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"Måste våga bara vara
med minnet av det barn,
som lät livet välja,
och våga säga ja."

– Eva Dahlgren

To my father

ABSTRACT

Helka Koivu

Total ankle replacement: Clinical, radiological, and biochemical assessment with special reference to osteolysis

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End-stage ankle arthritis may be managed surgically with either ankle fusion or total ankle replacement (TAR). The results of total ankle replacement have improved over the recent decades, but challenges remain. Peri-implant osteolysis has been major problem, as it compromises the stability of the implant components and can lead to aseptic loosening and implant failure.

For this retrospective study, 164 ankles (34 Scandinavian Total Ankle Replacement (STAR) and 130 Ankle Evolutive System (AES)) operated on in single institution during 1997–2008 were followed clinically and radiologically. Histological samples were collected from ankles revised due to periprosthetic osteolysis. Analysis from the data covering the years 1997–2006 of the Finnish Arthroplasty Registry was conducted.

The peri-implant osteolysis was common in the AES total ankle implants: 70% of the ankles exhibited osteolysis at the latest follow-up. Dual-coating of the implant was associated with a 3.1-fold risk of osteolysis and of significantly earlier development of osteolysis compared to single-coating. Histology revealed a foreign-body reaction characterized by extensive soft and bone tissue necrosis. RANK/RANKL-mediated osteoclast and multinuclear foreign body giant cells contributed to peri-implant osteolysis, and there was increased expression of danger signals in the peri-implant tissues, suggesting an auto-inflammation mechanism behind osteolysis.

The annual incidence of TAR according to the Finnish Arthroplasty Registry was 1.5 per 10^5 inhabitants and overall implant survival was 83% at 5 years when any revision was the end point. The most common reasons for revision were aseptic loosening (39%) and instability (39%). In the registry study, there was no difference in the survival rates between the STAR and AES designs, nor was there any association between age, gender, diagnosis, or hospital volume and TAR survival.

The survival of the STAR implant was satisfactory, 93.8% (95% CI 77.5% to 98.4%) at 5 years, and 87.2% (95% CI 69.4% to 95.0%) at 10 and 15 years. There was no statistically significant association between implant survival and patient age, gender, BMI, or diagnosis. The overall rate of revisions was 44%, which includes all postoperative revisions for osteolysis, component and insert exchanges, and conversions to arthrodesis.

The survival of the AES implant was strongly affected by osteolysis and malalignment, and inferior compared to previously published results. The 5-year survival was 87.3% (95% CI 80.0% to 92.0%), and the 10-year survival 74.9% (95% CI 65.4% to 82.2%). Postoperative alignment of ≥10° of varus predicted a poorer outcome and was statistically significant for implant survival (p=0.0005). The revision rate for all revisions was 57% including all postoperative revisions for osteolysis, component exchanges, and conversions to arthrodesis. Osteolysis was the main reason for revisions and failure.

The survival of the STAR total ankle replacement was satisfactory in the long-term, but the results of the AES total ankle implants were strongly influenced by aggressive and early-emerging osteolysis. Future studies should focus on examining the mechanism behind the osteolytic process in TAR to avoid similar problems for implant development in the future.

Keywords: Total ankle replacement; Implant survival; Ankle arthritis; STAR; AES; Osteolysis; RANKL; autoinflammation

TIIVISTELMÄ

Helka Koivu

Nilkan tekonivel: Kliininen, radiologinen ja biokemiallinen seuranta

Turun yliopisto, Lääketieteellinen tiedekunta, Ortopedia ja traumatologia, Turun yliopiston kliininen tohtoriohjelma, Turku, Suomi

Ylemmän nilkkanivelen loppuvaiheen nivelrikkoa voidaan hoitaa nilkan luudutus- tai tekonivelleikkauksella. Viime parinkymmenen vuoden aikana nilkan tekonivelleikkaus tuhoutuneen ylemmän nilkkanivelen hoidossa on yleistynyt. Hankalin nilkan tekonivelen komplikaatio on viime vuosien aikana ollut osteolyysi eli luun liukeneminen tekonivelen ympäriltä, joka saattaa johtaa tekonivelen irtoamiseen.

Tässä takautuvassa tutkimuksessa analysoitiin yhdessä sairaalassa laitetun 164 nilkan tekonivelen (34 Scandinavian Total Ankle Replacement (STAR) ja 130 Ankle Evolutive System (AES)) kliiniset ja radiologiset seurantatulokset. Kudosnäytteet saatiin nilkoista, jotka oli jouduttu uusintaleikkaamaan osteolyysin vuoksi. Lisäksi analysoitiin Suomen Endoproteesirekisterin dataa ajalta 1997–2006 koskien nilkan tekoniveliä.

Osteolyysin määrä AES-nilkan tekonivelissä oli korkea, 70 % nilkoista viimeksi tehdyn analyysin mukaan. AES-tekonivelen kaksoispinnoite aiheutti yli kolminkertaisen riskin osteolyysin kehittymiselle sekä merkitsevästi aikaisemmin ilmaantuvaa osteolyysiä yksinkertaiseen pinnoitteeseen verrattuna. Mikroskooppitutkimuksessa todettiin vierasesinereaktio ja runsaasti kudoskuoliota.

Suomen Endoproteesirekisteriin perustuvassa tutkimuksessa nilkan tekonivelen vuosittainen ilmaantuvuus oli 1,5 tapausta 100.000 asukasta kohti. Nilkkaproteesin kokonaispysyvyys oli 83 % 5 vuoden aikana, kun päätetapahtumana oli mikä tahansa uusintaleikkaus. Uusintaleikkauksen yleisimmät syyt olivat aseptinen irtoaminen (39 %) ja epävakaus (39 %). Rekisteritutkimuksen mukaan implanttimallilla, potilaan iällä, sukupuolella, diagnoosilla tai sairaalan leikkausvolyymilla ei ollut yhteyttä implantin pysyvyyteen.

STAR-nilkan tekonivelen pysyvyyden todettiin olevan erittäin hyvä, 93.8 % viiden vuoden ja 87,2 % kymmenen ja viidentoista vuoden aikana. Potilan iällä, sukupuolella, painoindeksillä tai diagnoosilla ei todettu yhteyttä tekonivelen pysyvyyteen. Uusintaleikkausten määrä oli 44 % sisältäen kaikki uusintaleikkaukset osteolyysin vuoksi, komponenttien vaihdot ja tekonivelen vaihdot luudutukseen.

AES-nilkan tekonivelen pysyvyys oli huonoa, ja siihen vaikuttivat sekä runsas osteolyysin määrä että nilkan virheasento. Viiden vuoden pysyvyys oli 87.3 % ja kymmenen vuoden 74.9 %. Leikkauksen jälkeisen nilkan virhelinjauksen todettiin ennustavan tilastollisesti merkitsevästi huonompaa tulosta. Uusintaleikkausten määrä oli 57 % sisältäen kaikki uusintaleikkaukset osteolyysin vuoksi, komponenttien vaihdot ja tekonivelen vaihdot luudutukseen. Osteolyysi aiheutti suurimman osan uusintaleikkauksista ja epäonnistumisista.

STAR-tekonivelen pysyvyys oli hyvä pitkällä aikavälillä, mutta AES-tekonivelen tuloksia huononsi merkitsevästi erittäin aikaisessa vaiheessa ilmaantunut aggressiivinen osteolyysi. Tulevaisuudessa tutkimusten tulisi keskittyä selvittämään tarkemmin osteolyysin mekanismeja, jotta vastaavat ongelmat voitaisiin jatkossa välttää tekonivelien kehitystyössä.

Avainsanat: Nilkkatekonivel; pysyvyys; nilkka-artroosi; STAR; AES; osteolyysi; RANKL; autoinflammaatio

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ABBREVIATIONS

AES	Ankle Evolutive System
AOS	Ankle Osteoarthritis Score
AOFAS	American Orthopedic Foot and Ankle Society
ASA	American Society of Anesthesiologist
AP	Anteroposterior
BEI-SEM	Back-scattered electron imaging of scanning electron microscopy
BMI	Body mass index
BMP-7	Bone morphogenetic protein-7
CBCT	Cone beam computed tomography
CCI	Ceramic Coated Implant
CD105	Endoglin
CI	Confidence interval
CoCr	Cobalt-chromium
COFAS	Canadian Organization of Faculty Association Staff
CT	Computed tomography
DAMP	Damage-associated molecular patterns
DMARD	Disease-modifying antirheumatic drug
EDXA	Energy dispersive radiographic analysis
EDL	Extensor digitorum longus
EHL	Extensor hallucis longus
FAAM	Foot and Ankle Ability Measure
FDL	Flexor digitorum longus
FGF	Fibroblast growth factor
FHL	Flexor hallucis longus
HA	Hydroxyapatite
HIF-1α	Hypoxia-inducible factor-1 alpha
HMGB1	High-mobility group protein 1/High mobility group box 1 protein
ICLH	Imperial College of London Hospital
IL-1	Interleukin-1
IL-6	Interleukin-6
MCP-1	Monocyte chemoattractant protein-1
MMP	Matrix metalloproteinase
MOXFQ	Manchester-Oxford Foot Questionnaire
MRI	Magnetic resonance imaging
mSv	millisievert
NF-κB	Nuclear transcription factor-kappa B

OA	Osteoarthritis
OPG	Osteoprotegerin
PGE2	Prostaglandin E2
PMMA	Polymethyl methacrylate
PRR	Pattern recognizing receptors
PROM	Patient reported outcome measure
RA	Rheumatoid arthritis
RAGE	Receptor for advanced glycation end products
RANKL	Receptor activator of nuclear kappa B ligand
RANK	Receptor activator of nuclear kappa B
ROM	Range of motion
RSA	Radiostereometric
SF-36	Medical Outcomes Shortform-36
SEFAS	Self-reported Foot and Ankle Score
SPECT-CT	Single-photon emission computed tomography
STAR	Scandinavian Total Ankle Replacement
TAR	Total ankle replacement
^{99m}Tc DPD	^{99m}Technetium dicarboxypropane disphosphonate
Ti	Titanium
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4
TMTA	Trabecular Metal Total Ankle
TNF-α	Tumor necrosis factor alpha
TPR	Thompson-Parkridge-Richards
UHMWPE	Ultra high molecular weight polyethylene
VAS	Visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals (I–VI):

I Koivu H, Kohonen I, Sipola E, Alanen K, Vahlberg T, Tiusanen H. Severe periprosthetic osteolytic lesions after the Ankle Evolutive System total ankle replacement. *J Bone Joint Surg Br* 2009;91-B:907-914.

II Skyttä E, Koivu H, Eskelinen A, Ikävalko M, Paavolainen P, Remes V. Total ankle replacement: a population-based study of 515 cases from the Finnish Arthroplasty Register. *Acta Orthop* 2010;81(1):114-118.

III Koivu H, Mackiewicz Z, Takakubo Y, Trokovic N, Pajarinen J, Konttinen YT. RANKL in the osteolysis of AES total ankle replacement implants. *Bone* 2012;51(3):546-552.

IV Koivu H, Takakubo Y, Mackiewicz Z, Al-Samadi A, Soininen A, Peled N, Kukis M, Trokovic N, Konttinen YT. Autoinflammation Around AES Total Ankle Replacement Implants. *Foot Ankle Int* 2015;36(12):1455-1462.

V Koivu H, Kohonen I, Mattila K, Löyttyniemi E, Tiusanen H. Long-term results of STAR total ankle replacement. *Foot Ankle Int* 2017, DOI:10.1177/1071100717698695

VI Koivu H, Kohonen I, Mattila K, Löyttyniemi E, Tiusanen H. Medium to long-term results of 130 Ankle Evolutive System total ankle replacements–Inferior survival due to peri-implant osteolysis. *Foot Ankle Surg* 2017, DOI:10.1016/j.fas.2017.03.016.

1. INTRODUCTION

End-stage ankle arthritis may be managed surgically either by ankle fusion or total ankle arthroplasty. Both procedures have their advantages and disadvantages, but neither of them has been proven superior. Ankle fusion leads to biomechanical changes and the risk of arthritic changes of the surrounding joints and the complication rate is quite high. Total ankle replacement enables nearly normal gait and the long-term results are improving (Hintermann 2005; Doets 2009; Hsu & Haddad 2014). However, total ankle replacement is a demanding procedure and requires adequate experience of the operating surgeon, and the risk for revision or additional surgery is high. Despite all potential problems, patient satisfaction is high for both ankle fusion and total ankle arthroplasty.

