

Familial osteorarthritis : risk factors and determinants of outcome Riyazi, N.

## Citation

Riyazi, N. (2006, November 22). Familial osteorarthritis: risk factors and determinants of outcome. Buijten & Schipperheijn, Amsterdam. Retrieved from https://hdl.handle.net/1887/5416

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Osteoarthritis: an introduction to the disease





## Osteoarthritis: an introduction to the disease

Osteoarthritis refers to a heterogeneous group of conditions ranging from the hereditary form of disabilitating osteoarthritis before the age of forty, and the relative early onset osteoarthritis of the middle aged to the very common form of this disorder found in more than 80% of the elderly population. These conditions are generally marked by a slow progression of articular cartilage degeneration and related changes in the underlying bone at the joint margins (1). The joint groups most often affected by osteoarthritis are the hands, knees, hips, metatarsophalangeal joints and the apophyseal joints of the spine. Disc degeneration, considered by some to be the result of osteoarthritis, is also very common. In familiar forms of osteoarthritis multiple joint groups are often affected, the so-called generalised osteoarthritis (2). The construct of generalised osteoarthritis, described clinically by Kellgren and Moore in 1952, was defined by Lawrence in population-based epidemiological studies, as the occurrence of radiographic changes of osteoarthritis in either 3 or more joint groups (3). A well-recognised form of familiar osteorthritis is polyarticular hand osteoarthritis, characterised by the presence of Heberden's en Bouchard's nodes. Stecher found a two-to three-fold increased risk of the presence Heberden's nodes in mothers and sisters of probands with Heberden's nodes (4). In several subsequent studies familial aggregation has been reported for hand osteoarthritis (4, 5), knee osteoarthritis (6), hip osteoarthritis (7, 8) and disc degeneration (9, 10). Combinations of joint groups with osteoarthritis have most often been reported for the hands with the knees (11), and thee hands with the hips (12). In spite of these observations there is no clinically accepted classification in OA on the basis of joint site or severity.



Clinically, osteoarthritis is characterised by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable degrees of inflammation or effusions. Measurements of structural abnormalities in the affected joints can be performed by radiographic methods, while the current gold standard still is plain radiographic examination (13). Radiological characteristics of osteoarthritis are defined by the presence of osteophytes on the joint margins, joint space narrowing, subchondral sclerosis, bony cysts and altered shape of the bone ends (14). Although radiographic classification of osteoarthritis is widely used, especially in epidemiological studies, the significance of clinical criteria in defining this disorder has been recognised since the 1980s. Criteria for osteoarthritis were established by the Diagnostic and Therapeutics Criteria Committee of the American College of Rheumatology and are aimed to identify patients with clinical osteoarthritis. The major criterion for classification of osteoarthritis is joint pain on most days of the prior month (15) in combination with structural changes, like radiological abnormalities or the presence of bony swellings (Tables 1-3).







Table 1. Checklist of the American College of Rheumatology criteria of hand osteoarthritis

- Hand pain, aching or stiffness for most days of the prior month 1.
- 2. Hard tissue enlargement of  $\geq 2$  of the 10 selected hand joints
- MCP swelling in  $\leq$  2 joints 3.
- 4. Hard tissue enlargement of >1 DIP
- Deformity of ≥ 1 of 10 selected¹ hand joints 5.

Osteoarthritis present\* 1, 2, 3, 4 or 1, 2, 3, 5

Abbreviations: MCP, metacarpophalangeal joint; DIP, distal interphalangeal joint

<sup>1</sup>2<sup>nd</sup> and 3<sup>rd</sup> DIP, 2<sup>nd</sup> and 3<sup>rd</sup> proximal interphalangeal joint (PIP) and 1<sup>st</sup> carpometacarpal joint (CMC) of both hands

\*Minimal criteria for classification

Table 2. Checklist of American College of Rheumatology criteria for the classification of knee osteoarthritis, based on clinical and radiographic characteristics

