PERIARTICULAR CHANGES IN ASSOCIATION WITH OSTEOARTHRITIS IN THE HIP, KNEE OR SHOULDER

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"The more you know, the more you know you don't know"
Aristotle

CONTENTS

I. ABSTRACT

The aim of this thesis was to evaluate the presence of degenerative changes in the periarticular tendons in association with osteoarthritis (OA) in the hip, knee or shoulder. Moreover, changes in bone mineral density (BMD) in the hip, spine and calcanei were investigated after total hip arthroplasty (THA).

Study I is a case control study comprising 26 patients, in which the macroscopic, histological, morphological and ultrastructural changes in tissue samples from the long head of the biceps and subscapularis tendons of the shoulder were examined. The tendon fibril diameter and histological total degeneration score (TDS) were assessed. The biceps tendon in patients with OA of the shoulder revealed more macroscopic and morphological degenerative changes compared with the control group. This indicates that OA in the shoulder might be associated with tendinopathy in the periarticular tendons.

Study II is a case control study comprising 41 patients, in which the histological, morphological and ultrastructural changes in tissue samples from the semitendinosus tendon were examined. The tendon fibril diameter and histological total degeneration score (TDS) were assessed. The semitendinosus tendon in patients with OA of the knee revealed no more degenerative changes compared with the control group. No association was found between the presence of degenerative tendon changes and OA of the knee.

Study III is a case control study comprising 100 patients, in which the histological and ultrastructural changes in tissue samples from the gluteus medius (GMED) tendon were examined. The GMED tendon revealed more ultrastructural degeneration in patients who undergo hip revision arthroplasty than in patients with primary OA of the hip and control patients. Furthermore, patients who had previously undergone primary THA through a direct lateral approach revealed more ultrastructural GMED tendon degeneration than patients who had previously undergone THA through a posterior approach. The direct lateral revision group had a higher total degeneration score (TDS) histologically compared with the primary hip OA group. An association was found between the presence of GMED degenerative changes and previous THA but not between GMED degenerative changes and OA of the hip.

Study IV is a prospective study comprising 42 patients. BMD was measured in the spine, hip and calcanei before and after THA. BMD decreased postoperatively in both calcanei, in both male and female patients, despite an improvement in physical activity and quality of life as measured with the Tegner activity score and EQ-5D.

Keywords
Arthroplasty, Osteoarthritis, Osteoporosis, Tendinopathy, Tendinosis

II. SAMMANFATTNING PÅ SVENSKA

Syftet med denna avhandling var att utvärdera förekomsten av degenerativa förändringar i peri-artikulära senor i samband med artros (OA) i höft-, knä- eller skulderled. Vidare, undersöka förändringar i benmineraldensitet (BMD) i höft, rygg och hälben efter total höftartroplastik (THA).

Studie I är en fall-kontrollstudie omfattande 26 patienter, där makroskopiska, histologiska, morfologiska och ultra-strukturella förändringar i vävnadsprover från långa biceps- och subscapularis-senan undersöktes. Diametern hos senfibriller och total degeneration scoren (TDS) bedömdes. Bicepssenan hos patienter med OA uppvisade makroskopiska och morfologiska förändringar i högre grad jämfört med en kontrollgrupp. Resultatet talar för ett samband mellan tendinopati i peri-artikulära senor och OA i skulderleden.

Studie II är en fall-kontrollstudie omfattande 41 patienter, där histologiska, morfologiska och ultra-strukturella förändringar i vävnadsprover från semitendinosus-senan undersöktes. Diametern hos senfibriller och TDS bedömdes. Semitendinosus-senan hos patienter med OA uppvisade ingen skillnad i degenerativa förändringar jämfört med en kontrollgrupp. Inget samband mellan tendinopati i de peri-artikulära senorna och OA i knäleden kunde påvisas.

Studie III är fall-kontrollstudie omfattande 100 patienter, där histologiska och ultrastrukturella förändringar i vävnadsprover från gluteus medius (GMED) senan undersöktes. GMED senan visade en ökad ultrastrukturell degeneration hos patienter som genomgick höftrevision jämfört med patienter med primär OA i höftleden och kontrollpatienter. Vidare, hade patienter som tidigare genomgått primär THA med lateralt snitt en ökad ultrastrukturell degeneration av GMED senan jämfört med patienter som tidigare genomgått THA med bakre snitt. Gruppen med tidigare lateralt snitt hade också histologiskt högre TDS jämfört med den primära OA gruppen. Det fanns ett samband mellan degenerativa förändringar i GMED senan och tidigare genomgången THA, men inte mellan degenerativa förändringar i GMED and OA i höftleden.

Studie IV är en prospektiv studie omfattande 42 patienter. BMD uppmättes i höften, ryggen och hälbenen före och 5 år efter THA. BMD minskade postoperativt i båda hälbenen, hos både män och kvinnor trots förbättringar i fysisk aktivitet och livskvalité, mätt med Tegner aktivitets score och EQ-5D.

III. LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **More tendon degeneration in patients with shoulder osteoarthritis**
Ibrahim M, Kartus JT, Steigen SE, Olsen R, Meknas K.
Knee Surg Sports Traumatol Arthrosc. 2019;27(1):267-275

II. **No significant histological or ultrastructural tendinosis changes in the hamstring tendon in patients with mild to moderate osteoarthritis of the knee?**
Ibrahim M, Meknas K, Steigen SE, Olsen R, Sernert N, Ejerhed L, Kartus JT.
Knee Surg Sports Traumatol Arthrosc. 2020;29(4):1067-1074

III. **More histological and ultrastructural changes in the gluteus medius tendon after hip arthroplasty**
Ibrahim M, Hedlundh U, Sernert N, Meknas K, Haag L, Movin T, Papadogiannakis N, Kartus JT.
Journal of Orthopaedic Surgery and Research. 2021;16(1):339

IV. **Despite increased physical activity levels, bone mineral density decreases after total hip arthroplasty**
Ibrahim M, Sernert N, Kartus JT, Ejerhed L
Translational Sports Medicine. 2018;2(1):32-38

IV. ABBREVIATIONS

AB/PAS	Alcian blue/periodic acid Schiff
ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
BMD	Bone mineral density
DXA	Dual-energy X-ray absorptiometry
DXL	Dual-energy X-ray absorptiometry and laser technology
ECM	Extracellular matrix
GAGs	Glycosaminoglycans
GMED	Gluteus medius
HE	Hematoxylin-eosin
HTO	High tibial osteotomy
MRI	Magnetic resonance imaging
n.s.	Non-significant
OA	Osteoarthritis
SD	Standard deviation
TDS	Total degeneration score
TEM	Transmission electron microscopy
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
VAS	Visual analogue scale
QCT	Quantitative computed tomography
WHO	World Health Organization

V. BRIEF DEFINITIONS

ACL reconstruction	Reconstruction of the ruptured ACL using a graft
EQ-5D	A standardized measurement of health status developed to provide a simple, generic measurement of health for clinical and economic appraisals
Glycosaminoglycans	Polysaccharides, a major component of the extracellular matrix in tendons
Hemiarthroplasty	Surgery in which the femoral head is removed and replaced with artificial materials
Hip revision	Surgery in which part(s) or the whole of a previously implanted artificial hip joint, or prosthesis, is replaced with a new prosthesis
p-value	The probability of obtaining a result equal to or more extreme than that actually observed
Power	The probability of finding a significant association when one truly exists
Tendon fibril	An electron-microscopically clearly visible unit. A bunch of collagen fibrils form a collagen fibre
Total hip arthroplasty	Surgery in which the diseased ball and socket of the hip joint are completely removed and replaced with artificial materials
T-score	The difference in the number of standard deviations between the mean bone mineral density value of the individual and the mean of a group of young healthy adults of the same sex
Z-score	The difference in the number of standard deviations between the mean bone mineral density value of the individual and a group of people of the same age and sex

01 INTRODUCTION

1.1 SUMMARY

Osteoarthritis (OA) is a common global problem. Despite the fact that OA has been thoroughly studied, there are still gaps in knowledge in this field. Interesting findings in the form of periarticular changes in neuromuscular function 1, muscle strength [2-5] and muscle fatty infiltration have been observed in association with OA[6].

For this reason, one important issue in the understanding of this disease is to investigate whether degenerative changes may occur in periarticular tendons in patients with OA in different joints. The presence of alterations in the periarticular tendons would justify a treatment directed towards tendinopathy as a separate or supplementary part in relieving pain and improving function in patients with OA.

Over a period lasting several decades, total hip arthroplasty (THA) has become a more common treatment alternative for patients, often elderly, with advanced OA of the hips. For this reason, it is also of interest to investigate whether a deterioration in bone mineral density (BMD) with a theoretical increase in fracture risk may occur after surgical treatment of OA of the hip with THA in this population.

1.2 OSTEOARTHRITIS (OA)

OA is the most common form of arthritis [7-9]. It is regarded as a disease of the whole joint, involving not only cartilage degradation but also subchondral bone sclerosis, osteophyte and cyst formation, together with synovitis and joint effusion. Periarticular structures like muscles and ligaments may also be afflicted by OA (Fig. 1) [2, 5, 10].

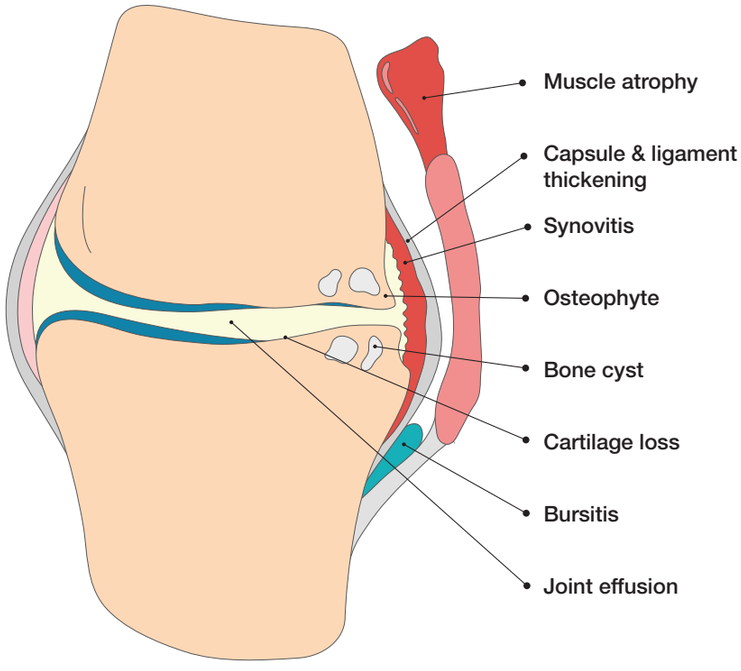

Figure 1. *Illustration of structural changes associated with OA. © M Kartus*

The hand, knee and hip are most frequently affected by OA [11]. In 2003, the World Health Organization (WHO) scientific group estimated that 10% of the world's population aged > 60 years had significant clinical problems that could be attributed to OA [12]. OA is the third main contributor (343 million), after low back pain and fractures, to the global burden of musculoskeletal disorders [13, 14]. Moreover, OA of the hip, knee and hand is ranked among the 30 leading global causes of disability in females living in countries with a high and high-middle sociodemographic index, as well as males living in countries with a high sociodemographic index, according to the WHO in 2019 [14].

