness, and limping which ultimately results with inability to perform activities of daily living. Thus, hip osteoarthritis significantly affects patients' quality of

Abbreviation:

AAOS	– American Academy of Orthopaedic Surgeons
ACR	– American College of Rheumatology
ADL	– Activities of daily living
BAG6	– BCL2-associated athanogene 6 gene
BMI	– Body mass index
CE	– Center-Edge
CSR	– Croatian Society for Rheumatology
CT	– Computed tomography
DMOADs	– Disease-modifying osteoarthritis drugs
EULAR	– European League Against Rheumatism
FAM46A	– family with sequence similarity 46, member A gene
GRO	– Growth-related oncogene
GWAS	– Genome-wide association studies
HERS	– Heart and Estrogen/Progestin Replacement Study
HRT	– Hormone replacement therapy
IL1	– Interleukin-1 gene
IL-1	– Interleukin-1
IL-6	– Interleukin-6
IL-8	– Interleukin-8
IL-17	– Interleukin-17
IL-18	– Interleukin-18
JSN	– Joint space narrowing
K-L	– Kellgren-Lawrence
LIF	– Leukemia inhibitory factor
MCP-1	– Monocyte chemoattractant protein-1
MRI	– Magnetic resonance imaging
NIA	– National Institute on Aging
NIAMS	– National Institute of Arthritis and Musculoskeletal and Skin Diseases
OA	– Osteoarthritis
OARSI	– Osteoarthritis Research Society International
OREF	– Orthopaedic Research and Education Foundation
ROM	– Range of movement
ROS	– Reactive oxygen species
SNPs	– Single nucleotide polymorphisms
THR	– Total hip replacement
TKR	– Total knee replacement
VNTR	– Variable number tandem repeat

life and represents a major public health problem. Because of its high incidence, prevalence and significant medical, social, and economic impact on society as a whole, in this review article we will describe and discuss terminology, classification, epidemiology, etiopathogenesis, clinical presentation, diagnosis, treatment, and prevention of hip osteoarthritis.

INTRODUCTION

The hip joint, including the small joints of the hand and the knee, is one of the most commonly affected joints with osteoarthritis (OA) *(1)*. Clinically, hip OA is characterized by fluctuating pain, crepitation, and decreased range of motion, which results with walking disability of the patient. The clinical features are generally associated with particular radiological changes of the hip joint. The latter are present in different stages of severity of OA comprising joint narrowing, subchondral bone sclerosis, bone cysts, and osteophytes formation. The aforementioned clinical and radiological features of hip OA consequently lead to patient disability in performing activities of daily living (ADL) and have a significant impact on their quality of life, which require treatment. Currently, there are three basic modalities of hip OA therapy: non-pharmacological, pharmacological, and surgical *(2)*. However, the contemporary efficiency of treatment is limited to pain relief, improvement in mobility and performance of ADL, and attempts to repair damaged cartilage with cell-based therapies *(3)*. Furthermore, current treatment regimens are only partially effective, and that is the main reason for physician's dissatisfaction in treating hip OA with such therapies.

Since the cause (etiology) of OA is still not fully elucidated, the etiological treatment is not possible. Therefore, the main goal of treatment is to slow down, or at best, to halt disease progression. Numerous previous studies have improved our understanding of the causes, risk factors, pathophysiological pathways, and mechanisms responsible for the onset and progression of OA [for a review, see *(4-8)*]. A better understanding of the disease pathophysiology will allow the identification of new therapeutic targets in the treatment of OA. However, there is a problem not only for patients with OA and doctors who treat such patients, but also for the society as a whole, due to inability to cope with the medical needs in finding adequate treatment of this disease. So, one of the major challenges in the future will be to find the most appropriate treatment for OA, or a collection of very suitable therapeutic regimens that can perhaps border with goals of personalized medicine.

OSTEOARTHRITIS OR OSTEOARTHROSIS?

Genomic analysis of osteoarthritis renewed the debate about whether it is proper to call this disease osteoarthritis or osteoarthrosis, due to semantic problems in the definition of inflammation present in cartilage *(9, 10)*. Namely, the term osteoarthritis (suffix *-itis* is added to the root of the word) refers to the fact that this disease has an inflammatory component in the pathophysiological process, unlike the term osteoarthrosis (suffix *-osis* is added to the root of the word), which points to the fact that a degenerative process is the dominant one. Thus, in the post-genomic era of molecular medicine, this issue is not just a question of semantics (that studies solely the meaning of the word) *(10)*, but also of synonymy (that studies semantic relationship between two lexemes belonging to the same type of a word, which have a different expression but hold the same content). In other words, are they similar terms, as it is often stated in literature *(11)*? In addition, it has been s suggested that the question referred to the name of this disease is actually a difference in expression in the Anglo-Saxon or German speaking area, justifying the interpretation by the appearance of disease symptoms as a result of dual (chemical and mechanical) action of joint cartilage detritus *(12)*. For example, in German speaking countries, osteoarthrosis pathology will include the occurrence of synovitis (inflammation of the synovial membrane), which arises as a consequence of degenerative changes (e.g. shearing) of cartilage, whereas in the Anglo-Saxon literature this disease is called osteoarthritis *(13)*. The question is what is primary and what is secondary in osteoarthritis? Namely, if the inflammation in osteoarthritis occurs, does it contain all the classic signs of inflammation, according to the 20-century-old definition proposed by the Roman physician Cornelius Celsius, such as the presence of redness and swelling with warmth and pain (from the Latin *rubor et tumor cum calore et dolor*), or some of these signs do not manifest themselves in this disease *(10, 14)*? The answer was given by gene-expression analysis by chip-technology, which showed that avascular, alymphatic, and aneural human articular cartilage affected by osteoarthritis (sometimes even before a stronger clinical manifestations of the disease) contains cells in cartilage like activated macrophages, which show superinduction of inflammatory mediators, but without other signs of inflammation *(10)*. Given the proven presence of inflammatory mediators, in the post-genomic era of molecular medicine, it has been proposed to call this disease osteoarthritis, rather than osteoarthrosis.

