The association between obesity, low-grade inflammation, self-reported knee symptoms and radiographic knee osteoarthritis in individuals with knee pain

A longitudinal cohort study

Alma Buer
Abstract

Background

One of the earliest signs of knee osteoarthritis (OA) is knee pain which correlates with inflammation and disease severity. Knee OA affects 260 million worldwide, and is in similarity with obesity, characterized by ongoing low-grade inflammation. The low grade-inflammation affects the knee-joint area and associations to cartilage degradation and bone remodelling have been shown. Most individuals, however, seek medical care for the first time when they experience knee pain. At this stage, the destruction of the knee is often irreversible. The inflammatory marker C-reactive can be found in both individuals who are obese and individuals with knee OA. It would be beneficial for the many individuals with knee pain at risk of developing knee OA, to be identified at an earlier stage and start treatment and hence slow down the progression of the disease.

Purpose

The purpose was to study associations between obesity, low-grade inflammation, self-reported knee symptoms and the outcome of radiographic knee OA in Swedish individuals with knee pain. Three research questions were formulated.

Methods

The design of this two-year longitudinal cohort study included Swedish individuals with present knee pain. Data was used to assess obesity and analyse inflammation to determine presence and/or severity of radiographic knee osteoarthritis and evaluate long- and short-term and symptoms and function of the knee. Original data were retrieved from the Cohort profile: the Halland osteoarthritis (HALLOA) cohort–from knee pain to osteoarthritis: a longitudinal observational study in Sweden. Individuals were recruited from healthcare clinics and newspaper advertisement. Age ranged from 32–63 and included data from 60 individuals after two years. Obesity was assessed where body composition was analysed with a bioelectrical impedance analysis. Level of C-reactive protein (CRP) was analysed with ELISA method. The outcome of radiographic knee OA was graded with Ahlbäck classification system in combination with physical
examinations of the knees. Self-reported knee symptoms and function were measured with the questionnaire knee injury and osteoarthritis outcome score (KOOS). The data were analysed with the statistical computer software IBM SPSS Statistics.

Results

No significant associations were found between the obesity, low-grade inflammation and the outcome of radiographic knee OA in Swedish individuals with knee pain. However, significant associations were found between the odds of developing radiographic knee OA assessed with KOOS for the subgroups pain (p = 0.032), symptom (p = 0.016), Sport/Rec (p = 0.02) and QOL (p = 0.038).

Conclusion

KOOS questionnaire should be used for individuals with knee pain to identify individuals at risk of developing knee OA and ensue the disease progression, along with exercise and weight reduction if needed. CRP is not a good marker to measure inflammation in knee OA or use as a predictor tool.
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Introduction

Osteoarthritis (OA) is the most common joint disease globally and characterized by pain and low-grade inflammation (Mahmoudian et al. 2021; Kanthawang et al. 2021; Bosch 2019). OA is known to be one of the oldest diseases, and there are signs of the pathology present in ancient human skeletons and even in the skeletons of dinosaurs (Bosch 2019). Joints that are frequently affected are the knees, hands, and hips (Cui 2020). OA usually progresses slowly (Jacobs et al. 2020). Individuals that are currently affected worldwide by OA are 500 million (Hunter, March & Chew 2020). Out of these 500 million individuals, knee OA accounts for 260 million. One of the earliest and most central symptoms of knee OA is knee pain (Cui 2020; Hunter & Bierma-Zeinstra 2019; Carlesso et al. 2021). The disease breaks down the cartilage and changes the underlying bone (Zhang & Wen 2021). The pain that characterizes knee OA is one of the most disabling factors (Bosch 2019; Hunter & Bierma-Zeinstra 2019; Cui 2020; Hunter et al. 2020). Individuals often seek treatment due to knee pain, but effective treatment at this stage is often too late (Mahmoudian et al. 2021; Yang et al. 2020). Radiographic knee OA is visible on radiographic imaging and display the severity of bone attrition and joint space narrowing (Wing et al. 2021). Knee OA can be spotted on a radiograph, but individuals who experience knee pain does not always have radiographic knee changes (Cui 2020). Frequent symptoms are stiffness, decreased range of motion and bony enlargement whereas example of physical symptom is swelling (Stoddart et al. 2021; Runhaar et al. 2021; Hunter & Bierma-Zeinstra 2019).

Examples of common risk factors for developing knee OA are obesity, sex and injury (Mahmoudian et al. 2021; Hunter & Bierma-Zeinstra 2019). The increased risk of developing knee OA is also linked to the life-threatening co-morbidities cardiovascular disease, metabolic syndrome, stroke and diabetes (Hunter & Bierma-Zeinstra 2019; Zeddou 2019). Obesity put excessive weight on joints and alter biomechanical patterns (Donell 2019; Collins et al. 2018). Obesity is in similarity with knee OA, also characterized by low-grade inflammation (Kanthawang et al 2021; Martel-Pelletier et al. 2019). Obesity is a risk factor for developing knee OA and is linked to both the incidence and progression of knee OA (Mora et al. 2018; Senol et al. 2019). According to WHO, being obese or overweight kills over 4 million and has grown into an epidemic.
The physical implications of obesity further increase the risk of morbidity and mortality (Mora et al. 2018). Obesity is also connected to joint injuries that cause pain (Roemer et al. 2022). The combination of knee OA and obesity inhibit individuals' physical activity in everyday life (Mahmoudian et al 2021; Mora et al. 2018). The disabling condition of knee OA have noteworthy implications for the individual and are challenging for the health care (Hunter & Bierma-Zeinstra 2019; Kanthawang et al 2021; Mora et al. 2018). The inflammation that involves both obesity and individuals with knee OA, may also play an important role in the increased severity of radiographic knee OA and the connection, needs to be studied (Roemer et al. 2022; Bosch 2019).

**Background**

The most frequently affected joints for individuals with OA are the knee joints (Alissa, Alzughaibi & Marzouki 2020). Knee pain is one of the earliest symptoms of knee OA and is also a hallmark (Cui 2020; Di Francesco et al. 2022; Alissa, Alzughaibi & Marzouki 2020). Knee OA is a complex degenerative and progressive joint disease that breaks down the cartilage and cause structural alternation in the affected joint (Di Francesco et al. 2022; Hunter & Bierma-Zeinstra 2019). Physical symptoms such as the joint-relating pain, bony enlargement and swelling, joint instability, morning stiffness, muscle weakness, fatigue and psychological pain-related stress are all parts of knee OAs’ disease picture (Hunter & Bierma-Zeinstra 2019). Observations of the radiographs can help determine the width of the joint space and evaluate thickness of the articular cartilage (Weidow, Cederlund, Ranstam & Kärrholm 2006; Ahlbäck 1968).

