On how obesity links with osteoarthritis

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Chapter 9

Summary, discussion and future direction

9.1. SUMMARY

Osteoarthritis (OA) is the most common joint disease and obesity is one of the strongest risk factors for development and progression of OA. The main aim of this thesis is to give more insight on how obesity leads to OA. Gaining more insight on the effect of obesity on OA is important because we are losing the battle against the world epidemic of obesity. Simply public health measures seem not enough to lower the number of obese people. By understanding more about the pathophysiology of obesity in OA, we might be able to 'treat' OA by modifying the effect of obesity. This approach might be more effective.

After the introduction, the first three chapters of this thesis presented the results of the studies on the structures involved in OA and the studies on OA progression. Studies on OA progression investigated how to stratify OA patients at an early stage. Stratifying (i.e. differentiating) patients who will progress from patients who will not progress, is useful for the selection of the study population that will benefit most from OA treatment in future clinical trials.

In **chapter 2**, we investigated the association between joint tissue damage seen on magnetic resonance imaging (MRI) and pain. MRI can visualize the whole joint, not only cartilage but also bone and synovium. Showing which structures are associated with pain will lead to a rational therapeutic target. In this chapter, we summarized published studies to learn which tissue damage is associated with OA. We concluded in this systematic review that bone marrow lesion (BML) and synovitis/ effusion were associated with knee pain. The level of evidence of this association was moderate. The consequence of these findings is that bone marrow lesion and synovitis/ effusion have the potential to be used as target in treating OA.

In **chapter 3**, we changed the view for a while, from OA defined by pathology to OA defined by joint symptoms. In this population with clinical OA either in the knee or hip, we investigated the factors associated with the clinical progression and good prognosis of lower limb OA. In this study, we found that more than half of the

patients showed progression during a 6-years period (defined as having total joint replacement or worsening self-reported pain or function above predefined criteria) and nearly one fourth had good prognosis of lower limb OA. Factors associated with the progression of lower limb OA in long term were: worsening of self-reported pain and function in one year, limited total range of motion and higher osteophytes and JSN scores. Factors associated with a lower chance to have good prognosis were: worsening in self-reported pain and function score in 1- year. The findings described in this chapter can be used in the clinic to inform patients with regard to their OA prognosis. Knowing which OA patients who will deteriorate at a very early stage is also very helpful in clinical trial on OA drugs or therapy: OA patients with progression are actually the main target in OA therapy.

In **chapter 4**, we investigated the use of multiple measurements of biomarkers to monitor the progression of OA and as a method to predict the progression of OA at multiple sites. The study presented in chapter 4 was unique due to several reasons. Firstly, we used data on multiple measurements of biomarkers. Secondly, we assessed OA at multiple joints. When investigating biomarkers as predictor for progression or as measure of OA change, not only large joint such as knee or hip should be considered but also smaller joints such as hand joints. All synovial joints in the body contribute to the measured biomarkers. Among five biomarkers, we found that multiple measurements of uCTX-II were associated with progression of OA. The predictive power of multiple measurements uCTX-II levels at 0-6 months for OA progression at 2 years is highly promising, implicating that this marker can be use to differentiate patient with and without progression at an early stage. Again, this will be helpful in selecting patient population to participate in clinical trials on treatment of OA. Moreover, since multiple measurements of this uCTX-II were associated with the progression of cartilage defects on radiographs, this biomarker can also be used to evaluate the efficacy of OA therapy. uCTX-II may also be used as one of the outcomes in clinical OA trials and lowering its level may be one of the aims in OA trials.

The following three chapters in this thesis presented results of the studies that tried to answer several questions on how obesity influences the development and progression of OA. In **chapter 5**, we performed a systematic review and showed that obesity was associated with the development of hand OA. The level of evidence of this association was moderate. Since we do not walk on our hands (no added mechanical force in hands of obese people), the results presented in chapter 5 suggest that metabolic factors associated with fat, such as adipokines might also play a role in OA.