CLASSIFICATION

Although many classifications of OA exist, the most common one used in literature is that of the Subcommittee on Classification Criteria of Osteoarthritis, a subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association from 1986 (Table 1) *(15)*. OA can be divided into primary and secondary. Primary OA is a disease of unknown etiology (but with pro-inflammatory character), which occurs in the elderly. Secondary OA occurs predominantly at a

TABLE 1
Classification of subsets of osteoarthritis (OA) [15].

I. Primary (idiopathic)	II. Secondary
A. Localized	***A. Post-traumatic***
1. Hands: nodal (Heberden's and Bouchard's nodes), non-nodal (erosive IP arthritis), S-MC, S-T	***B. Congenital or developmental diseases***
2. Feet: hallux valgus, hallux rigidus, hammer/cockup toes, talo-navicular joint	1. Localized
3. Knee:	a. Hip diseases: LCPD, DDH, SCFE, shallow acetabulum
a. Medial compartment	b. Mechanical and local factors: obesity, leg length inequality, extreme valgus/varus deformity, hypermobility syndromes, scoliosis
b. Lateral compartment	2. Generalized
c. Patellofemoral compartment	a. Bone dysplasias: epiphyseal dysplasia, spondylo-apophyseal dysplasia
4. Hip:	b. Metabolic diseases: hemochromatosis, ochronosis, Gaucher's disease, hemoglobinopathy, Ehlers-Danlos disease
a. Eccentric (superior)	***C. Calcium deposition disease***
b. Concentric (axial, medial)	1. Calcium pyrophosphate deposition disease
c. Diffuse (coxae senilis)	2. Apatite arthropathy
5. Spine (especially cervical and lumbar)	3. Destructive arthropathy (shoulder, knee)
a. Apophyseal	***D. Other bone and joint disorders***: avascular necrosis, rheumatoid arthritis, gouty arthritis, septic arthritis, Paget's disease, osteopetrosis, osteochondritis
b. Intervertebral (disc)	***E. Other diseases***
c. Spondylosis (osteophytes)	1. Endocrine diseases: diabetes mellitus, acromegaly, hypothyroidism, hyperparathyroidism
d. Ligamentous (hyperostosis [Forestier's disease, or DISH])	2. Neuropathic arthropathy (Charcot joints)
6. Other joints: shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular	3. Miscellaneous: frostbite, Kashin-Beck disease, Caisson disease
B. Generalized (includes 3 or more areas listed above)	
1. Small (peripheral) and spine	
2. Large (central) and spine	
3. Mixed (peripheral and central) and spine	

Legend: DDH – Developmental Dysplasia of the Hip; DISH – Diffuse idiopathic skeletal hyperostosis; IP – Interphalangeal; LCPD – Legg–Calvé–Perthes Disease; SCFE – Slipped Capital Femoral Epiphysis; S-MC – Scapho-metacarpal; S-T – Scapho-trapezial

younger age, and it is usually a consequence of other diseases or conditions with a known cause such as developmental disorders, trauma, or the like, which leads to the process also characterized by the appearance of inflammatory mediators *(16)*.

EPIDEMIOLOGY

Epidemiological principles can be used to describe the distribution of OA in the population, and also to assess the impact of risk factors on the onset and progression of the disease *(17)*. For the purposes of epidemiological research, OA can be defined pathohistologically *(18)*, radiologically *(19)*, or clinically *(15, 20)*. Radiological definition of OA has long been considered as the reference standard *(17)*. In fact, there are several ways to define radiologically this disease *(15, 19-24)*. The most common method for radiological definition of OA is the Kellgren-Lawrence (K-L) grading scale for radiological assessment of OA *(19)* and atlas of individual radiographic features in OA *(25)*. Other radiological measurements, including a semi-quantitative assessment of individual radiographic features (such as osteophytes and joint space narrowing [JSN]) or direct measurement of the distance between two bones that form a particular joint (as an indicator of joint space width in knees and hips), are used for the analysis of OA progression in epidemiological studies and in clinical trials of drugs that modify the course of the disease (disease-modifying osteoarthritis drugs – DMOADs) *(26, 27)*. More sensitive imaging method for evaluating the severity of OA is the magnetic resonance imaging (MRI), by which one can visualize more structures within the joint, define different stages of OA, and detect potential DMOADs efficacy in much faster way than by conventional radiological techniques *(21, 28)*.