Risk factors of developing knee OA are obesity, sex, age, genetics, race, trauma, injury, and repetitive work (Mahmoudian et al. 2021; Hunter & Bierma-Zeinstra 2019). Genetics increase the chance of getting OA by 40-80% and the risk, compared to knee OA, is even bigger for hand and hip OA (Hunter & Bierma-Zeinstra 2019). To be over 65 years old or African American furthermore increase the risk by 35% (Mora et al. 2018). Knee OA and hand OA are both more common in women than in men (Bosch 2019; Hunter & Bierma-Zeinstra 2019). An increased risk of developing knee OA is also linked to the life-threatening co-morbidities cardiovascular disease, stroke, diabetes
and metabolic syndrome including increased central obesity (Hunter & Bierma-Zeinstra 2019; Zeddou 2019). The association between obesity and knee OA has historically, been understood as a result of excessive joint load (Kanthawang et al. 2021). The association between OA and obesity, has however, been observed in non-weight bearing joints as well, and is yet not fully understood (Alissa, Alzugaibi & Marzouki 2020; Kanthawang et al. 2021). According to Kanthawang et al (2021), knee OA have been associated in a few studies with metabolic syndrome. The association has, however, not been found for hip OA and implies a deeper complexity (Kanthawang et al 2021).

Knee OA and obesity are both characterized by low-grade inflammation (Kanthawang et al 2021). Inflammation is the body’s biological response to disease, injury or an infection and lead to the activation of the immune system (Matsuda, Huh & Ji 2019; Mora et al. 2018). Individuals with knee OA can experience an increased joint sensation due to increased responsiveness of peripheral nociceptors, which is caused by the ongoing inflammation in the joint tissue (Hunter & Bierma-Zeinstra 2019). It is however, not known, if it is the actual inflammation cause the knee OA structural alterations or if it is the knee structural alternations that cause the inflammation (Moria et al. 2018; Hunter & Bierma-Zeinstra 2019). What is known however, is that when the immune system has been activated it starts to produce inflammatory cytokines resulting in cartilage destruction as well as bone remodeling (Mora et al. 2018; Donell 2019). Cytokines can be detected in the body fluids before individuals are experiencing any symptoms of knee OA (Jacobs et al 2020; Mahmoudian et al. 2021). Inflammatory cytokines such as interleukin-6 (IL-6), trigger the production of C-reactive protein (CRP) that has been seen in early stages of knee OA (Alissa, Alzugaibi & Marzouki 2020). CRP is a protein that both responds to inflammation and play a central role in the inflammatory process that is central in both knee OA and obesity (Zeddou 2019).

Individuals with knee OA associated symptoms can be evaluated with the help of knee injury and osteoarthritis outcome score (KOOS) questionnaire (Appendix 2). KOOS consists of five subscales that separately analyse symptoms, pain, activities of daily living (ADL), sport and recreation function (Sport/Rec) and knee-related quality of life (QOL). KOOS can be used for young and old individuals with consistent results (Collins et al. 2016). However, the validity for different subcategories has been
questioned (Collins et al. 2016). The subscale ADL, for example, has a higher validity for older individuals and Sport/Rec seem to have a higher validity for younger individuals. The subscale pain is moreover, better applicable for painful conditions (Collins et al. 2016). In addition, KOOS have been evaluated in a cohort study by Larsen et al. (2019), with obese individuals and a body mass index (BMI) over 35. The subscales pain, ADL, Sport/Rec and QOL were significantly worse for individuals with a BMI over 35, compared to a reference population (Larsen et al. 2019). Reference population-based data were retrieved from a national population register (Paradowski et al. 2006). KOOS score also detected more severe radiological changes for obese individuals (Larsen et al. 2019). Symptoms of knee OA, for example decreased range of motion and stiffness can in some cases lead to that individuals can no longer work or perform daily activities (Mahmoudian et al. 2021). Unfortunately, the current gap in research that involves the difficulty of identifying individuals at risk, makes this group vulnerable (Mahmoudian 2021). Further research is required to be able to diagnose and provide an early treatment (Hunter & Bierma-Zeinstra 2019). Therefore, a better understanding of the associations between obesity, low-grade inflammation, self-reported knee symptoms and the outcome of radiographic knee OA is therefore needed.

The pathophysiology of knee osteoarthritis

The knee synovial joint is the largest joint in humans and connects the three bones, the femur, tibia and patella (Alissa, Alzughaibi & Marzouki 2020). Knee OA affects the whole joint and involve structural alterations in the articular cartilage, subchondral bone, synovial membrane, capsule, ligaments, and periarticular muscles (Alissa, Alzughaibi & Marzouki 2020; Mora et al. 2018; Lombardi et al. 2021; Donell 2019). The articular cartilage is one of the main components of the knee- and hip-joint (Di Francesco et al. 2022). The articular cartilage in the knees, covers the bone ends of the femur and tibia. It absorbs mechanical loads and contributes to friction-free movement (Di Francesco et al. 2022). The cartilage is avascular and are thereby lacking blood vessels (Mora et al. 2018).

Chondrocytes are cells that are responsible for the homeostasis in the joint and can be found within the cartilage (Di Francesco et al. 2022). To maintain homeostasis in OA knees, the chondrocytes synthesize the articular cartilage (Gupta et al., 2019). Synovial
membrane surrounds both bone ends of the femur and tibia (Mathiessen & Conaghan, 2017). The synovial membrane produces synovial fluid which acts as a protective barrier between the two bones (Mora et al. 2018; Di Francesco et al. 2022; Mathiessen & Conaghan, 2017). Synovial fluid lubricates the knee joints and provides nutrients to the cartilage (Mora et al. 2018). Both the membrane surrounding the joint, and the synovial fluid work to reduce friction between the two bone ends during joint load (Di Francesco et al. 2022). However, as knee OA progresses it leads to a culmination of inflammatory cytokines in the synovial fluid and surrounding tissues, resulting in loss of lubrication and cartilage breakdown (Loeser, Collins & Diekman 2016; Di Francesco et al. 2022).

Osteochondral junction is the tissue that connects the subchondral bone with the cartilage in the joint. The osteochondral junction can be found in the tissue layer between the underlying subchondral bone and the deep layers of the articular cartilage (Lombardi et al. 2021). Microfractures seen in the osteochondral junction, progress with abnormal joint loading, contribute to cartilage degradation and enables the synovial fluid and cytokines to penetrate the subchondral bone (Donell 2019; Zhang & Wen 2021). The microfractures together with the cartilage degradation, expose the subchondral bone and weaken the joint as the disease progress (Donell 2019; Zhang & Wen 2021). As a result of the exposed subchondral bone, the cartilage gets invaded by vessels and nerves (Grässel & Aszodi 2019; Lombardi et al. 2021). Endochondral ossification has a distinct role in knee OA, and is the process, where bone formation replaces cartilage (Yamaguchi et al. 2018; Donell 2019). The development of knee OA increases significantly with the ossification contributing to subchondral bone damage and cartilage lesions (Lombardi et al. 2021; Zang & Wen 2021).