- 1. Knee pain for the most days of prior month
- 2. Radiographic osteophytes at the joint margins
- Synovial fluid of osteoarthritis (at least 2: clear, viscous, WBC <2,000 cells/mL) 3.
- 4. Synovial fluid not available; age ≥ 40 years
- 5. Morning stiffness of the knee ≤ 30 minutes
- 6. Crepitus on active joint motion

Osteoarthritis present\* 1,2 or

> 1, 3, 5, 6 or 1, 4, 5, 6

Abbreviation: WBC, white blood count

\*Minimal criteria for classification

### Table 3. Checklist of American College of Rheumatology criteria for the classification of hip osteoarthritis, based on clinical and radiographic characteristics

- Hip pain for most days of the prior month 1.
- 2. ESR ≤ 20 mm/h
- 3. Radiographic femoral and/or acetubular osteophytes
- 4. Radiographic hip joint space narrowing

Osteoarthritis present\* 1, 2, 3 or 1, 2, 4 or

1, 3, 4

Abbreviation: ESR, erythrocyte sedimentation rate

\*Minimal criteria for classification







In osteoarthritis, there is a poor association between clinical symptoms and radiological abnormalities. Only 20 to 40% of subjects with radiological osteoarthritis have signs and symptoms in concurrent joint sites. The cause of pain in osteoarthritis is unclear. Since there are no pain receptors in cartilage, cartilage degeneration in itself cannot lead to pain. The origin of the pain is thought to be due to stimulation of pain receptors in the synovium and surrounding tissues, such as periost, subchondral bone, entheses and tendons. However, some of the pain experienced in and around the joints is referred pain or sympathetic efferent pain (16). Additionally the ability to cope with pain has been suggested to also be related to the pain intensity. Catastrophising, a measure of helplessness and magnification of pain and inability has been shown to play a substantial role in the affective response in osteoarthritic pain (17). Loss of function is in addition to pain an important determinant of disability in osteoarthritis.

# **Epidemiology**

The prevalence of osteoarthritis increases with age and is higher in women than in men, especially among the elderly (18). The majority of prevalence surveys on the frequency of osteoarthritis have focused on radiological disease and on osteoarthritis per joint group. The prevalence of radiological osteoarthritis, as assessed in a random population of 917 women in Rotterdam between the ages of 55 to 70 years on the basis of Kellgren & Lawrence scaling grade ≥2, was 21% in the knees, 10% in the hips and 69% in the hands (9). In this population the prevalence of radiological osteoarthritis at multiple sites was 16% in the cohort of 55-65 years and 23% in the cohort of 55-70 years. Symptomatic osteoarthritis is less common than radiological osteoarthritis, especially in the hands. Incidence rates for osteoarthritis at multiple sites are not known. The prevalence of symptomatic osteoarthritis, as diagnosed by the ACR criteria, in an Italian population-based study in 697 older adults (≥ 65) was estimated to be 29.8% in the knees, 7.7% in the hips and 14.9% in the hands. Less than 30% of the subjects with symptomatic osteoarthritis, 9% of the total population, were affected with symptomatic osteoarthritis at multiple joint groups (19). The age- and sex-standardised incidence rate of symptomatic osteoarthritis at different joint groups based on the American College of Rheumatology (ACR) criteria (20) has reported to 100/100,000 person-years (CI95 86-115) in the hands, 88/100,000 person-years (CI95 75-101) in the hips and 240/100,000 (CI95 218-262) in the knees (Figure 1).

# **Pathogenesis**

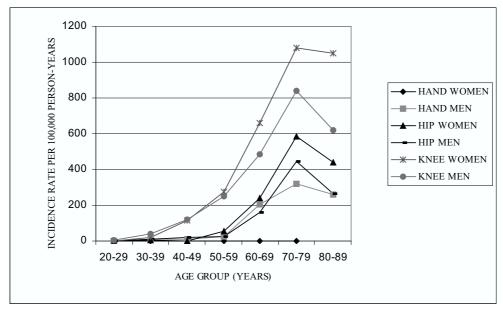
In human articular cartilage, chondrocytes are responsible for the generation of the extra-cellular matrix and the maintenance of tissue homeostasis (21). In osteoarthritis, destruction and failure of the extra-cellular matrix takes place, generally as a result of imbalance in the physiochemical resisting properties of the articular cartilage and applied mechanical stress. The osteoarthritic cartilage