First generation total ankle arthroplasty implants were introduced to the market four decades ago, but were abandoned shortly after because of a high failure rate. However, implants were developed further and modern third generation implants have proved to yield satisfactory results. Although long-term implant survival of total ankle replacement is still inferior compared to hip and knee replacement, it is approaching the same level. The use of third generation total ankle implants was started in Finland at 1997. During the study period 1997–2008, the number of total ankle replacements has varied from 4 to 89 per year and was on average approximately 62 replacements per year (Finnish National Institute for Health and Welfare). In the Paimio Hospital, the number of replacements during that period was approximately 13 per year (range 1–32). In comparison, the current total annual number knee replacements is approximately 10 000 and of total hip replacements 9000, compared to 50 ankle replacements per year in Finland (Finnish National Institute for Health and Welfare/ Finnish Arthroplasty Register).

The most disturbing complication of total ankle replacements has been peri-implant osteolysis, which is a common problem for all total joint implants. Numerous factors may contribute to the development of osteolysis, and, in addition to wear particles from the implant itself and implant coating materials, also local damage to the blood supply, joint fluid pressure and flow, and local anatomic-physiological and mechanical factors presumably affect the process (Purdue et al. 2006). The AES total ankle implant was withdrawn from the market at 2008 because of preliminary findings of peri-implant osteolysis.

The purpose of this study was to investigate the survival and failure mechanisms, especially osteolysis, associated with the introduction of third generation mobile-bearing total ankle implants.

2. REVIEW OF THE LITERATURE

2.1 Overview

The tibiotalar joint forms a unique anatomical and biomechanical complex compared with the other major lower extremity joints. The thickness and tensile properties of the cartilage in the ankle joint are different from cartilage in the hip and knee. Although the ankle joint is subjected to the highest forces per square centimeter and injured more commonly than any other joint in the body, primary ankle osteoarthritis is rare (Stauffer et al. 1977; Cushnaghan & Dieppe 1991). The most common cause of ankle arthritis is secondary to previous trauma or inflammatory arthritis. The ankle joint is affected in nearly half of the rheumatoid patients at some point, but rarely early in the course of the disease (Kirkup 1990). The kinematics of the ankle is strongly connected to the joints of the hindfoot and the leg, and any changes in ankle movement will affect the kinematics of the hindfoot. The surgical treatment for end-stage ankle arthritis is either tibiotalar fusion or total ankle replacement. The first-generation total ankle replacements were a major failure in terms of implant survival, but modern third generation total ankle implants are providing satisfactory results which are nearly comparable in terms of survival to hip and knee replacement.

2.2 Normal ankle

The ankle joint complex comprises the tibiotalar, talocalcaneal, and transverse tarsal joints, which act together to form a kinetic linkage between the lower leg and the foot allowing the lower limb to interact with the ground.

2.2.1 Ankle anatomy

2.2.1.1 Bones and ligaments

The tibiotalar joint consists of three sets of articulating surfaces from three bones, the tibia, fibula, and talus. This forms unique anatomical and biomechanical characteristics compared with the other major lower extremity joints. The contact area of the joint at load is approximately 350mm^2 (Kimizuka et al. 1980; Beaudoin et al. 1991), which is much less compared with the hip or the knee. The tibia and fibula form the ankle mortise, which encloses the talus firmly. The mortise is supported by the tibiofibular syndesmosis, which consists of tight anterior and posterior ligaments together with an interosseous membrane. The convex distal tibial articular surface matches the concave superior articular surface of the talus. The talar dome forms a segment of a cone, since it is wider anteriorly than posteriorly and the radius is smaller medially than laterally. The medial compartment of the joint consists of the medial articular surface of the

talar dome and the medial malleolus, and the lateral compartment consists of the lateral articular surface of the talar dome and the lateral malleolus, which lies slightly more posterior and extends more distal compared with the medial malleolus. Medially, the joint is supported by a strong ligamentous complex of deep and superficial layers of deltoid ligaments, which are the most important passive stabilizing structures of the ankle joint. The lateral ligament complex consists of the anterior and posterior talofibular and calcaneofibular ligaments. Together with the joint capsule, these tight ligament complexes stabilize the talus to the ankle mortise, and permit simultaneous movement of the ankle and subtalar joint. The bony anatomy, ligaments, and joint capsule together guide and restrain movement in the ankle and create a continuously changing rotational axis of the talus relative to the ankle mortise. In addition, there are mechanoreceptors in both lateral and medial ligaments (Michelson & Hutchins 1995), which are important for the proprioceptive features of the ankle.

The subtalar joint, between the talus and the calcaneus, is a triplanar, uniaxial joint. The geometry of joint with convex and concave articular surfaces allows inversion and eversion of the ankle. The main stabilizer of the joint is the thick interosseous talocalcaneal ligament between the bones.

The transverse tarsal joint is composed of the talonavicular and calcaneocuboid joints, which share a common axis of motion contributing to the eversion-inversion motion of the foot.

2.2.1.2 Tendons and neurovascular structures

The tendons around the ankle can be divided into different compartments by their function. Anterior to the ankle there are the tendons of the dorsiflexors tibialis anterior, extensor hallucis longus (EHL), extensor digitorum longus (EDL), and peroneus tertius. Laterally run the tendons of the evertors peroneus longus and peroneus brevis, and posteromedially the tendons of the invertors and plantar flexors tibialis posterior, flexor hallucis longus (FHL), and flexor digitorum longus (FDL). Posterior to the ankle is located the main plantar flexor, the Achilles tendon.

There are two main neurovascular bundles in the ankle. In the anterior compartment, the anterior tibial artery runs in the midline of the ankle together with the deep peroneal nerve and its branches supply blood to the anterior, medial, and lateral side of the ankle. This bundle is at risk during anterior surgical approaches to the ankle joint, which is common in total ankle replacement. The other main branch is located posteromedial behind the medial malleolus and is formed by the posterior tibial artery and the tibial nerve. In addition, there are subcutaneous branches of the superficial peroneal nerve in the anterior part of the ankle, which must also be considered when the ankle is approached anteriorly.

2.2.1.3 Cartilage

The thickness and tensile properties of the cartilage in the ankle joint are different from the cartilage in the hip and knee. The thickness of ankle cartilage ranges from less than one mm to less than two mm (Athanasiou et al. 1995), whereas the articular cartilage thickness of the knee ranges from at least 3 up to 6 mm (Ateshian et al. 1991). However, the tensile properties of the articular cartilage of the ankle are not affected by age to a similar extent as of the other joints. The tensile fracture stress and tensile stiffness of the ankle articular cartilage deteriorate less rapidly with age than of the hip cartilage (Kempson 1991), and the incidence of full-thickness cartilage defects in the knee is 20-fold compared to the ankle (Meachim 1975). The differences may be explained by several factors. Compared to the knee, ankle cartilage has a higher content of proteoglycans and water, as well as higher proteoglycan turnover. Furthermore, the chondrocytes of the ankle have decreased responsiveness to catabolic cytokine interleukin-1 (IL-1), which inhibits proteoglycan synthesis by the chondrocytes (Chubinskaya et al. 1996; Huch et al. 1997; Aurich et al. 2006; Kuettner & Cole 2005). However, chondrocytes of the ankle cartilage synthesize proteoglycans in response to trauma at a higher rate than chondrocytes in the knee (Kuettner & Cole 2005). The cartilage of the ankle joint has also different acoustic properties compared to the knee joint (Hattori et al. 2005).

2.2.2 Ankle biomechanics

Despite the relatively congruency, the ankle has movement in three planes. The combined motion from the tibiotalar and the subtalar joint is usually defined as dorsiflexion and plantar flexion in the sagittal plane, inversion and eversion in the frontal plane, and abduction and adduction in the transverse plane. Combinations of these motions of the ankle joint complex create three-dimensional motions supination and pronation. The tibiotalar joint axis is obliquely oriented and allows horizontal rotations to occur in the foot or the leg with movements of the ankle. The subtalar joint is a single axis joint with an oblique hinge and motion from medial to lateral and in the horizontal plane with great individual variations. The range of motion (ROM) of the ankle joint is approximately 40 - 50 degrees of plantar flexion and 10–15 degrees of dorsiflexion (Roaas & Andersson 1982). The ankle ROM seems to decrease with age (Nigg et al. 1992). Approximately 24–30 degrees of combined ROM is needed for normal walking, and 37 degrees for ascending, and 55 degrees for descending stairs (Murray et al. 1964). The kinematics of the ankle is strongly connected to the joints of the hindfoot and the leg, and therefore any changes in ankle movement will affect the kinematics of the hindfoot.

During stance phase, the maximal load is transmitted through the superior articular surface of the talus, where the contact area is the largest while ankle is in neutral or slightly dorsiflexed position (Deland et al. 2000). The rest of the load is transmitted

through medial and lateral facets. The average tibiotalar cartilage contact area is minimal at heel strike, 272 mm^2, and maximal at midstance, 417 mm^2 (Wan et al. 2006). As little as 1 mm lateral shift of talus was shown to decrease the tibiotalar contact area even 40% in a classic biomechanical study using a constrained ankle model (Ramsey & Hamilton 1976), which was considered to advocate for anatomic stabilization of all ankle fractures. However, further studies with dynamic or unconstrained models have failed to reproduce the finding. Up to 6 mm lateral displacement of talus has not been shown to cause significant difference in tibiotalar contact area, but sectioning the deep deltoid ligament reduces the contact area significantly (Clarke et al. 1991; Curtis et al. 1992; Pereira et al. 1996). Therefore, it seems that the primary stabilizers of the joint are medial and with displaced fibular fracture the talus does not follow fibula unless there is insufficiency of the deltoid ligament (Daniels & Thomas 2008). Loading results to increased joint congruency, as the ankle tends to adopt a stable position when loaded (Daniels & Thomas 2008).

2.3 Ankle arthritis

2.3.1 Epidemiology and etiology

Although the ankle joint is subjected to the highest forces per square centimeter and is injured more often than any other joint in the body, the incidence of symptomatic ankle osteoarthritis is much lower than of the hip and knee (Stauffer et al. 1977; Cushnaghan & Dieppe 1991). The exact incidence of ankle osteoarthritis is not known. The frequency of full-thickness cartilage defects at random autopsy biopsies of ankles is much smaller than of the knees, and the changes do not seem to progress to symptomatic osteoarthritis, as is the case for the knee joint (Daniels & Thomas 2008). In rheumatoid arthritis the ankle joint is affected up to half of the patients at some point of the disease (Kirkup 1990; Michelsson et al. 1994).

2.3.1.1 Osteoarthritis

Osteoarthritis is defined as a multifactorial disease affecting all tissues around the joint, including cartilage, bone, and synovium of the joint itself, as well as ligaments and muscles surrounding the joint. In addition to the degenerative process, there is also local inflammation as a part of an active response to injury, which drive the pathological process of leading to remodeling of joint tissue (Loeser et al. 2012). The common pathology of the affected joint includes destruction of the cartilage, subchondral bone alterations with sclerosis and cyst formation, osteophyte formation, and synovial inflammation (Loeser et al. 2012). The thickness of the subchondral bone plate is increased in ankle osteoarthritis (Nakasa et al. 2014). Primary osteoarthritis is defined as joint destruction developing without any evident cause, and epidemiological

studies show that the incidence of primary osteoarthritis of the ankle joint is low (Cushnaghan & Dieppe 1991; Huch et al. 1997; Barg et al. 2013a). The most common cause of ankle osteoarthritis is secondary osteoarthritis due ankle trauma, either fracture, ligamentous injury, or repetitive trauma due to ankle instability (Saltzman et al. 2005). The risk of posttraumatic osteoarthritis after ankle fracture is very high, up to 40% (Lübbeke et al. 2012). In an epidemiologic study, the predisposing factors for posttraumatic ankle osteoarthritis are a history of rotational ankle fracture (37.0% of the cases), recurrent sprains (14.6%), single sprain (13.7%), pilon fracture (9.0%), tibial shaft fracture (8.5%), and osteochondral lesion of the talus (4.7%) (Saltzman et al. 2005). As the incidence of ankle trauma has increased during the recent decades (Daly et al. 1987; Jensen et al. 1998; Doherty et al. 2014), the incidence of posttraumatic ankle arthritis is probably increasing. Chronic functional instability of the ankle causes changes in cartilage T2-relaxation times in magnetic resonance imaging, especially in the medial side of the talus (Golditz et al. 2014). The adult human ankle cartilage increases both proteoglycan-4 release and biosynthetic activity as an immediate cellular response to injury (Shekhawat et al. 2016), and many synovial cytokines, including aggrecan, BMP-7, bFGF, and CD105, may be demonstrated in ankle joints with osteoarthritis (Schmal et al. 2014; Schmal et al. 2015). Differences in the incidence and etiology of osteoarthritis suggests that the ankle joint is more resistant to primary osteoarthritis than many other joints, probable due to metabolic characteristics, tensile properties, congruency, and restrained movement, but at the same time the ankle is less adaptable to incongruity, instability, and increased stresses caused by traumatic events (Daniels & Thomas 2008; Barg et al. 2013a).