Osteocytes regulate the bone homeostasis in the knee and is triggered by osteocytes, but the activity of osteocytes in an OA knee is irregular (Yan et al. 2020; Zhang & Wen 2021). In an OA knee, osteophytes work to maintain homeostasis, by recruiting bone-forming- and bone resorbing cells (Dai et al 2020). These bone-forming- and bone resorbing cells can be seen on plain imaging as bone spurs (Donell 2019; Zhang & Wen 2021). More severe radiological changes are inevitable as the disturbances in the bone metabolism continues with the progression of the disease (Donell 2019).
Obesity

There are multifactorial links between knee OA and obesity and excessive weight contributes to a wear and tear condition (Kanthawang et al 2021). The definition of being overweight or obese is to have abnormal or excessive fat accumulation (WHO 2023). Overweight individuals are defined by WHO with a BMI higher than 25 and obese individuals with a BMI higher than 30 (WHO 2023). BMI is a tool that can define normal weight in a population, as well as weight of obese and overweight individuals (Lahav, Goldstein & Gepner 2021). One limitation is, however, the inability to measure obesity-related morbidities connected to fat mass (Lahav, Goldstein & Gepner 2021). Associations have been found between knee OA and BMI in women in a study presented by Alissa, Alzughaibi & Marzouki (2020). Being overweight or obese, can in addition of leading to the musculoskeletal disorder knee OA, also cause diabetes and metabolic syndrome (Alissa, Alzughaibi & Marzouki 2020). Having an excessive weight also increases the risk of developing cardiovascular disease such as stroke and heart disease which are the leading causes of death (Alissa, Alzughaibi & Marzouki 2020; WHO 2023; Hunter & Bierma-Zeinstra 2019). The device Inbody 770 is a bioelectrical impedance analysis (BIA). The height is entered manually on the BIA, which then calculates the BMI according to a pre-programmed formula. BIA continues to analyze the body composition such as fat mass, fat-free mass, segments, bone content and fluid balance (Lahav, Goldstein & Gepner 2021; Brewer et al. 2021; InBody 2023). The advantage with BIA is that it is time efficient, can measure changes over time, is relatively inexpensive and does not require educated personnel (Lahav, Goldstein & Gepner 2021; Brewer et al. 2021). A limitation of BIA is its sensitiveness of the bodys’ water status (Lahav, Goldstein & Gepner 2021). As skeletal muscles contain more water than fat mass it can affect the measurement (Lahav, Goldstein & Gepner 2021). According to Brewer et al. (2019), BIA also underestimate of fat percentage and overestimate of fat-free mass. Another study confirmed that body fat was especially underestimated in women (Lahav, Goldstein & Gepner 2021).

Adipose tissue works as an endocrine organ (Carrión et al. 2019; Kanthawang et al. 2021). It is an active tissue responsible for cellular reactions and a part of the whole-body metabolism (Unamuno et al. 2018). Adipocytes are fat cells that consists of lipid
droplets and can be found in the adipose tissue (Rosenwald & Wolfrum 2014; Wronska and Kmiec 2012). Adipose tissue grows in response to an increased number of adipocytes (Unamuno et al. 2018). Adipocytes are involved in the regulation of inflammation in obese individuals as well as other immune functions (Unamuno et al. 2018). Adipocytes can in response to different signals secrete adipokines (Belluzi et al. 2016). Adipokines are involved in the regulation of the inflammation and immune function and have an important role in the glucose and lipid metabolism (Unamuno et al. 2018). Adipokines are also involved in bone and cartilage metabolism and homeostasis (Xie & Chen 2019). Excessive weight creates dysfunctional adipose tissue with intolerable levels of adipokines, resulting in lipid accumulation in the adipose tissue (Carrión et al 2019: Collins et al. 2018). The lipid accumulation in the adipose tissue, further increases metabolic stress in insulin sensitive tissues (Carrión et al 2019; Qiao et el. 2019; Collins et al. 2018). The lipid accumulation in obese individuals, creates a state of ongoing low-grade inflammation (Kanthawang et al 2021). Low-grade inflammation in obese individuals can, moreover, enhance catabolism in knee OA tissues (Martel-Pelletier et al. 2019; Kanthawang et al 2021). The low-grade inflammation is characterized by the production of Interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF) (Carrión et al 2019). Moreover, IL-1, IL-6 and TNF are proinflammatory cytokines and are all linked to both obesity and knee OA (Wanga and He, 2018). In a study by Jacobs et al (2020), elevated inflammatory maker, such as cytokines, lead to cartilage degradation, bony remodeling, and increased pain. This is partly supported by Josef et al. (2023) as their study linked obesity and knee OA with increased pain and joint space narrowing.

The knee joints are subjected to alterations for individuals with a higher BMI (Kanthawang et al 2021; Romer et al. 2022). The connection between BMI and knee OA have been found in two other studies and support the link between BMI and knee OA (Roemer et al. 2022; Zeddou 2019). A study by Baghban et al. (2021) showed that lower BMI leads to increased physical function, decreased joint stiffness, decreased pain and lower levels of CRP. Knee pain has also been linked to BMI, where individuals knee OA and lower levels if adiposity experienced milder pain compared to individuals with knee OA and higher level of adiposity (Zeddou 2019; Martel-Pelletier et al. 2019). According to a study by Roemer et al (2022), the presence of inflammation
in overweight or obese women have a higher risk of developing radiographic knee OA. The excessive weight that overweight and obese individuals put on their knee joints, further increases the risk of developing radiographic knee OA (Banuls-Mirete et al. 2021; Romer et al. 2022; Collins 2018). According to Joseph et al. (2023), the relationship between weight and radiographic knee OA has already been established. Several studies have confirmed that decreased weight on knee joints lead to improvements in pain and a delay in progression of joint structural damage in individuals with knee OA according to Collins et al. (2018). In addition, the authors found significant association between body fat, weight circumference measured with and knee OA (Collins et al. 2018). A group of women with a BMI over 25 with a mild to moderate risk of developing knee OA were divided into groups of diet and exercise. Individuals who had lost more than 5% in weight over 96 months had a slower cartilage degeneration independent of group (Gersing et al. 2019). Since adipose secretion contributes to the production of inflammatory cytokines and affect levels of CRP the result of this study is of importance (Carrión et al 2019; Martel-Pelletier et al. 2019).

**Inflammation and inflammatory markers**

It is generally accepted that inflammation is present in the pathogenesis of knee OA (Bosch 2019). The inflammation in individuals with knee OA is suggested to play a role in the initiation of the disease (Hsueh et al. 2021; Zeddou 2019). The low-grade inflammation stimulates the immune cells monocytes and macrophages and leads to the production of inflammatory markers e.g. cytokines (Bosch 2019; Ansari, Ahmad & Haqqi 2020; Misra et al. 2019; Zeddou 2019). Examples of inflammatory markers are the cytokines IL-6, TNF and IL-1. IL-6, TNF and IL-1 are key elements in the progression and the development of knee OA (Hsueh et al. 2021; Zeddou 2019). According to Kanthawang et al (2021), inflammatory markers in the knee synovial joint are more prevalent and sever in overweight and obese individuals. Furthermore, their study found a clear link between inflammation markers in the knee synovial membrane, cartilage and knee structural degeneration in individuals with knee OA (Kanthawang et al 2021). Increased synovial inflammation likely occur, due to catabolic enzyme activity or trauma leading to the production of cytokines by synovial cells (Bosch 2019). Immune cells present in the synovium, together with inflammatory cytokines found in tissues and fluids, break down the cartilage (Bosch 2019; Ansari, Ahmad & Haqqi
2020; Misra et al. 2019; Zeddou 2019; Yang et al. 2020). Another study found that the immune cells and the production of cytokines drove the inflammation in the synovial membrane and correlated with the severity of radiographic knee OA (Hsueh et al. 2021). Similar results were found by Roemer et al. (2022) using an MRI. The MRI enabled the researchers to spot inflammation in the joint. Inflammation visible with MRI was associated with increased odds of radiographic knee OA (Roemer et al. 2022).

