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Familial osteorarthritis : risk factors and determinants of outcome

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Summary and Discussions

Introduction

This thesis focuses on the development of osteoarthritis and the ensuant disability.
In *Chapter I* a general introduction on osteoarthritis has been given. Osteoarthritis is the most common rheumatic disorder, affecting the integrity of articular cartilage and the subchondral bone. It is a heterogeneous disease consisting of several subtypes, including generalised osteoarthritis and osteoarthritis at specific joint sites, such as the hand, knee or hip. Osteoarthritis is in general a slowly progressive disease leading to pain and functional loss (1).
Osteoarthritis development is thought to have a multicausal etiology involving systemic, genetic and local biomechanical risk factors. In this multicausal etiologic model systemic risk factors, such as age, sex, hormonal status and the like as well as genetic factors, determine an individual's susceptibility to the impact of local risk factors, like obesity, meniscectomy and labour intensive occupations (2-5). A number of genetic risk factors have been identified for various definitions of osteoarthritis. It is yet unclear which specific osteoarthritis subtypes exist and whether gene variants also act as contributory in these specific subtypes.
Epidemiological studies have revealed that some definitions of osteoarthritis, including generalised osteoarthritis, hand OA and disc degeneration of the spine, are especially determined by familial influences (6-8). Hence, these definitions are of particular benefit to the study of genetic risk factors for osteoarthritis as well as for the recognition of the interaction between genetic and non-genetic risk factors. A better understanding of the risk factors for osteoarthritis development would increase the understanding of the pathogenetic mechanisms in osteoarthritis development and may subsequently lead to new targets for therapeutic interventions.

Etiological Studies in Osteoarthritis at Multiple Joint Sites

In *Chapter II* the so-called GARP (Genetic ARtrhrosis and Progression) study is described; a study set up to investigate genetic risk factors for osteoarthritis. In this investigation, conducted between June 2000 and March 2003, sib pairs (191 patients recruited via rheumatologists, orthopedic surgeons and general practitioners with 191 sisters or brothers) with familial symptomatic osteoarthritis at multiple joint sites were included. The majority were females (82%), with a mean age of 60 years and a mean body mass index of 26.5 kg/m^2. The osteoarthritis status of these patients was evaluated in detail by history taking, physical examination of all joint sites, standardised radiographs of spine, hands, knees and hips and by questionnaires on symptoms and functions, such as the Health Assessment Questionnaire, Western Ontario and McMaster Universities osteoarthritis index (WOMAC), Australian Canadian Hand osteoarthritis index (AUSCAN), RAND-36 and biomarkers. Symptomatic osteoarthritis was found 72% in the hands, 80% in the cervical or lumbar spine, 34% in the knees and 24% in the hips. In the siblings of the GARP study familial aggregation was evident for osteoarthritis in the hand, odds ratio (OR)=4.4 (95% confidence interval (CI95) 2.0-9.5), as well as for osteoarthritis in the hip (OR=3.9, CI95 1.8-8.4) and spine (OR=2.2, CI95 1.0-5.1), but remarkably not for osteoarthritis in the knee (OR=1.0, CI95 0.5-2.0). The risk for siblings to be affected in the same joint site combination as the proband were increased for the combination of hand and hip osteoarthritis (OR 3.4, CI95 1.1-10.4) or spine and hip osteoarthritis (OR 4.7, CI95 2.1-10.4). These results indicate that genetic mechanisms may contribute to the development of osteoarthritis phenotypes based on isolated hip osteoarthritis or hip osteoarthritis in the context of a much more generalised phenotype. It is possible that genetic heterogeneity may underlie these different clinical endpoints. Indeed, the same gene variant in the frizzled-related protein (FRZB) gene was found to contribute to the risk of hip osteoarthritis in a UK study (9, 10) and osteoarthritis at multiple sites in GARP (10). It is possible that genetic heterogeneity may underlie the truly different clinical endpoints. Currently used definitions of osteoarthritis can however not yet be considered as distinct clinical subtypes, since osteoarthritis may arise in increasing numbers of joints with aging.

In our search for the risk factors for the development of familial osteoarthritis at multiple sites in the middle-aged, we present the results of two studies in *Chapters III and IV*.