The non-surgical management of OA includes patient education, physiotherapy, weight loss, the use of anti-inflammatory drugs and/or intra-articular steroid injections. Surgery is reserved for the patients who suffer due to pain and impaired joint function despite receiving the above-mentioned treatments.

Hip replacement (Fig. 2). In 2019, approximately 19,500 primary THAs, 4,000 primary hemiarthroplasties and 2,000 hip revision arthroplasties were carried out in Sweden. Hip fractures accounted for 6,000 of these. Sweden is one of the countries with the highest incidence of hip arthroplasties. At the end of 2019, 3.6% of the

Swedish population aged 40 and over had a hip prosthesis (4.1% females & 3.0% males). Females are overrepresented in the group of patients undergoing THA due to hip fracture where patients are generally older. This could be a contributory factor to the difference in prevalence between genders. Twenty-seven per cent of all hip prosthesis bearers have undergone bilateral arthroplasty [15].

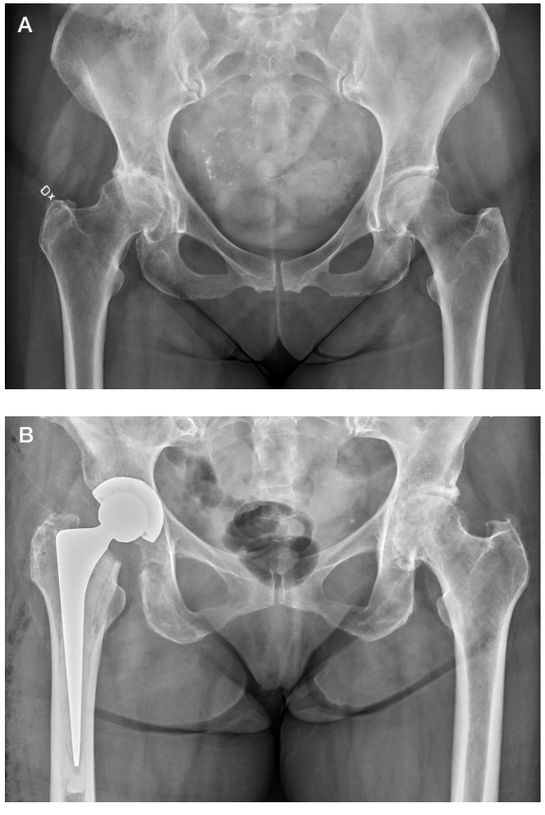

Figure 2 A & B. *A is an X-ray showing OA in the right hip joint, B is an X-ray showing OA in the left hip joint and THA in the right hip. © M Ibrahim*

There are different surgical approaches to THA [16]. The two most commonly used approaches in Sweden are the posterior (57%) and the lateral (36%) approaches [15]. The most commonly utilised approach internationally is the posterior approach [17]. The posterior approach necessitates the surgical division of the small external rotators of the hip, as well as the posterior hip capsule (Fig. 3), while the GMED tendon is spared. The direct lateral (transgluteal) approach, on the other hand, necessitates both the partial surgical division of the GMED tendon at its insertion on the greater trochanter and the partial splitting of the GMED muscle, as well as the surgical division of the anterior hip joint capsule to access the hip joint (Fig. 4) [18].

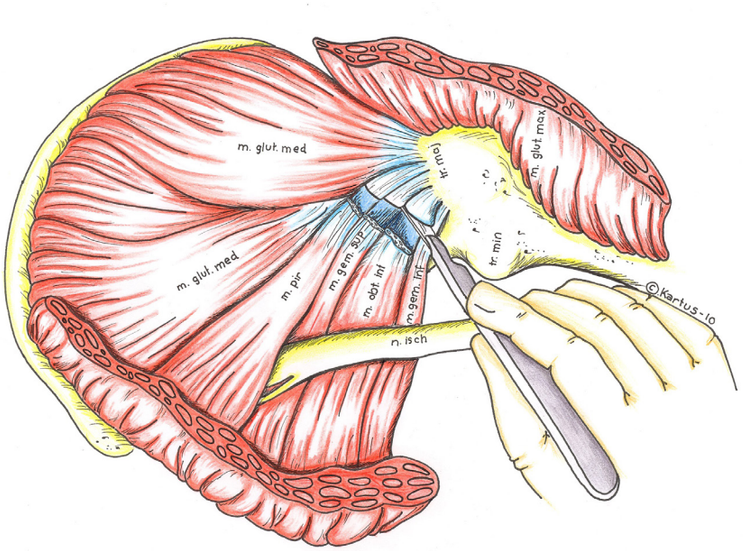

Figure 3. *Illustration of the posterior surgical approach to THA in which the small external rotator muscles are divided but not the GMED tendon. © M Kartus and C Kartus*

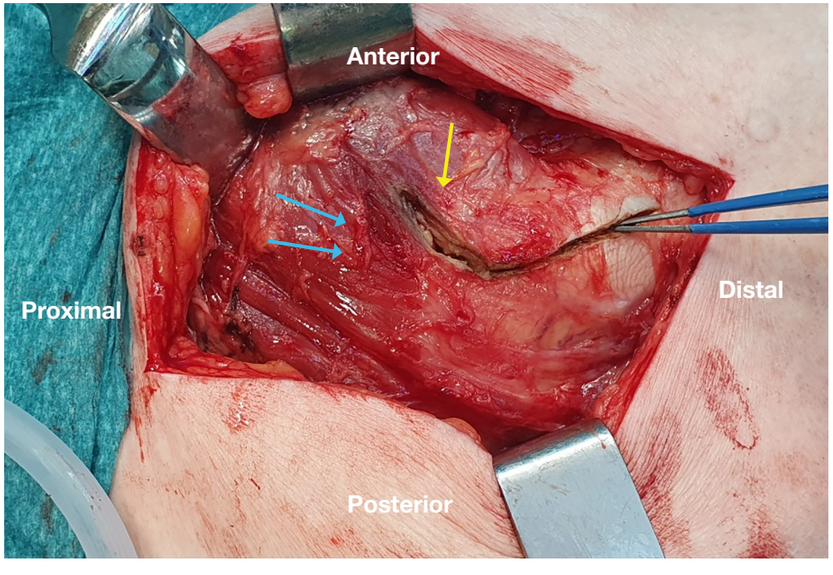

Figure 4. *Illustration of the direct lateral surgical approach to THA in which the GMED tendon and muscle are partially divided and a diathermy forceps is pointed at the division site. The yellow arrow is pointing at the anterior one third of the GMED tendon and the blue arrows are pointing at the posterior two thirds of the GMED tendon. © M Ibrahim*

Each approach has its own advantages and disadvantages. Patients who underwent THA through the posterior approach experienced a greater improvement in mean satisfaction values postoperatively compared with the direct lateral approach [19]. Likewise, they experienced a greater improvement in function evaluated with the Oxford Hip Score [20] and superior outcomes one to three years postoperatively, including self-reported limping [21]. Nevertheless, several studies have reported a higher risk of postoperative dislocation with the posterior approach [22-25]. Interestingly, the risk of dislocation within the first two years after THA via the posterior approach was declining according to the Swedish hip registry, contrary to what Andrew N. et al. have reported [26].
The overall gait function did not show a greater improvement after THA via the posterior approach than via the direct lateral approach. In spite of this, those patients who underwent THA via the posterior approach experienced more improvement in hip abductor and flexor muscle strength at the 12-month postoperative follow-up [27].

On the other hand, the direct lateral approach has been reported to confer a lower overall risk of mechanical complications, such as dislocation, aseptic loosening and periprosthetic fracture, within the first two years postoperatively compared with the posterior approach [25].

Moreover, in a recently published study, the direct lateral approach showed the lowest risk for the development of lateral trochanteric pain compared with other approaches at the 12-, 24- and 36-month time points [28].

Hip prosthesis revision surgery may be required after a failed primary THA. The most common indications for revision include loosening of the cup and/or the stem, recurrent dislocation of the hip prosthesis, wear to or failure of the prosthesis and deep infection.

In a large study from the Norwegian Arthroplasty Register, no differences were found regarding two- and five-year survival rates or a relative risk of revision between these two surgical approaches [29]. Likewise, in a study from the Australian Orthopaedic Association National Joint Replacement Registry, there was no difference in the early rate of revision between these surgical approaches [30]. However, patients who have undergone both primary THA and a single successful debridement, antibiotics and an implant retention (DAIR) operation for deep infection via the posterior approach have less limping, a better functional outcome, better health-related quality of life and greater patient satisfaction compared with those who have undergone both primary THA and a single successful debridement, antibiotics and an implant retention operation for deep infection using the direct lateral approach [31].

High tibial osteotomy (HTO) is a surgical treatment alternative for moderate medial tibiofemoral OA in patients under 60 years of age. The principle of HTO is the redistribution of the weight-bearing load from the arthritic portion in the medial compartment of the knee joint to the viable articular cartilage portion in the lateral compartment of the knee joint. In 2019, 176 osteotomies were reported to the Swedish knee osteotomy register [32].

Knee arthroplasty has seen an exponential increase in numbers since 1975. In 2019, a total of almost 17,000 primary knee arthroplasties were reported, a 9.7% increase as compared to 2018. According to the annual report from the Swedish knee arthroplasty register in 2020, it is expected that the volumes will continue to increase as the age distribution of the population will most probably increase the demand for this type of surgery. Knee arthroplasty is more common in females than in males, 56.5% and 43.5% respectively [32].

Shoulder arthroplasty is indicated for patients with impaired shoulder function that markedly limits their daily activities and/or is associated with intractable pain. Primary OA of the glenohumeral joint is relatively uncommon. It is more common in women and in patients over the age of 60 [33]. Previous trauma, such as dislocation, humeral head or neck fracture and large rotator cuff tendon tears (cuff tear arthropathy), may lead to secondary OA of the glenohumeral joint. In 2019, more than 2,000 primary shoulder arthroplasties were carried out in Sweden. Approximately one third of the operations is due to OA of the shoulder joint and approximately one fourth of the operations is one forth due to shoulder fracture. The number of shoulder arthroplasty operations has increased steadily during the last 20 years [34].

An anterior cruciate ligament reconstruction (ACLR) is performed to stabilise the knee after ACL injury in patients with knee instability despite physiotherapy. The incidence of anterior cruciate ligament (ACL) injuries based on a number of studies is 32-80/100,000 inhabitants/year [35]. In Sweden, almost 4,000 patients (46% females and 54% males) underwent primary ACL reconstruction in 2019. The average age for the female patients undergoing ACL reconstruction was 28 years, while it was 29 years for the male patients [35]. The average time between injury and surgery was 400-500 days. Approximately 50% of patients with an ACL injury develop radiological signs of knee OA within 10-15 years after the injury [35].