The combination of inflammation, inflammatory cytokines and the loss of lubrication and cartilage breakdown, cause pain and difficulty to load the joint (Alissa, Alzughaibi & Marzouki 2020; Bosch 2019; Donell 2019; Deroyer et al. 2022; Di Francesco et al. 2022). The experienced pain might be connected to specific inflammatory markers found in individuals with knee OA and/or obesity (Martel-Pelletier et al. 2019). Inflammatory markers connected to knee symptoms are therefore important to identify (Martel-Pelletier et al. 2019).

C-reactive protein

The inflammatory marker CRP is a protein that is triggered by the inflammatory cytokine IL-6 (Zaki et al. 2020; Alissa, Alzughaibi & Marzouki 2020; Nehring, Goyal & Patel 2022). CRP is synthesised by the liver and have anti- and pro-inflammatory properties. CRP can activate pathways that is a part of the immune system. The activation of phagocytic cells helps to remove damaged, apoptotic cells and foreign pathogens. The activation of phagocytic cells can also become pathogenic and worsen tissue damage and activate of inflammatory cytokines. Levels of CRP can rise or fall rapidly, due to inflammatory stimuli. Inflammatory conditions have consistently elevated levels of CRP (Nehring, Goyal & Patel 2022).

The first study that discovered the association between serum levels of CRP and knee OA was made 1975 (Acheson & Collart 1975). Low levels of CRP were found with the blood-test high-sensitivity CRP (hs-CRP) (Kondo et al. 2021). This type of blood-test was new during that time and enabled individuals with low grade inflammation to be detected (Kondo et al. 2021). Elevated levels of CRP have been spotted in early stage of knee OA and significantly higher serum levels of CRP have been found in individuals
with knee OA and obesity (Alissa, Alzughaibi & Marzouki 2020; Martel-Pelletier et al. 2019). Hs-CRP has in another study been associated with elevated levels of CRP in the synovial fluid and knee structural abnormalities in individuals with knee OA (Yang 2020). A higher level of CRP confirms the presence of inflammation in individuals with knee OA (Alissa, Alzughaibi & Marzouki 2020; Yang et al. 2020). In addition, CRP levels are also associated with BMI and co-morbidities such as cardiovascular disease and metabolic syndrome (Yang et al. 2020; Go et al. 2022). The relationship between CRP, excessive fat accumulation known as adiposity and pain was found to be associated (Martel-Pelletier et al. 2019; Bosch 2019). Individuals with lower levels of CRP and lower level of adiposity have less severe pain than individuals with higher level (Martel-Pelletier et al. 2019). A study looked closer at how diet affected CRP in women. A 12-week program with a low-calorie diet, resulted in decreased levels of CRP, increased physical function, decreased stiffness and pain. The decreased level of CRP is an interesting finding, since similar associations have been found between CRP, pain, function, and symptoms in obese individuals (Martel-Pelletier et al. (2019). The progression of the disease is unpredictable and most individuals with knee OA get diagnosed when the destruction of the joint is irreversible (Yang et al. 2020). Elevated levels of CRP might help to identify individuals with ongoing low-grade inflammation at an earlier stage, and hence improve preventative, diagnostic and therapeutic intervention (Yang et al. 2020).

Purpose

The purpose of this study was to study associations between obesity, low grade inflammation, self-reported knee symptoms, and the outcome of radiographic knee osteoarthritis in Swedish individuals with knee pain.

Research questions:

- Is there an association between radiographic knee osteoarthritis and obesity for Swedish individuals with knee pain?
- Is there an association between radiographic knee osteoarthritis and C-reactive protein for Swedish individuals with knee pain?
• Is there an association between radiographic knee osteoarthritis and patient reported outcomes assessed by knee injury and osteoarthritis outcome score?

Methods

Cohort

The design of this two-year longitudinal cohort study included Swedish individuals with present knee pain. The study compared baseline data with data after two years. Baseline data were collected from the study Cohort profile: the Halland osteoarthritis (HALLOA) cohort-from knee pain to osteoarthritis during 2017-2018 (Andersson et al. 2022). Data after two years were collected from the same individuals year 2019-2020 by Andersson et al. (2022). Individuals with present knee pain from southeast Sweden were enrolled. The recruitment took place when (1) seeking care for knee pain in health clinics and (2) from advertisement in local newspapers. The exclusion criteria were previously known OA, knee injury, cruciate ligament or rheumatological disorder as confirmed by a general practitioner. Pregnant women and/or individuals with medical implant were also not included (Andersson et al. 2022).

There were 60 individuals who had generated data at both baseline and after two years. The age of the individuals at baseline until two years after were between 30 to 63 years. Two individuals were younger than 30 (29 and 24) and three individuals were older than 63 (two is 66 and one is 73). Because of the big age span, these individuals were excluded due to bias. Data from baseline and data after two years have been used for analyses in this paper.

Assessment of obesity

The definition of central obesity was set in accordance with the international diabetes federation (International diabetes federation [IDF] 2006). It was defined by a waist circumference measure of ≥ 94 cm for men and ≥ 80 cm for women (IDF 2006). A measuring tape was used for abdominal range. To assess body composition, Inbody 770 (InBody Co. Ltd., Seoul, Korea), BIA was used. Visceral fat area (VFA) was assessed,
and the level of having too much, was set to be $\geq 100$ cm$^2$ (Thorstensson et al. 2009). BIA can be used repeatedly and has been found to be a valid, reliable by previous studies it was found to be suitable device for the purpose of this study (Lahav, Goldstein & Gepner 2021; Brewer et al. 2019; Marra et al 2019). BIA sends a low-voltage electric current through the body and register the resistance through electrodes (Sergi et al. 2017). For the measurement to take place, the individuals were instructed to wear thin pants and t-shirt and use the bathroom before using the machine. Thereafter, they were instructed to step up on metal footpads in bare feet and to grasp a pair of electrodes that was fixed on a handle. Both arms were extended sideways. After standing for couple of minutes, weight (kg), VFA (cm$^2$), fat percentage (%) and BMI (kg/ m$^2$) were calculated according to a preprogramed formula. The data were presented on the BIA device screen.

Analysis of C-reactive protein

Blood samples were collected annually and used to analyse present inflammation and inflammation over time (Andersson et al. 2022). CRP levels above 1 mg/L were analysed at the department for laboratory medicine at the hospital of Halmstad using the turbidimetry method with Cobas 8000 (Roche). Levels of CRP below 1 mg/L were analyzed with the sandwich ELISA method (Enzyme-Linked ImmunoSorbent Assay). High sensitive-CRP (hs-CRP) in serum was measured using hs-CRP ELISA kit with a limit of detection of 0.10mg/L (Abnova 2017). The reproducibility of ELISA is high but large volume of sample is required for testing and there is a risk of false positive (Churchman et al. 2012).