2.3.1.2 Inflammatory arthritis

The other major cause of ankle joint destruction is inflammatory arthritis, most commonly rheumatoid arthritis (RA). Rheumatoid arthritis is an autoimmune disease affecting approximately 1% of the population characterized by joint inflammation, pain, and stiffness (Feldman et al. 1996; Firestein 2003). The exact etiology of the disease is unclear, but various epigenetic, genetic, and environmental factors contribute to emergence and progression of RA (Ritchlin et al. 2004). A pivotal feature of RA is the osteodestructive process, which leads to bone loss in three ways: periarticular osteopenia (described as focal bone loss at the joint margins and in subchondral bone), erosions (presenting as localized resorption at the synovial attachment to bone), and generalized osteoporosis of the skeleton (Goldring & Gravallase 2000). Joint erosion is driven by the inflammatory synovial tissue or 'pannus', a hyperplastic, locally invasive tissue, which consists of fibroblasts, monocytes, and T-lymphocytes, mast cells, and numerous blood vessels (Ritchlin et al. 2004). The cells of this tissue produce many inflammatory mediators including cytokines, interleukins, prostaglandins, reactive

oxygen species, and matrix metalloproteinases, which damage the extracellular matrix of the joint by direct and indirect mechanisms (Ritchlin et al. 2004).

Another inflammatory joint disease that often causes major damage to the joints is psoriatic arthritis, which occurs in 10–15% of the patients with psoriasis (Mease 2002).

The ankle joint is affected at some point in time in 15–52% of RA patients, but rarely in the early course of the disease (Kirkup 1990; Michelson et al. 1994). The joints of the forefoot and midfoot are usually affected earlier, which very often results in valgus malalignment of the ankle. As the ankle is damaged later in the disease, it is often accompanied with osteoporosis, fragile skin, and a poor soft-tissue envelope around the ankle because of the disease and prolonged medication. Polyarticular rheumatoid arthritis also reduces the ability of patients to adapt to biomechanical alterations following ankle procedures, *e.g.*, arthrodesis. The special features of inflammatory arthritis need to be considered when planning the treatment. These features include the condition of skin and other soft tissue, medication that might have a significant impact on healing, and the state of the mobility of the patients due to involvement of other joints.

2.3.2 Diagnosis and clinical features

The diagnosis of ankle arthritis is based on symptoms, including pain and stiffness of the ankle, physical examination, and radiologic imaging.

End-stage ankle arthritis leads to reduced ankle ROM, walking speed, and altered ankle moments on gait analysis (Brockett & Chapman 2016). Ankle osteoarthritis changes hip kinematics significantly to compensate for a lack of plantar flexion of the ankle, and osteoarthritis in any of the lower extremity joints (hip, knee, or ankle) results in reduced peak vertical forces and extension and plantar flexion moments, which require compensatory gait mechanisms throughout the lower extremity (Schmitt et al. 2015).

Radiographs should be taken standing with hindfoot alignment view. There are several different radiological grading systems of the severity of the disease. The most popular one is the Kellgren-Lawrence system for osteoarthritis, and the Larsen system for inflammatory arthritis, both of which rely on radiographies.

Cross-sectional imaging is widely used, in addition to radiography, for diagnostic purposes and planning of treatment of ankle arthritis. Computed tomography (CT) shows the bony structures in great detail and, with intra-articular contrast medium, accurate visualization of the articular surfaces is possible. The technique is useful for determining preoperatively the presence or absence of degenerative cysts or geodes in the bones. An additional advantage of CT is good resolution near retained metal hardware with metal artefact reducing algorithms. The radiation dose of ankle CT is

negligible, because the ankle is peripherally located and there are no radiosensitive organs in or close to the imaged area. The mean effective dose of one CT examination of the ankle is 0.07 mSv, which is even less than in what a conventional chest radiograph generates (approximately 0.08 mSv) (Biswas et al. 2009). Cone beam technology (CBCT), a new method in the field of musculoskeletal radiology, allows weight-bearing imaging of the ankle. MRI is useful for evaluating the soft tissues around the ankle and the quality of bone, *e.g.*, to assess the presence or absence of osteonecrosis, and MRI is the best imaging modality for cartilage evaluation.

In the recent years, single-photon emission computed tomography (SPECT-CT) has been used for diagnosing osseous pathology of the foot and ankle. (Coughlin et al. 2014; Paul et al. 2015). Bone scintigraphy with bone-seeking radiotracers, mostly ^{99m}technetium dicarboxypropane disphosphonate (^{99m}Tc-DPD) combines the high sensitivity of functional imaging with the high specificity of structural imaging, and is especially useful when joint preserving surgery is considered, *e.g.*, when osteotomy of a varus or valgus ankle is planned (Paul et al. 2015). SPECT positive areas of subchondral bone in end-stage OA are characterized by a pathologic bone-remodeling process (Paul et al. 2015).

2.3.3 Treatment

2.3.3.1 Conservative treatment

Conservative treatment of a diseased ankle is as for other joints. Physical activity is recommended, although high-impact sports should probably be avoided. Pain can be managed with non-steroidal anti-inflammatory drugs, local ice packs, and rest. Physiotherapy may be useful for maintaining the normal gait and range of motion of the joint, and shoe modifications and orthoses may relieve symptoms.

Systemic treatment to slow the progression of joint damage of patients with rheumatoid arthritis includes disease-modifying antirheumatic drugs (DMARDs) and, if needed, biologic agents (American College Rheumatology 2015). Intra-articular corticosteroid injections are efficient in mollifying the symptoms of ankle and foot arthritis (Ward et al. 2008), and are recommended in the treatment of rheumatoid arthritis (American College Rheumatology 2002). Viscosupplementation with hyaluronic acid might be a treatment alternative for the ankle, as it is for the knee, but robust data is lacking regarding its use and dosing (Migliore et al. 2011)

2.3.3.2 Other surgical treatment than arthroplasty

Arthroscopic surgery

There is fair evidence-based data to support the use of ankle arthroscopy for the treatment of ankle impingement, osteochondral lesions, and ankle arthrodesis (Glazebrook et

al. 2009; Phisitkul et al. 2013). Arthroscopic treatment including soft tissue and bone debridement, removal of loose bodies, and microfracturing in case of grade III to IV cartilage lesions has been proposed for treating ankle osteoarthritis. There are some promising results regarding the use of arthroscopic surgery in mild to moderate disease (Osti et al. 2016), but otherwise data is inconsistent, especially with more advanced arthritic changes (Glazebrook et al. 2009). For comparison, arthroscopic debridement of the knee to treat osteoarthritis is of no benefit to the patients, and is no longer recommended for the treatment of knee osteoarthritis (Moseley et al. 2002; Kirkley et al. 2008) Arthroscopic synovectomy of the ankle in rheumatoid arthritis seems to be helpful, but the best outcome is achieved in the early course of the disease when there is minimal evidence of cartilage degeneration (Choi et al. 2013).

Distraction ankle arthroplasty

Distraction arthroplasty has originally been described as an alternative surgical treatment for hip arthritis, and has also been adapted to the ankle joint as a less invasive procedure after which ankle fusion and replacement are still viable options in case distraction fails (Smith et al. 2012). Distraction arthroplasty is performed with either a fixed or hinged distractor frame for approximately three months. There are some encouraging results in the treatment of posttraumatic ankle arthritis, although the level of evidence is still insufficient (Smith et al. 2012). The motion distractor has been found to be advantageous over fixed distraction in the short term (Saltzman et al. 2012). A longer-term follow-up of the same study showed that approximately half of the patients treated with distraction needed ankle fusion or replacement during a median follow-up time of eight years (Nguyen et al. 2015).

Supramalleolar osteotomy

Supramalleolar osteotomy is a joint-preserving treatment option of asymmetric valgus or varus ankle osteoarthritis. The purpose of the procedure is to realign the relationship between the talus and tibia to restore joint loading and correct the altered biomechanics. Additional procedures to balance the soft tissues, as well as hindfoot osteotomy and arthrodesis, may be combined with osteotomy to realign the joint (Hintermann et al. 2016). The literature regarding supramalleolar osteotomy demonstrates good clinical outcomes for asymmetric ankle osteoarthritis, especially varus ankle osteoarthritis, and improvement of functional outcomes in mid- to long-term follow-up (3.6 to 7.1 years) (Barg et al. 2013b; Lee 2016; Al-Nammari & Myerson 2016; Krähenbühl et al. 2016). In addition to reducing pain and improving function and radiographic signs of osteoarthritis, supramalleolar osteotomy delays the time to ankle arthrodesis or total joint replacement (Krause et al. 2016). Based on limited evidence, a grade I treatment recommendation has been given for supramalleolar osteotomy to treat mild to moderate ankle osteoarthritis with distal tibial malalignment (Krause et al. 2016).

Tibiotalar fusion

The traditional surgical treatment for end-stage ankle arthritis has for decades been tibiotalar fusion. It is a reliable procedure with good patient satisfaction, but it is also associated with a high complication rate relayed especially to infections and non-union. Arthroscopic ankle arthrodesis has decreased the time to union and provided equivalent or higher union rates, less blood loss, less morbidity, earlier mobilization, lower cost, and shorter hospital stay compared to open arthrodesis (Myerson & Quill 1991; O´Brien et al. 1999; Winson et al. 2005; Nielsen et al. 2008; Peterson et al. 2010; Townshend et al. 2013; Pakzad et al. 2014; Elmlund & Winson 2015; Jain et al. 2016). Arthroscopic arthrodesis is especially advantageous when the soft tissues are compromised, *e.g.*, in patients with inflammatory or posttraumatic arthritis. It seems to produce reliable results even when there is preoperative deformity, as long as the forefoot can be reduced parallel to the ground (Dannawi et al. 2011; Elmlund & Winson 2015).

Ankle arthrodesis results in substantial alterations to the biomechanics of the joints in the hindfoot, midfoot, and knee joint (Coester et al. 2001; Bayert et al. 2004; Thomas et al. 2006; van Engelen et al. 2010; Bruening et al. 2016). In a study by Thomas et al. (2006) almost one fifth of the patients had significant gait alterations during short-term follow-up, and in the long-term (over 20 years of follow-up) (Coester et al. 2001) almost all patients have a significant limp. There is a risk of knee instability after ankle arthrodesis, as 63% of the patients with previous ankle arthrodesis had instability of medial collateral ligament of the knee in a long-term study with an average of 10.4 years of follow-up (Buck et al. 1987). The altered biomechanics could predispose to degenerative arthritis of the joints of the hindfoot and midfoot (Takakura et al. 1999; Coester et al. 2001; Fuchs et al. 2003; Thomas et al. 2006). The main range of motion of the ankle after tibiotalar arthrodesis seems to be due to sagittal hypermobility of the talonavicular joint (Bruening et al. 2016; Pedowitz et al. 2016). Although some authors have suggested that ipsilateral hindfoot and midfoot arthritis is already present in patients with arthritis of the ankle and the changes are not consequence of ankle arthrodesis (Sheridan et al. 2006), there seems to be an apparent relationship between ankle arthrodesis and arthritis of the other ankle joints (Thomas et al. 2006; Fuentes-Sanz et al. 2012; Vaughan et al. 2015). Furthermore, fusion of the subtalar or talonavicular joints or triple arthrodesis predispose to tibiotalar arthritis for more than 70% of patients (Mann et al. 1998; Ebalard et al. 2014).

The non-union rates after tibiotalar fusion has varied from 0 to 40% in different studies (Coughlin et al. 2014). In addition to problems with union, the most common complaints after ankle fusion are varus or valgus malunion with equinus deformity or limb-length discrepancy (Katsenis et al. 2005). The well-known risk factors for failure of the tibiotalar fusion are smoking, diabetes, and neuromuscular imbalance (Coughlin et al. 2014; Jain et al. 2016; Taylor et al. 2016). Age, female gender, higher

ASA grade, multiple medical comorbidities, rheumatoid arthritis, lower SF-36 scores, and open surgery prolong the duration of the hospital stay (Pakzad et al. 2014). Previous tibiotalar arthrodesis also decreases significantly the rate of union of subsequent subtalar arthrodesis (Easley et al. 2000; Zanolli et al. 2015).