1.3 TENDINOPATHY AND TENDON CHANGES ASSOCIATED WITH TENDINOPATHY

Tendinopathy is a degenerative condition of the tendon characterised by pain and disability. Epicondylitis (tennis and golf elbow) and Achilles, rotator cuff, patellar, gluteal and proximal hamstring tendon tendinopathies are some examples. The presence of periarticular tendinopathy in association with OA is not clearly outlined. Meknas et al. showed that the internal obturator tendon in patients with OA of the hip had a more degenerative appearance compared with those without OA [36].

Macroscopically, the tendinopathic tendon is grey or brown, soft and fragile, while the normal tendon is shiny white with a firm fibroelastic texture [37,38].

Histologically, the normal tendon has organised parallel collagen bundles, while the tendinopathic tendon often shows the disorganisation of collagen fibres. A tendinopathic tendon also has an increase in the number of vessels and sensory nerves, a breakdown of tissue organization and the haphazardly arranged proliferation of collagen fibres (Fig. 5). Moreover, there are frequent areas of cell death and/or fibroblast reaction. At cellular level, there are increased numbers of both leukocytes (especially macrophages and mast cells) and vascular cells. Macrophages with accumulations of hemosiderin in their cytoplasm are more prevalent in tendinopathic tendons than in normal tendons. Hemosiderin is thus an indicator of prior injury. Histochemical analyses of pathological tendons have revealed an increase in the glycosaminoglycan (GAGs) content of the extracellular matrix of the tissue compared with normal tendons (Fig. 6) [39,40].

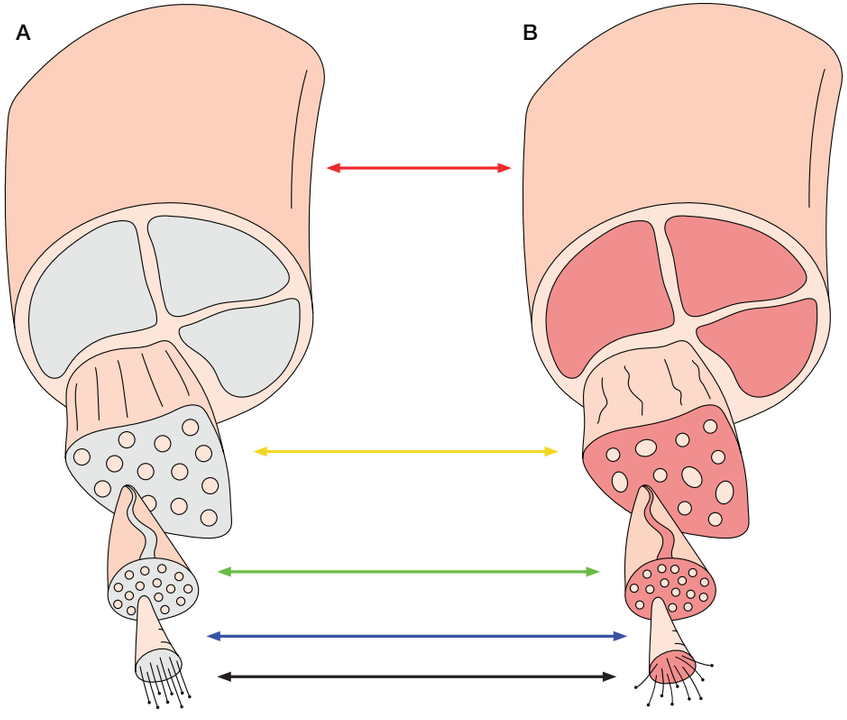

Figure 5 A & B. *Illustrate some differences between a healthy (A) and a tendinopathic tendon (B). Red double arrow pointing at the tendons, orange double arrow pointing at the fascicles 20–200 µm, green double arrow pointing at collagen fibres 50–100 µm, blue double arrow pointing at collagen fibrils 200–500 nm and black double arrow pointing at collagen microfibrils. In Fig. 5A the collagen microfibrils are tightly bundled type I collagen. Fig 5B shows collagen microfibril disarray, type I collagen fibres mixed with smaller in diameter type III collagen fibrils. © M Kartus*

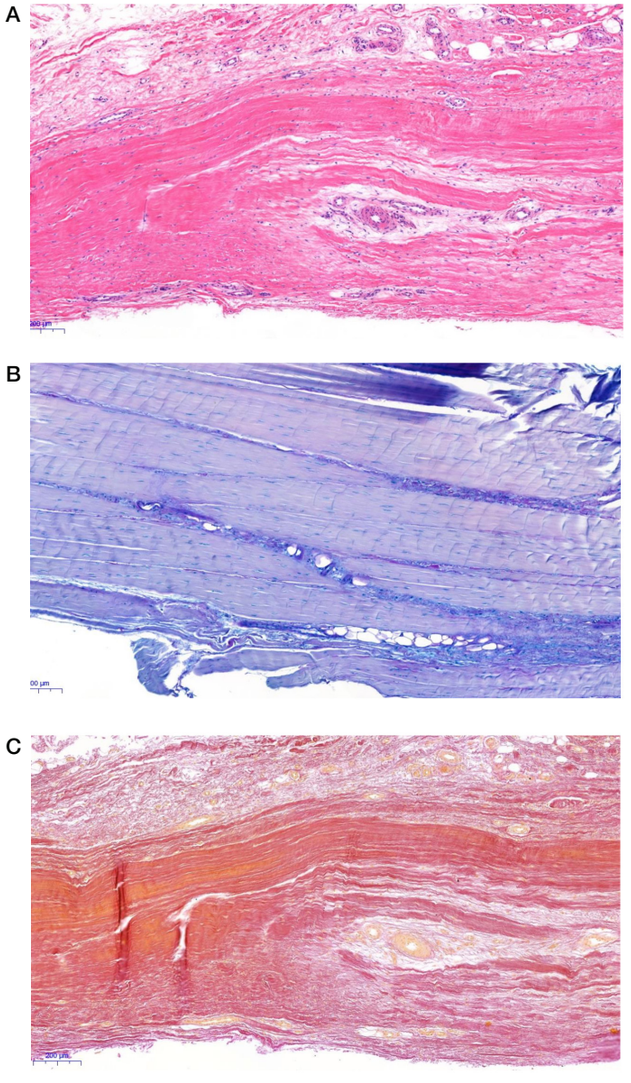

Figure 6 A, B & C. *Semitendinosus tendon from patients in Study II. A shows the separation and deterioration of the fibres. An increase in vessels within the tendon tissue.* ***Hematoxylin-eosin stained*** *for fibre structure, cellularity & vascularity, B shows a slight to moderate increase in alcianophilia (light blue stain) between the fibrous connective tissue.* ***Alcian blue/periodic acid Schiff*** *stained for GAGs, C shows no convincing evidence of scar tissue.* ***Elastin van Gieson*** *stained for collagen.*

Morphologically, the extracellular matrix (ECM) of a tendon is composed of collagen and elastic fibres, ground substance and anorganic components [41]. The ECM endows the tissue of tendons with its mechanical and biochemical properties [42]. The ECM in a normal tendon has a parallel alignment with the organised stacking of cells. The linear organisation of the ECM in a normal tendon is severely disrupted (perturbed) in a tendinopathic tendon. Moreover, the cells are separated from the ECM by electron-lucent regions (Fig. 7) [43].

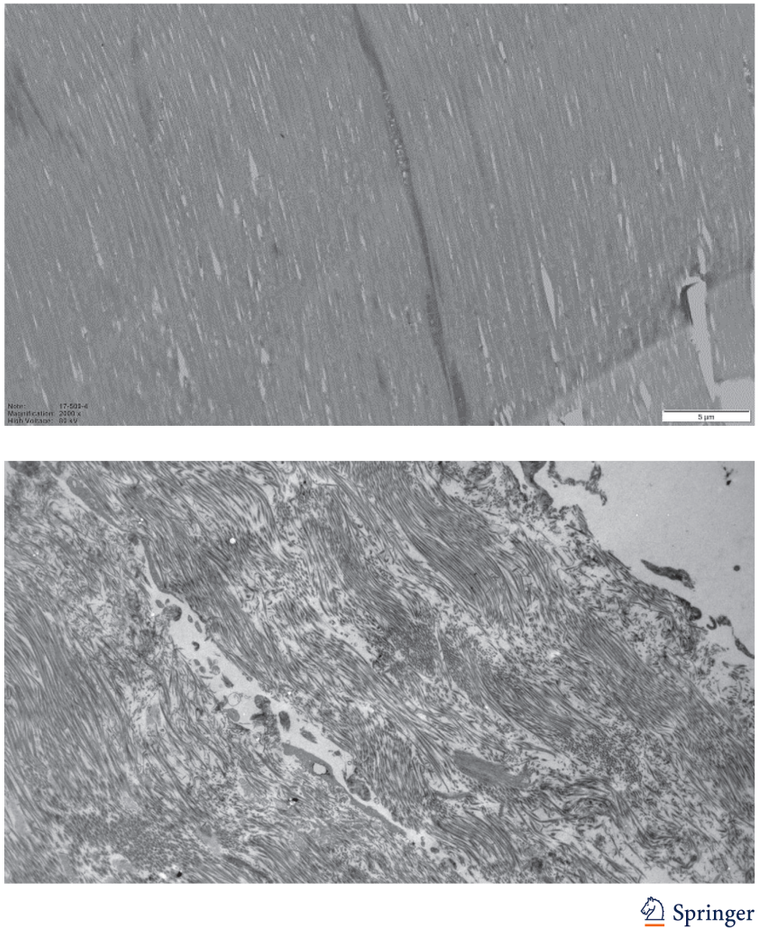

Figure 7 A & B. *Semitendinosus tendon from patients in Study II. A) A homogeneous ECM with collagen fibrils running in the same direction in a normal tendon. Original magnification X 2,000, B) collagen fibrils oriented in different directions and an irregular ECM in a tendinopathic tendon. Original magnification X 2,000.*

Ultrastructurally (Fig. 8), the fundamental constituent of a tendon is collagen and it accounts for 70% of the dry weight of a tendon [44]. Type I collagen is the main type of collagen in a normal tendon and it accounts for approximately 90%, while less than 5% is type III collagen [45]. Only small amounts of Type II collagen are present in tendon, mostly concentrated close to the bone insertion 46. There are other types of collagen, but they present in very small amounts.

At the electron-microscopic level, the formation of type III collagen fibrils accompanies tendon degeneration. This type of collagen fibril has a smaller diameter than type I collagen fibrils, the main collagen type in tendon tissue. As a result, the distribution of fibril diameters in tendinopathic tendons displays a shift towards smaller diameters (Fig. 9) [43].