Radiographic scoring

The presence of radiographic knee OA was determined by standing radiographic examinations according to Ahlbäck classification system (Table 1) (Ahlbäck 1968). Clinical examinations of the knees were made annually as well as radiographs of the knee (Andersson et al. 2022). Clinical examinations included measurements of range of motion in flexion and extension of the knee and foot. Palpations of the knees assessed alignment and evaluated bony enlargement and crepitation (Andersson et al. 2022).
Patellofemoral joints were radiographed in a skyline view. Tibiofemoral joints were radiographed posteroanterior in weight bearing positions with flexed knee (Weidow, Cederlund, Ranstam & Kärrholm 2006; Ahlbäck 1968).

Joint space narrowing, bone attrition and the outcome of radiographic knee OA were graded into five levels according to Ahlbäck (Ahlbäck 1968) (Table 1).

Table 1. Five grading levels and the outcome of radiographic knee OA

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Joint space narrowing (less than 3 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Joint space obliteration</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Minor bone attrition less than (0-5 mm)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Moderate bone attrition (5-10 mm)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Severe bone attrition (10-15 mm)</td>
</tr>
</tbody>
</table>

Self-reported knee function

To evaluate long-term and short-term symptoms as well as the function of the knee, the questionnaire knee injury and osteoarthritis outcome score (KOOS) was used in this study (Roos & Lohmander 2003; Gandek et al. 2019). The individuals participated in the study were asked to fill in the KOOS questionnaire annually (Appendix 2) (Andersson et al. 2022). The KOOS questionnaire helped assess the health-related outcomes (Andersson et al. 2022; Roos & Lomander 2003). The 5 subscales separately analysed pain, symptoms, ADL, Sport/Rec and QOL. Each outcome was transformed into 0-100 scale with 0 representing extreme knee problems and 100 representing no knee problems (Gandek et al. 2019). KOOS is an instrument that is self-administrated with high reliability and validity for individuals with knee related problems and deemed suitable for the purpose of this study (Roos & Lomander 2003).

Ethical and social considerations

This research aimed to generate knowledge regarding the development and the effects of the disease, understand causes and consequently improve diagnostic, preventative-
and therapeutic interventions. The declaration of Helsinki was developed by the World medical association (Declaration of Helsinki 2013). The declaration contains principles for medical research that involve human subjects and research data and was taken into consideration when conducting the study (Declaration of Helsinki 2013). A research protocol was submitted to the research ethics committee Regional ethical review board in Lund, Sweden (EPN-application number 2016/229 for approval, comment and guidance before the study began. The committee ensured that laws and regulations in the country were followed and the health, rights and integrity for the participating individuals were continually safeguarded. Coded lists containing test results were stored in a computer to ensure the individuals privacy and protect sensitive information. The individuals who agreed to participate in the study gave their consent by signing a consent form (Appendix 1). They were informed about their right to withdraw at any time. The participating individuals had access to their own results during the study and after. They were informed about the research aim of generating knowledge and their own contributions. By signing a consent form, they approved to the used method, aim, potential benefits and risks, eventual discomfort they might experience and other aspects relevant to the study.

**Statistics**

The statistical computer software IBM SPSS Statistics (Version 21.0 statistical software IBM Corp., Armonk, NY, USA) was used to analyse the data. The data was calculated in the same way for men and women, with a median and a min-max. Shapiro-Wilk test was used for continuous data to study the distribution of normality. The majority of data were not normally distributed, therefore, non-parametric tests were used. The significance level was set at < 0.05. Chi-2 tests or Mann-Whitney U-tests were used for nominal/ordinal data between groups and tested if two categorical variables were associated. If an association was found it was presented with a p-value <0.05. Univariate binary logistic regression was used for the regression analysis. The regression analysis used odds ratio (OR expB). Individuals who had developed knee OA after two years had an odds ratio over 1.0.
Results

The data that were collected calculated the associations between obesity, CRP, self-reported outcomes and the outcome of radiographic knee OA in Swedish individuals with knee pain over two years. The result of the data is presented in three tables below.

The data from 66 individuals at baseline were divided into two columns: individuals with no radiographic knee OA and individuals with radiographic knee OA. The p-value is presented in the third column (Table 2). At this point of the study, there were 21 individuals who had developed radiographic knee OA (N=21). The remaining 45 had not developed radiographic knee OA (N=45). No significant differences between the two groups were found in variables measuring abdominal range or body composition (obesity, VFA, fat percentage, BMI) or CRP. Individuals who had developed radiographic knee OA were older (p=0.013) (Table 2). Among the individuals with radiographic knee OA, a higher percentage were women (M/W, % = 29/71). The group who had developed radiographic knee OA reported more symptoms compared to the group who had not developed radiographic knee OA (Table 2).

**Table 2.** Descriptive variables at baseline for study-participants with and without radiographic knee OA

<table>
<thead>
<tr>
<th></th>
<th>No radiographic knee OA Median (Min-Max)</th>
<th>Radiographic knee OA Median (Min-Max)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>45</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52 (30-61)</td>
<td>56 (48-61)</td>
<td>0.013</td>
</tr>
<tr>
<td>Sex (M/W, %)</td>
<td>38/62</td>
<td>29/71</td>
<td>0.465</td>
</tr>
<tr>
<td>Abdominal range (cm)</td>
<td>94.0 (65.6-132)</td>
<td>88.8 (67.5-152)</td>
<td>0.669</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>79.5</td>
<td>90.0</td>
<td>0.304</td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td>94.4 (36.9-238)</td>
<td>99.8 (45.1-290.8)</td>
<td>0.798</td>
</tr>
<tr>
<td>Fat percentage (%)</td>
<td>28.5 (13.3-47.3)</td>
<td>31.4 (10.6-52.5)</td>
<td>0.382</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (17.9-41)</td>
<td>24.9 (22.6-47.7)</td>
<td>0.715</td>
</tr>
</tbody>
</table>
CRP (mg/L) 1.20 (0-8.5) 1.30 (0.08-10.5) 0.298  
KOOS pain (1-100) 75.0 (39-100) 63.9 (36-94) 0.086  
KOOS symptom (1-100) 71.4 (39-100) 57.1 (21-96) 0.019  
KOOS ADL (1-100) 88.2 (47-100) 76.5 (37-97) 0.086  
KOOS Sport/Rec (1-100) 50 (0-100) 27.5 (0-75) 0.002  
KOOS QOL (1-100) 56.3 (19-94) 43.8 (6-81) 0.023  

N Number; VFA: Visceral fat area; BMI: Body mass index; CRP: C-reactive protein; KOOS: Knee injury and OA outcome score (worst to best); ADL: activities of daily living, Sport/Rec: Function in sport and recreation; QOL: knee related quality of life

The same variables were used for comparisons after two years (Table 3). When the compilation of the data was complete after two years, there were 60 individuals who had generated data at both baseline and after two years. Individuals who had developed radiographic knee OA after two years, were older (p = 0.038), and had more pain (p = 0.001) (Table 3). No significant differences between the two groups were found in variables measuring sex, abdominal range or body composition (obesity, VFA, fat percentage, BMI) or CRP. In addition, the result show worse symptoms (p = 0.01) lower knee quality of life (p = 0.008) as well as a lower value of Sport/Rec (p < 0.001) for the group with radiographic knee OA (Table 3).