Despite all complications, patient satisfaction after ankle arthrodesis has been high in all studies, even when the procedure is made on both sides (Vaughan et al. 2015; Henricson et al. 2016a).

2.3.3.3 Clinical evaluation of treatment

There are several reporting tools available for the clinician to evaluate the results of treatment of the foot and ankle conditions (Naal et al. 2010). The most widely used tool is the American Orthopedic Foot and Ankle Society's (AOFAS) ankle-hindfoot score (Kitaoka et al. 1994), which gives points for pain, function, and alignment. The scoring system has not been validated, and it has been criticized for correlating poorly with the validated Medical Outcomes Shortform-36 score (SF-36) (SooHoo et al. 2006). Other popular scoring systems include the Kofoed Ankle Score (Kofoed 1986; Kofoed 1995). Neither of these are patient reported outcome measure (PROM) tools, which have become more popular as it has been suggested that PROMs provide more valuable information about the outcome than clinician reported scores. The PROMs do improve communication between clinician and patient in clinical practice, and they can therefore influence care and outcomes (Cook et al. 2011). The recently developed Self-Reported Foot and Ankle Score (SEFAS) is a patient-reported outcome measure, which yields similar or better outcomes as the AOFAS score, but can be completed 3 times faster (Cöster et al. 2014). Other common PROMs include the Manchester-Oxford Foot Questionnaire (MOXFQ) (Isis Innovation Ltd, Oxford, UK), which has been validated for clinical trials involving foot surgery (Dawson et al. 2011; Dawson et al. 2012), and the Foot and Ankle Ability Measure (FAAM) (Martin et al. 2005), which is not validated for ankle disorders related to osteoarthritis or rheumatoid arthritis.

2.4 Total ankle replacement

2.4.1 History of total ankle replacement

The interest towards ankle arthroplasty began in the 1960s with the development of knee and hip arthroplasty. The first total ankle implant was invented by Lord and Marotte at 1970, who used a hip implant with a femur component in tibia and acetabular component in talus (Lord & Marotte 1980). Between 1970 and 1989 several total ankle implants were introduced. All of them were fixed with cement, but the design varied from non-constrained to constrained. The first results were promising,

and patient satisfaction was high, but different studies reported failure rates of 36% to 52%, and loosening in up to 93% of the cases (Dini & Bassett 1980; Lord & Marotte 1980; Stauffer & Segal 1981; Newton 1982; Bolton-Maggs et al. 1985; Kirkup 1985; Unger et al. 1988; Wynn & Wilde 1992; Wood et al. 2000). The largest study on the Mayo Total Ankle was published by Kitaoka and Patzer (1996) with 204 ankles and average nine years of follow-up. Of the ankles, 36% were failures, and only 19% were rated as good. Loosening was the main problem on the talar side: 57% of the components were loose. This led the authors to draw the conclusion that total ankle implants should not be used at all (Kitaoka & Patzer 1996).

Retrospectively, there were many reasons why the first-generation ankle implants failed. The surgical instruments were poor or non-existent. The design of the implants did not respect ankle anatomy or biomechanics, as the implants were either too constrained or too unstable. Indications may have been lax, as in some series there were patients with osteonecrosis of the talus, which today is a relative contraindication to ankle replacement. In addition, the implants were fixed with cement, which is now known to be associated with inferior survival (Takakura et al. 1990; Kofoed 2004).

In Finland, these first-generation total ankle implants were used between 1976 and 1987, the most popular one was the Imperial College of London Hospital (ICLH) ankle (Finnish National Institute for Health and Welfare). There is one Finnish study by Kaukonen and Raunio (1983) including 22 Thompson-Parkridge-Richards (TPR; Richards International, Memphis, TN, USA), five ICLH, and one St. Georg-Buchholz total ankle implant; loosening was detected in 5 of the 56 cases (9%).

There are three different total ankle implants, which may be considered second generation implants: The Agility (DePuy, Warsaw, IN, USA), the first generation of the STAR, and the Buechel-Pappas (Endotec, Orange, NJ) implant which was developed from the New Jersey Low Contact Stress implant. The results of these implants have been acceptable (Rippstein 2002).

2.4.2 Third generation total ankle replacement

Since the 1990s, the development of total ankle implants has continued, and with better implant designs and developed instrumentations there is renewed interest toward the procedure. The current total ankle implants are called third generation implants, and they have been used in Finland since 1997.

2.4.2.1 Implants

The modern third generation total ankle implants are semi-constrained and available with either mobile or fixed polyethylene bearings. There is a difference between

Europe and the US regarding the bearings, as most implants in Europe are with mobile bearings, whereas in the US mainly fixed bearing implants are used. For many years, the only total ankle implant approved by the FDA was the Agility (DePuy, Warsaw, IN, USA), which is often referred to as a second-generation total ankle implant, and its use requires quite extensive bone resections and a syndesmodesis.

The implant is usually fixed without cement, as cement fixation is associated with inferior device survival (Takakura et al. 1990; Kofoed 2004). The required bone resections are small and this avoids component subsidence and migration, which is especially important at the tibial side, as the strength of subchondral bone in distal tibia decreases rapidly proximally from joint line. Compression resistance in the proximal one centimeter of bone is approximately 600 N, decreases to approximately 125–250 N when moving further, and at three centimeters is nearly zero (Aitken et al. 1985). There are several designs on the market, of which at least the Scandinavian Total Ankle Replacement (STAR; Stryker GmbH, Selzach, Switzerland), Ankle Evolutive System (AES; Biomet, Warsaw, Indiana, USA), Mobility (DePuy Synthes, Warsaw, IN, USA), Hintegra (Integra, Plainsboro, NJ, USA), CCI (Ceramic Coated Implant; Wright Medical Technology, Arlington, TN, USA), and TMTA (Trabecular Metal Total Ankle, Zimmer, Warsaw, IN, USA) have been or are currently used in Finland.

2.4.2.2 Indications and contraindications

The indication for total ankle replacement is painful end-stage ankle arthritis. As the results of both total ankle replacement and tibiotalar fusion are comparable, the decision as to which procedure is chosen has to be discussed individually with each patient. Most contraindications to total ankle replacement are relative. Prior infection has often been stated as an absolute contraindication to TAR (Chou et al. 2008; Bonasia et al. 2010), although there are also opposite results (Coughlin et al. 2014). In a recent retrospective analysis of 22 TAR operations, a history of ankle joint sepsis or osteomyelitis was not associated with postoperative infection (Shi et al. 2015). Neuromuscular diseases, neuroarthropathy (*e.g.,* Charcot´s disease), or pathological joint laxity should be considered as absolute contraindications to TAR (Coughlin et al. 2014). Preoperative malalignment does not seem to affect the result of TAR, if the alignment is reduced to the normal pre- or perioperatively (Queen et al. 2013). Osteonecrosis or poor bone stock of the talus must be taken into consideration when planning TAR, as they may lead to aseptic loosening or subsidence of the talar component (Coughlin et al. 2014). Smoking is associated with a statistically significant increased risk of wound breakdown, and smokers have also an increased rate of infection, revision surgery, and nonrevision surgery, and worse outcome scores compared with nonsmokers or former smokers (Lampley et al. 2016).

2.4.2.3 Surgery and treatment protocol

Most of the modern total ankle replacements are implanted through the anterior approach, between the tibialis anterior and EHL tendon or between the EHL and EDL tendons. The anterior neurovascular bundle must be identified and preserved. The TMTA implant (Tantal Metal Total Ankle, Zimmer, Warsaw, IN, USA) requires a lateral approach through fibular osteotomy, where the distal fragment of the osteotomized fibula is turned caudally. Two-staged surgery may be useful when malalignment is present, but osteotomies, tendon or ligament procedures, or fusions to correct the alignment may also be performed at the same time as the total ankle replacement (Coughlin et al. 2014).

One of the most important requirements for a successful outcome of total ankle replacement is accurate positioning of the components. Coronal plane deformity and the overhang between the components resulting from this may contribute to aseptic loosening and implant failure by postoperative edge loading. Sagittal malalignment and version of the components is also important. Anterior translation of the talus is related to ankle osteoarthritis, especially in posttraumatic situations caused by ankle instability. This sagittal malalignment may be one cause for failure of total ankle replacement, probably due to lift-off of the polyethylene bearing (Tochigi et al. 2006 a,b). The relative component rotation caused by malalignment between the components seems to increase the pressure between the components and may predispose to polyethylene wear (Espinosa et al. 2010). In an *in vitro* study by Fukuda et al. (2010), malrotation of the talar component caused increased peak pressure and rotational torque and reduced the contact area between the components. Clinically, it has been shown that patients with suboptimal positioning of the talar components have a higher rate of persisting pain and worse ankle mobility (Barg et al. 2011a). Intraoperative referencing is traditionally done under fluoroscopic guidance, but nowadays also patient-specific instrumentation is available.

There is an obvious effect of the learning curve to the success of TAR. According to Swedish Registry data, the survival of TAR was significantly lower for the surgeon's first 30 operations compared to later (Henricson et al. 2007), and the same effect has been shown in many other studies (Myerson & Mroczek 2003; Saltzman et al. 2003; Haskell&Mann 2004; Schubert et al. 2006; Lee et al. 2008; Schimmel et al. 2014). The volume of procedures is also important, as early revision rates have been significantly higher in low-volume centers operating < 20 ankle replacements per year (Zaidi et al. 2016). Surgeons performing > 21 TAR cases per year have had less overall complications, lower rate of medial malleolar fractures, decreased length of hospital stay, and decreased hospital charges compared to low volume surgeons (Basques et al. 2016).

2.4.2.4 Complications

The complications of the total ankle replacement can be classified in many ways. Traditionally, the complications may be categorized based on time as intraoperative, *e.g.,* perioperative fracture, nerve and tendon laceration; early postoperative, *e.g.,* wound healing complication, postoperative stress fracture, and deep infection; and delayed complications, *e.g.,* component migration, aseptic loosening, osteolysis, heterotopic ossification, residual pain, polyethylene wear, insert luxation, insert fracture, and late hematogenic deep infection, or based on their severity as minor or major. A recent systematic review claims that there is inconsistency in reporting the revisions and complications associated with TAR (Mercer et al. 2016). Glazebrook et al. presented a classification of the complications related to total ankle replacement based on the severity of each complication or on the potential impact of the outcome (Glazebrook et al. 2009). Based on failure rate, the complications were classified as high-grade, intermediate-grade, and low-grade (Glazebrook et al. 2009). High-grade complications with > 50% of failure rate included implant failure, aseptic loosening > 2 mm, periprosthetic osteolysis, and deep infection; intermediate-grade with < 50% failure rate included technical error, subsidence, postoperative bone fracture, and medial impingement; and low-grade as rare included intraoperative bone fracture, and wound healing problems (Glazebrook et al. 2009). However, one retrospective review on complications used the classification of Glazebrook et al. reported that all complications, except intraoperative bone fracture and wound healing, had a failure rate of at least 50%, and the authors proposed that complications should be labeled as carrying either a high or low risk for early failure of TAR (Gadd et al. 2014).

Recently, a new coding system for reoperations was proposed by Younger et al. (2016) based on the reoperation rates from a multicenter database after both TAR and ankle fusion. Vulcano & Myerson have presented a diagnostic and treatment algorithm for painful total ankle replacement (Vulcano & Myerson 2017).

The most common complications and their incidence listed by different classifications are presented in Table 1. The most disturbing complication in recent years has been peri-implant osteolysis, which will be discussed in detail in Chapter 2.4.7.

Table 1. The most common complications with incidence figures for third-generation total ankle replacements. Complications are classified based by time and severity (system proposed by Glazebrook et al. 2009).