Studies that examine the symptomatic OA may be more clinically relevant, because all patients with radiologically diagnosed OA do not have symptomatic OA, and *vice versa*, all patients with symptomatic OA need not necessarily have a potentially radiologically diagnosed one

(29). Given this variability in assessing the diagnosis, each set of clinical and radiological criteria can differently define OA in the same person *(29)*.

The prevalence and incidence of hip osteoarthritis

The prevalence (proportion of patients in the population dependent on the incidence and duration of the disease) and incidence (number of new patients in relation to the number of vulnerable people that can become ill from particular disease within a certain population over a given period) of primary hip OA increases with age *(30-32)*. The prevalence of hip OA varies among the studies in relation to the definition of hip OA, but also according to the characteristics of the observed population in the study *(17)*.

Radiologically diagnosed (radiographic) hip OA was less frequent in relation to radiographic hand or knee OA. For example, about 7% of women aged ≥ 65 years had radiographic hip OA in The Study of Osteoporotic Fractures Research Group *(33)*. However, the incidence of radiographic hip OA was much higher in The Johnston County Osteoarthritis Project, with 27% of respondents aged at least 45 years, showing radiological evidence of the severity of hip OA by K-L scale 2 or more *(34)*. Possible explanation for the differences between those studies are differences in the observed populations, differences in the definition of OA, distribution of risk factors for the development of OA, as well as differences among observers who assessed the degree of radiographic severity of OA *(17)*.

Symptomatic OA is generally defined by the presence of pain and limited mobility of the affected joint with certain radiological characteristics (JSN, osteophytes, subchondral cysts, and subchondral bone sclerosis), and in dependence of the degree of OA severity *(17)*. The prevalence of symptomatic OA also increases with age *(35)*. Specifically, about 9% of respondents in The Johnston County Osteoarthritis Project had symptomatic hip OA *(34)*.

Oliveria *et al. (31)* in their study reported that the incidence of symptomatic OA of the hip, knee and hand standardized by age and sex is 88, 240, and 100 per 100 000 person yearly in subjects from the Massachusetts health maintenance organization. The incidence rate of symptomatic hand, knee or hip OA is rapidly growing around the age of 50, and the same is then equalized after 70 years of age.

Risk factors for the development of hip osteoarthritis

Osteoarthritis has a multifactorial etiology. In addition, there are multiple genetic risk factors. The development of OA can be seen as a result of the interaction between systemic and local risk factors *(36)*. For example, a person may have inherited predisposition for the development of OA, whereas the similar outcome can occur only if that person suffers an injury to a joint *(17)*. The relative importance of risk factors may vary for different joints, for different stages of disease, for the development in relation to disease progression, and for the radiologically diagnosed OA in the relation with symptomatic OA *(17)*. There is evidence that suggests that some risk factors may act independently according to some individual radiographically-defined disease characteristics, such as osteophytes and JSN *(36)*.

Multiple risk factors exist for the development of primary hip OA, such as age, sex, ethnicity, obesity, occupational *(37)* and genetic factors for which are believed to be associated with the development and progression of this disease *(38)*. All risk factors were classified into two groups: systemic and local.

Systemic risk factors for the development of hip osteoarthritis

Systemic risk factors for the development of hip OA include age, gender, hormones, race/ethnicity, genetics, congenital/developmental abnormalities, and nutrition.

Age is one of the strongest risk factors for the development of OA in all joints including the hip *(36, 39, 40)*. The increase in incidence and prevalence of OA with age increase was probably consequence of cumulative exposure to various risk factors and biological changes that occur with aging *(17)*. Those biological changes may decrease functional abilities of particular joint during the action of certain unfavorable circumstances, such as thinning of the articular cartilage, muscle power loss, poor proprioception, and oxidative damage *(17)*.

Women, not only have a possibility to develop OA more often than men, but also with a more severe form *(41)*. Increased incidence of OA in women during menopause has prompted research on whether hormonal factors play a role in the occurrence of OA. However, the results of observational studies on the impact of endogenous or exogenous estrogen on the occurrence of OA are contradictory *(42-44)*. For example, in the Heart and Estrogen/Progestin Replacement Study (HERS) *(45)*, a randomized, double-blind, placebo-controlled trial, there was no significant effect of 4 years of combined estrogen and progestin hormone replacement therapy (HRT) compared with placebo on knee pain and related disability. On the contrary, data from the Women's Health Initiative *(46)*, placebo-controlled, double-blind, randomized trials have shown that women on estrogen-alone HRT have 15% less chance for total knee replacement (TKR) or total hip replacement (THR) surgery compared to those women without such therapy. Additionally, combined estrogen and progestin HRT was not associated with the risk for TKR or THR surgery.

