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Chapter 7

Summary and General Discussion
Chapter 1 provides a general introduction. The main aim of this thesis is to determine which prognostic factors for knee OA development can be identified in a 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 osteoarthritis (OA) early in life. Additionally, we investigated the short-term and long-term clinical effects of surgical management of traumatic meniscal tears.

In Chapter 2 we defined localized development of knee osteoarthritis OA that arises from anterior cruciate ligament (ACL) and meniscal injuries identified on 0.5T MR images performed a decade ago in patients with sub-acute knee symptoms. Also the effect of surgical management of these lesions on OA development was investigated. A follow-up study was performed in 326 patients (mean age 42 years, 33% female) who were all 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 mean follow-up was 10 years. Initial findings and differences in treatment were compared with follow-up radiographs and 3.0T MR scans. Odds ratios (OR) with 95%CI confidence intervals were used to identify effects between variables.

Patients with ACL ruptures had an increased risk of developing joint space narrowing (JSN), cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts medially or laterally (OR, 2.4–9.8). Patients with medial meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, and bone marrow lesions medially (OR, 2.0–15.3). Patients with lateral meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts laterally (OR, 2.1–10.5). Meniscectomy and ACL reconstruction had no effect on the risk of developing OA.

We conclude that localized development of knee OA arises from ACL and meniscal lesions identified on MR images a decade earlier in patients with sub-acute knee symptoms and that surgical treatment of ACL and meniscal lesions have no effect on the development of OA.

In Chapter 3 we validated a newly developed quantification method that automatically detects and quantifies the joint space width (JSW) in hand radiographs. Decrease of JSW is considered to be an important marker of cartilage damage, one of the main characteristics of OA. Repeatability, accuracy
and sensitivity to changes in JSW were determined and the influence of joint location and joint shape on the measurements was tested.

A mechanical micrometer set-up was developed to define and adjust the true JSW in an acrylic phantom joint and in human cadaver-derived phalangeal joints. Radiographic measurements of the JSW were compared to the true JSW. Repeatability, systematic error (accuracy) and sensitivity (defined as the smallest detectable difference (SDD)) were determined. The influence of joint position on the JSW measurement was assessed by varying the location of the acrylic phantom on the X-ray detector with respect to the X-ray beam and the influence of joint shape was determined by using morphologically different human cadaver joints.

The mean systematic error was 0.052 mm in the phantom joint and 0.210 mm in the cadaver experiment. In the phantom experiments, the repeatability was high (SDD = 0.028 mm), but differed slightly between joint locations ($p = 0.046$), and a change in JSW of 0.037 mm could be detected. Dependent of the joint shape in the cadaver hand, a change in JSW between 0.018 and 0.047 mm could be detected.

The automatic quantification method is sensitive to small changes in JSW. Considering the published data of JSW decline in the normal and osteoarthritic population, the first signs of hand OA progression with this method can be detected within one or two years.

In Chapter 4 we identified risk factors for knee osteoarthritis (OA) development in a young to middle-aged population with sub-acute knee complaints in order to define high risk patients who may benefit from early preventive or future disease modifying therapies. The relationship between known OA risk factors from literature described in older study populations and OA development and knee function (Knee injury and Osteoarthritis Outcome Score (KOOS)) in 319 relatively young knee patients (mean age 41.5 years) was investigated. OA development visible on radiographs and MR images and KOOS knee function outcome scores 10 years after sub-acute knee complaints were assessed. Associations between OA development and age, gender, activity level (Tegner Scale), Body Mass Index (BMI), meniscal or ACL lesions, OA in first-degree relatives and radiographic hand OA were determined using multivariable logistic regression analysis. KOOS knee function outcomes were compared to normal population reference values and associations with age, gender, activity level, BMI, and ACL or meniscal lesions were determined using MANCOVA analysis.
OA on radiographs and MR in the tibiofemoral compartment (TFC) is associated with increased age (OR: 1.10, 95%CI 1.04-1.16 and OR: 1.07, 95%CI 1.02-1.13). TFC OA on radiographs only is associated with ACL and/or meniscal lesions (OR: 5.01, 95%CI 2.14-11.73), presence of hand OA (OR: 4.69, 95%CI 1.35-16.32) and higher Tegner activity scores at baseline before the complaints (OR: 1.20, 95%CI 1.01-1.43). The presence of OA in the TFC diagnosed only on MRI is associated with a family history of OA (OR: 2.44, 95%CI 1.18-5.06) and a higher BMI (OR: 1.13, 95%CI 1.04-1.23). OA in the patellofemoral compartment (PFC) diagnosed on both radiographs and MR is associated with an increased age (OR: 1.06, 95%CI 1.02-1.12 and OR: 1.05, 95%CI 1.00-1.09). PFC OA diagnosed on radiographs only is associated with a higher BMI (OR: 1.12, 95%CI 1.02-1.22). The presence of OA in the PFC diagnosed on MR only is associated with the presence of hand OA (OR: 3.39, 95%CI 1.10-10.50). Compared to normal reference values, the study population had significantly lower KOOS scores in all different subscales. Lower KOOS scores in all subscales were associated with an increased BMI (Effect size reaching from 0.024-0.064). TFC OA according to the Delphi criteria was associated with lower outcomes in the subscales Sports and Recreation and Quality of life (Effect size 0.027 and 0.021). The presence of JSN and osteophytes in the PFC was associated with lower Quality of life scores (Effect size 0.017). Higher Tegner Activity scores at baseline were associated with higher scores in the subscales Pain and Sports and recreation (Effect size 0.018 and 0.019). A higher age was associated with lower scores in the subscales ADL and Pain (Effect size 0.018 and 0.048). The presence of ACL and/or meniscal lesions was associated with lower Symptoms scores (Effect size 0.019).