Complication	Classification	Incidence	References
Delayed wound healing	Early postoperative Low-grade	0 – 17.4%	Stengel et al. 2005 Gougoulias et al. 2010 Coughlin et al. 2014
Deep infection	Early postoperative/ Delayed High-grade	0 – 6.9%	Stengel et al. 2005 Gougoulias et al. 2010 Zhao et al. 2011 Coughlin et al. 2014 Patton et al. 2015
Fractures (Perioperative/ postoperative)	Intraoperative/ Early postoperative Low-grade/Intermediate grade	11.4 – 20%	McGarvey et al. 2004 Stengel et al. 2005 Wood et al. 2007 Choi et al. 2013 Jung et al. 2015
Broken/ dislocated PE insert	Early postoperative Delayed	0.5 – 14.3%	Anderson et al. 2003 Wood et al. 2008 Wood et al. 2009 Brunner et al. 2013
Osteolysis	Delayed High-grade	0 – 48%	See 2.4.7.1
Nerve injury	Intraoperative	0 – 77%	Rodriguez et al. 2010
Tendon laceration	Intraoperative	4 – 21%	Myerson & Mroczek 2003 Knecht et al. 2004
Aseptic loosening	Delayed High-grade	4 – 8.6%	Myerson & Mroczek 2003 Stengel et al. 2005 Fevang et al. 2007 Hosman et al. 2007 Henricson et al. 2011b Zhao et al. 2011
Heterotopic ossification/ Impingement	Delayed Intermediate-grade	5.2 – 38%	Stengel et al. 2005 Zhao et al. 2011 Brunner et al. 2013 Sadoghi et al. 2013 Jung et al. 2015 Jung et al. 2016
Subsidence	Delayed Intermediate-grade	9.1 – 78%	Stengel et al. 2005 Choi et al. 2013 Jastifer & Coughlin 2015
Residual pain	Delayed	5 – 60%	Knecht et al. 2004 Buechel et al. 2004 Gougoulias et al. 2010

2.4.2.5 Additional and revision surgery

There is often a need for additional procedures in connection with total ankle replacement, especially when there is malalignment. It is necessary to align the foot in a neutral position to reassure that the procedure provides an optimal outcome. Either a two-staged or one-staged approach can be chosen, but if malalignment is severe, as in pes planovalgus, the two-staged method is often preferable. Additional procedures requiring separate incisions do not apparently increase the rate of complications (Criswell et al. 2016). Coincident fusion of the subtalar joint may yield satisfactory results (Usuelli et al. 2016), as may secondary subtalar, talonavicular, double, or triple arthrodesis (Gross et al. 2016a).

Compared to total hip or knee arthroplasty, it is much more common to do revision procedures after total ankle replacement. Impingement caused by heterotopic ossification associated with reduced ankle motion occurs often after TAR, and revision surgery for impingement is often needed (Lee et al. 2011; Jung et al. 2016). The impingement can be managed either by open surgery or arthroscopically (Overley et al. 2015; Gross et al. 2016b; Gross et al. 2017). Traditionally, the polyethylene insert has been exchanged regardless of the condition of the insert in connection with any open procedure and this should not be considered as implant failure (Henricson et al. 2011a). Polyethylene insert fracture and dislocation are relatively common–especially mobile bearings are prone to fracture in case they extrude across the edge of metal components (Coughlin et al. 2014). The dislocation is usually related to instability or malalignment. Exchanging the mobile bearing is a relatively easy procedure, but if the ankle is unbalanced, bony alignment should be corrected at the same time (Coughlin et al. 2014).

A large worldwide registry data shows that the most common reasons for revisions after TAR are aseptic loosening (38%), technical errors (15%), pain (12%), and septic loosening (9.8%) (Sadoghi et al. 2013).

2.4.3 Function after total ankle replacement

2.4.3.1 Range of motion

Ankle arthroplasty does not increase the range of movement of the ankle but rather preserves the movement present before surgery (Wood & Deakin 2003; Coetzee & Castro 2004; Wood et al. 2008; Brigido et al. 2015). In a study by Coetzee and Castro (2004) there was a statistically significant difference between the preoperative and postoperative ROM (P=0.0037), but the overall improvement of ROM was only five degrees. Therefore, the most favorable results considering postoperative ROM are likely to be obtained in ankles with a good preoperative ROM. The overall sagittal

range of movement of the ankle after total ankle replacement consists of both tibiotalar and talonavicular movements, but the relation of these movements is closer to normal than after tibiotalar fusion, where the only movement is of the talonavicular joint (Pedowitz et al. 2016).

2.4.3.2 Kinematics

A fluoroscopic study with ten Agility ankle implants showed that all implants demonstrated less posterior-to-anterior translation during the stance phase than normal ankles (3.5 mm vs. 6 mm), but more variability in eversion and inversion and internal and external rotation, which might cause edge loading and high contact stress (Conti et al. 2006). Another fluoroscopic study showed that the mean range of flexion was approximately 17 degrees, the antero-posterior translation 3.2–3.3 mm, and the inclination angles similar to the normal ankle (Cenni et al. 2012).

Queen et al. conducted a kinematic study with 51 TAR ankles before surgery and 1 and 2 years after surgery about pain, function, and gait, and found that all measured variables improved significantly across all of time points but there was no difference in the ROM of the ankle (Queen et al. 2012).

Doets et al. (2007) have published several studies regarding the gait patterns after total ankle replacement. In their study from 2007 the gait pattern in terms of joint kinematics of the knee, ankle, and foot after ankle replacement was near normal, although the EMG activity and the ground reaction forces had not fully normalized (Doets et al. 2007). In subsequent studies, there has been no difference in mechanical loading of the ankle after ankle replacement, despite small differences in internal work at the ankle compared to normal (Houdijk et al. 2008). Although the gait patterns after TAR are nearly normal, patients have still experienced impaired lower leg function and increased mechanical energy dissipation during the step-to-step transition, and an increased metabolic demand of walking (Doets et al. 2009). In a study by Singer et al. comparing gait patterns after TAR and ankle arthrodesis, ankle moments and power remained reduced for both groups, although the gait pattern resembled the normal gait more closely after TAR than ankle arthrodesis (Singer et al. 2013). The abnormalities in gait mechanisms observed in valgus or varus aligned ankles preoperatively become normal when ankle alignment has been restored by total ankle replacement (Grier et al. 2016).

2.4.3.3 Return to sports activities

There are several studies addressing the clinical outcome after TAR with respect to return to sports. Valderrabano et al. (2008) analyzed 152 ankles of 147 patients who underwent Hintegra TAR. The mean follow-up time was 2.8 years. They found a statistically significant difference in the proportion of patients active in sports before and after surgery (36% vs. 56%). They also found that sports-active patients had statistically significantly higher postoperative AOFAS hind-foot scores than patients not active in sports. The most common sports were hiking, biking, and swimming. In a study by Naal et al. with 101 patients on average 3.7 years after TAR, two-thirds were active in sports and there was no association between sports participation, increased physical activity levels, and the appearance of periprosthetic radiolucencies (Naal et al. 2009). Bonnin et al. (2009) evaluated 179 Salto TARs with a self-administered questionnaire at a mean of 53.8 months after TAR and found that 76% of the patients had returned to light recreational activities (Bonnin et al. 2009). The authors concluded that nonimpact sports, but probably not high-impact sports or strenuous recreational activities, were generally possible after TAR (Bonnin et al. 2009).

2.4.4 Survival of total ankle replacement

There is some inconsistency in reporting the outcome and survival of total ankle replacements, which makes the comparison of different studies difficult. The terms revision and failure are both used as end-points of implant survival, and many studies present failure and revision rates. It has been suggested that isolated exchange of the polyethylene insert should not be considered as implant failure (Henricson et al. 2011a). However, some authors define failure as exchange of metallic components or conversion to fusion, others include all polyethylene insert exchanges, and some use any revision as an end-point. For total knee and hip implants, the acceptable level of 10-year survival is 95%. The literature regarding survival of the third-generation total ankle replacements implants is presented on Table 2.

Table 2. Studies on the most common third-generation TAR implants with survival analyses. Review studies are marked with *. Register studies are presented separately. In some reports, survival in presented only for component revisions and conversion to fusion, and in some with all types of revision as the end-point.

Implant	FU (years)	No of ankles	Survival (95% CI)	References
STAR, BP, LCS, RAMSES, ESKA	5	1107	90.6% (84.1 – 97.1%)	Stengel et al. 2005*
Agility	6	1105	86% (60 – 99%)	Gougoulias et al. 2010*
STAR	5		89% (74 – 99%)	
BP	12		92% (89 – 95%)	
AES, Salto, Hintegra	5.9	592	88% (39 – 100%)	Besse et al. 2010*
STAR	5	2088	85.9% (80.9 – 90.3%)	Zhao et al. 2011*
	10		71.1% (60.9 – 81.5%)	
STAR	5	51	70% (-)	Anderson et al. 2003
STAR	5	200	92.7% (86.6 – 98.8%)	Wood & Deakin 2003
STAR	12	25	95.4% (91.0 – 99.9%)	Kofoed 2004
STAR	5	84	96% (89 – 99%)	Mann et al. 2011
	10		90% (79.6 – 95.1%)	
STAR	5	82	93.9% (-)	Nunley et al. 2012
	8		88.5% (-)	
STAR	10	77	70.7% (-)	Brunner et al. 2013
	14		45.6% (-)	
STAR	12	18	94.4% (-)	Jastifer & Coughlin 2015
STAR	10	134	78% (63 – 88%)	Kerkhoff et al. 2016
AES	3.5	93	90% (-)	Henricson et al. 2010
AES	6	38	94.7% (80.3 – 98.7%)	Morgan et al. 2010
AES	2	38	79% (56 – 98%)	Kokkonen et al. 2011
Hintegra	5	684	94% (-)	Barg et al. 2013
	10		84% (-)	
Hintegra	3.75	50	90% (-)	Deleu et al. 2015
BP	8.3	31	93% (-)	San Giovanni et al. 2006
BP	5	30	87.6% (-)	Dhawan et al. 2012
Salto	6	98	94.9 – 98% (-)	Bonnin et al. 2004
Salto	9	87	85% (75 – 95%)	Bonnin et al. 2011
Salto	5	218	85.1 – 95.6% (-)	Schenk et al. 2011
BOX	3.5	62	91.9% (81.4 – 99.9%)	Bianchi et al. 2012
Mobility	3	100	97% (91 – 99%)	Wood et al. 2010
	4		93.9% (84.7 – 97.4%)	
BP, LCS	20	40	74.2% (-)	Buechel et al. 2004
	12		92% (-)	
BP, LCS	8	93	84% (-)	Doets et al. 2006
STAR, BP	2.7	58	92% (-)	Van der Heide et al. 2009
STAR	6	100	95% (87.2 – 98.1%)	Wood et al. 2009
BP		100	79% (63.4 – 88.5%)	
BP, CCI	6	90	79 (63 – 94%)	Nieuwe Weme et al. 2015
			87% (74 – 99%)	
Hintegra	4.5	209	92% (-)	Lefrancois et al. 2017
Agility		75	83% (-)	
STAR		75	92% (-)	
Mobility		92	81% (-)	

Register	Implants	FU (years)	No of ankles	Survival	References
Sweden	BP, STAR, AES, Mobility, Hintegra, CCI	5	531	78% (74 – 82%)	Henricson et al. 2007
Norway	TPR, STAR	5	257	89% (84 – 93%)	Fevang et al. 2007
		10		76% (-)	
New Zealand	Agility, RAMSES, STAR, Mobility	5	202	86% (-)	Hosman et al. 2007
Sweden	BP, STAR, AES, Mobility, Hintegra, CCI	10	780	69% (67 – 71%)	Henricson et al. 2011b
Sweden	STAR	12	324	64% (57 – 71%)	Henricson & Carlson 2015
		14		47% (38 – 66%)	

BP=Buechel-Pappas (Endotec, Orange, NJ), LCS=Low Contact Stress (DePuy, Warsaw, IN), RAMSES (Fournitures Hospitaliers, Mulhouse, France), ESKA (ESKA Orthodynamics, Lübeck, Germany), BOX=Bologna-Oxford (Finsbury Orthopaedics Ltd, Leatherhead, UK), Salto (Tornier, Saint Martin, France), CCI=Ceramic Coated Implant (Wright Medical Technology, Arlington, TN), TPR=Thompson Parkridge Richards (Smith & Nephew, Memphis, TN)

2.4.4.1 Clinical studies

The survival rates of total ankle replacements have become more satisfactory, but are generally considered to be inferior compared to total hip or knee arthroplasty. The reported survival rates have varied from 5-year survival rates of 70% to 95% to 10- to 12-year survival rates of 85%–95% (Anderson et al. 2003; Wood & Deakin 2003; Buechel et al. 2004; Kofoed 2004; Bonnin et al. 2004; Knecht et al. 2004; Spirt et al. 2004; Doets et al. 2006; San Giovanni et al. 2006; Wood et al. 2008; Wood et al. 2009; Wood et al. 2010; Bonnin et al. 2011; Mann et al. 2011; Schenk et al. 2011; Nunley et al. 2012; Dhawan et al. 2012; Barg et al. 2013c; Jastifer&Coughlin 2015; Nieuwe Weme et al. 2015; Kerkhoff et al. 2016; Lefrancois et al. 2017). Some of the variation is due to variable definitions of implant failure.