The prevalence of OA as well as localization of individual joints affected by OA differs among racial and ethnic groups *(17)*. Results from „The Johnston County Osteoar-

thritis Project" showed that the prevalence of hip OA in African American women (23%) was similar to that of Caucasian women (22%), while the prevalence of OA of the same localization in males was slightly higher in African Americans (21%) than in Caucasians (17%) *(47)*. An interesting fact from the same study is that the prevalence of individual radiographic features of hip OA varied between African Americans and Caucasians. Namely, JSN in the upper part of the hip joint as well as the occurrence of osteophytes in the lateral part of the hip joint is more common in African Americans than in Caucasians. However, the racial/ethnic difference related to the anatomical variations of femoral head and acetabulum, could be an important risk factor in radiographic hip OA in Caucasians *(48, 49)*, and this remains a problem for research in the future.

Numerous studies have demonstrated the importance of heredity for the development of primary OA, as well as heredity variation with regard to OA localization *(50-55)*. Studies of monozygotic and dizygotic twins, as well as family studies have shown that hereditary component for the development of OA estimates ranging approximately from 50 and 65% with a greater genetic influence for the development of hand and hip OA than the knee OA *(50-52)*. Furthermore, MacGregor *et al. (55)* examined the genetic contribution to radiogarphic hip OA in women and concluded that the genetic factors have a significant contribution for the development of hip OA and account for approximately 60% of the variability in the population.

Some congenital or developmental disorders (such as developmental dysplasia of the hip, Legg-Calvé-Perthes disease, or slipped capital femoral epiphysis) are associated with the occurrence of hip OA later in life *(56-58)*. Given the fact that previously mentioned disorders are rare, it can be assumed that they have little impact on the incidence of hip OA in the general population *(17)*. Several studies have investigated the subclinical form of acetabular dysplasia (which was defined by values of Center-Edge (CE) angle of Wiberg ranging 20-25° in people without clinical symptoms in the hip joint), which is the common and milder form of developmental disorder of the hip, and its correlation with the development of hip OA, with contradictory results *(59-63)*. Lane *et al. (59)* in their study showed that the abnormal CE angle of Wiberg and acetabular dysplasia are associated with approximately threefold increased risk for early development of hip OA in women, suggesting that subclinical form of acetabular dysplasia could be a significant risk factor for the development of hip OA.

Nutritional factors, which represent one of the systemic risk factors for the development of OA, are the subject of great interest of researchers who seek to clarify their role in the development of OA. One of the dietary factors assumed to influence the development of OA is vitamin D. However, results of these studies are contradictory *(64-67)*. Namely, without the sufficient amounts of vitamin D in the body, bones can become thin, brittle, or deformed. In the Study of Osteoporotic Fractures Research Group *(65)*, women with medium (23-29 ng/ml) and the lowest (8-22 ng/ml) levels of 25-vitamin D in serum are three times more likely to develop incident radiographic hip OA (defined by JSN) compared to women with the highest values (30-72 ng/ml) of this vitamin in the serum. Also, the same study has shown that low serum levels of 25-vitamin D were not associated with risk for the development of osteophytic form of incident radiographic hip OA, and that serum levels of 1,25-vitamin D were not associated at all with radiographic changes of hip OA.

Local risk factors for the development of hip osteoarthritis

The local risk factors for the development of hip OA include overweight and obesity, previous injury and/or surgery, occupation, physical activity, and sport.

Obesity (body mass index [BMI] ≥30) and overweight (BMI 25.0-29.9) have been long time ago recognized as risk factors for the development of OA, particularly knee OA *(36)*. However, the relationship between overweight and obesity with hip OA is inconsistent. If the impact on the development of hip OA exists, such a linkage is less pronounced than in patients with knee OA *(68, 69)*. However, it was shown that obesity increases the risk for the development of bilateral radiographic, as well as symptomatic hip OA *(70)*. In the study of Karlson et al. *(71)* it was observed that increased BMI (especially at the age of 18 years) is significantly associated with increased risk for THR. The increased joint loading is probably the main, but not the only mechanism by which obesity could cause knee or hip OA; namely, excessive loading of the knees and hips can lead to the joint damage with the concomitant loss of ligamentous and other structural support *(17)*.

Previous injury and/or surgery of the hip joint can lead to increased incidence and earlier development of hip OA. Namely, in the study of Cooper et al. *(72)* it was observed that an increased incidence of hip OA occurs in a population with a previous hip injury. Such hip injury is more associated with an earlier development of unilateral hip OA in men than in women. Furthermore, it was stated that time from the hip injury to the onset of symptoms (pain and limited mobility) is on average 13 years. Therefore, the conclusion is that previous hip injury represents a risk factor for the development of hip OA.

Highly repeated overuse of joints in performing various work activities is associated with increased risk for the development of OA *(17)*. Explicitly, the increased risk for hip OA was observed in workers who frequently lift and carry heavy loads, such as construction workers and farmers *(73)*. Also, there was a positive correlation between frequent stair climbing during work activities and increased incidence for hip OA. On the other hand, increased incidence of hip OA as a consequence of frequent ladder climbing was not proven. With regard to the long-term kneeling

TABLE 2

List of selected epidemiological studies of osteoarthritis in the period from 1941. – 2000.