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**Figure 1.** Incidence of symptomatic osteoarthritis of the hand, hip and knee, in members of the Fallon Community Health plan, 1991-1992, by age and sex (Oliveria, Arthritis Rheum 1995).





degeneration has been suggested to consist of a three-step cellular reaction pattern, not necessary in sequence. First, chondrocytes activate or deactivate their synthetic-anabolic activity. Second, chondrocytes undergo phenotypic modulation, leading to a severely altered gene-expression profile of the cells in the diseased tissue. Third, the chondrocytes can die or they can proliferate in an attempt to compensate for cell loss or in order to increase their synthetic activity (22). Despite the low proliferative activity of chondrocytes the tissue repair that takes place does not seem to be very efficient, since the resulting cell clusters do not appear to add substantially to the matrix anabolism (23).

#### **Mediators of inflammation**

In osteoarthritic cartilage, chondrocytes display enhanced and coordinated expression of proinflammatory cytokines and inducible nitric oxide synthase (iNOS), the enzyme responsible for NO production (24). Pro-inflammatory cytokines and NO inhibit the synthesis of cartilage matrix molecules and enhance metalloproteinases (MMPs) activity (25). MMPs, and in particular collagenase 3 (MMP 13) are a potent proteolytic enzyme that play a major role in the degradation of type II collagen (26). Although pro-inflammatory cytokines are pivotal in the initiation and development of osteoarthritis, a shift in the balance between the pro- and anti-inflammatory cytokines contribute to the loss of integrity of the articular cartilage (25). Of the pro-inflammatory cytokines, interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  are the most prominent in ostheoarthritis.





These cytokines in vitro stimulate the production of other cytokines such as IL-8, IL-6, leukaemia inhibitory factor as well as their own production, which in its turn contribute to the accelerated damage of articular tissue (25). Studies in animal models suggest that cartilage destructive processes are mainly IL-1 $\beta$  driven, whereas TNF- $\alpha$  is involved in the early stages of inflammation (27). A number of cytokines such as IL-4, IL-10 and IL-13 inhibit, in vitro, the activity of pro-inflammatory cytokines (28). Further, these anti-inflammatory cytokines are found in increased levels in synovial fluid of osteoarthritis patients (25). Hence, the metabolic state of chondrocytes is under influence of a complex network of cytokines. However, in osteoarthritis, the exact roles of other cytokines than IL-1 $\beta$  and TNF- $\alpha$  in the activation and modulation of possible cascade reactions have not yet been clearly established (28).

# **Etiology**

Osteoarthritis is no longer regarded simply as a "wear and tear " disease but as a disease with a complex etiology. Systemic factors determine an individual's susceptibility to the impact of local biomechanical factors in developing osteoarthritis (Figure 2). Well-known systemic factors are age, female sex and genetic predisposition(29). Of the local biomechanical factors, physically demanding occupations (30), a history of joint trauma and meniscectomy (31) are factors most commonly associated with osteoarthritis. Obesity is also an important risk factor for osteoarthritis not only due to its local biomechanical properties associated with knee osteoarthritis (32) but also due to its metabolic attributes, such as the production of adipokines, that have been suggested to contribute to the susceptibility of hand osteoarthritis (33).