2.4.4.2 Review studies

In a systematic meta-analysis by Stengel et al. the weighted 5-year implant survival rate averaged 90.6%, secondary surgery was performed in 12.5%, and secondary arthrodesis was necessary in 6.3% (Stengel et al. 2005). The most frequent implant in the analysis was STAR (Stengel et al. 2005). In a systematic review of the literature on TAR survival Gougoulias et al. reported an overall failure rate of 9.8% (95% CI 3.1–16.5%) and a survival analysis varying from 67% at 6 years to 95.4% at 12 years (Gougoulias et al. 2010). The most common complication was residual pain in up to two thirds of the patients (Gougoulias et al. 2010). In another systematic review, the pooled mean implant survival rate was 85.9% at five years, and 71.1% at ten years, and the pooled failure rate was 11.1% during a mean follow-up time of 52 months (Zhao et al. 2011). In a review study by Zaidi et al. (2013) the overall survivorship was 89% at 10 years with an annual failure rate of 1.2% (95% CI, 0.7 to 1.6%), and TAR had a positive impact on the quality of life of the patients, as judged by reduced pain and improved function, as well as improved gait and increased range of movement (Zaidi et al. 2013).

2.4.4.3 Register studies

Labek et al. (2011) published an interesting study, where they compared the revision rates after TAR between register studies and sample-based clinical studies, and found the average revision rates from register studies to be approximately 2-fold compared to clinical studies being. The rates were 21.8% at 5 years, and 43.5% at 10 years. In addition, they showed that implant developers were over-represented in scientific publications with almost a half of the published content, and the inventors of STAR and BP total ankle implants published data which was statistically significantly superior to the outcome achieved in average patients as documented in registries. The implant developers are surely expected to be able to produce the best result of an implant, but with a high number of operated ankles and different surgeons, register data might

provide a more realistic view on the real situation. The limitations of register studies are potential deficiencies of coverage of the recorded data, as all implantations and revisions might not be reported adequately, and, in addition, a notable number of complications are treated without implant component exchange and not thus covered by the register. The terminology in reporting the complications is also highly variable (Mercer et al. 2016). Therefore, it would be essential to standardize data collection and evaluation and to develop a methodology addressing the specific needs of total ankle replacement (Labek et al. 2013).

Currently, there are published data on the survival of total ankle replacement from five different national registries: Sweden, Finland, Norway, New Zealand, and the UK (Fevang et al. 2007; Henricson et al. 2007; Hosman et al. 2007; Henricson et al. 2011b; Henricson & Carlsson 2015; Zaidi et al. 2016). The results of the Finnish register are presented in Chapter 5.2.

Five-year survival analyses are available from the registries of Sweden, Norway and New Zealand: the survival rate has varied from 78% to 88% and the revision rate from 7% to 19% (Fevang et al. 2007; Henricson et al. 2007; Hosman et al. 2007). The 10-year survival rate in Swedish and Norwegian registries was 62% to 72%, and aseptic loosening the most frequent reason for revision representing 31–48% of all revisions (Fevang et al. 2007; Henricson et al. 2007).

The largest registry data with the longest long-term follow-up comes from Sweden with 780 cases was updated at 2011, where the revision rate was 22%, and the 10-year survival rate was 69% (95% CI 67%–71%) compared to first report with estimated 5-year survival rate of 81% (95% CI 79%–83%) and 10-year survival rate of 62 % (95% CI 52%-72%) (Henricson et al. 2007). They also found that women below 60 years of age with osteoarthritis were at a higher risk for revision, but neither age nor gender affected the outcome of rheumatoid arthritis patients (Henricson et al. 2011b). The data was updated in 2015 with a follow-up of up to 20 years. Now the 14-year survival of the single-coated STAR was 47%, and the 12-year survival of the double-coated STAR was 64% (Henricson & Carlsson 2015). The most unsatisfactory results were obtained from the single-coated implant, as in a previous study from the same register (Henricson et al. 2011b), and many failures were associated with polyethylene wear or breakage, which is expected when the follow-up time becomes extended.

The largest cohort of ankle replacements from a joint registry is available from the UK, where the UK National Joint Registry was started at 2003, and which contains the data of total ankle replacements since 2010. The first short-term results were published in 2016: the 30-day readmission rate was 2.2%, and 6.6% of the primary TAR patients required a reoperation within 12 months of the index operation (Zaidi

et al. 2016). Early revisions were significantly more common in low-volume centers operating < 20 ankle replacements per year (Zaidi et al. 2016) than centers with a bigger volume. A similar effect of the volume of operations performed was shown in a study by Basques et al. from the US, where surgeons performing > 21 TAR cases per year had overall fewer complications, lower rate of medial malleolar fractures, decreased length of hospital stay, and decreased hospital charges (Basques et al. 2016).

There is a report evaluating the incidence, complications, and survival rates of TAR from the New York State Department of Health database, which is very close to registry data, although no national registries are available in the US (Seaworth et al. 2016). In that study, the rate of failure was 13.8%, and surgery for failure was only associated with younger age (Seaworth et al. 2016).

2.4.4.4 Studies addressing malaligned ankles

Numerous authors have suggested that the total ankle arthroplasty should be performed only when there is < 10–15 degrees of varus or valgus (Wood & Deakin 2003; Haskell & Mann 2004; Doets et al. 2006; Wood et al. 2008). The revision rate after TAR increases when varus deformity is present before surgery (Henricson et al. 2007). However, there are further studies where the outcome of preoperative varus alignment > 10 degrees has been comparable with neutral aligned ankles when appropriate additional procedures have been carried out (Kim et al. 2009; Shock et al. 2011). The most recent study shows that preoperative malalignment does not affect the result of TAR, if the alignment is reduced to the normal pre- or perioperatively (Queen et al. 2013). The current recommendation is that the deformity should be addressed with bony procedures, *e.g.,* supramalleolar or calcaneal osteotomies or subtalar fusion. Ligament releases and reconstructions, and tendon transpositions may be added to the treatment, when necessary (Coughlin et al. 2014).

2.4.4.5 Studies addressing different diagnoses

In many studies, survival of the total ankle replacement has been satisfactory in rheumatoid patients (Doets et al. 2006; Wood et al. 2007; van der Heide et al. 2009; Kraal et al. 2013; Pedersen et al. 2014), and there have not been differences between RA and OA patients regardless of the potential risks related to the inflammatory disease (Henricson et al. 2007; Pedersen et al. 2014). In some studies, the results have been superior in rheumatoid patients compared with osteoarthritis patients (McGuire et al. 1988; Bonnin et al. 2009). In studies comparing the survival rates of total ankle replacement of patients with different types of posttraumatic arthritis or primary and posttraumatic arthritis outcomes have been similar (Bonnin et al. 2009; Bai et al. 2010; Nieuwe Weme et al. 2015).

2.4.4.6 Studies addressing patient-related factors

The age of the patient does not seem to be associated with the survival of total ankle replacement, although older age might be related to fewer complications (Spirt et al. 2004; Hintermann et al. 2012; Demetracopuolos et al. 2015; Henricson & Carlsson 2015). In a study by Henricson & Carlsson (2015) a subgroup including women younger than 60 years with osteoarthritis, had a statistically significantly higher risk of revision when compared to men, women over 60 years, and other diagnoses than OA. In a study from the relevant New York State Department of Health database failure was associated with younger age (Seaworth et al. 2016).

There are diverse results on the effect of high BMI (>30) on the survival of total ankle replacement. In some studies, obesity has not had any effect on implant survival (Barg et al. 2011b; Bouchard et al. 2015), although successful TAR does not reduce obesity postoperatively (Penner et al. 2012). However, obesity has been shown to be associated with reduced long-term survivorship especially in patients with primary osteoarthritis (Schipper et al. 2016), and in a large national register study, obesity was associated with complications after both total ankle replacement and ankle fusion (Werner et al. 2015).

The effect of diabetes is not distinct. In a large study considering over 800 total ankle replacements, diabetes was not associated with a higher complication or infection rate in the short-term (Gross et al. 2015). In another study with a minimum follow-up time of two years involving 173 TAR implants, diabetes was associated with lower AOS and AOFAS scores, a higher rate of delayed wound healing, a higher failure rate, and a higher incidence of periprosthetic osteolysis, especially in patients with poor glycemic control (Choi et al. 2014).

As mentioned, smoking is associated with a statistically significantly increased risk of wound breakdown (Lampley et al. 2016). Although not statistically significant, smokers have an increased rate of infections, of revision surgery, of nonrevision surgery, and of worse outcome scores compared with nonsmokers or former smokers (Lampley et al. 2016).

2.4.4.7 Survival of STAR implants

There are several short-term and long-term survival studies of the STAR implant and they have provided satisfactory results (Andersson et al. 2003; Wood & Deakin 2003; Valderrabano et al. 2004; Schutte & Louwerens 2008; Wood et al. 2008; Henricson et al. 2007; Henricson et al. 2011b; Mann et al. 2011; Nunley et al. 2012; Brunner et al. 2013; Jastifer & Coughlin 2015; Daniels et al. 2015; Henricsson & Carlsson 2015; Kerkhoff et al. 2016), although in some studies the results seem to deteriorate over time (Brunner et al. 2013; Henricson & Carlsson 2015).

In the systematic review by Stengel et al. the weighted 5-year implant survival rate averaged 90.6%, and the most popular implant in the analysis was the STAR (Stengel et al. 2005). In a systematic review by Zhao et al. with exclusively STAR implants, the pooled mean implant survival rate was 85.9% at five years, and 71.1% at ten years, and the pooled failure rate was 11.1% during a mean follow-up time of 52 months (Zhao et al. 2011). Of the different generations of the STAR implant, the survival of the single-coated implant seems to be inferior compared to the double-coated version, and there also seems to be differences in the results between the double-coated version used in Europe compared to the version used in North America. In the studies conducted in North America, Nunley et al. presented the mean survival rate of 93.9% at 60.7 +- 21 months, and 88.5% at 107 months (Nunley et al. 2012), Mann et al. reported a probability of implant survival of 96% at 5 years and 90% at 10 years (Mann et al. 2011), and Jastifer & Coughlin showed an overall implant survival of 94.4% at a mean follow-up time of 12.6 years (range 10.2 to 14.6) (Jastifer & Coughlin 2015). In recent long-term European studies, the cumulative survival rate at 10 years of follow-up was 78% (Kerkhoff et al. 2016), and the probability of implant survival was 70.7% at 10 years and 45.6% at 14 years in a series of 77 ankles with single-coated STAR (Brunner et al. 2013). The longest follow-up to date has been published on data from the Swedish Ankle Registry with a follow-up of up to 20 years with both single- and double-coated implants; the 14-year survival of the single-coated STAR was 47% and the 12-year survival of the double-coated STAR was 64% (Henricson & Carlson 2015) However, most of the unsatisfactory results were related to the single-coated implant, as has been reported previously (Henricson et al. 2011b), and many failures were associated with polyethylene wear or breakage. In addition, the worse results might be explained by the nature of the study, as the results of registry studies are inferior to single-center studies (Labek et al. 2011). The differences in coating might explain the inferior results obtained in a series of solely single-coated STAR implants (Brunner et al. 2013).

The failure rate has varied from 14.9% in double-coated implants to 38% in single-coated implants (Brunner et al. 2013; Kerkhoff et al. 2016). Daniels et al. analyzed the revision rates of 111 ankles with double coated STAR implants with mean follow-up of 9 +- 1 years, and found that 12% of the ankles required metal component revision and 18% underwent polyethylene bearing exchange (Daniels et al. 2015).

2.4.4.8 Survival of AES implants

There are only few reports regarding the survival of the AES implant. In a study by Henricson et al. 93 AES implants were followed up for a mean time of 3.5 years; the estimated 5-year survival was 90% and only 3 cases of osteolysis occurred (Henricson et al. 2010). Morgan et al. (2010) reported their results of 38 AES implants: six-

year survival was excellent (94.7%), and the postoperative AOFAS and pain scores were good (Morgan et al. 2010). Although the clinical results were encouraging, 9 patients had osteolytic lesions (24%) (Morgan et al. 2010). In a study of Rodriguez et al. from 2010, 21 patients were followed for a mean time of 39.4 months during which the mean AOFAS score improved from 52.2 to 86.6, but osteolysis was present in 14 (77%) patients (Rodriguez et al. 2010). The authors concluded that the lesions were best identified by CT scanning, and recommended regular follow-up with CT (Rodriguez et al. 2010). Besse and co-workers reported their results from 50 AES ankles with a follow-up time of 39.9 months. Clinical outcome was good and the AOFAS score improved statistically significantly, but the rate of osteolysis was high (Besse et al. 2009). Peri-implant osteolysis was found in 62% of the ankles on the tibial side, and 43% on the talar side, and the lesions tended to be more severe with the dual-coating compared with the first-generation model (Besse et al. 2009). Kokkonen et al. published their findings on osteolysis in AES implants in 2011. The two-year survival was 79%, but there were osteolytic lesions in 19 (50%) ankles, which were especially large around the dual-coated prosthesis (Kokkonen et al. 2011).

