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Chapter 1

General Introduction
Of musculoskeletal disorders, knee complaints are the second most frequent reason (after spine related pain) for consulting the general practitioner (1). Knee Osteoarthritis (OA) is a common chronic medical condition leading to progressive structural damage of the joints and subsequent functional disability (2). Until the age of 45 knee OA is rarely diagnosed and knee complaints are often related to (sports) injury and patellofemoral knee pain (1). In older adults, there is a significant increase of the incidence and prevalence of knee OA (incidence in the age groups of 45 to 64 years, from 65 to 74 years and 75 years and older in men: 1.9, 4.1 and 7.3, respectively in women; 3.2, 10.9 and 13.9 per 1000 people per year). Above the age of 74 years, the prevalence in men is 47.3 and 19.7 in women per 1,000 persons per year (1).

Knee OA may develop after knee injury (3), whereas in other patients knee OA develops in a more generalized way without specific trauma, affecting multiple other joints. Known risk factors for the development of OA are mechanical forces including trauma, age, female gender, family history of OA, genetics, obesity, morphologic changes and OA localization in another joint (2;4-9). To date no effective disease modifying medical therapy is available (10).

Since OA is a disease affecting the elderly, studies investigating factors involved in OA development are usually performed in older populations with mean ages ranging from 50 to 80 years (5;11-13). Determining which risk-factors of OA development can be distinguished early in life may help to define high-risk knee patients for the development of knee OA. This could be of clinical importance because high risk patients may benefit from slowing down or even stopping the OA process by early preventive exercise therapy or in the future to develop disease modifying medication, since to date no effective disease modifying medical therapy is available (10;14-16).

To identify risk factors for OA early in life, we conducted a study to investigate knee function and knee OA development after 10 years in 326 patients (mean age 32, SD 7.7) with a history of subacute knee complaints. Inclusion criteria 10 years ago were: persistent knee complaints e.g. pain, swelling and instability lasting for more than four weeks. Exclusion criteria were: knee complaints lasting less than four weeks, clinical symptoms of a locked knee, known inflammatory diseases such as rheumatoid arthritis, moderate to severe radiographic knee OA and a history of knee surgery. All patients were part of a cohort of 855 knee patients who participated in a study on the cost-effectiveness of 0.5T magnetic resonance (MR) imaging relative to diagnostic arthroscopy
The main objective of the study was to determine which prognostic factors for knee OA development could be identified in this relatively young population with a history of knee complaints. Identifying these specific prognostic factors may help to distinguish high-risk knee patients for the development of knee OA early in life, and to develop ways to slow down OA progression towards end stage disease.

In Chapter 2 we investigated the role of anterior cruciate ligament (ACL) and meniscal lesions and subsequent change in biomechanics of knee movement in the development of osteoarthritic changes visible on radiographs and MR imaging. Until recently, knee OA has been primarily visualized and assessed on radiographs by using the Kellgren and Lawrence (KL) scoring system (18). Investigators in large prospective studies have used radiographs with follow-up times of 10–22 years to assess the effect of meniscal and anterior cruciate ligament (ACL) lesions on the development and progression of knee OA (19–22). Magnetic resonance (MR) imaging, owing to its ability to depict cartilage damage, subchondral bone, and bone marrow lesions, has however potential advantages in assessing the development of OA (23;24). Being a relatively new imaging modality, most MR imaging studies have been cross-sectional or have involved a maximal follow-up time of only 3 years (25–28). Since no long-term MR studies were available, we wanted to determine the relationship between knee OA development detected on both radiographs and 3.0-T MR images after 10 years and the presence of ACL ruptures or meniscal tears and the effect on OA development of surgical management of these lesions. The advantages of MR imaging could be useful in determining early OA changes in a relatively young study population.

In Chapter 3 the accuracy and sensitivity to change in hand joint space width (JSW) measurements by a newly developed quantification method is investigated. Being a multi-factorial disease, relationships between knee OA development and the presence of OA in other joints, especially the hands have been described (29). Hand radiographs are used commonly to diagnose and monitor hand OA because of their wide availability and the relatively low costs. Since cartilage cannot be visualized by radiography, decrease of joint space width (JSW) is used as a surrogate marker for cartilage defects. Semi-quantitative methods with standard
Atlases are the bench tools used by clinicians to determine changes in JSW (18;30). However, there is a limitation in reproducibility due to the difficulty to standardize the scoring between different readers. Since OA is a slowly progressive disease, an accurate and reproducible method is needed to detect subtle changes throughout follow-up, especially when evaluating new therapies. A newly developed JSW quantification method automatically detects the interphalangeal (IP) and metacarpophalangeal (MCP) joints and quantifies the JSW in hand radiographs (31). We assessed the accuracy and sensitivity to change in JSW of this quantification method by comparing the automatically determined JSW to the true distance between bony contours of the finger joints. Being able to detect small changes in JSW would make this method ideal for determining early OA changes in the hand and relate these changes to knee OA development in our relatively young study population.

In Chapter 4 we investigated which of the following OA risk factors: ACL and/or meniscal lesions, age, female gender, body mass index (BMI), activity level before knee complaints, a family history of OA and the presence of hand OA could be related to OA development in our relatively young study population. Furthermore, subjective knee function 10 years after knee complaints was determined in relation to osteoarthritic changes, age, gender BMI and activity level before the knee complaints.

In Chapter 5 the effect of surgical intervention on OA development shown on radiographs and MR imaging is reported in Chapter 2. Additionally, we investigated the short-term and long-term clinical effects of surgical management of the knee complaints in knee patients with traumatic knee complaints but without knee locking. Meniscectomy is commonly performed in patients with knee complaints and meniscal tears (32). Recent publications showed no benefits of meniscectomy compared to conservative therapy in patients with degenerative meniscal tears (33-35). It is suggested that knee locking in patients with meniscal tears could be considered an indication for surgical treatment but there remains controversy on the surgical management of traumatic meniscal lesions, especially in those patients without locking symptoms (36). We evaluated the long term clinical effect of meniscectomy in patients with knee complaints without
ACL lesions and with at least one traumatic tear but without symptoms of knee locking.
Differences in knee function and symptoms scores at ten year follow-up were compared between surgically and non-surgically treated patients.

The purpose of this study described in Chapter 6 was to examine the contribution of the OA susceptibility genes ASPN, GDF5, DIO2 and the 7q22 region to radiographic development of knee osteoarthritis (OA) in patients with a mean age of 40.6 years ± 7.9 (SD) who suffered from non-acute knee complaints a decade earlier. A dose response association of 4 SNP’s on the susceptibility genes ASPN, GDF5, DIO2 and the 7q22 locus were determined by comparing 36 patients who showed development of OA on radiographs with 88 patients who had no development of OA on radiographs and normal cartilage on MRI. OA development was defined as a Kellgren and Lawrence (K&L) score >1. Multivariate logistic regression analysis including the variables age, gender, body mass index (BMI) and reported knee trauma was performed to determine associations between OA development and the presence of the risk alleles.

Reference List

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