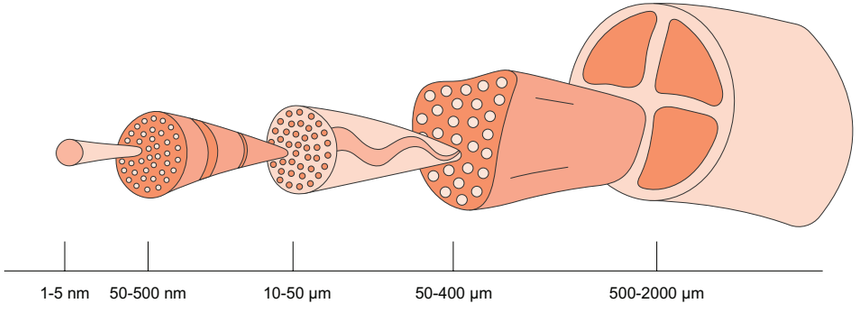

Figure 8. *Illustration of the tendon structure, tropocollagen molecules aggregate into microfibrils and then into collagen fibrils which are visible using an electron microscope. A group of collagen fibrers forms a collagen fibre, which is visible using a light microscope. A group of collagen fibres makes up a primary fibre bundle, while a bunch of primary fibre bundles makes up a secondary fibre bundle. A bunch of secondary fibre bundles makes up a tertiary bundle, while the tertiary bundles form the tendon. © M Kartus*

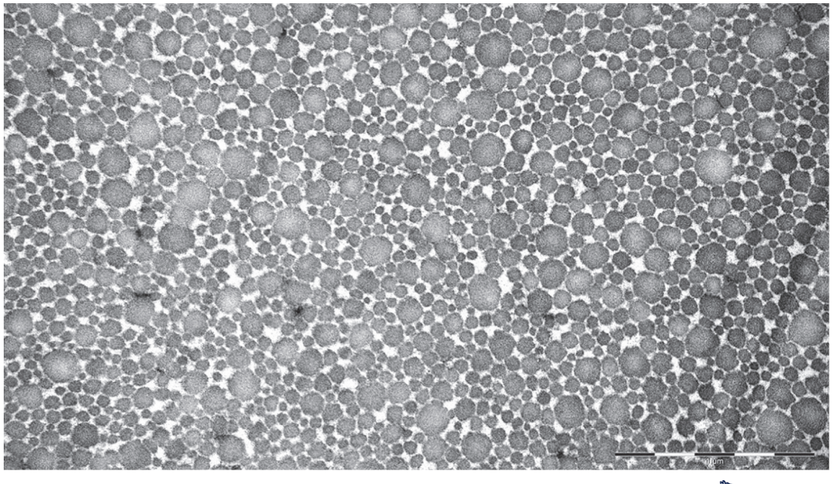

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Figure 9. *Example of a transmission electron microscope at 50,000 x magnification. The fibril diameters were measured in the biopsy with the best transverse orientation.*

1.4 OSTEOPOROSIS

Osteoporosis is a systemic disease characterised by low bone mass with reduced bone strength [47]. Osteoporosis is a global problem, especially in the Scandinavian countries, where the incidence of fragility fractures is high [48, 49]. The incidence of fragility fracture in Sweden is approximately 120,000/year [50]. The causes are unknown, but possible explanations could be that women in this region are generally taller with a lower body weight compared with women from other countries. In addition, ethnicity like Northern European and insufficient UVB-light exposure for dermal vitamin D synthesis due to high latitudes should also be considered [51]. Another hypothesis is that white skin and weaker bones might be an adaptation to northern environments [52].

The definition of osteoporosis is based on the T-score for BMD measured by Dual-energy X-ray Absorptiometry (DXA) at the femoral neck and lumbar spine and is expressed as a T-score of ≤ -2.5 SD [47]. A low BMD is an independent risk factor for low-energy fractures [53-55]. At the age of 65 years, the risk ratio for fragility fractures increases by a 1.4 per SD decrease in the Z-score of BMD, irrespective of measurement site [56]. The most common sites of fragility fracture are the spine, hip, wrist and proximal humerus. The relative risk of fracture increases as bone mineral density (BMD) decreases.

The main risk factors for fragility fractures include age, female gender, low body mass index (BMI), prior fragility fracture, history of parental hip fracture, glucocorticoid therapy and, lastly, excessive alcohol and/or smoking [57]. Fractures of the spine and hip in elderly individuals are associated with chronic pain, deformity, depression, disability and death. According to the literature, one-year mortality after a hip fracture is 8-36% [58-60]. In Sweden, the 30-day mortality after hip fractures in females and males is 6% and 11% respectively [61]. Patients > 60 years old with a displaced femoral neck fracture, usually a fragility fracture, are frequently treated with hemi- or total hip arthroplasty, depending on their age and activity level.

1.4.1 BONE MINERAL DENSITY (BMD)

Bone strength is determined by BMD and bone quality. One of the factors that determine bone quality is the bone macro- and micro-architecture, including bone shape, size, geometry, trabecular and cortical thickness and porosity. Other factors that determine bone quality include bone turnover, damage accumulation, matrix properties and mineralisation [62]. After advanced age, low BMD is a strong predictor of future fractures [63].

DXA is the the most widely accepted and validated technique, according to the WHO, and it can be applied to biologically relevant sites, including the hip, spine and forearm. It is used for the diagnosis of osteoporosis and for monitoring changes in BMD over time. The measurement of hip BMD also has the highest predictive value for hip fracture. In addition, if pharmacological therapy is planned, the measurement of spine BMD is useful, as it shows less variability and is able to detect responses to therapy earlier than hip BMD. The diagnosis of osteoporosis is made according to the lowest T-score measured.

The T-score is the difference in the number of standard deviations between the mean BMD value of the individual and the mean of a group of young healthy adults of the same sex.

Another score which is helpful in the assessment of osteoporosis is the Z-score, which is the difference in the number of standard deviations between the mean BMD value of the individual and a group of people of the same age and sex.

In spite of the fact that the reference standard for the diagnosis of osteoporosis is BMD at the femoral neck, according to the initial WHO report in 1994, other sites such as the lumbar spine and total hip can be used for diagnosis in clinical practice, according to the WHO scientific group on the assessment of osteoporosis at the primary health care level in 2005 [65]. Calcaneal BMD is also a useful way to assess osteoporosis [63, 66]. Studies suggest that BMD measurements with Dual X-ray and laser technology (DXL) may well reflect the actual BMD [67, 68].

02 AIMS

The overall purpose of the studies was to evaluate the presence of degenerative changes in the periarticular tendons in association with OA in the hip, knee or shoulder. Moreover, the purpose was to evaluate changes in the BMD of the hip, spine and calcanei after THA.

Specific aims

Study I
The aim of this case control study was to investigate the degenerative changes in the subscapularis and long head of the biceps tendon in patients with OA of the shoulder and to compare them with tendon from patients with fractures of the proximal humerus but without OA.
The hypothesis was that tendon samples from the patients with OA in the shoulder joint would reveal a larger proportion of macroscopic, histological, morphological and ultrastructural tendon pathology compared with samples from control patients with a fracture of the proximal humerus.

Study II
The aim of this case control study was to investigate the degenerative changes in the semitendinosus tendon in a group of patients with mild to moderate knee OA and to compare them with changes in the semitendinosus tendon in a control group, patients with knee instability without OA of the knee.
The hypothesis was that tendon samples from the patients with OA in the knee joint would reveal a larger proportion of histological, morphological and ultrastructural tendon pathology compared with samples from control patients with an ACL injury but without knee OA.

Study III
The aim of this case control study was to investigate the degenerative changes in the GMED tendon and to determine whether OA or previous THA lead to more degeneration in the GMED tendon compared with a control group.
The hypothesis was that patients who undergo revision hip arthroplasty are expected to have more GMED tendon degeneration than patients who undergo primary THA. Moreover, patients who had previously undergone primary THA through a direct lateral approach were expected to have more GMED tendon degeneration than patients who had previously undergone THA through a posterior approach.

Study IV
The aim of this prospective study was to evaluate the BMD changes in the spine, hip and calcanei after THA.
The hypothesis was that more BMD loss would be found in the lumbar spine, non-operated hip and both calcanei in patients who undergo THA compared with the expected normal age-dependent BMD loss.

03 PATIENTS

The allocation of patients to the studies

		Female/male	Age at operation years mean (range)	Surgical indication
Study 1 (shoulder)	**Group OA** n=13	8 / 5	66 (52-84)	OA shoulder
	Group fracture n=13	11 / 2	69 (51-84)	Proximal humeral fracture
Study II (knee)	**Group OA** n=21	11 / 10	51 (33-63)	OA knee
	Group ACL n=20	12 / 8	42 (31-57)	ACL injury
Study III (hip)	**Group DLR** n=22	10 /12	73 (46-89)	Revision after direct lateral (DLR) THA
	Group PR n=24	11 / 13	76 (60-88)	Revision after posterior (PR) THA
	Group OA n=29	19 / 10	70 (50-89)	Primary OA
	Group fracture n=25	19 / 6	73 (61-80)	Hip fracture
Study IV (BMD)	**Group THA** n=42	22 / 20	69 (54-85) 68 (50-80)	THA
	Group sample from the normal population n=1452	993 / 459	48 (15-85) 47 (19-85)	N.A.

**N.A. = not applicable*

Study I
Between 2015-2017, twenty-six consecutive patients were included from the Orthopaedic Department in Tromsø, Norway. Thirteen patients with OA of the shoulder and 13 control patients with a fracture of the proximal humerus. The inclusion criteria were patients with OA in the shoulder joint with indications for a shoulder prosthesis and patients with a proximal humerus fracture with indications for a shoulder prosthesis or fracture fixation with osteosynthesis. The exclusion criterion was patients with advanced organ failure.

Study II
Between 2016 and 2017, forty-one consecutive patients were included from the Orthopaedic Department, NU Hospital Group, Trollhättan/Uddevalla. Twenty-one patients with OA of the medial compartment of the knee were included in the HTO group and twenty patients with knee instability were included in the ACLR group. The inclusion criteria were primary medial compartment Ahlbäck grade 1-3 OA [69] of the knee with an indication for HTO or an unstable knee joint due to ACL rupture verified by MRI or a clinical examination,

with an indication for ACLR. The exclusion criteria were secondary arthritis of the knee, a more than grade II local chondral lesion according to the Outerbridge classification [70], multi-ligament injuries, previous fracture or surgery on the lower extremities and lastly age over 65 years. No patient in the ACLR group displayed radiographic OA changes pre-operatively.