Ordinal number	Geographical origin	Osteoarthritis localization
1	USA	Hand OA
2	USA	Hand OA
3	UK	Hand OA
4	UK	Hand OA
5	UK	Generalized OA
6	UK	Generalized OA
7	UK	Generalized OA
8	USA	Generalized OA (Hand and knee OA)
9	UK	Generalized OA (Hand and knee OA)
10	Sweden	Hip OA
11	UK	Knee and hip OA
12	UK	Hip OA
13	Iceland	Hip OA
14	USA	Spine OA
15	Japan	Spine OA
16	Italy	Spine OA
17	USA	Spine OA
18	UK	Hand and knee OA
19	UK	Cervical and lumbar spine OA
20	UK	Hip OA

Legend: OA – Osteoarthritis, UK – United Kingdom; USA – United States of America.

and squatting while performing work activities and hip OA, so far, there was also no established correlation.

Previous studies that have examined the relationship between sports activities and the consequent development of OA have yielded inconsistent results *(17)*. However, there are indicators in the literature, which point to the fact that there is an increased risk for the development of hip OA in competitive long-distance runners *(74, 75)*. Even more surprising is the fact that general physical activity can also increase the risk for hip OA. For example, the study by Lane et al. *(76)* reported that women with higher than „normal" level of physical activity also had higher prevalence of hip OA.

In the introductory part of the subsection about factors for the development of hip OA, all risk factors were classified into two groups: systemic and local. However, what is important to emphasize, from the clinical perspective, is the fact that particular risk factors for the development of hip OA are modifiable, such as patient hormonal status, nutrition, overweight and obesity, preceding injury and/or surgery, occupation, physical activity and sport. The remaining risk factors, such as age, sex, race/ethnicity, genetics and congenital/developmental abnormalities are non modifiable. Therapeutic action on modifiable factors can positively influence prevention of hip OA if risks were reduced.

Genetic epidemiology of hip osteoarthritis

Genetic epidemiology studies the genetic factors that determine the distribution and dynamics of particular disease in the population using different methods of analysis *(77)*. With the advent of high-throughput genotyping, it has become possible to genotype (i.e. analyze variations of DNA sequences) over a million single nucleotide polymorphisms (SNPs) per person and genotyping dozens or thousands of people in a single study *(78)*. The previously mentioned arguments, and the fact that current SNP markers cover over 85% of the genome in the Caucasian population *(79)*, mean that access to association analysis of the genome has the potential to reveal the genetic contribution in complex human diseases such as osteoarthritis *(78)*. Etiological insights that might stem from such research should lead to improved diagnostic

TABLICA 3

Clinical criteria for the diagnosis of hip osteoarthritis (OA) *(20)*.

Traditional criteria
Hip pain in the presence of one of the following criteria: – ESR <20mm/hour – radiographic femoral or acetabular osteophytes – radiographic JSN (superior, axial, and/or medial)
The criteria according to the classification tree
Hip pain and radiographic femoral and/or acetabular osteophytes or Hip pain with radiographic axial JSN and ESR ≤20mm/hour
Legend: ESR – Erythrocyte sedimentation rate; JSN – Joint space narrowing.

and prognostic capabilities and enable the development of more specific therapies for osteoarthritis of large joints.

One of the earliest indications that genetic predisposition for the development of OA exists has been known since 1941 (Table 2, Study under ordinal number) *(80)*. Namely, Stecher noticed frequent occurrence of Heberden nodes (spindle thickening of the hand distal interphalangeal joints) in particular families. In its work, Stecher concludes that this phenotype is inherited as a dominant trait with a strong preponderance in favor of the female sex, and sets the concept that the OA is the hereditary disease. Further family studies (Table 2, studies under ordinal numbers 2-7) have shown that the nodal OA (sudden appearance of swelling, pain and redness in the area of the distal interphalangeal joints of the hands in women older than 45 years) often occurs as part of generalized OA and, based on the results of those studies, it has been proposed polygenic inheritance for OA, defining thus OA as a complex (polygenic) disease *(81-86)*.

To confirm the role of different genes in the development of OA, further epidemiological studies were conducted (Table 2, studies under ordinal numbers 8-17) *(52, 87-95)*. Those studies included families with frequent occurrence of hand, knee, hip and spine OA. The results of these studies confirmed the significant impact of heritage in the development of OA. However, epidemiological studies usually have two basic weaknesses: insufficient data and the possibility that on the risk for the development of OA may affect environmental factors which are unknown, unrecorded, or are difficult to verify because they are obtained from patient medical history (e.g. patient occupation, etc.).

For these reasons, the genetic background for the development of potentially hereditary diseases (in this case OA) can be proved with twin studies (Table 2, studies under ordinal numbers 18-20) *(51, 55, 96)*. These studies compare the frequency of disease occurrence between monozygotic and dizygotic twins. Namely, as monozygotic twins share 100% of their genetic material, observed concordance in the incidence of disease directly shows the level of influence of genetic risk on the development of such diseases. Based on this, risk for the development of such disease is calculated and compared to the observed concordance in dizygotic twins, which share only 50% of their genetic material. The results of these studies have shown, after the correction with known confounding factors (such as obesity, occupation, sports activity, etc.), that development of 60% radiographic hip OA in women can be attributed to genetic factors independent of known predisposing (environmental or demographic) factors *(78)*.