Table 3. Descriptive variables after two years for study participants with and without radiographic knee OA

<table>
<thead>
<tr>
<th></th>
<th>No radiographic knee OA Median (Min-Max) after two years</th>
<th>Radiographic knee OA Median (Min-Max) after two years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>54 (32-63)</td>
<td>57 (50-63)</td>
<td>0.038</td>
</tr>
<tr>
<td>Sex (M/W, %)</td>
<td>39/61</td>
<td>26/74</td>
<td>0.337</td>
</tr>
<tr>
<td>Abdominal range (cm)</td>
<td>96.0 (66.0-115.0)</td>
<td>93.5 (80.0-150.0)</td>
<td>0.949</td>
</tr>
</tbody>
</table>
Age was significantly associated with an increased odds of developing radiographic knee OA after two years (Table 4). No significant association were found between the two groups and an increased odds of developing radiographic knee OA and the other variables measuring sex, abdominal range, body composition (obesity, VFA, fat percentage, BMI) or CRP. A significant association were found between pain (p = 0.032), symptom (p = 0.016), Sport/Rec (p = 0.02) and QOL (p = 0.038) and an increased odds of developing radiographic knee OA (Table 4).

**Table 4.** Age, sex, abdominal range, body composition, CRP, and self-reported knee symptoms and the odds of developing radiographic knee OA after two years

<table>
<thead>
<tr>
<th></th>
<th>OR (expB)</th>
<th>95% CI (lower-upper)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.133</td>
<td>1.010-1.270</td>
<td>0.033</td>
</tr>
<tr>
<td>Sex (M/W, %)</td>
<td>1.792</td>
<td>0.541-5.941</td>
<td>0.340</td>
</tr>
<tr>
<td>Abdominal range (cm)</td>
<td>1.006</td>
<td>0.968-1.045</td>
<td>0.760</td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td>1.005</td>
<td>0.995-1.016</td>
<td>0.340</td>
</tr>
<tr>
<td>Fat percentage (%)</td>
<td>1.039</td>
<td>0.974-1.107</td>
<td>0.245</td>
</tr>
</tbody>
</table>
**BMI (kg/m²)** 1.066 0.948-1.199 0.283
**CRP (mg/L)** 1.034 0.801-1.334 0.797
**KOOS pain (1-100)** 0.961 0.926-0.997 0.032
**KOOS symptom (1-100)** 0.955 0.920-0.992 0.016
**KOOS ADL (1-100)** 0.974 0.939-1.010 0.161
**KOOS Sport/Rec (1-100)** 0.954 0.926-0.983 0.002
**KOOS QOL (1-100)** 0.965 0.933-0.998 0.038

*Number; VFA: Visceral fat area; BMI: Body mass index; CRP: C-reactive protein; KOOS: Knee injury and OA outcome score (worst to best); ADL: activities of daily living, Sport/Rec: Function in sport and recreation; QOL: knee related quality of life*

### Discussion

**Discussion result**

The individuals with knee pain participating in this study were supposedly representing a group with risk of developing radiographic knee OA (Carlesso et al. 2021). After collecting data from individuals at baseline, there were 21 individuals who had already developed radiographic knee OA. No associations were however, found between obesity, C-reactive protein and the development of radiographic knee OA at baseline or after two years. The lack of association was surprising, since previous studies have showed that obesity is a known risk factor of developing knee OA (Alissa, Alzughaibi & Marzouki 2020). Excessive weight that alters the biomechanical patterns and the increased number of individuals who developed radiographic knee OA after two years, did, however, coincide with increased percentage in obesity. The median of obesity were higher for individuals with radiographic knee osteoarthritis at baseline and after two-year. The increased numbers of obese individuals and the increased number who had developed radiographic knee OA, is supported by earlier studies (Donell 2019; Collins et al. 2018). The link between BMI and knee OA has also been supported in other studies (Roemer et al. 2022; Zeddou 2019; Alissa, Alzughaibi & Marzouki; 2020; Kanthawang et al 2021). The median of the variables of abdominal range (cm), VFA
(cm²) and fat percentage (%) did increase after two years for individuals who had developed radiographic knee OA and might indicate, that a result might have been significant for more of the data parameters, with a higher number of participating individuals.

It is known that the inflammatory marker CRP rise in response to inflammation. Obesity and adipose secretion affect production of IL-6 and hence CRP, and the increased levels of CRP have been found in early stages of knee OA (Carrión et al 2019; Martel-Pelletier et al. 2019; Alissa, Alzugaibi & Marzouki 2020). Interestingly enough, the median measurement of CRP at baseline, 1.30 mg/L (table 2), show a higher level for individuals who had developed radiographic knee OA, than after two years, which measured 1.1 mg/L (table 3). Median value is affected by the highest (as well as the lowest) value. Since there was a drop in number of participants who had developed radiographic knee OA counting from baseline until two years after, the drop in numbers might explain these divergent measurements. Among the individuals who had developed radiographic knee OA, a higher percentage were women, which is consistent to other studies in this area (Bosch 2019; Hunter & Bierma-Zeinstra 2019). Studies have confirmed that radiographic knee OA is more common in women compared to men (Bosch 2019; Hunter & Bierma-Zeinstra 2019). Women who are overweight or obese are also subjected to a higher risk of developing radiographic knee OA (Roemer et al. 2022). This might explain the increase in radiographic knee OA in this group. A similar association and the risk of developing radiographic knee OA, has not been found in either men or in women of normal weight.

Moreover, age is a known risk factor for developing knee OA and was, in similarity with the results in this study, significantly associated with an increase in odds of developing radiographic knee OA. KOOS pain (p = 0.032), symptom (p = 0.016), Sport/Rec (p = 0.02) and QOL (p = 0.038) were all significantly associated with an increase in odds of developing radiographic knee OA. In this study, the self-reported instrument KOOS were associated with increased odds of developing radiographic knee OA. Significant associations were also found between pain (p= 0.001), symptom (p = 0.01), Sport/Rec (p <0.001) and QOL (p = 0.008) and the development of knee OA after two years.
Pain is a big part of the disease picture and so therefore is pain management. Exercise have shown to slow down the progression of OA, reduce pain and relieve symptom. Even if the optimal type of exercise for this patient groups is not yet known, current recommendation involves joint strength exercises with whole range of motion (ROM) movements (Jordan et al., 2003). Aerobic exercise moderate-intensity is good, 40-59% of HRR five days a week with a goal of 30 minutes per day (ACSM, 2014). Future studies should suggestively involve a bigger number of individuals as the results of this study were likely impinged by the smaller number of individuals. Rather than focusing on CRP, emphasis should be placed on inflammatory markers and in combination with KOOS, with hope of identifying individuals with low-grade inflammation and individuals at risk of developing knee OA at an earlier stage.