Study III
Between 2016 and 2019, a total of one hundred patients were recruited preoperatively from the Orthopaedic Department, NU Hospital Group, Trollhättan/Uddevalla and were included in one of four groups. The first group is called the revision direct lateral group (n=22), comprising patients who were scheduled for hip revision arthroplasty and had previously undergone primary THA through a direct lateral approach (involving sectioning of the GMED). The second group, which is called the revision posterior group (n=24), comprised patients who were scheduled for hip revision arthroplasty and had previously undergone primary THA through a posterior approach (leaving the GMED tendon intact). The third group is called the primary OA group (n=29), comprising patients who were scheduled for primary THA due to OA of the hip and, lastly, the fourth group is called the fracture group (n=25), comprising patients who were scheduled for primary THA due to femoral neck fracture.
The main inclusion criterion for both revision groups was loosening of the hip prosthesis. Two patients were included due to recurrent hip prosthesis dislocation and one patient underwent revision surgery due to the failure of metal-on-metal hip resurfacing arthroplasty. For the primary OA group, the inclusion criterion was primary OA of the hip, while, for the fracture group, it was a displaced non-pathological femoral neck fracture without OA of the hip. The exclusion criteria were secondary hip arthritis, previous hip surgery (other than primary THA), fragile patients with severe comorbidity, dementia or cognitive impairment, widespread malignancy diseases, patients with conditions that affect the neuromuscular function of the lower extremities, osteonecrosis of the femoral head and systemic corticosteroid treatment for more than three months. In addition, for the revision groups, patients with hip dysplasia, a postoperative infection after the primary THA and a revision within one year of the primary THA were excluded.

Study IV
Between November 2004 and February 2008, 42 consecutive patients scheduled for THA due to symptomatic osteoarthritis/rheumatoid arthritis were included from the Orthopaedic Department, NU Hospital Group, Trollhättan/Uddevalla, and followed for five years. The exclusion criteria were secondary hip arthritis, previous hip surgery, diseases or conditions that affect the neuromuscular function of the lower extremities (polio, stroke, multiple sclerosis etc.), osteonecrosis of the femoral head, fragile patients with severe comorbidity or severely ill patients (ASA 4, according to the American Society of Anesthesiologists physical status classification system), dementia or cognitive impairment, widespread malignancy and systemic corticosteroid treatment for more than three months.

04 METHODS

4.1 BIOPSY PROCEDURE

Studies I, II & III: At the index operation in the study, two to four biopsies, each 2-5 mm in diameter, were harvested close to the tendon insertion of the subscapularis on the proximal humerus and from the long head of the biceps tendon (Study I), 4 cm proximal to the semitendinosus tendon insertion on the medial aspect of the proximal tibia (Study II) and from the GMED tendon close to its insertion on the trochanter major (Study III). Immediately after harvesting the biopsies, one to two of them were immersed directly in one to two tube(s) filled with formaldehyde and one to two biopsies were immersed directly in a tube(s) filled with a solution containing 3% glutaraldehyde and 0.15 M cacodylate buffer. The biopsies which were immersed in formaldehyde were kept at room temperature and sent to the pathologist for a light-microscopic examination, while those immersed in the other solution were kept in a refrigerator at + 4 to + 6 degrees Celsius until all the study samples had been collected and they were then sent for an electron-microscopic examination.

The biopsies in Studies I & II were examined and analysed at the University of Tromsø, Norway, while the biopsies in Study III were examined and analysed at the Karolinska Institute, Stockholm, Sweden.

4.2 MACROSCOPIC EVALUATION (STUDY I)

Based on the thickness, fraying and stiffness, the tendons were dichotomously classified as degenerated or not degenerated. The macroscopic evaluation was performed by the surgeon and the surgeon's assistant.

4.3 HISTOLOGICAL EVALUATION

Studies I & II
The samples for light microscopy were fixed in 4% formalin, embedded in paraffin blocks and sectioned at 4µm. The sections were stained with hematoxylin-eosin (HE) to evaluate the fibre structure, cellularity and vascularity. Alcian blue/periodic acid Schiff (AB/PAS) was used to detect sour/neutral mucins for GAGs. Elastin staining was performed, staining collagen fibres red for easier detection. Furthermore, Perl's, van Gieson and van Kossa stains were performed to identify hemosiderin, collagen and calcium deposits respectively. All the stainings were performed automatically (BenchMark Special Stains, Tucson, USA). The fibre structure, cellularity and vascularity and the presence of GAGs were classified according to a semi-quantitative scoring system (Table 1) [71]. It consists of four different elements, such as the fibre structure, cellularity, vascularity and GAGs. Each element can obtain between 0 and 3 points. This procedure and evaluation system have been performed in multiple previous studies [36, 72-75].

Table 1 *Total degeneration score (TDS)*

	Grade 0	Grade 1	Grade 2	Grade 3
Fibre structure	Straight, parallel, packed fibres, with slight waviness	Slight separation of fibres, increased waviness	Separation of fibres, deterioration of fibres	Complete loss of fibre structure and hyalinisation
Cellularity	< 100 cells/high-power field (HPF)	100-199 cells/HPF	200-299 cells/HPF	> 300 cells/HPF
Vascularity	Vessels running parallel to the collagen fibre bundles in the septa	Slight increase in vessels, including transverse vessels in the tendon tissue	Moderate increase in vessels within the tendon tissue	Markedly increased vascularity with clusters of vessels
Glycosaminoglycans	No alcianophilia	Slight alcianophilia between the collagen fibres	Moderate increase in alcianophilia	Markedly increased alcianophilia forming blue lakes

Subsequently, the TDS was calculated. The TDS can result in values between 0 (no degeneration at all) and 12 points (extremely high degeneration). The TDS is similar to a scoring concept previously described by Movin et al. [76] and used in a biopsy analysis of the Achilles tendon. The score has also undergone satisfactory intra-observer reliability testing [76].

The staining for hemosiderin and calcium deposits was dichotomously classified as positive/negative. The amount of scar tissue in the sample was estimated as a percentage of the field of view.

The histological evaluations of two samples from each patient were performed by one independent pathologist with extensive experience. The pathologist was blinded to the group of specimens. The histological evaluations were conducted using a light microscope at a magnification of X20 in Study I and X50 in Study II.

Study III

The samples for light microscopy were fixed in 10% neutral-buffered formalin, embedded in paraffin blocks and sectioned at 4-5µm. The sections were stained with HE to evaluate the fibre structure, cellularity and vascularity. AB/PAS was used for the detection of GAG-rich areas. The histological evaluations of two samples from each patient were performed by a pathologist and an orthopaedic surgeon with a special interest in pathology together, using a light microscope (Leica DMRBE, Wetzlar, Germany) at a magnification of approximately X100.

The examiners were blinded in terms of the group to which the patient belonged.

The fibre structure, cellularity and vascularity and the presence of GAGs were classified according to a semi-quantitative scoring system previously mentioned (Table 1). Subsequently, the TDS was calculated by adding the mean values of the two biopsies for the four elements.

4.4 MORPHOLOGICAL EVALUATION (STUDIES I & II)

The morphology of the ECM was evaluated using a transmission electron microscope (TEM) and it was dichotomously classified as homogeneous or irregular at a magnification of X3,000 in Study I and X2,000 in Study II.

4.5 ULTRASTRUCTURAL EVALUATION

TEM was used to assess the ultrastructure of the tendon.

Studies I & II

The specimens were fixed in 8% formaldehyde in Hepes buffer. The biopsies were cut into small cubes and half the material was immersion fixed in McDowell's fixative for electron-microscopic studies [77]. After primary fixation, the tissue was washed with Sorensen's phosphate buffer, post-fixated in 1% aqueous OsO4, washed and stained "en-bloc" with 2% uranyl acetate, dehydrated in a graded series of ethanol, embedded in an Epon substitute (AGAR: AGAR 100, MNA, DDSA) and DNP-30 with propylene oxide as a transitional solvent, according to standard procedures. Semithin and ultrathin sections were cut using a Leica Ultracut S (Vienna, Austria) on glass or diamante knives (Diatome, Biel, Switzerland). Ultrathin sections were mounted on formvar-coated 100 mesh copper grids and contrasted with 5% uranyl acetate, followed by Reynold's lead citrate [78]. Micrographs were obtained using a Jeol JEM 1010 (Tokyo, Japan) with a Morada camera system (Olympus Soft Imaging Systems, Münster, Germany). For sampling, two blocks from each patient were sectioned and mounted on carbon-coated formvar films on copper grids. Micrographs for measuring the fibril diameters were obtained at random, from one to three groups of cross-sections from each block. The diameter of a minimum of 100 fibrils was measured using the Soft Imaging System (Olympus, Münster, Germany) at a magnification of X50,000. The relative fibril diameter distribution was calculated in per cent. The diameters were grouped in six size classes (0-30, 31-60, 61-90, 91-120, 121-150 and > 150nm). The accuracy of the measurements was 1/100th of an nm, but, in the results, an accuracy of 1/10th of an nm was chosen. This method has been used in a previous publication [36].

The micrographs were evaluated by one independent technician with extensive experience of using the TEM. The technician was blinded to the group of specimens.

Two samples were scanned, but only the one with the best images was evaluated.

Study III

Specimens were collected and immediately fixed in 2% glutaraldehyde and 1% paraformaldehyde in 0.1 M sodium cacodylate buffer containing 0.1 M sucrose and 3 mM CaCl2 (pH 7.4) at room temperature for 30 min, followed by storage at 4°C. The specimens were rinsed in 0.1 M sodium phosphate buffer (pH 7.4) prior to post-fixation in 2% osmium tetroxide in 0.1 M sodium phosphate buffer (pH 7.4) at 4°C for two hours. The specimens were then dehydrated stepwise in ethanol, followed by acetone and LX-112 (Ladd) embedding. Ultrathin sections (approximately 60-80nm) were prepared and contrasted with uranyl acetate followed by lead citrate and examined in a Tecnai G2 Spirit BioTWIN electron microscope (FEI) operated at 80 kV and equipped with a 2k x 2k Veleta CCD camera (Olympus Soft Imaging System). Four randomly acquired images in areas showing transversely sectioned collagen fibrils were used for image analysis and fibril diameter measurement. The fibril diameters were measured manually on images acquired at X49,000 magnification (1.14nm/px) using Fiji software (https://imagej.net/ImageJ) and the Bio-Formats plugin.

The fibrils were grouped in intervals of 10nm and presented as the relative distribution. One hundred fibrils were analysed in each specimen and the mean value was calculated with an accuracy of 1/10th of a nanometer. Two biopsy specimens from each patient were scanned; however, the fibril diameters were only measured in the

biopsy with the best transverse orientation, while the other biopsy was left unmeasured. The micrographs were evaluated by one independent technician with extensive experience of using the TEM and this technician was blinded to the group of specimens.

4.6 BMD EVALUATION

DXA (Study IV)
The patient was positioned on a padded table which has a movable C-arm with a radiographic tube below the patient and a detector above the patient (Fig. 10). Photon beams with two different energy levels are generated by the radiographic tube. The difference in the attenuation of the two photon beams as they pass through body tissue with different compositions distinguishes bone from soft tissue and makes the quantification of bone mineral density possible. BMD was measured using DXA in both hips and the lumbar spine before surgery and after six months, 18 months, three years and five years. The DXA examination and measurements in both hips and the lumbar spine were carried out at the Osteoporosis Unit at Uddevalla Hospital using a standard DXA machine (Lunar Prodigy Advance, GE Healthcare Lunar, Madison, WI, USA).