This issue was elaborated further by investigating the association between adipokines and the progression of radiographic hand OA in **chapter 6**. Among the adipokines investigated: leptin, adiponectin and resisitin, higher level of adiponectin was shown to be associated with a lower risk for hand OA progression (increased JSN as measured on radiographs). Patients with adiponectin levels in the highest tertile had a 3 times lower risk to have hand OA progression compared to patients with adiponectin levels in the lowest tertile. This suggests that adiponectin is an attractive target for prevention of hand OA progression by increasing adiponectin levels through pharmaceutical or lifestyle intervention.

In **chapter 7**, we investigated the association between obesity and pain in patients who visited orthopedic surgeons to discuss the possibility of getting hip or knee replacements. We found that BMI, as a measure of obesity was associated with pain. We also found that the effect of BMI on pain was different in hip and in knee OA. In hip OA, the effect of BMI was directly associated with pain experience, while in knee OA the effect of BMI on pain was mediated by structural damage. These results suggest the complexity of the relation between obesity and total joint replacement (TJR). It is not merely the sequence: obesity leads to structural damage, consequently structural damage leads to pain, and consequently pain leads to TJR. These findings can have a consequence in treatment of OA. In hip OA, losing weight may not reverse the joint damage already done, but it may be enough to lessen the pain. In contrast, in knee OA, influencing structural damage may be as important as losing weight.

In **chapter 8**, we investigated the possible interaction between obesity and another strong factor of OA, i.e. malignment in their association with the progression of knee OA. Overweight and malalignment are mechanical factors that exert its force on the knee. Arguably, when these two forces: overweight and malalignment are present together in one knee, the risk of having knee OA progression will be increased. In this study, obesity, as well as malalignment was indeed shown to be associated with the progression of knee OA. Obesity was also shown to have small interaction with malalignment. These findings have the implication that clinical trials on the effect of weight loss, and studies on the effects of physical therapy in reducing stress due to malalignment in preventing knee OA progression, can be done in separate trials or simultaneously to look at synergistic effects.

9.2. DISCUSSION AND FUTURE DIRECTION

9.2.1. New targets in OA treatment

OA is a disease without pathognomonic findings. That OA has no pathognomonic findings is perhaps disappointing but also not surprising. Pain is caused by stimulation of nociceptors in areas of tissue damage. The search of the origin of pain in OA is actually to find which tissues are damaged. Cartilage has been thought for a long time as the source of pain despite the knowledge that cartilage is not innervated. This explains why many studies failed to show the association between structural damage in OA with pain. The emerging studies using MRI have shown that BML and synovitis/ effusion are potential targets for OA treatment because of their association with pain (**chapter 2**). Trials on medicine targeting these structures should be pursued in the future.

Although it seems promising, more studies are still needed to understand how BML and synovitis/ effusion lead to pain in OA. The level of evidence in our study in chapter 2 is only moderate. The damage on subchondral bone and synovitis does not give a clear-cut answer on the source of pain in OA. There are several explanations and studies in the future should take these factors into account. Firstly, pain in OA comes and goes and this is often not taken into account in the studies. Ideal future studies

are studies with case-crossover design. In those studies, imaging is performed in a patient when he had pain, and this is compared to the imaging on the same patient when he does not have pain. Secondly, it is likely that pain is more complex than structural damage, and that psychosocial factors, such as coping mechanism might also be involved. These factors are much more difficult to cope in future studies. A possible solution is performing studies with the patient population consisted of patients with OA on one side and without OA on the other side (e.g. OA on right knee and normal left knee). The effect of OA on pain can then be compared in the same patients. The use of new imaging techniques such as functional MRI (fMRI) to investigate the pain mechanism in the brain can also be considered.

9.2.2. Stratifying OA patients

Many clinical trials failed to show the efficacy of medicine in treating OA progression. One of the reasons is the mixed study population in these trials. We know that patients with OA have different prognosis at long term after the diagnosis. Some of them will progress, some will stay the same and some will be better. When patients from all these subgroups are included, it will lead to underestimation of the effect in a clinical trial. Efforts to stratify patients are needed to select patients that will progress at an early stage since these patients are the patients who will have benefit from a medicine in OA.