There are several possible strategies that can be used to investigate the role of genetics in the development of hip OA, such as: family studies, twin studies, candidate gene studies, genome-wide association studies (GWAS), and meta-analyzes *(78, 97-102)*. Due to the facts that extensive literature exists regarding the role of genetics in the development of hip OA (using previously listed strategies) and its extent is beyond the scope of this subsection, we refer the reader to the additional literature regarding this topic.

Previous studies regarding genetic predisposition for the development of hip OA in the Croatian population *(103, 104)*, carried out in multicentre collaboration (University Hospital for Orthopaedics and Traumatology Lovran, School of Medicine, University of Rijeka, Croatia; Department of Physiology and Immunology, School

TABLE 4

Kellgren-Lawrence grading scale for radiological assessment of osteoarthritis (OA) *(19)*.

Radiographic grade	**0**	**I**	**II**	**III**	**IV**
Classification	Normal	Doubtful	Mild	Moderate	Severe
Description	– no radiographic features	– minute osteophytes – doubtful significance	– definite ostephytes – normal joint space	– definite ostephytes – moderate joint space narrowing	– definite ostephytes – severe joint space narrowing – subchondral sclerosis

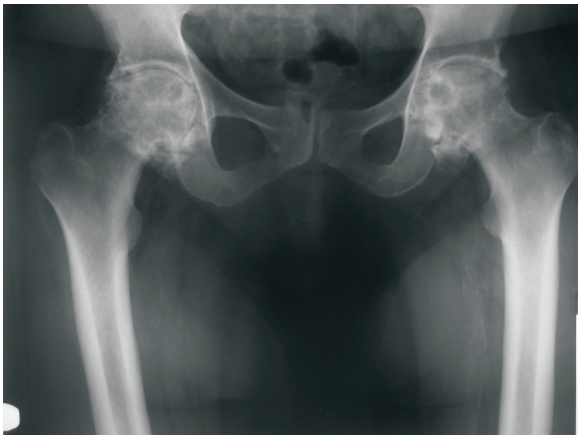

Figure 1. *Antero-posterior X-ray of the pelvis and both hips showing advanced bilateral hip osteoarthritis with the presence of classical radiographic findings, such as joint space narrowing, subchondral sclerosis, osteophytes, and subchondral cysts.*

of Medicine, University of Rijeka, Croatia; Clinical Institute for Transfusion Medicine, University Hospital Center Rijeka, School of Medicine, University of Rijeka, Croatia; Department of Oral Biology, Molecular Genetics Laboratory, University of Oslo, Norway) showed that 1-1-1-2 haplotype of the interleukin-1 (IL1) gene locus could be associated with a predisposition for the development of hip OA *(104)*. Our results corroborate the published studies in a German *(105)*, Dutch *(106)*, and UK *(107, 108)* population, in which haplotype 1-1-1-2 has been found to be associated with susceptibility to hip OA. On contrary, our study contradicts a latter UK study *(109)* which described lack of association with susceptibility to hip OA in persons with 1-1-1-2 haplotype. Possible explanations for such contradictory outcomes between our and other published association studies regarding susceptibility to hip OA could be the differences in complex inheritance variability and environmental exposures in diverse populations. Our further research *(110)* has shown the connection between variable number tandem repeat (VNTR) polymorphism in the second exon of the family with sequence similarity 46, member A (FAM46A) gene and BCL2-associated athanogene 6 (BAG6) gene rs3117582 SNP with predisposition for the development of the large joint (hip and knee) OA in the same population. In conclusion, aforementioned results show that the IL1 gene locus, as well as FAM46A and BAG6 genes in „collaboration" with some unknown gender-specific factors, not excluding other genetic or epigenetic factors, are involved in the pathogenesis of primary hip OA.

ETIOPATHOGENESIS

The last and still valid definition of osteoarthritis is the one from 1995 *(111)*, established by consensus of experts in the area of this disease from the American Academy of Orthopaedic Surgeons (AAOS), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Aging (NIA), Arthritis Foundation, and the Orthopaedic Research and Education Foundation (OREF), which reads as follows:

„Osteoarthritis (OA) represents a group of different overlapping diseases that can have various causes, but similar biological, morphological and clinical outcome. The pathophysiological process in this disease affects not

TABLE 5

Guidelines of non-surgical (non-pharmacological and pharmacological) and surgical treatment of hip osteoarthritis (OA).