Chapter III provides evidence suggesting that a proportion of the genetic susceptibility for osteoarthritis may be encoded for by variation in innate cytokine activity. Subjects with a high innate *ex vivo* production of interleukin (IL)-1β and IL-1 receptor antagonist (Ra) and low IL-10 production upon lipopolysaccharide (LPS) stimulation had an increased risk of familial osteoarthritis at multiple sites with the following OR: (IL)-1β, OR 3.3 (CI95 1.4-7.9), IL-1(Ra), OR: 8.0 (CI95 3.7-17.4) and IL-10, OR: 3.1 (CI95 1.5-6.5). A high innate *ex vivo* production of TNF-α did not increase the risk of osteoarthritis. Innate variations in the production of IL-1β, IL-1Ra and IL-10 all appeared to contribute to osteoarthritis susceptibility in familial cases. These results complement data obtained from *in vitro* studies and animal models pointing at IL-1β as the prominent cytokine involved in the cartilage destructive process (11, 12). These findings also stimulate research in treatment possibilities with structure-modifiers using IL-1 inhibitors such as Diacerein (13). Moreover, the results of this study

warrants investigations into the role of IL-10, functional IL-10 polymorphisms, as well as IL-1β and IL-1 Ra. The ongoing studies in GARP, however, do not show the expected relationship between the relevant genetic variation at these loci, the stimulated cytokine production in vitro and the presence of osteoarthritis (Meulenbelt personal communications).

It is not clear whether the multifcausal etiological model, believed to be important in the development of osteoarthritis, also applies to familial osteoarthritis. In the few studies that have investigated the role of systemic and local risk factors for osteoarthritis in addition to genetic risk factors, the genetic risk factor has merely been defined, as the co-existence of hand osteoarthritis or Heberden`s nodes (4, 14-15).

As described in *Chapter IV* we examined the association of systemic and local risk factors involved in osteoarthritis in cases with familial osteoarthritis at multiple sites. This study was based the GARP study, which had identified several genetic risk factors. For this purpose 345 healthy control subjects (mean age of 57 years (range 40-76), 64% were women) were recruited by a random sampling taken from the population by telephone. Familial osteoarthritis was associated with married status: OR=2.1 (CI95 1.3-3.4), smoking was negatively associated: OR=0.65 (CI95 0.4-1.0). In women age at natural menopause was associated with etc (age before 45 years compared to the reference category 45-52 years: OR=3.1 (CI95 1.6-6.3)). Physically demanding jobs were associated with an increased risk of familial osteoarthritis in men: OR=2.6 (CI95 1.3-5.3). A higher risk of familial osteoarthritis was observed with increasing body mass index (BMI) (kg/m^2): BMI 25-30, OR=1.8 (CI95 1.3-2.6) and BMI >30, OR=2.0 (CI95 1.3-3.2), compared to BMI <25. The risk of familial osteoarthritis decreased with an increase in height: 160-170 cm: OR=0.51 (CI95 0.3-0.9), 170-180 cm: OR=0.47 (CI95 0.2-0.9) and >180 cm: OR=0.33 (0.1-0.8), all compared to those shorter than 160 cm. In addition, a history of meniscectomy was found to be strongly associated with familial osteoarthritis at multiple sites involving the knees. This study underscores the multicausal etiology of osteoarthritis.

Etiological studies in hand osteoarthritis

Chapters V and VI present the results of two investigations into the association of genetic risk factors with radiological distal interphalangeal (DIP) osteoarthritis, i.e., HLA-DR alleles and IL-10 SNPs. These determinants were studied in consecutive patients with and without radiological DIP osteoarthritis aged 40-70 years from a cohort of subjects with different types of arthritis in an early stage referred to as Early Arthritis Clinic (EAC).

Chapter V demonstrates that HLA-DR2 was more frequent in patients with DIP osteoarthritis than in patients with no radiological evidence of DIP osteoarthritis. We also found a lower prevalence of DIP osteoarthritis in HLA-DR4 positive patients. One would tend to hypothesize a direct role of HLA-DR antigens in osteoarthritis. HLA-class II molecules are involved in the communication between T cells and antigen-presenting cells (16). Osteoarthritis, though not generally considered to be an autoimmune disorder with an inflammatory nature, several studies suggest a role for T-cells and HLA class II molecules in osteoarthritis (17, 18).

In Chapter III it has been shown that subjects with a low innate *ex vivo* production of IL-10 upon LPS stimulation had an increased risk of familial osteoarthritis at multiple sites. This finding prompted us to investigate whether IL-10 polymorphisms, constitutive of the four ancient IL-10 haplotypes and likely reflective of IL-10 production, are a risk factor for osteoarthritis of the DIP joints. The results of the study described in *Chapter VI* indicate that this is not the case. In short, we have observed both in the EAC and in GARP, that the tested Il-10 polymorphisms do not associate with DIP osteoarthritis (Chapter VI) or with osteoarthritis at multiple sites (personal communication Meulenbelt, in prep.). Whereas, these polymorphisms, as shown in other study designs, do associate with production levels and production levels in the GARP study associate to osteoarthritis. This discrepancy may possibly be due to the fact that not all of the genetic variations in IL-10 production are dictated by IL-10 haplotypes of the tested polymorphisms. It may be that the genetic factors dictating interindividual IL-10 production differences that are not located in the IL-10 locus, are the ones relevant for DIP osteoarthritis.