2.4.5 Total ankle replacement versus ankle arthrodesis

There are several studies comparing total ankle replacement with ankle arthrodesis, and the result seems to be that neither of the procedures is better. Most of the studies are neither prospective nor randomized, but recently, a prospective multicenter randomized controlled trial comparing the outcome of total ankle replacement and arthrodesis has been registered in UK (TARVA; Goldberg et al. 2016).

An early study by McGuire et al. (1988) compared 25 TAR patients with 18 arthrodesis patients and found that the complication frequency was 30% higher in the arthrodesis group (McGuire et al. 1988). The result of TAR was better for rheumatoid patients compared with patients with osteoarthritis. Kofoed and Stürup published a study with 14 TAR and 14 arthrodesis patients whom they followed for an average of 84 months of follow-up in 1994, and concluded that TAR provided better pain relief, a better functional result, and a lower infection frequency compared with the arthrodesis group (Kofoed & Stürup 1994). In a large study by SooHoo et al. in 2007, 4705 ankle arthrodeses and 480 total ankle replacements from 1995 to 2004 were analyzed for complications, and there were more revision operations in the TAR group both at one and at five years of follow-up (SooHoo et al. 2007). The number of subtalar arthrodesis was higher in the arthrodesis group. The data was updated at 2016 with new data from 2005 to 2010, and, interestingly, the TAR patients had now a significantly lower rate of readmission and periprosthetic joint and wound infections than the arthrodesis patients (Stavrakis & SooHoo 2016). Haddad et al. published a systematic review of studies on ankle arthrodesis and total ankle replacement, where they included 39

studies with 1262 patients who had undergone ankle arthrodesis with a mean follow-up time of 5.3 (1.9–23.0) years and 10 studies with 852 patients who had undergone total ankle replacement with a mean follow-up time of 4.7 (2.3–9.0) years. There were no differences between the procedures regarding the AOFAS Ankle-Hindfoot Scale, subjective score, implant survival, and revision rate (Haddad et al. 2007). There are two comparative studies by Saltzman et al. (Saltzman et al. 2009; Saltzman et al. 2010). The first one is a prospective controlled study with a large number of patients who underwent 606 total ankle replacement and 482 ankle arthrodeses with a follow-up time of 24 months. Pain relief between the groups was similar, but the functional result was better in the TAR group (Saltzman et al. 2009). In second study, there were 49 total ankle replacements that were compared with 29 arthrodeses with an average follow-up of 4.2 years. Here, the clinical results regarding clinical scores and radiographic evaluation were similar, but pain relief was superior in the TAR group (Saltzman et al. 2010). The quality of life was analyzed in a study by Slobogean et al. and there were no differences between patients who had undergone total ankle arthroplasty and ankle arthrodesis (Slobogean et al. 2010). In a study by Esparragoza et al. (2011) the quality of life was slightly better after TAR compared to arthrodesis measured by the AOFAS score and the short form (SF)-36 questionnaire (Esparragoza et al. 2011). Pedowitz et al. analyzed the arc of movement and functional outcomes of 41 TAR patients and 27 arthrodesis patients, and found that the range of motion after ankle arthrodesis was achieved at the talonavicular joint (Pedowitz et al. 2016). As expected, there was a significant difference in sagittal plane movement and talonavicular motion between the groups, but also the functional scores VAS and FAAM were significantly higher in the TAR group (Pedowitz et al. 2016). The postoperative performance on uneven surfaces of patients who had undergone total ankle arthroplasty and ankle arthrodesis was analyzed in a prospective study by Jastifer et al., who measured the ability of the patients to walk in stairs, an inclined ramp, and on uneven surfaces 6 and 12 months postoperatively (Jastifer et al. 2015). They found that the TAR group had a significantly better outcome in the Buechel Pappas scale, AOFAS score, VAS score, other functional scores, ankle dorsiflexion, plantar flexion, walking upstairs, downstairs and downhill, but patient satisfaction was good in both groups (Jastifer et al. 2015). In Sweden, a comparison between TAR and ankle fusion was made of 16 patients who had undergone TAR on the one ankle and fusion on the other ankle; the patients were equally satisfied with both procedures (Henricson et al. 2016b).

The worst results for total ankle replacement were reported in a comparative study by Daniels et al., where they analyzed the revisions and complications of 232 TAR and 89 arthrodesis patients as a part of a COFAS prospective multicenter study, and found that the rates of reoperation and major complications were higher after ankle replacement (Daniels et al. 2014), although the AOS and SF-36 scores were similar

between the groups (Daniels et al. 2014). The inferior result of the TAR group could partly be explained by a large amount on Agility (DePuy, Warsaw, IN, USA) implants on the group, which is known to have higher complication rate compared with more modern total ankle implants (Knecht et al. 2004; Spirt et al. 2004; Criswell et al. 2012; Roukis 2012).

2.4.5.1 Conclusion: Patient selection

Of the preceding review of the literature (section 2.4.2.2 – 2.4.5) one may draw a conclusion that total ankle replacement appears to be the optimal choice for a patient with the following characteristics: middle-aged or older, has rheumatoid arthritis, is of normal weight, does not smoke, has no significant comorbidities, and has an ankle that is with a well aligned with good bone stock and a good range of motion. Arthrodesis, on the other hand, might be a better option for a patient whose ankle is markedly deformed, who has bone loss, has had a previous infection, is heavier and physically active, and has neuroarthropathy or pathological joint laxity.

2.4.6 Radiology of total ankle replacement

2.4.6.1 Conventional radiography

Traditionally, total joint replacements, including total ankle replacements, have been followed by conventional radiography. Standing radiographs including anteroposterior and lateral views are used (Figure 2.); non-weight-bearing lateral ankle views in maximal plantar and dorsiflexion can be used to measure the range of motions between the components. The radiographs provide information on the anatomic relationships between the components, bone loss or ectopic bone formation, postoperative range of motion, component migration and subsidence, fractures, and impingement.

Studies on total hip replacement have shown that radiographs underestimate the size of periprosthetic osteolytic lesions (Puri et al. 2002; Walde et al. 2005) and some of the existing lesions may even remain undetected on radiographs (Looney et al. 2002). In total ankle replacements, CT has been shown to be superior in detecting osteolytic lesions around the components compared to radiographs (Hanna et al. 2007; Rodriguez et al. 2010; Kohonen et al. 2013a; Viste et al. 2015).

2.4.6.2 Computed tomography

CT is useful for imaging the ankle after TAR when the patient has implant-related symptoms or when periprosthetic osteolysis is suspected and the condition cannot be determined with radiography. Keogh et al. (2003) and Cahir et al. (2007) have shown

the usefulness of CT for imaging the painful total hip replacement. Studies on total ankle replacement have shown that radiographs provide only limited information on periprosthetic osteolytic lesions (Besse et al. 2009; Hanna et al. 2007; Rodriquez et al. 2009; Kohonen et al. 2013a) and that CT reveals osteolytic changes in ankle better than radiographs (Hanna et al. 2007; Rodriguez et al. 2010; Kohonen et al. 2013a; Viste et al. 2015), especially beneath the talar component (Kohonen et al. 2013a) (Figure 6). CT is also useful for defining the exact locations of osteolytic lesions when revision surgery for a failed TAR is being planned, and CT could be included for the follow-up of every TAR patient to detect osteolytic lesions as early as possible (Rodriguez et al. 2010; Kohonen et al. 2013a). CT may also be useful in other total ankle replacement related conditions, *e.g.,* periprosthetic fracture, subluxation and dislocation of prosthesis components, infection, impingement, and heterotopic ossification. CT should also be considered before total ankle replacement to determine the presence of any degenerative cysts or geodes in distal tibia, fibula, or talus so that such lesions will not later be interpreted as osteolysis.

Every metal instrument causes artifacts in CT images, and to minimize the artifacts caused by prosthesis components, orientation of the components, and acquisition parameters of CT-imaging should be optimized. Orientation is critical: the long axis of the tibia should be aligned parallel with the CT scan table (Kohonen et al. 2013b). At optimal orientation, a 100 kVp tube voltage is sufficient to evaluate periprosthetic bone structure (Kohonen et al. 2013b). Modern CT scanners have image reconstruction algorithms, *e.g.*, iterative reconstruction, which helps in minimizing metal artifacts. Radiation exposure of the patient is inconsequential due to the peripheral location of ankle joint (Biswas et al. 2009).

2.4.6.3 Magnetic resonance imaging

MRI has also been used to evaluate periprosthetic bone structure. Although metal implants do cause artifacts on MRI and impair image quality, there are metal artifact reduction sequences available which help to obtain diagnostic images from joints with prosthesis components (Potter et al. 2005; Potter & Foo 2006; Vessely et al. 2006).

2.4.6.4 Radiostereometric analysis

Plain radiographs provide limited information on implant migration, and Braito et al. have shown that the accuracy between plain radiographic measurements of prosthetic migration and alignment is poor (Braito et al. 2015). Radiostereometric analysis (RSA) provides the most accurate measurement of implant migration and is mainly used for monitoring osteointegration of the implant (Selvik et al. 1983; Kärrholm 2012). There are some RSA-studies on early migration of TAR implants and these studies

show rapid initial migration of the implants, which usually stabilizes by 6 months after surgery (Carlsson et al. 2005; Nelissen et al. 2006; Dunbar et al. 2012).

2.4.7 Peri-implant osteolysis

A major problem related to total ankle replacement has been and still is peri-implant osteolysis. Osteolysis is a process where biological or mechanical factors initiate a local immune response in the periprosthetic tissue, which ultimately results in implant loosening and failure. Although a common complication in all total ankle implants, early and severe osteolysis has been a special problem with AES implants (Besse et al. 2009; Rodriguez et al. 2010; Morgan et al. 2010; Kokkonen et al. 2011).

2.4.7.1 Peri-implant osteolysis in total ankle replacement

Besides AES, osteolysis occurs with many total ankle implants, most frequently with Hintegra (Integra, Plainsboro, NJ, USA) implants (Yoon et al. 2014; Deleu et al. 2015). A study by Doets et al. from 2006 included 19 New Jersey low contact stress (LCS; DePuy Orthopaedics Inc, Warsaw, IN, USA) and 74 Buechel-Pappas (BP, Endotec, South Orange, NJ, USA) implants and radiolucency was seen in 39 ankles, and six had a complete radiolucent line over one millimeter (Doets et al. 2006). Wood and co-workers published their results on 100 STAR and 100 BP implants. Patients were followed for at least 36 months, and the authors report that there were osteolytic cavities in 7% of the ankles (Wood et al. 2009). Of other reports on osteolysis related to the STAR implant, the highest rate was reported by Schutte and Louwerens with 20% lesions in 49 STAR implants during a mean follow-up time of 28 months (Schutte & Louwerens 2008). In a study by Nieuwe Weme et al. with 15 BP and 75 CCI (Ceramic Coated Implant; Wright Medical Technology, Arlington, TN) implants and a mean follow-up time of five years, osteolysis was the most frequent failure mechanism, as there was lesions over ten millimeters in 23/90 (26%) of the ankles, six of which required salvage fusion (Nieuwe Weme et al. 2015). In a histological study regarding osteolysis with samples from four different TAR implants the majority of the samples were from the CCI implants (van Wijngaarden et al. 2015). Osteolysis related to the Hintegra implant has been reported in one study in 24 of 50 ankles (48%) (Deleu et al. 2015), and in 37% of the ankles in another study during a mean follow-up of 40.8 months (Yoon et al. 2014). Lucas y Hernandez and associates found small osteolytic lesions in 67% of the CT scans, and large lesions in 9% of the 127 ankles with an AKILE® (Lavender Medical Limited, UK) implant during a mean follow-up time of 81 months (Lucas y Hernandez et al. 2014). Osteolysis has also been common for the Agility (DePuy, Warsaw, IN, USA) implant, which is known to have a higher complication rate than modern total ankle implants (Knecht et al. 2004; Spirt et al. 2004; Roukis 2012; Criswell et al. 2012). At least one case report has been published

of osteolysis in an INBONE I® (Wright Medical Technology Inc, Memphis, TN, USA) ankle implant (Roukis 2015).