Figure 10. *DXA is the tool for the diagnosis of osteoporosis and the monitoring of changes in BMD over time © M. Ibrahim*

DXL (Study IV)
One foot at a time was placed on the footstep of the apparatus (Fig. 11). In addition to DXA examination of the heel, a laser scan is performed to measure the heel thickness. This allows better exclusion of adipose tissue present inside or outside the calcaneus than with DXA alone. DXL thus has the potential to present a more accurate measurement of bone mineral mass than standard DXA [79]. BMD was measured using DXL in both heels before surgery and after six months, 18 months, three years and five years. The DXL examination and measurements in both heels were carried out at the Orthopaedic Department at Uddevalla Hospital using Calscan (Dual X-ray and laser technology, Demetech AB, Sweden).

A

B

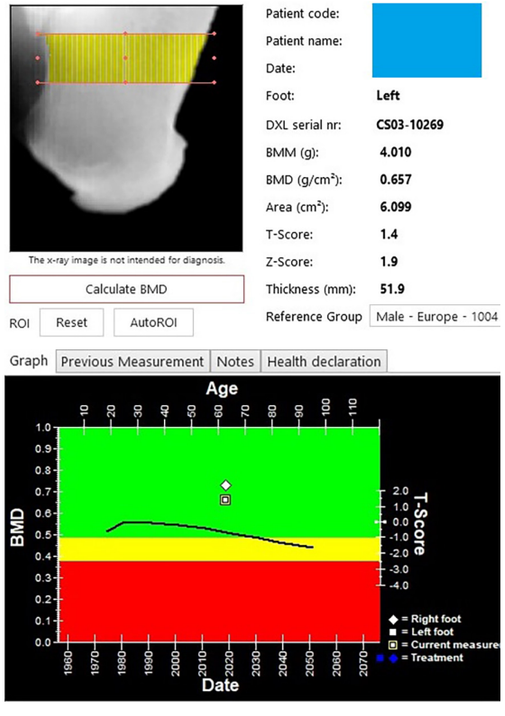

Figure 11, A & B. *BMD measurement with DXL. Fig 11 B shows how the results of BMD at the calcaneus are presented. A T-score value in the green zone indicates normal BMD, while a T-score value in the yellow and red zones indicates osteopenia and osteoporosis respectively © N. Sernert*

7.4 PATIENT-REPORTED OUTCOME MEASUREMENTS

The Tegner activity score was published in 1985 as a new rating system in the evaluation of knee ligament injuries. It is a self-report questionnaire in which work and sport activities are graded numerically on a 0-10 scale. Level 0 corresponds to sick leave or disability pension because of knee problems and level 10 corresponds to competitive sports at national elite level 80. To the best of the author's knowledge, the Tegner activity score was a sufficient outcome measurement of physical activity at the time the study was designed for the study population.

EQ-5D L3 The EuroQol Group 5-Dimension is a standardised measurement of health status developed by the EuroQol Group in order to provide a simple, generic measurement of health for clinical and economic appraisal. It contains two parts; the first is the descriptive system section of the EQ-5D questionnaire, which produces a five-digit health state profile that represents the level of reported problems in each of the five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three levels: no problems, some problems, extreme problems. The second part of the EQ-5D is the visual analogue scale (VAS) for overall health and it can be used as a quantitative measurement of health. The EQ-5D-3L descriptive system can be converted into a single index value. The index values are presented in country-specific value sets [81,82]. In Study IV, the British value set was used to calculate the EQ-5D index.

4.8 REHABILITATION (STUDY IV)

All patients followed a standardised training (rehabilitated according to standard protocol) programme and underwent rehabilitation postoperatively by an experienced group of physiotherapists during the hospital stay. Patients were instructed to avoid more than ninety degrees of hip flexion on the operated side and to avoid adduction and rotation of the operated lower limb during the first postoperative months. The patients were referred to local physiotherapists to continue rehabilitation. Follow-up was carried out by one senior orthopaedic surgeon three months postoperatively.

4.9 STATISTICAL METHODS

Studies I, II & III
Mean (standard deviation, SD) and/or median (range) values are presented for the age of patients. A relative number of specimens were presented, as (%) mean (SD) values are presented for the TEM findings. For the histological findings, median (range) values are presented. An unpaired t-test was used to compare the TEM findings between the OA and the control groups. The Mann-Whitney U-test was used to compare the histological findings between the OA and control groups. Dichotomous comparisons were made using Fisher's exact test. When all four groups in Study III were compared with each other, the ANOVA test was used for the TEM finding, whereas the Kruskal-Wallis test was used for the TDS findings.
A p-value of < 0.05 was regarded as statistically significant.

The power analysis in all three studies was based on the assumption that a difference of 5 nm in fibril diameter would be of interest to detect. If the SD were as large as 40 nm, just over 1,000 fibrils would need to be measured in each sub-group analysis to reach a power of 80%.

Study IV
Mean (range) values are presented for the age of patients. Median (range) values are presented for the Tegner activity score, T-score (the number of standard deviations (SD) above or below what is normally expected in a healthy young adult) and Z-score (the number of SD above or below what is normally expected for someone of a specific age, gender, weight and ethnic or racial origin). Mean values and 95% confidence intervals were used for the BMD results. The paired t-test was used to compare the preoperative and postoperative BMD values and to compare the BMD on the operated and non-operated sides. A BMD reduction during the five-year follow-up is also shown as the percentage decrease from the preoperative values. The mean and range were used for the EQ-5D. Wilcoxon's signed rank test was used to compare the Tegner activity score and EQ-5D index changes over time and to analyse the T-score and Z-score. A p-value of < 0.05 was considered statistically significant.
The power of the study was estimated to be greater than 80% with 25 patients and was based on standard deviations and BMD reductions found in patients after ACL surgery [83,84].

4.10 OUTCOME MEASUREMENTS

Primary outcome measurements were fibril diameter TEM (Studies I, II & III) and BMD in the hip, spine and calcanei (Study IV).

Secondary outcome measurements were TDS (Studies I, II & III), tendon structure morphology (Studies I & II), Tegner activity score and the EQ 5D (Study IV).

4.11 ETHICS

Ethical approval was obtained for all four studies from the Human Ethics Committee at the Medical Faculty at the University of Gothenburg and Regionale komiteer for medisinsk of helsefaglig forskningsetikk, Oslo, Norway. All the patients gave their written informed consent.

Dnr 2014/1773 (Study I)
Dnr 381/15 (Studies II & III)
Dnr 107/04 (Study IV)

05 RESULTS

Study I
Macroscopic degeneration was found more often in the OA group compared with the control group, 15 and 7 respectively (p=0.048) (Table 3, Paper I, Page 270). Histologically, there was no significant difference in the total degeneration score (TDS) between the study groups (Table 4, Paper I, Page 271).
Morphologically, there were more samples with a non-homogeneous extracellular matrix (ECM) in the OA group compared with the control group (p=0.048) (Table 3, Paper I, Page 270).
Ultrastructurally, the OA group revealed a significantly larger fibril diameter in the long head of the biceps tendon (p<0.0001) compared with the control group. However, no such difference between the groups was shown for the subscapularis tendon (Table 5, Paper I, Page 272) [85].

Study II
The histological, morphological and ultrastructural evaluation of the semitendinosus tendon failed to reveal any significant difference between patients in the HTO and ACLR groups, with the exception of the presence of more hemosiderin in the ACLR group (Tables 3,4,5,6 Paper II, Pages 1070-1071 respectively). There was no significant difference for the TDS between the study groups (Table 7, Paper II, Page 1072) [86].

Study III
Histologically, a significantly higher TDS was found when the direct lateral revision group was compared with the primary hip OA group (p=0.004) (Table 4, Paper III, Page 6). Moreover, one TDS value in the primary THA group was missing.
Ultrastructurally, both revision groups had significantly more collagen fibrils with smaller diameters compared with the fracture and primary THA groups (p<0.0001). Furthermore, more collagen fibrils with smaller diameters were found in the direct lateral revision group compared with the posterior revision group (p<0.0001) (Table 3, Paper III, Page 4).
No significant difference in fibril diameter between the fracture and primary THA group was revealed (Table 3, Paper III, Page 4) [87].

Study IV
The female patients lost 10-12% BMD and the male patients 8-9.3% BMD in their calcanei (p=0.002 and p=0.003 respectively) (Table I, Paper IV, Page 34). Similarly, the BMD in the calcanei of the unilaterally operated patients reveals a significant reduction bilaterally at both 36 and 60 months post-operatively (Table 4, Paper IV, Page 36). No significant loss was found in the contralateral hip (Table 2, Paper IV, Page 35), whereas a slight yet significant increase in BMD was found in the lumbar spine in male patients (Table 3, Paper IV, Page 35). The Tegner activity score and EQ-5D increased significantly from six months (p=0.002 and p=0.001 respectively) and were maintained during the follow-up period. Male patients had a higher EQ-5D index at six and 18 months than female patients (p=0.009 and p=0.04 respectively) [88].

06 DISCUSSION

1. General discussion

The main finding in Studies I, II and III was that there was no association between the presence of degenerative changes in the periarticular tendons in the shoulder, knee or hip and the presence of OA in these joints. Other important findings in Studies III and IV were the presence of degenerative changes in the GMED tendon after THA, as well as a deterioration in BMD measured at the heels. This may elicit a possible negative effect of surgery, namely the THA, on the adjacent and remote tissues.
Although primary OA and degenerative tendinopathy are two distinct diseases, they have staggering similarities. Both have a multifactorial pathogenesis, share several common risk factors and are more prevalent in middle-aged individuals, females and the elderly [13, 15, 32, 34]. The causes of pain in both OA [89-93] and tendinopathy [94-97] are yet not completely understood. Moreover, the degeneration of the ECM is a common histopathological feature [98]. Due to these similarities and the paucity of high-quality studies addressing the potential role of changes in periarticular tendons in association with OA, there is an unmet need to obtain a deeper understanding of this pathological condition.

THA and total knee arthroplasty (TKA) are among the highly successful surgical procedures performed in orthopaedics. Approximately 85% and 86% of the patients who have undergone THA and TKA respectively are satisfied or very satisfied, while the other 14-15% are not [15, 32, 99]. Persistent pain and functional limitation are the two most dominant causes of postoperative dissatisfaction in patients who have undergone THA or TKA [100, 101]. Persistent pain accounts for 41% of all the reasons for dissatisfaction after THA and TKA. Functional limitations account for 26 and 35% of the reasons for dissatisfaction after TKA and THA respectively. Female patients are more prone to these adverse effects [101, 102]. According to the Swedish Hip Arthroplasty Register in 2013, women over 55 years of age were more dissatisfied than men, along with a tendency towards poorer results as patients got older. Moreover, preoperatively, women had a higher VAS pain value and a lower level on the EQ-5D compared with men [103]. Based on the reasons mentioned above, it is possible to speculate that periarticular tendon degeneration might play a causal role in postoperative dissatisfaction, given that gluteal tendinopathy is more prevalent in females and the elderly.
Most tendon pathology and pain occur adjacent to the tendon-bone interface, as in patellar tendinopathy, but it may also arise at the mid-portion of a tendon, as in Achilles tendinopathy. However, the cell matrix changes in both cases are identical [104, 105].