Outcome Studies

The final chapters address the disability resulting from osteoarthritis. In these chapters, the modifying effects of illness perceptions and mental health on the association between impairments in body structures and functions due to osteoarthritis and limitation in activities in the lower extremities and in the hands were investigated, using the International Classification of Functioning, Disability and Health as framework (19). The self-reported limitations in activity have been assessed in the lower extremities by the WOMAC and in the hands by the AUSCAN. For each patient an expected WOMAC and AUSCAN function score has been calculated, using an equation based on a multivariate model of the association of body structures and functions with limitations in activity. We have separately examined the modifying effect of contextual factors in patients reporting less, and patients reporting more, limitation in activities than what would be expected based on impairments in body structures and body functions.

Chapter VII shows that illness perceptions and mental health are important contextual factors in osteoarthritis in the lower extremities. It is further demonstrated that lumbar spine degeneration and exercise as well as physical therapy are contextual factors. Chapter VIII shows that illness perceptions also play a role as contextual factors in hand osteoarthritis. In addition, age, educational level, shoulder pain and pain at other joint sites also appear to be contextual factors. We found different contextual factors to play a role in patients reporting less or more limited activities as measured by the WOMAC or AUSCAN function test than would than would be calculated based on impairments in body structures and body functions. This finding suggests that different mechanisms underlie the discrepancies in the effects of the modifying factors in these two groups of patients. Furthermore our study suggests that future rehabilitation programs to preserve hand function may benefit from improvements in the psychological well being, rather than from focusing solely on improvement in medical status.

Future perspectives

This thesis underscores the multicausal etiology of osteoarthritis, and especially of osteoarthritis with a hereditary background. In this middle-aged patient population with osteoarthritis at multiple sites, systemic risk factors such as hormonal status and local risk factors are shown to be important additional risk factors in the susceptibility of this phenotype. The identification of environmental and systemic risk factors in familial osteoarthritis not only leads to a better understanding of the pathophysiology of this disorder, but also provides us with management options in affected families, i.e. weight reduction, prevention of trauma or job advice. This is important since patients with this phenotype are believed to have a faster disease progression and consequent disability, constituting a patient population with an important social and economic impact as a result of osteoarthritis. Studies to evaluate these management options are to be encouraged.
In search of risk factors for osteoarthritis with a genetic basis, we showed subjects with a high innate *ex vivo* production of interleukin (IL)-1β and IL-1 receptor antagonist (Ra) and low IL-10 production upon lipopolysaccharide (LPS) stimulation to have an increased risk of familial osteoarthritis at multiple sites. The candidate gene variants that may form the genetic basis for this effect, were not associated to osteoarthritis. Whether or not innate *ex vivo* production also translates to cytokine levels, as measured in the peripheral blood and the joints, is to be investigated. It would then be possible to consider the plausibility of treatment options and clinical trials with IL-1 inhibitors such as Diacerein and other biologicals.

We found HLA-DR antigens to be associated with radiological DIP osteoarthritis, a form of osteoarthritis with a strong familial predisposition. Whether HLA-antigens also play a role in the GARP population has to be determined. A genome wide linkage scan is being performed to locate and identify the major loci contributing to osteoarthritis in GARP. We have found that the FRZB locus though not the major locus, contributes to osteoarthritis in GARP (10). In addition to the identification of genetic markers in the future, we have observed cartilage degradation markers in urine to be associated with variations in radiological abnormalities in GARP at baseline (20).
The results presented in this thesis are founded on cross-sectional data on the development of osteoarthritis. From a clinical perspective the short-term and long-term follow-ups to measure the progression of osteoarthritis is a far more interesting subject. The GARP study has already been set up to follow-up a proportion of the patients over a period of 2 years. This will provide us with the opportunity to study which risk factors and biomarkers are associated with progression and to improve clinimetry. The long-term follow-up will give us more relevant information on the progression of osteoarthritis. Since osteoarthritis is in general a slowly evolving disease, information of a longer follow-up period, i.e. an interval of 5 years will be of additional significance in improving our insight in mechanisms involved in progression. To our knowledge there are very few long-term longitudinal studies of osteoarthritis and even fewer are the studies of progression of osteoarthritis at multiple joint sites.

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