Non-pharmacological treatment
It is recommended that patients do the following: – cardiovascular (aerobic) and/or resistance exercise – exercise in water – body weight reduction (for obese) *It is conditionally recommended that patients do the following*: – participation in programs of self-medication – manual therapy in combination with a controlled exercises – psychosocial support – instruct patients about local heat application – use of walking aids (if needed) *No recommendation regarding the following*: – participation in balance exercises or in combined balance and strength exercises – participation in tai chi programs – application of manual therapy as the only treatment
Pharmacological treatment
It is conditionally recommended that patients should use one of the following: – paracetamol – oral NSAIDs – tramadol – IA corticosteroid injections *It is conditionally recommended that patients should not use the following*: – chondroitin sulfate – glucosamine *There is no recommendation regarding the use of the following*: – topical NSAIDs – IA hyaluronate injections – duloxetine – opioid analgesics
Surgical treatment
Depending on the severity of OA: – hip arthroscopy – open hip debridement – osteotomies around hip joint (pelvic and/or proximal femoral osteotomies) – total hip replacement

Legend: IA – Intra-articular; NSAIDs – Non-steroidal anti-inflammatory drugs.

only the joint cartilage, but involves the whole joint including subchondral bone, ligaments, joint capsule, synovial membrane and periarticular muscles. Finally, degeneration of articular cartilage occurs with fibrillation, fissures, and ulceration, which ultimately leads to loss of full cartilage thickness up to the subchondral bone. OA is a result of interaction of mechanical and biological events that destabilize the equilibrium of degradation and synthesis of chondrocytes and extracellular matrix of the articular cartilage, as well as subchondral bone. Several factors, such as genetic, developmental, metabolic, and traumatic lead to initiation of this disease. Changes during OA affect all tissues of the diarthrodial joints. In its final stage, OA is manifested by morphological, biochemical, molecular, and biomechanical changes of cells and matrix which lead to a softening, fibrillation, ulceration and loss of joint cartilage, sclerosis and eburnation of the subchondral bone, formation of osteophytes and subchondral cysts. When it becomes clinically evident, OA is manifested by pain, tenderness, limited range of movement, crepitus and occasional swelling of the affected joint, as well with a variable degree of inflammation without systemic effects."

According to Brandt *et al. (112)* this inclusive definition offers something for everyone, but is not helpful in understanding the etiopathogenesis of OA. OA is the most common disease of the musculoskeletal system in middle and old age in developed countries *(113)*. Therefore, it is of particular importance to study pathogenesis, clinical aspects and treatment of this disease, because it has a high incidence, prevalence and significant medical, social and economic impact on society. The etiology of OA is still unclear, and thus the etiological treatment of this disease is not possible. Given the fact that the etiology of OA remains unclear, the main goal of treatment is to slow down, or at best, halt progression of OA *(2)*.

Numerous previous studies have improved our understanding about the causes, risk factors, pathophysiological pathways, and mechanisms responsible for the onset and progression of OA *(2)*. If we talk about the molecular pathogenesis of OA, this disease affects the whole joint *(114)*. Namely, the cartilage, synovial membrane, and bone may be the main place of production of cytokines, growth factors, chemokines, and inflammatory mediators that promote the occurrence of inflammation and progressive destruction of joints affected by OA *(115, 116)*. Joint destruction affected by OA is primarily characterized by the destruction of cartilage as a result of, at first, subclinical inflammatory changes in the cartilage detectable only at the molecular level *(10, 115)*. Abnormal mechanical loading seems to „wake up" chondrocytes from the state of low metabolic activity *(117)* and stimulates these cells to produce proinflammatory mediators, many of which are produced by macrophages during the response to injury or infection *(10)*. These inflammatory mediators include numerous cytokines and chemokines such as interleukin-1 (IL-1), IL-6, IL-8, IL-17, IL-18, monocyte chemoattractant protein-1 (MCP-1), leukemia inhibitory factor (LIF), growth-related oncogene (GRO) and oncostatin M (OSM), as well as reactive oxygen species (ROS) such as nitric oxide, superoxide, hydrogen peroxide and peroxynitrite *(116)*. All previously mentioned mediators of inflammation along with derivatives of arachidonic acid (prostaglandins and leukotrienes) increase catabolic activity of chondrocytes, which results in production and release of a number of proteolytic enzymes, including matrix metalloproteinases and aggrecanase, leading to degradation of the cartilage matrix *(116)*.

Finally, the research should be directed at better understanding of the etiology and pathophysiology of this disease in the future, which will eventually allow the identification of new therapeutic targets and successful treatment of patients with OA.

CLINICAL PRESENTATION

Discomforts related to the occurrence of OA are described as the presence of symptoms and signs of the disease in certain patients whose joint (or joints) is affected by osteoarthritis. Symptoms of the disease are defined as the subjective experience of the patients, while signs of the disease are objective indicator of certain diseases. Symptoms of OA is the cause that bring the patient to the physician, and the physician observes signs of OA upon examining patients with OA of particular joint (or joints).

The most common symptoms of the disease associated with the occurrence of OA are pain in the affected joint, morning stiffness of the joint that lasts up to 30 minutes, instability or deformity of the joint, and limited joint function or loss of joint function *(118)*.

The most common signs of the disease associated with the occurrence of OA in the affected joint are bone prominence, limited or blocked joint mobility, crepitus and/or pain during movement, and malalignment (incorrect positioning of bones of the joint) and/or deformity of the joint *(118)*.