The choice of the tendons from which the biopsies were taken in Studies I, II and III was based on the ease of accessing these tendons during the operation and avoiding inflicting unnecessary harm to the patients. Moreover, there are well-identified painful pathologies related to the tendinopathy of the gluteal medius and the long head of the biceps [106]. Assuming that no consideration was taken to minimise damage, more invasive procedures would be applied to obtain biopsies from other tendons. Possible

tendinopathic changes in the supraspinatus tendon would be interesting to investigate in association with OA of the shoulder joint, because of the clinical relevance and the high prevalence of involvement of this tendon in shoulder joint pathology [107]. Moreover, the short external rotators of the hip, patellar and quadriceps tendons would also be interesting to examine in the presence of OA in the hip and knee joint respectively, because of their anatomical proximity to these joints.

The full-thickness tendon biopsies were harvested close to the studied joints, because there is evidence indicating that degenerative ruptures are more common at this localisation for the GMED tendon (Fig. 12) [108, 109, 110]. Likewise, a common site for degenerative tendon changes in the shoulder is the origin of the long head of the biceps tendon at the glenoid [111].

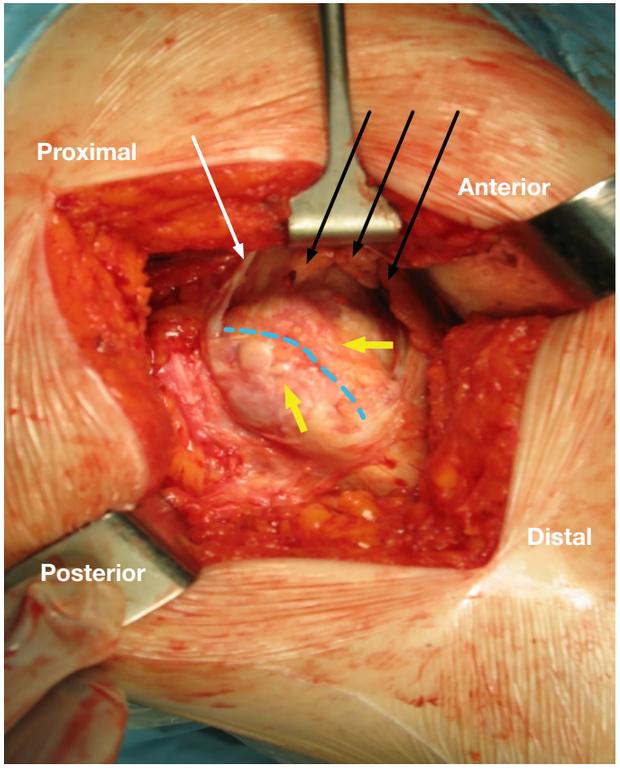

Figure 12. *Illustration of the total rupture of the anterior superior two-thirds of the GMED tendon. The black arrows are pointing at the ruptured end, as well as the atrophied and retracted GMED tendon, the white arrow is pointing at the atrophied, albeit not ruptured edge of the superior-posterior part of the GMED tendon, the yellow arrows are pointing at the bare irregular surface of the trochanter major and the dark-blue dotted line shows where the ruptured GMED tendon was attached. © M Ibrahim*

The handling and storage of the biopsies after harvest was done in the same way in both the studies conducted in Sweden and Norway. However, there are some differences in biopsy preparation and staining. It is the opinion of the research group that these differences did not have a substantial impact on the external validity of the results, as the biopsies from both the OA group and the control group in each separate study were prepared, examined and assessed by the same laboratory.

2. Macroscopic evaluation (Study I)

Significantly more tendons showed macroscopic changes, indicating tendinopathy in the OA group compared with the control group.

A direct perioperative macroscopic evaluation of the long head of the biceps and subscabularis tendons was made in Study I by one senior orthopaedic surgeon and his assistant. Evaluating the tendons macroscopically without blinding or reliability testing should be regarded as a confounding factor. This might have been prevented if the person who made the evaluation was not directly involved in the study.

An examination of the tendons macroscopically was not made in Studies II & III because of the difficulty involved in obtaining a reliable evaluation by the unblinded orthopaedic surgeon who harvested the tendon biopsy.

3. Histological evaluation (Studies I, II & III)

The main histological findings in these studies were that there were no significant differences in the periarticular tendon in patients with shoulder, knee or hip OA compared with the control patients without OA. These findings, as mentioned above, also contradict the (expected) hypothesised association between the presence of degenerative changes in periarticular tendon and OA.

The results of Study III revealed a significantly higher TDS when the direct lateral revision group was compared with the primary hip OA group. These results are in line with the results of other studies [112-114]. It was also expected that tendons in the direct lateral revision group would show more degenerative findings than those in the posterior revision group. This is basically because the GMED tendon is partially divided during THA through the direct lateral approach, resulting in a local surgical trauma at the insertion of the GMED tendon and scar formation in the tendon tissue. This damage was not expected to occur, at least not to the same extent as the abductor attachment at the trochanter major, which is supposed to be spared when THA is performed through the posterior approach.

In the two revision groups, the time interval between the primary THA and the revision operation was not significantly different and could not explain the disparity in TDS between these groups.

Based on a macroscopic evaluation, Howell et al. have reported a 20% prevalence of degenerative tears of hip abductors in patients undergoing hip arthroplasty due to OA of the hip [115]. Bunker et al. have reported that 11 of 50 (22%) patients with a fracture to the neck of the femur had a tear at the insertion of hip abductors [116]. The results of Study III have not revealed findings that support the findings of the two previously mentioned studies, neither histologically nor ultrastructurally.

Both HE staining for fibre structure, cellularity and vascularity and AB/PAS staining for GAGs were used in Studies I, II and III. At the same time, four additional stainings, elastin, Perl's, Van Gieson and Van Kossa, of the tendon samples were only conducted in Studies I and II to detect collagen fibres, hemosiderin, scar tissue and calcium deposits respectively. This difference was due to some discrepancy at the two laboratories in

preparing and evaluating the tendon samples. However, this did not have any significant impact on the results of the studies other than the finding of the presence of more hemosiderin in the ACLR group compared with the OA group in Study II.

4. Morphological evaluation (Studies I & II)

Significantly more morphological degenerative changes were found in the OA group compared with the control group in Study I, supporting the hypothesis that OA may be associated with degenerative tendon changes, but this was not shown in Study II.

5. Ultrastructural evaluation (Studies I, II & III)

The main ultrastructural findings in these studies were that there were no significant differences in the periarticular tendon in patients with shoulder, knee or hip OA compared with the control patients without OA. The only exception was that larger tendon fibrils were present in the long head of the biceps tendon in patients with OA of the shoulder compared with the control group.
These findings contradict the hypothesised association between the presence of degenerative changes in the periarticular tendon and OA.
These results differ partially from a previous similar study in this field, in which ultrastructural changes have been shown in periarticular tendon in the hip in association with OA [36]. Nonetheless, there is an interesting similarity between the ultrastructural finding in the internal obturator tendon of the hip by Meknas et al. and that in the long head of the biceps tendon in the shoulder in Study I, as both these studies revealed fewer small and medium-sized collagen fibrils in the OA group compared with the controls. This is contrary to what is expected, as tendon degeneration leads to the formation of type III collagen fibrils which have smaller diameters than the original mainly type I collagen fibrils of tendon tissues [43].
One essential difference in the Study II population is that preoperatively the OA group had relatively less severe OA based on the X-ray (radiological) findings compared with the OA groups in Studies I and III. This might have influenced the result of Study II, because fewer degenerative changes in the periarticular tendon are theoretically to be expected with less severe OA and vice versa.
Another finding was that more ultrastructural changes were shown in the periarticular tendon in patients who had previously undergone arthroplasty surgery due to OA compared with patients with primary OA of the hip or femoral neck fracture, as reported in Study III. This indicates that the prior surgical division of the tendon caused more degeneration than OA itself.

Tendon damage and muscle fatty atrophy of the GMED and hip external rotator have been shown after THA through the direct lateral and posterior approaches respectively [112]. GMED muscle fatty atrophy and tendon defects were more prevalent findings in patients with residual trochanteric pain and limping after THA compared with an asymptomatic control group [117]. Numerous surgical insults accompanying multiple hip revision operations result in more GMED muscle atrophy [113]. Patients with asymptomatic GMED pathology undergoing THA because of OA of the hip have recently been shown to have inferior two-year postoperative patient-reported outcomes compared with a matched group [118].

Interestingly, Wang et al. have shown more three-dimensional MRI morphological changes in the GMED in terms of muscle atrophy and fatty infiltration after THA via a minimally invasive posterior approach compared with a modified direct lateral approach [119]. These findings are in line with the results of Study III, as both indicate that injury to the abductors after THA via the posterior approach cannot be negligible.

6. BMD evaluation (Study IV)

Despite a postoperative increase in quality of life and activity level in patients who underwent THA, a significant bone mineral loss was found in the calcanei, on both the ipsilateral and the contralateral side, after THA. No reduction in BMD was found in the contralateral hip. However, this result should be interpreted with caution due to the relatively large number of dropouts and bilaterally operated patients.
To minimise any possible influence of bilateral OA of the hip, the BMD in the calcanei of the unilaterally operated patients was analysed separately. Similar changes have been shown in the BMD of the calcanei, with a significant reduction bilaterally at both 36 and 60 months postoperatively in this subgroup.
The bone loss in the calcanei was significantly higher than the expected natural age-dependent bone loss during the study period in both females and males [68]. A similar BMD decrease in the calcanei has been shown after ACL reconstruction and after shoulder arthroscopy [84, 120, 121]. A systemic response to surgery could be the cause, as it occurs distant to the operated body part and is bilateral. The local postoperative tissue inflammation, hyperaemia and an increase in metabolism may lead to a bone remodelling process with mobilisation of the bone mineral. The calcaneus appears to provide a sensitive location to measure changes in BMD, probably because it consists of 90% cancellous bone with high metabolic activity. Contrary to the findings in the present study, Adolphson et al. used quantitative computed tomography (QCT) to measure BMD and reported a decrease in vertebral BMD after hip arthroplasty [122]. In addition, a slight increase in the BMD of the entire limb after THA with a cemented stem was shown by Linder et al. [123].
Unlike DXA, QCT has the ability to assess volumetric BMD [124]. Some studies argue in favour of the superiority of QCT over DXA in predicting vertebral strength and having higher sensitivity, thereby distinguishing patients with osteoporosis from those without it [125-127]. Notwithstanding the above, DXA is still the standard tool in clinical practice in the diagnosis of osteoporosis. DXA exposes the examined person to a smaller dose of ionising radiation, has a simpler scanning procedure, is more available and has lower costs than QCT [124].
DXA might not be the optimal method for measuring BMD in the spine of elderly people, as vertebral compression, aortic calcification and spondylarthrosis can reveal a false increase in BMD in the lumbar spine. The use of quantitative computed tomography might result in more accurate measurements of BMD in the spine.