Discussion methods

BIA was used in this study to analyze body composition. Several studies have confirmed that BIA is a valid instrument with a high reliability (Brewer et al. 2019; Lahav, Goldstein & Gepner 2021). However, BIA underestimates fat percentage especially in women, and also overestimate of fat-free mass (Brewer et al. 2019). Water is another component that can affect the readability. The individuals were therefore required to accurately follow the instructions, and not drink excessively amount of water before the reading. After weighing pros and cons of using BIA, it was decided that BIA was a good device to use for the purpose of this study.

The data in this study presented significant results for four of the KOOS subgroups for individuals with knee pain. According to Roos & Lohmander (2003), the KOOS questionnaire, that were used in this study, has a high validity and reliability. KOOS has in addition been tested for obese individuals and with high validity (Larsen et al. 2019). Collin et al (2016) did however questioned the validity and reliability of KOOS and the three of subscales pain, ADL and Sport/Rec in their systematic review and meta-analysis. According to them, the subscale ADL, had a higher validity for older individuals whereas the validity for Sport/Rec were higher for individuals who were younger. Since younger individuals might participate in sports more than older
individuals it may explain the higher validity for young people in the Sport/Rec subcategory. Interestingly enough, the strongest significant association overall, in the study by Collins et al. (2016), was found for the subscale Sport/Rec. As for the validity of ADL it seems more plausible, that elders reflect more on the ability to fend for themselves, compared to younger individuals. No significant association was however found in this study for this subcategory. In regard to the subscale pain, it had higher validity for individuals with painful conditions. As pain itself is hard to estimate, it is difficult to write if and how, it affected the result in this study. Noteworthy is that the review by Collins et al. (2016), included groups with or without OA and groups with different types of knee injuries such anterior cruciate ligament (ACL) injuries and those who had undergone a total knee replacement or articular cartilage repair. Since the comparison involved groups with different types of injuries/diseases, the difficulties posed by these injuries/diseases look different. Moreover, the outcome in terms of function and pain, also differs and thus likely affect the result of the study (Collins et al. 2016). Collins et al. (2016) writes that even if additional evaluation is required, they agreed that KOOS is both a valid and reliable tool. In summary, all three studies described above agreed upon the validity and test reliability and the usage of KOOS and its subgroups (Collins et al 2016; Roos & Lohmander 2003; Larsen et al. 2019). In this study, everyone with OA-related symptoms were required to assess both the symptoms and experienced pain when filling in the KOOS questionnaire. The choice of combining KOOS with physical examination and the obtainment of radiographs, to minimized bias, was therefore good.

Conclusion

The significant associations that were found between the four subscales of KOOS support that KOOS is good for identifying individuals at risk of developing radiographic knee OA as well as ensue the disease progression. KOOS should therefore be used early and continuously for individuals who are experiencing knee symptoms. CRP was not a good marker to measure inflammation or to be used as a predictor tool in knee OA. Moreover, exercise and weight reduction along with educational programs and coping strategies should be encouraged. Future studies should involve a bigger number of individuals and focus at finding inflammatory markers, that could improve
the chances of identifying individuals at an earlier stage with low-grade inflammation and at risk of developing knee OA.
Reference list

Abnova (2023). CRP (Human) ELISA Kit.


WHO (2023). Obesity Overview. https://www.who.int/health-topics/obesity/#tab=tab_1 [20240304]

WHO 2023. Obesity Complications. https://www.who.int/health-topics/obesity/#tab=tab_2 [20240304]


https://doi.org/10.1155/2019/2037484

https://doi.org/10.3390/ijms22126522.

Appendix 1
Prediktion av sjukdomsförloppet och dess relation till samsjuklighet vid symptomatisk knäartros - En studie av artrosfenotyper och deras biomarkörer

Bakgrund och syfte
Studier har visat att vissa personer med smärta i knäna utvecklar knäartros. Tidigare ansågs artros främst bero på slitage av ledbrosket. Studier har dock på senare år visat att artros kan bero på andra saker; man har t ex sett samband mellan artros, fetma, diabetes, hjärtsjukdomar, ämnesomsättningsrubbningar och utbredd smärta. Det gemensamma för dessa tillstånd är en låg grad av inflammation. Det är dock okänt om inflammationen startar sjukdomarna eller om det är en konsekvens av dem. För att kunna studera dessa samband mer noggrant behöver vi följa personer med knäsmärta under en längre tid och med täta uppföljningar.

Förfrågan om deltagande
Vi vänder oss till dig som har varit på besök på vårdcentral och har besvär med smärta i knäna.

Hur går studien till?
Studien innebär att du en gång om året under fem års tid kommer att kallas till tre olika undersökningstillfällen: undersökning av knäna, röntgen av knäna samt blodprovstagning. Vid dessa undersökningar kommer följande att utföras:

- Du kommer att få svara på ett frågeformulär med frågor om bl.a. smärta, smärtupplevelse samt livsstilsfaktorer (kost, rökning, alkoholvanor, fysisk aktivitet). I formuläret ställs även frågor kring dina knäbesvär, eventuella handbesvär samt allmän hälsa.
- Du får lämna blodprover för analys av ditt blodsocker, blodfetter samt för att se om du har en inflammation i kroppen.
Vilka är riskerna?

Det finns inga risker med att delta. Blodproverna och undersökningen av knäna kommer att utföras av utbildad personal. Röntgenundersökningen av dina knän bedöms ej medföra några risker.

Finns det några fördelar?

Du kommer att få ta del av dina resultat från samtliga tester.

Hantering av data och sekretess


Hur får jag information om studiens resultat?

Kunskapen från studieresultatet kommer att resultera i vetenskapliga artiklar, som kommer att skickas in till internationella reumatologiska tidskrifter samt till vetenskapliga kongresser. Alla resultat kommer att redovisas i grupp. Resultaten kommer även att delas med personal på vårdcentraler vid personalföreläsning samt föreläsningar för patientföreningar och kommer därmed att komma patienter till gagn.

Försäkring, ersättning

Patientskadeförsäkring gäller. Ingen ersättning för förlorad arbetsinkomst eller andra utgifter kopplade till projektet kommer att kunna utbetalas.

Frivillighet

Deltagande i forskningsprojektet är frivilligt och du kan när som helst, utan särskild förklaring, avbryta ditt deltagande. Du har rätt att begära att insamlad data och prover förstörs eller märks så att de inte längre är möjliga att spåra till dig. Om du väljer att inte delta i studien eller avbryter studien kommer detta inte att påverka din behandling/omhändertagande.
FoU Spenshult, som är huvudman för studien lyder under personuppgiftslagen enligt vilken du har rätt att återkalla lämnat samtycke till att dina personuppgifter används i en studie. Lagen föreskriver också att du varje kalenderår kan få kostnadsfri information om vilka av dina personuppgifter som behandlas. Du kan även begära rättelse av personuppgifter. För begäran om rättelse eller information om personuppgifter kontakta Maria Andersson (se nedan).