The most common symptom of hip OA is the appearance of pain in the hip joint. Usually such pain develops gradually, in the beginning it is of lower intensity and intermittent, but over time became much more severe and more frequent. However, sudden onset of pain was described in the patients with hip OA *(118)*. Pain and stiffness of the hip joint can be more pronounced in the morning or after a long sitting *(20)*. Over time, painful episodes become more frequent and occur during sleep or during the night. Additional symptoms and signs of the disease that can occur in patients with hip OA are pain in the groin or thigh extending in the ipsilateral gluteal region or knee, pain that worsens with activity of daily living, limited range of movement (ROM) of the hip joint which hinders the patient mobility, blockages in the area of the

hip joint (because of the presence of intra-articular loose bodies) with crepitus (due to wear of the cartilage), limited active and passive hip motion (especially internal rotation – it is usually earliest affected movement in the patient with hip OA!) that affects the mobility of hip and leads to limping and disturbed dynamics of walking, as well as aggravation of described symptoms during changes in weather conditions *(20, 118)*.

At the physical examination of patient with hip OA, one should pay attention to dynamics of the walking and the presence or absence of a limp from affected hip. In the area of the hip affected by OA tenderness and pain that increases during hip mobility is usually present. Similarly, during examination of affected hip ROM, limited and painful active and passive mobility is also usually observed *(20)*. Namely, the passive internal rotation is the most painful and the most limited movement in the hip joint *(20)*. Moreover, crepitus can occur during the movement in the hip joint.

DIAGNOSIS

All patients with OA of certain joint (or joints) can be classified into two groups: 1) patients with radiographic OA who are asymptomatic and are discovered incidentally on the basis of radiographic imaging findings of affected joint(s), and 2) patients with symptomatic OA, whose complaints, such as pain, restricted mobility and a reduction or loss of function of the affected joint(s), brings them to the physician. Symptomatic OA, as mentioned above, is generally defined by the presence of pain and limited joint(s) mobility with certain radiological characteristics (e.g. JSN, osteophytes, subchondral cysts, and subchondral bone sclerosis), depending on the degree of the severity of OA *(17)*.

The diagnosis of hip osteoarthritis is made on the basis of medical history, clinical presentation, physical examination, as well as basic and (if necessary) additional diagnostic imaging techniques. The most commonly used clinical criteria for the diagnosis of hip OA are the criteria of the American College of Rheumatology for the diagnosis and classification of hip OA (Table 3) *(20)*.

Basic diagnostic imaging techniques for patients with suspected hip OA includes antero-posterior (AP) X-ray of pelvis with both hips (Figure 1) and axial X-rays of the pelvis with both hips („Frog-leg position") *(119)*. The most commonly used radiological criteria for the diagnosis of hip OA is Kellgren-Lawrence scale for radiological assessment of OA (Table 4) *(19)*. In the case of initial osteoarthritic changes in the hip with uncertain signs of OA (radiographic stage I according to K-L scale) additional diagnostic imaging techniques are indicated, such as ultrasound, computed tomography (CT), bone scan, or MRI of the hip (the most sensitive and most specific of all additional diagnostic imaging techniques) *(120)*.

TREATMENT

Current modalities for the treatment of osteoarthritis, such as a non-surgical (non-pharmacological and pharmacological) or surgical treatment do not cure the cause, but the consequences of OA (such as pain and loss of function) *(121)*. To date, numerous guidelines for the treatment of OA have been described in literature. The table 5 shows a synthesis of recent published guidelines for non-surgical (non-pharmacological and pharmacological) and surgical treatments of hip OA from The European League Against Rheumatism (EULAR) *(122)*, The Osteoarthritis Research Society International (OARSI) *(123)*, American College of Rheumatology (ACR) *(124)*, and Croatian Society for Rheumatology (CSR) *(125)*.

Treatment of patients with hip OA depends on intensity of symptoms, limitation of hip mobility, degree of disability in activities of daily living, and sleep disorders. The use of non-surgical (non-pharmacological and pharmacological) treatment is always indicated in the initial stages of the disease. In advanced stages of the disease, when applied non-surgical treatment did not give satisfactory results, surgical treatment of patients with hip OA is indicated. Total hip replacement surgery should be applied as the last method of treatment in patients with hip OA, i.e. after the failure or inability to use (due to the severity of the disease) all remaining methods of treatments.

PREVENTION

Osteoarthritis, as the most common disease of the musculoskeletal system today, has significant social, economic, and medical impact on society as a whole *(2)*. Preventive strategies to reduce the impact and burden of the society by OA should be aimed at potentially modifiable risk factors in order to reduce their frequency. Reducing the risk for the development of OA is most effective when risk factors are modified in the risk population *(39)*.

When considering preventive possibilities, evaluation of risk factors for the development and progression of OA is of great importance. Age is the strongest predictor for the development and progression of radiographic OA. In a population at risk for the development of OA are persons aged 50 years and those who are obese, with abnormal joint biomechanics, or with previous joint damage *(126)*.

Prevention strategies that are recommended in patients with OA (and this also applies to the patients with hip OA) are education, elimination of unhealthy behaviors and promoting healthy habits, weight reduction, preservation of function of the affected joint(s), psychosocial support, treatment of comorbidities, rehabilitation measures, reducing the discomforts with self-medication (pharmacological interventions), and well-timed referral to surgical intervention *(126)*.

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