These results show that knee OA development in young to middle aged patients with a history of subacute knee complaints is associated with the presence of known risk factors for knee OA. OA is already visible on radiographs and MRI after 10 years. These high risk patients may benefit from adequate OA management early in life.

In **Chapter 5** we investigated the short-term and long-term clinical effects of surgical management of traumatic meniscal tears in knee patients without knee locking symptoms. A 10 year follow-up in 118 patients with sub-acute knee complaints (mean age 32 years SD 7.8) was performed. Clinical outcome measures of surgically and conservatively treated patients were compared using the Noyes and KOOS knee questionnaires.

There were no differences in short- and long-term Noyes scores and long-term cross-sectional KOOS Pain, Symptoms, ADL and Quality of life outcomes. KOOS Sports and Recreation outcomes were
significantly better in surgically treated patients (19.2 points, 95\% CI 1.5; 36.8, \( p=0.033 \)). Higher activity levels before the start of the complaints improved this effect.

Therefore, partial meniscectomy of traumatic meniscal tears may result in better Sports and Recreation related long-term clinical outcomes. This effect is positively associated with higher activity levels before injury. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.

In Chapter 6 we examined the contribution of the OA susceptibility genes ASPN, GDF5, DIO2 and the 7q22 region to radiographic development of knee osteoarthritis (OA) after 10 years in patients with 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 \( \geq 1 \). 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. A dose response association of DIO2 SNP rs225014: odds ratio (OR) 2.3, 95\% CI 1.1-4.5 (\( P=0.019 \)) and GDF5 SNP rs143383: (OR) 2.0, 95\% CI 1.1-3.8 (\( P=0.031 \)) was observed with knee OA development. The ASPN and 7q22 SNPs were not associated with OA development.

We conclude that the presence of the risk alleles of the DIO2 SNP rs225014 and the GDF5 SNP rs143383 are associated with OA development in a relatively young study population 10 years after knee complaints. Determining DIO2 and GDF5 genotypes significantly improves risk prediction towards clinical relevant values.

**General Conclusion**

In this thesis we demonstrated that several known risk factors for knee OA development i.e. ACL ruptures, meniscal tears, the presence of hand OA and increased BMI, are already associated with knee OA development as demonstrated on radiographs and MR images early in life. Identifying these factors in young to middle aged patients suffering from knee complaints helps to define high risk patients who may benefit from early preventive exercise therapy or maybe disease modifying drugs which might be developed in the future.
Meniscectomy and ACL reconstruction have no effect on knee OA development after 10 years in patients with sub-acute knee complaints.

The in this thesis validated automatic JSW quantification method is sensitive to small changes in JSW of the finger joints. The first signs of hand OA development with this method can be detected within one or two years.

In patients with traumatic meniscal tears but without knee locking symptoms, there may be some benefits from treatment with meniscectomy in long-term Sports and Recreation knee function outcomes compared to conservative treatment. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.