

Novel Treatment Targets in Early-stage Osteoarthritis

Objectives

The meniscus is an important shock absorber in the knee, whose breakdown is an early event in the development of osteoarthritis (OA). Our aims are:

- ✓ To learn about the molecular breakdown of the meniscus that causes it to tear
- ✓ To develop new means to detect and monitor meniscus breakdown and early OA prior to onset of symptoms
- ✓ To identify novel drug targets for new treatments that slow or cure the breakdown of meniscus tissue, to thereby prevent OA

Background

Osteoarthritis, a degenerative joint disease, is a major cause of musculoskeletal pain in the middle-aged and elderly. However, there is currently no disease-modifying treatment against OA. Our research focuses on meniscal breakdown, one of the most common causes of OA. Our work shows that meniscus tears are most often part of a slowly developing degenerative disease, not usually the outcome of acute knee injury as previously considered. We further found that these early meniscus tears are strongly linked with development of knee OA. Detection and prevention of meniscal breakdown could therefore be a promising new target for early diagnosis and treatment of OA.

Methods and approach

In this project, we will characterize the early molecular and structural changes associated with meniscal breakdown and knee OA. By studying the meniscus from patients with torn menisci using advanced instrumentation called *mass spectrometry*, we will identify protein changes that accompany meniscus breakdown. These changes will identify possible markers of early-stage OA that may be detectable in joint fluid or blood, for easy diagnosis of risk of disease.

We will further monitor early-stage, structural changes in the knee of patients at risk for OA using a new, ultra high-resolution 7-Tesla magnetic resonance imaging (MRI) machine in Lund, Sweden. These images will enable us to observe changes in cartilage *quality*, i.e. the very early changes of the disease, and monitor the progression of the structural features associated with OA.

Combining our results from the two methods, we can understand which molecular changes in the meniscus lead to meniscal tearing and development of OA, to discover new targets for pharmaceutical intervention against meniscal breakdown and OA disease.

Recruitment of participants

Participants who contribute tissue samples to our study are adult patients scheduled for knee surgery due to meniscus tears or total knee joint replacement. They must understand either Swedish or English and provide informed consent for the study. Additionally, a subset of patient volunteers with meniscus tears who contribute tissue samples for molecular analysis will also undergo MRI scanning up to 3 times over a period of 5 years, for structural analysis of OA progression. Exclusion criteria for MRI include patients with pacemakers and other metallic foreign objects or devices, as well as patients with severe claustrophobia.

Burden for patients participating in this study

Patients contribute tissue samples for proteomic analysis in our study. These samples are discarded from knee surgeries that the patients undergo for medical reasons, collected after informed consent. Some patients also volunteer to undergo up to 1 hour-long MRI imaging sessions, up to 3 times. MRI scanning is not invasive and safe. Our study is expected to pose minimal burden to patient participants.

Expected benefits for patients

OA research so far has mainly focused on loss of hyaline cartilage, which lines the surface of bones in joints. However, loss of hyaline cartilage occurs at a late stage of the disease. We have evidence that knee OA often starts much earlier with tearing of the meniscus, the loss of its protective function leading to joint failure. Previously, meniscus tears were treated by arthroscopic removal of torn meniscus, but our research has suggested that such surgery may even increase the risk for OA. Instead, we focus on the molecular breakdown of the meniscus to identify biomarkers and drug targets that enable early detection of OA risk, for non-surgical management, include exercise therapy and for development of the first *disease-modifying OA drug*.

Expected benefits for society

OA has a profound burden on public health. Especially in Europe, as the population of elderly and obese continues to increase, the incidence of OA is expected to surge. Early diagnosis and disease-modifying therapeutics would help address this important health issue.

Patient involvement in the design and conduct of the study

We have worked with two patient research partners in the design of this study. We have received positive feedback from them on our project goals and design, and will continue working with them as the study progresses.