Several clinical factors, such as worsening of self-reported pain and function in short term, limited total range of motion, and higher osteophytes and JSN scores can be used to identify patients who will have progression on the long term (six years in our study, described in **chapter 3**). In future clinical trials on a novel drug or treatment, the study population can be selected by including patients who have factors that increase the risk of progression. This 'enriched' population will increase the chance to show the effect of a working novel drug. Moreover, since the long-term progression (i.e. 6 years) can be predicted by using progression short-term progression (i.e. 1 year), a trial can also be performed over a shorter period of time. There is no need to perform a long term trial when it is known that patients who will progress at the long term will also progress at shorter term. Short-term progression can be used to estimate long-term progression.

The clinical factors could also be combined with the use of biomarkers such as uCTX-II in stratifying patients who will have OA progression. To have a prediction model that combine clinical factors with biomarkers future studies should have a large number of participants. The outcome of progression in such studies can be clinical, radiological and combination of clinical and radiological.

Remarks can be made on imaging as outcome in studies on progression of OA. Despite its widespread use, imaging as an outcome in a study has an important limitation that it is simply a snapshot of the end results of processes in a joint. Imaging gives no information about ongoing process in structures involved in OA. Measurement of a single level of biomarkers is also a snapshot. Therefore, multiple measurements of OA are likely a better option to monitor OA progression. Since multiple measurements of uCTX-II are associated with increasing cartilage thinning measured on radiograph (**chapter 4**), it has the potential to be used as a replacement of radiograph as an outcome in observational studies and clinical trials. Future studies should also explore the use of other structures than cartilage that involved in OA such as BML and synovitis/ effusion as outcome in studies. Reducing BML and synovitis/ effusion can be tested as a goal of a novel drug.

9.2.3. Excess of fat affects OA in multiple ways

Based on the results presented in this thesis, we can conclude that excess of body fat exerts its effect not only by extra mechanical force on weight bearing joint, but also by producing metabolic factors (adipokines) that could damage joints. Adiponectin is one of the adipokines produced by fat tissue. Interestingly, obesity has an inverse relationship with adiponectin: more fat leads to lower level of adiponectin. Lower level of adiponectin seems to be bad for cartilage, as described in **chapter 6**. While adiponectin is shown to be associated with progression of OA pathology, no association is found between adiponectin with pain level and worsening of pain level (data are not shown). Probably, adipokines do not stimulate the nociceptor directly. Adipokines might lead to cartilage damage first and subsequently lead to pain. The difference of the effect of adipokines on cartilage damage progression and on pain experience brings back the discussion that damage associated with OA is not always

related to pain. It is still the holy grail in studies in OA to find the solution on this discrepancy.

The observation that the effect of obesity in knee OA but not in hip OA is mediated by structural OA (**chapter 7**), implies that the mechanical effect of obesity on OA should not be totally put aside (knee is considered to be more weight bearing joint than hip). It should be realized in future studies on the effect of excess of fat in OA that the choice of which joints to be studied means investigating different effects of obesity. Possibly, hand joints are where metabolic effect plays the most prominent role, and knee joint is where mechanical effect has most important role. Considerably, the hip joint endures a mixed metabolic and mechanical effect.

A remark should also be made on measurement of excess of fat. BMI that is commonly used in epidemiological studies on OA is actually just only a proxy of human body fat. Therefore, the product of fat itself should be used in future epidemiological studies. Using the products of fat tissue as the measurements of excess of fat will bring us to the closer end of the causal path on the association between obesity and OA. Apart from adipokines, other measurement of fat products such as cholesterol and triglycerides should be pursued in the studies on OA.

Future basic research should investigate the effect of adipokines on the inflammatory states of structures involved in OA. The structures shown on MRI that related with pain in OA: BML and synovitis/ effusion are linked with inflammatory states. Interestingly for knee OA, more research can be done on the role of Hoffa's fat pad. The knee joint is unique since it is in the approximation of a collection of fat tissue. This fat pad has been shown to have inflammatory characteristics.

9.3. IN SEVERAL SENTENCES

OA is a progressive disease that can be defined as pathology or symptom where excess of fat plays an important role in its development and progression. Whether the effect of excess of fat predominantly mechanical or metabolic, depends on which

joint involved. Measurement of the fat itself or fat products should be performed in addition to, or instead of BMI in studies on the effect of obesity in OA. These fat products and its receptors are the potential therapeutic target in treating OA in the future.