**Ansvariga**

Kontaktperson och projektledare:

Maria Andersson, BMA, Forskare vid FoU Spenshult
E-post: maria.andersson@spenshult.se, 0735-187043

Stefan Bergman
Leg läkare,
Forskningschef vid FoU Spenshult
Telefon 0735-187040 (sekr)

Ann Breman
Leg sjukgymnast,
Bitr. forskningschef vid FoU Spenshult

Samtyckesblankett

Prediktion av sjukdomsförloppet och dess relation till samsjuklighet vid symptomatisk knäartros - En studie av artrosfenotyper och deras biomarkörer

☐ Jag har fått information om studien, dess syfte och fått möjlighet att ställa frågor. Jag deltar frivilligt i studien och kan när som helst avbryta min medverkan.

Ort och Datum:
________________________________________________________________________

________________________________________________________________________

Namnteckning

________________________________________________________________________

Namnförtydligande
Appendix 2

KOOS
Frågeformulär för knäpatienter


Symptom
Tänk på de symptom Du haft från ditt knä under den senaste veckan när Du besvarar dessa frågor.

S1. Har knät varit svullet?
<table>
<thead>
<tr>
<th>Aldrig</th>
<th>Sällan</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Alltid</th>
</tr>
</thead>
</table>

S2. Har Du känt att det mäler i knät eller hör Du klickande eller andra ljud från knät?
<table>
<thead>
<tr>
<th>Aldrig</th>
<th>Sällan</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Alltid</th>
</tr>
</thead>
</table>

S3. Har knät hakat upp sig eller låst sig?
<table>
<thead>
<tr>
<th>Aldrig</th>
<th>Sällan</th>
<th>Ibland</th>
<th>Ofta</th>
<th>Alltid</th>
</tr>
</thead>
</table>

S4. Har Du kunnat sträcka knät helt?
<table>
<thead>
<tr>
<th>Alltid</th>
<th>Ofta</th>
<th>Ibland</th>
<th>Sällan</th>
<th>Aldrig</th>
</tr>
</thead>
</table>

S5. Har Du kunnat böja knät helt?
<table>
<thead>
<tr>
<th>Alltid</th>
<th>Ofta</th>
<th>Ibland</th>
<th>Sällan</th>
<th>Aldrig</th>
</tr>
</thead>
</table>

Stelhet
Följande frågor rör ledstelhet. Ledstelhet innebär svårighet att komma ighjung eller åkmat moiständ då Du böjer eller sträcker i knät. Markera graden av ledstelhet Du har upplevt i ditt knä den senaste veckan.

S6. Hur stelt har ditt knä varit när Du just har vaknat på morgonen?
<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Något</th>
<th>Måttligt</th>
<th>Mycket</th>
<th>Extremt</th>
</tr>
</thead>
</table>

S7. Hur stelt har ditt knä varit efter att Du har suttit eller legat och vilat senare under dagen?
<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Något</th>
<th>Måttligt</th>
<th>Mycket</th>
<th>Extremt</th>
</tr>
</thead>
</table>
Smärta
P1. Hur ofta har Du ont i knät?

<table>
<thead>
<tr>
<th>Aldrig</th>
<th>Varje månad</th>
<th>Varje vecka</th>
<th>Varje dag</th>
<th>Alltid</th>
</tr>
</thead>
</table>

Vilken grad av smärta har Du känt i ditt knä den senaste veckan under följande aktiviteter?

P2. Snurra/vrida på belastat knä

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P3. Sträcka knät helt

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P4. Böja knät helt

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P5. Gå på jämnt underlag

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P6. Gå upp eller ner för trappor

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P7. Under natten i sängläge (smärta som stör sömnen)

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P8. Sittande eller liggande

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

P9. Stående

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Svår</th>
<th>Mycket svår</th>
</tr>
</thead>
</table>

Funktion, dagliga livet

Följande frågor rör Din fysiska förmåga. Ange graden av svårighet Du upplevt den senaste veckan vid följande aktiviteter på grund av dina knäbesvär.

A1. Gå nerför trappor

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
</table>

A2. Gå uppför trappor

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
</table>

A3. Resa dig upp från sittande

<table>
<thead>
<tr>
<th>Ingen</th>
<th>Lätt</th>
<th>Mättlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
</table>
Ange graden av svårighet Du upplevt med varje aktivitet den senaste veckan.

A4. Stå stilla
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A5. Böja Dig, i ex för att plocka upp ett föremål från golvet
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A6. Gå på jämmt underlag
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A7. Stiga i ur bil
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A8. Handla/göra inköp
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A9. Ta på strumpor
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A10. Stiga ur själen
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A11. Ta av strumpor
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A12. Ligg i själen (vända dig, hålla knäet i samma läge under lång tid)
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A13. Stiga i och ur badkar/dusch
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A14. Sitta
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A15. Sätta dig och resa dig från toalettstol
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A16. Utföra tungt hushållsarbete (snöskötsling, golvvätt, dammsugning etc)
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor

A17. Utföra lätt hushållsarbete (målning, damming etc)
- Ingen
- Lätt
- Måttlig
- Stor
- Mycket stor
Funktion, fritid och idrott
Följande frågor rör Din fysiska förmåga. Ange graden av svårighet Du upplevt den senaste veckan vid följande aktiviteter på grund av Dina knäbesvär.

SP1. Sitta på luk

<table>
<thead>
<tr>
<th></th>
<th>Ingen</th>
<th>Lätt</th>
<th>Måttlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

SP2. Springa

<table>
<thead>
<tr>
<th></th>
<th>Ingen</th>
<th>Lätt</th>
<th>Måttlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

SP3. Hoppa

<table>
<thead>
<tr>
<th></th>
<th>Ingen</th>
<th>Lätt</th>
<th>Måttlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

SP4. Vrida/snurra på belastat knä

<table>
<thead>
<tr>
<th></th>
<th>Ingen</th>
<th>Lätt</th>
<th>Måttlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

SP5. Ligga på knä

<table>
<thead>
<tr>
<th></th>
<th>Ingen</th>
<th>Lätt</th>
<th>Måttlig</th>
<th>Stor</th>
<th>Mycket stor</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tbody>
</table>

Livskvalité

Q1. Hur ofta gör sig Ditt knä påmint?

<table>
<thead>
<tr>
<th></th>
<th>Aldrig</th>
<th>Varje månad</th>
<th>Varje vecka</th>
<th>Varje dag</th>
<th>Alltid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Q2. Har Du förändrat Ditt sätt att leva för att undvika att påfresta knäet?

<table>
<thead>
<tr>
<th></th>
<th>Inte alls</th>
<th>Något</th>
<th>Måttligt</th>
<th>I stor utsträckning</th>
<th>Totalt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Q3. I hur stor utsträckning kan Du lita på Ditt knä?

<table>
<thead>
<tr>
<th></th>
<th>Helt och hållet</th>
<th>I stor utsträckning</th>
<th>Måttligt</th>
<th>Till viss del</th>
<th>Inte alls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Q4. Hur stora problem har Du med knäet generellt sett?

<table>
<thead>
<tr>
<th></th>
<th>Inga</th>
<th>Smla</th>
<th>Måttliga</th>
<th>Stora</th>
<th>Mycket stora</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

Tack för att Du tagit dig tid att besvara samtliga frågor!