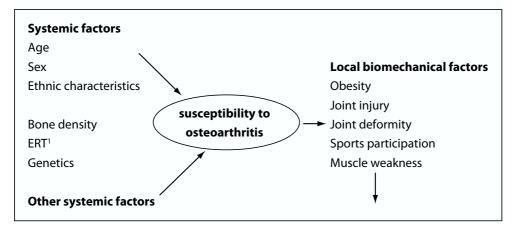
In recent years, there has been a rapid development in the field of osteoarthritis genetics and several chromosomal regions and gene variants have been identified to be important in osteoarthritis susceptibility. A hereditary basis for hand osteoarthritis has been documented already in the 1940s by Stecher and was later confirmed and extended for radiological generalised osteoarthritis by Kellgren et al (4, 34). Since then, heritabilities ranging from 10 to 70% were reported respectively for osteoarthritis in the knees, hands, hips and spine (6, 10, 11). It is unclear whether the varying heritabilities for the different joint groups imply that the genetic contribution to OA is joint-related or whether it is the result of heterogeneous phenotype definitions and study designs, or different prevalences of acquired risk factors. A number of genes encoding extra-cellular matrix components (such as collagen type II) cause Mendelian skeletal diseases and severe early onset osteoarthritis as one of the phenotypic components of the disease. However, these genes did not contribute by genetic variation of milder effects to primary OA arising at later ages. More recently a number of gene variants have been identified that do contribute to primary OA. These findings on the frizzled-related protein 3 gene (FRZB) (35, 36), the asporin (ASPN) gene and the calmodulin 1 (CAML1) gene indicate that genetic susceptibility to primary OA points at a role of signal transduction (37) and (local) inflammatory responses (38, 39) rather than the quality of the extra-cellular matrix.







Figure 2. Pathogenesis of osteoarthritis with putative risk factors (Felson, Ann Intern Med 2000)



<sup>&</sup>lt;sup>1</sup>Estrogen replacement therapy (in postmenopausal women)

### **Outline of the thesis**

The present thesis concerns osteoathritis in patients at middle age. The main objective is to identify risk factors that play a role in the development of osteoarthritis in order to gain further insight in the aetiology of osteoarthritis. The secondary objective is to investigate factors that determine the outcome in osteoarthritis.

In this thesis two phenotypes of osteoarthritis are studied, i.e., familial osteoarthritis at multiple joint sites and radiological osteoarthritis of the hands, both in patients of middle age. These phenotypes of osteoarthritis both have an important hereditary component. The Genetics, ARthrosis and Progression (GARP) study and the Early Arthritis Clinic (EAC) provided the framework for the studies in this thesis.

The GARP study is primarily aimed at the identification of genetic determinants of susceptibility and progression of osteoarthritis. It consists of 191 Caucasian probands aged 40 to 70 and their siblings with primary osteoarthritis at multiple joint sites, collected from 2000 to 2003. The studies described in Chapters II to IV and VIII and VIII are based on data from the GARP study. The EAC is part of an ongoing project that includes consecutive patients with arthritis in at least one joint with a short history of complaints. These patients were referred to the EAC by general practitioners. Each patient subsequently undergoes full clinical, biochemical and radiographic assessment. The studies described in Chapters V and VI are based on data from the EAC.

In Chapter II the GARP study is presented. Earlier studies showed that osteoarthritis in the hand, spine, hip and knee have hereditary components. Hand and spine osteoarthritis have the highest heritability and knee the lowest. In this chapter the familial aggregation of osteoarthritis of different joint sites is investigated within sibpairs with symptomatic osteoarthritis at multiple joint sites.





#### 14 Osteoarthritis: an introduction to the disease

Osteoarthritis is a multicausal disease. Which genetic factors play a role in the development of osteoarthritis is still largely unknown. In Chapter III genetic factors are looked for in patients with familial osteoarthritis at multiple sites included in the GARP study. Chapter III provides evidence suggesting that a proportion of the genetic susceptibility for osteoarthritis is encoded for by variation in innate cytokine activity.

Whether apart from genetic factors also other systemic risk factors and local biomechanical risk factors are etiologic factors in patients with familial osteoarthritis at multiple sites is investigated in Chapter IV.

Since hand osteoarthritis is a subtype of osteoarthritis with a strong familial background, this subtype is appropriate to look for genetic risk factors. In Chapters V and VI studies are presented investigating the association of radiological distal interphalangeal (DIP) osteoarthritis with a number of genes being HLA-DR alleles and IL-10 SNPs.

The final two chapters address the impact of osteoarthritis on the patient's functioning, disability and health. In osteoarthritis there is often a discrepancy between abnormalities due to osteoarthritis, such as radiographic abnormalities on the one hand and disability on the other hand. In Chapter VII and VIII factors that may modify the relationship between disease and disability in osteoarthritis of the hands and the lower extremities are investigated.







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