Osteophytes and subchondral bone sclerosis are associated with coxarthrosis and they increase the measured BMD. This may explain why the Z-score for the hip in the present study is higher than that for the normal population and that just two patients had an osteoporotic preoperative T-score value in the neck of the femur on the index side.

In the present study, an increase and improvement in the Tegner activity score and quality of life were shown after six months and were maintained by both genders during the five-year follow-up period. The improvement in EQ-5D in Study IV was in agreement with what was reported in the Swedish hip register in 2013 [103].

07 STRENGTHS AND LIMITATIONS

A common and major limitation in Studies I, II and III was the size of study samples and the fact that the studies might be under-powered, even though Study III involved 100 patients. In the power calculation for Studies II and III, a delta of 5nm in the mean fibril diameter was considered "meaningful", even though the authors have no evidence that 5nm has a clinical implication. Moreover, the power calculation was based on the number of collagen fibrils and not on the number of patients, as it should ideally be. This was because it is impossible practically to include about two thousand patients in each study.
The small size of the study groups in Studies I, II and III limits the reliability of the conclusions. However, the uniformity of the ultrastructural results in particular with the lack of a significant difference between OA and the control groups suggests that the findings have some validity.

Study I
The strength of this study is that the biopsies were obtained from living individuals.
The limitations include the fact that the patients in the control group were not healthy individuals. Moreover, there was a lack of information regarding signs or symptoms of tendinosis in the shoulders of patients in the control group before they suffered a proximal humeral fracture. A healthy age-matched control group would ideally have been better, but this was not possible for ethical reasons. The macroscopic assessment of the tendon biopsies was performed by the surgeon (co-author) and his assistant. No blinding or reliability tests were carried out (test-re-test, for example). A significantly higher female/male ratio in the fracture group compared with the OA group (11/13 and 8/13 respectively) is another weakness. The shift in the female/male ratio was the result of a normally higher incidence of proximal humeral fractures among elderly females than males.

Study II
The strengths of the study are that the biopsies were obtained from living individuals and that all the biopsies were only obtained by two senior orthopaedic surgeons. In addition, efforts were made to reduce the inherent age difference between the study groups. The age difference was inevitable and it is important to remember that age has not been an issue when comparing fibril diameters in both the hip and the shoulder in previous publications [36, 75].
The limitations of the study are the lack of preoperative symptom and activity level assessments of the knee joint. In addition, a non-optimal group of patients undergoing ACLR was used as controls. Ethically, it was not possible to take semitendinosus tendon biopsies from healthy age-matched individuals. The hamstring tendon has the ability to regenerate itself, as it does after being harvested during ACLR [128, 129]. For this reason, the hamstring tendon might not be the most optimal choice when studying tendon degeneration. It is probable that the quadriceps or patellar tendon might have been more appropriate for obtaining biopsies.
Assessments of the pre-operative X-ray of the knee were made by one orthopaedic surgeon without intra-observer reliability testing.

Study III
The strengths of the study include the fact that the biopsies were obtained from living individuals and that efforts were made to have as large a study cohort as practically possible. The whole study took five years to perform and a longer time period would not have been possible in order to execute the study. The limitations of the study include the fact that it was ethically not possible to obtain GMED tendon biopsies from healthy age-matched individuals. For this reason, patients with femoral neck fractures undergoing THA were used as controls, although this was not ideal. Three patients were included in the revision groups due to causes other than the main reason for inclusion, which was loosening of the hip prosthesis. Different inclusion criteria could be a confounding variable as it might be expected that repeated dislocations or wear debris may result in greater histological or ultrastructural changes as compared to primary THA. Not including a morphological evaluation of the tendon samples in this study is another weakness, as that evaluation would facilitate the assessment of the overall alignment of the ECM.

Study IV
The strengths of the study are that the BMD was measured and evaluated at three different locations in the body. Moreover, the prospective design of the study with a five-year follow-up period was a strength. The limitations of the study include the fact that 30% of patients underwent bilateral THA during the five-year follow-up period. This was a considerable natural dropout, not properly calculated during the planning of the study. In addition, the Tegner activity score was used to evaluate physical activity in elderly individuals. This was not ideal, mainly because of the floor effect. The University of California, Los Angeles activity scale (UCLA) would have been a better scale to use, because it has greater reliability, a higher completion rate and no floor effect compared with the Tegner activity score [130, 131]. A further weakness was the lack of a healthy age-matched control group in this study. Ethically, it is not acceptable to continue to treat patients suffering from OA of the hip conservatively for five additional years, when analgesics and physiotherapy have failed to relieve their symptoms. For this reason, the control group used in this study was a database for DXL measurements in the calcanei in healthy women and men from southern Sweden. Finally, DXA may not be the most accurate examination when measuring BMD in the spine in elderly people.

08 CONCLUSIONS

Study I
More macroscopic and morphological degenerative changes in the long head of biceps and subscapularis tendon were found in the OA group compared with the control group. This indicates that OA in the shoulder might be associated with tendinopathy.

Study II
The semitendinosus tendon in patients with mild and moderate medial compartment knee OA displayed no more degenerative changes than the semitendinosus tendon in patients without OA, as seen in both the light and the electron microscope.

Study III
More ultrastructural degenerative findings are shown in the GMED tendon in patients who undergo hip revision arthroplasty than in patients with primary OA of the hip and control patients who sustained a femoral neck fracture. In addition, more histological degenerative findings in the GMED tendon were shown in patients who had previously undergone primary THA through a direct lateral approach than in patients who suffer primary OA of the hip.

Study IV
A significant loss of BMD was found in the calcanei three and five years after THA, despite improvements in physical activity and quality of life postoperatively.

09 FUTURE PERSPECTIVE AND CLINICAL APPLICATION

Studies I, II & III
OA of the shoulder, knee or hip is less likely to be associated with periarticular tendinopathy, as no clear association was shown between the OA and the presence of histological or ultrastructural changes in the periarticular tendons. In spite of this, the results of the studies should be interpreted with caution, not only because of the small study populations but also because of other confounding factors, such as the use of non-optimal control groups and the lack of a preoperative assessment of the control groups regarding the possible presence of tendinopathy in the tendons.
The use of imaging modalities such as MRI or ultrasonography of the intended tendons might have helped to rule out these patients from Studies II and III.

As was hypothesised, the GMED tendon in the direct lateral revision group showed significantly more degenerative histological and ultrastructural changes. For this reason, it is possible to argue in favour of the posterior approach, not causing injury to the important hip abductor tendons.
Residual trochanteric pain and/or limping are well-known complications after THA. The results of the present studies objectively explain, at the ultrastructural and partially at histological levels, the changes that may cause these complications. The author feels this provides valuable knowledge and clinical implications both for patients suffering from these complications and for practising orthopaedic surgeons in their discussions with patients regarding possible causes of postoperative trochanteric pain and/or limping. One important question, based on the results in Study III, is whether rehabilitation programmes focusing on gluteal tendinopathy after THA may result in clinical and tendon structural improvements, as they did in patients with patellar tendinopathy [132, 133]. One finding supporting the possible beneficial effect of rehabilitation is that patients with gluteal tendinopathy, but without OA of the hip or having previously undergone THA, experienced improvements after receiving education and exercise. The physiotherapist-guided exercise and education relating to the appropriate amount of and gradual increase in tendon loading provided a higher rate of improvement and the positive effect lasted longer compared with a single-dose corticosteroid injection or a wait-and-see approach [134].

It is also possible to speculate that some degree of general deterioration in the periarticular soft tissue, including tendons and muscle, may occur as result of the THA operation itself, regardless of the approach.

The present studies have raised several unanswered and interesting questions that could be addressed in further studies. These questions include:

- Is there an association between supraspinatus tendinopathy and OA of the shoulder?
- Could a larger study population make a difference in the result?
- Is a radiologically more severe degree of knee OA associated with periarticular tendinopathy?
- Is there an association between other periarticular tendons, such as patellar or quadriceps tendinopathy, and OA of the knee?

Findings from patellar tendon biopsies after ACL reconstruction support this speculation [135].
Examining the morphology of the ECM of the GMED tendon was not included in Study III. The ECM comprises about 85% of tendons and it gives the tendon its mechanical and biochemical properties, so studying the morphological changes will add valuable information and enable a better evaluation of tendinopathies. Finally, it would be interesting to see whether there are any histological or ultrastructural findings that can explain pain and dysfunction after THA and TKA.

Study IV
Investigating how to prevent or reduce the postoperative deterioration in BMD found in the present study is an interesting perspective. The increased activity level in the present study was not enough to prevent the substantial bone loss found in both calcanei. A meta-analysis of randomised controlled trials supports the hypothesis that exercising a mixed loading impact is associated with an increase in BMD for the lumbar spine and femoral neck in older adults 136. This arises the question of whether these exercises after surgery have a more favourable effect on BMD.

Some other questions that have been arisen are as follows.

- Does the use of bisphosphonate postoperatively play a role in preventing BMD deterioration?
- Does this deterioration in BMD have a noticeable effect on the risk and incidence of osteoporosis fractures in clinical practice?
- Can surgical trauma be regarded as an independent risk of osteoporosis, like other well-known risk factors?

These are important question that need to be answered.

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12

PAPERS I-IV

I

More tendon degeneration in patients with shoulder osteoarthritis

Ibrahim M, Kartus JT, Steigen SE, Olsen R, Meknas K

Knee Surgery Sports Traumatology Arthroscopy. 2019;27(1):267-275

II

No significant histological or ultrastructural tendinosis changes in the hamstring tendon in patients with mild to moderate osteoarthritis of the knee?

Ibrahim M, Meknas K, Steigen SE, Olsen R, Sernert N, Ejerhed L, Kartus JT.

Knee Surgery Sports Traumatology Arthroscopy. 2020;29(4):1067-1074

III

More histological and ultrastructural changes in the gluteus medius tendon after hip arthroplasty

Ibrahim M, Hedlundh U, Sernert N, Meknas K, Haag L, Movin T, Papadogiannakis N, Kartus JT.

Journal of Orthopaedic Surgery and Research. 2021;16(1):339

IV

Despite increased physical activity levels, bone mineral density decreases after total hip arthroplasty

Ibrahim M, Sernert N, Kartus JT, Ejerhed L

Translational Sports Medicine. 2018;2(1):32-38