2.4.7.2 Osteolysis and the AES implant

Morgan et al. reported encouraging clinical results of 38 AES implants but osteolytic lesions were found in nine patients (24%) (Morgan et al. 2010). In a study of Rodriguez et al. from 2010 with 21 patients and a mean follow-up time of 39.4 months osteolysis was present in 14 (77%) patients (Rodriguez et al. 2010). The authors concluded that the lesions were best identified by CT, and recommended regular CT follow-up (Rodriguez et al. 2010). Besse and co-workers reported the results of 50 AES ankles after an average follow-up time of 39.9 months. The rate of peri-implant osteolysis diagnosed by plain radiography was high: 62% of the ankles on the tibial side and 43% of the ankles on the talar side (Besse et al. 2009). The lesions tended to be more severe with the dual-coating compared with first generation model (Besse et al. 2009). Kokkonen et al. reported osteolytic lesions in 19 (50%) ankles, and more cyst-like osteolysis and larger lesions around the dual-coated prosthesis (Kokkonen et al. 2011). The AES implant was withdrawn from the market in 2008 after the findings regarding periprosthetic osteolytic lesions around the components became known, albeit unpublished.

2.4.7.3 Mechanisms of osteolysis

Numerous factors have been suggested to contribute to the development of osteolysis, where the biological response of the surrounding host tissue cells is the principal cause (Gallo et al. 2013). Besides wear particles from the implant itself or implant coating materials, also local damage to blood supply, joint fluid pressure and flow, and local anatomic-physiological and mechanical factors presumably affect the process. At the cellular level, the major cell types involved are the monocyte/macrophage lineage cells, both by their phagocytic and pro-inflammatory mediator release features, and by acting as the key factor initiating the complex adverse local tissue reaction through interaction with wear debris (Bitar & Parvici 2015). An increased number of osteoclasts at the bone-implant interface, together with impairment of osteoblast function driven by multiple inflammatory pathways, affect bone resorption and lead to osteolysis. Genes regulating inflammation and osteoclastogenesis are involved in osteolysis (Veronesi et al. 2017).

Particles

Traditionally, peri-implant osteolysis has been considered to originate from a foreign body reaction caused by particles generated mostly from polyethylene wear, and the term “particle disease” was coined (Harris 1994). Wear particles are considered to be

the most important factor leading to osteolysis, but the specific nature of this process is dependent of the patterns of wear, type of prosthesis, and host-related factors (Purdue et al. 2006; Bitar & Parvici 2015). In addition to polyethylene, the wear particles may be bone, cement, metal, metallic corrosion products, or hydroxyapatite, which originate from wear and corrosion, and induce an inflammatory reaction with specific alterations to the host's immune response (Bitar & Parvici 2015; Sukur et al. 2016). The wear debris may be present as soluble ions or insoluble particles (Bitar & Parvici 2015). The degree of bone loss seems to be partly a function of the size, number, and origin of the particles (Sukur et al. 2016).

Wear particles activate an immune response, which leads to increased osteoclast activation (Bitar & Parvici 2015). The most important target of wear particles are the macrophages, as they actively phagocytose the particles, and in response express chemokines, cytokines, proteolytic enzymes, and other substances of inflammation, leading to a predominance of osteoclasts in induced periprosthetic bone tissue at the bone-implant interface (Purdue et al. 2006; Bitar & Parvici 2015).

In a histological light microscopy examination of the samples taken from the joint capsule at revision surgery of ballooning lysis around the STAR implant a mass of polyethylene particles was seen surrounded by foreign-body giant cells with an active appearance (Valderrabano et al. 2004). A similar histological finding was previously reported of aggressive granulomatous lesions associated with hip arthroplasty (Santavirta et al. 1990a,b). Other histological studies from failed total ankle replacements have revealed a foreign body reaction where the expression of multinuclear foreign body giant cells has been high, but considerable necrotic tissue and a low amount of PE and metal particles has been seen (Dalat et al. 2013; van Wijngaarden et al. 2015; Singh et al. 2016). In addition to macrophages, which have been the predominant cell type, also T-lymphocytes, B-lymphocytes, and dendritic cells have been identified in tissue from ankles with ballooning osteolysis (Singh et al. 2016). The role of the lymphocytes with respect to osteolysis is controversial (Purdue et al. 2006).

Most of the wear particles are smaller than the resolution of the light microscope and analysis of wear particles merely by light microscope may not be feasible (Savio et al. 1994). In a study of six recovered AES total ankle implants, electron microscopy was carried out in addition to other analyses, and the specimens showed marked signs of wear of both components thought to be due to hard foreign particles between the mobile and static parts of the implant. Aluminum particles were seen in the alloy-titanium coating interface (Cottrino et al. 2016). In addition, titanium particles were embedded in the mobile bearings and the periprosthetic tissues (Cottrino et al. 2016). The authors suggested that the cobalt-chromium (CoCr) alloy used in

the AES implants was brittle and became abraded, while the aluminum particles were caused by defective sand blasting. Together, these circumstances might have weakened the mechanical properties of the coating and induced stress leading to cracks in the titanium coating and to premature wear (Cottrino et al. 2016). The titanium alloy is less resistant against shear compared to other metal alloys (Gundapaneni et al. 2015).

Proinflammatory cytokines

The pathogenesis of osteolysis is multifactorial and diverse, but osteolysis is driven by proinflammatory enzymatic bone resorption, increased osteoclastogenesis, and decreased osteoblastogenesis with numerous proinflammatory cytokines participating the process (Bitar & Parvici 2015; Kandahari et al. 2016). Early local inflammation around the implant activates the production of several pro-inflammatory cytokines and chemokines, *e.g.,* tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), prostaglandin E2, (PGE2), monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinases (MMPs), which induce chronic inflammation, tissue fibrosis, tissue necrosis, and osteoclast activation (Geng et al. 2011; Nich et al. 2013). Inflammatory cytokines promote bone resorption, and TNF-α is a key proinflammatory cytokine that promotes particle-induced inflammation and osteolysis. The inflammatory cytokines can act directly on macrophages (Purdue et al. 2006). In addition, they may influence osteoclastogenesis indirectly via the expression of nuclear transcription factor-kappa B (NF-κB) (Purdue et al. 2006)

The nuclear transcription factor-kappa B (NF-κB) family is the key regulator in the expression of several genes controlling proinflammatory cytokine production and appears to be crucial in initiating the host reaction (Sukur et al. 2016). Receptor activator of NF-κB ligand (RANKL) binds to receptor activator of NFkB (RANK) expressed on cell surface, which is necessary for the differentiation of osteoclast precursors to mature functional osteoclasts (Nicholson et al. 2000). Osteoprotegerin (OPG) is a naturally occurring decoy receptor for RANKL, which downregulates osteoclastogenesis by binding RANKL and preventing its interaction with RANK (Simonet et al. 1997). The bone resorption rate is thus affected by the balance of RANKL and OPG (Boyle et al. 2003). The receptor activator of NF-κB ligand (RANKL) pathway and osteoprotegerin (OPG) have a prominent role in the development of osteolysis (Bitar & Parvici 2015; Sukur et al. 2016).

The alarmins or damage-associated molecular patterns (DAMPs) are endogenous molecules released by dead and dying cells that signal tissue and cell damage (Bianchi 2007; Bidwell et al. 2008). They are recognized by the cells of the innate immune

system by several families of pattern-recognizing receptors (PRR), mainly toll-like receptors (TLRs) (Bianchi 2007). The high mobility group box 1 (HMGB1) protein is a DNA-binding and regulating non-histone protein able to stimulate receptor equipped cells to produce various inflammation promoting chemokines and cytokines, and is considered to be the master cytokine in the alarmin family (Bianchi 2007; Bidwell et al. 2008). After release from necrotic cells, HMGB1 can alarm close-by cells via pattern-recognizing receptors RAGE, TLR2 and TLR4. The signaling pathway of toll-like receptors (TLRs) activates RANK mediated expression of various inflammatory cytokines (Bianchi 2007). Increased expression of the TLRs has been reported around loose total hip replacement implants (Takagi et al. 2007). In addition to particles, low pH and hypoxia can also contribute to the periprosthetic inflammatory state (Ioannou et al. 2011; Naylor et al. 2013; Brüne et al. 2013).

Several cytokines inhibit the differentiation of the osteoclasts. There is most information on interferon gamma, which downregulates RANKL-induced osteoclastogenesis (Takayanagi et al. 2000). Wear debris induces bone resorption also by decreasing the protective effects of antiosteoclastogenetic cytokines, as both titanium and polymethyl methacrylate (PMMA) cement particles have been shown to inhibit the actions of these cytokines (Rakshit et al. 2006). Titanium particles might also inhibit the formation and function of osteoblasts: titanium particles reduce the expression of type I and II collagen in osteoblasts, reduce the viability of the osteoblasts by inducing apoptosis, downregulate the differentiation of osteoblasts from the mesenchymal stem cells, and induce the apoptosis of the mesenchymal stem cells (Yao et al. 1997; Zambonin et al. 1998; Vermes et al. 2000; Vermes et al. 2001; Pioletti et al. 2002; Wang et al. 2002; Wang et al. 2003, Okafor 2006). Titanium and PMMA particles may also affect the generation and activation of osteoclasts by affecting the intracellular signaling molecules, mainly the MAP kinase family members (Purdue et al. 2006).

Micromotion

Micromotion and compressive stress at the bone-implant interface play an important role in the process of peri-implant bone resorption. Radiostereometric studies of hip implants imply that early migration of an implant predicts an increased risk of implant loosening (Kärholm et al. 1994). Considering wear particles, larger particles are generally produced because of surface fatigue (delamination as flaky debris, and pitting as round debris), while smaller, more biologically active particles generally arise by adhesion and abrasion through repeated rotational, rolling, and sliding motions on the bearing surfaces (Gallo et al. 2013). It has been suggested that the coating of AES total ankle implants may delaminate by fretting and that metal particles emerge from shear stress, which detaches particles from the coating (Dalat et al. 2013). It has also been shown that micromotion at the bone-implant interface upregulates

RANKL expression and downregulates OPG expression creating a bone resorption response in human bone (Stadelmann et al. 2008). Thus, osteoclastogenesis might be mechanically regulated at the cellular level via the RANKL-OPG-RANK pathway.

Fluid pressure

Fluid pressure and flow may contribute to osteolysis. In animal models a constant or intermittent fluid pressure under an implant results in massive bone resorption under the pressurized area (van der Vis 1998a; van der Vis et al. 1998b; Aspenberg & van der Vis 1998; Fahlgren et al. 2010; Johansson et al. 2011). This phenomenon may have contributed to clinical osteolysis according to a case report (Schmalzried et al. 1997).

High fluid pressures and flow may also be present within osseointegrated implants, as there may be high fluid pressures in pseudojoints after hip replacements in stable and loose implants (Hendrix et al. 1983; Robertsson et al. 1997; Alidousti et al. 2011). The cementless designs might allow easier access of fluid and debris into porous bone, at least in total hip arthroplasty (Schmalzried et al. 1992; Schmalzried et al. 1994).

Fluid pressure and flow in bone tissue changes the biochemical response of osteocytes, which raises the RANKL-to-OPG ratio (You et al. 2008; Sakai et al. 2009). Fluid pressure also induces osteoclasts proliferation at a different localization compared to titanium particles by a molecular pathway, which is less strongly associated with the innate system and TNFα (Nilsson et al. 2012).

2.4.7.4 Treatment of periprosthetic osteolytic lesions

There are no established treatment protocols for osteolytic lesions of the ankle. Curettage and bone or cement grafting in cases of large or continuously growing lesions have been proposed to prevent implant subsidence and loosening (Rodriguez et al. 2010; Gupta et al. 2010; Prissel & Roukis 2014; Roukis 2015; Gross et al. 2016c). However, some authors have suggested only follow-up, as the results of bone grafting have been poor (Besse et al. 2013). In a recent study based on data from the current study, 28% of the grafted lesions had good radiologic survival at a mean of 3.8 years of follow-up, but 68% of the lesions progressed (Kohonen et al. 2017). Generally, the follow-up should include a CT scan, as plain radiographs underestimate the lesions (Hanna et al. 2007; Rodriguez et al. 2010; Kohonen et al. 2013a; Viste et al. 2015).

Currently there are no validated biomarkers for early detection and monitoring of aseptic loosening or peri-implant osteolysis. Many biomarkers including RANKL, many interleukins, and bone resorption markers have been investigated, but none has worked clinically (Sumner et al. 2014).

Many medical treatments for osteolysis have been studies, but none of has so far been proven to be successful (Kandahari et al. 2016). Denosumab, a monoclonal antibody against RANKL, could theoretically be advantageous, since the RANKL pathway seems to be crucial for the development of osteolysis. Denosumab is currently in phase II clinical trials on efficacy in treating osteolysis (Kandahari et al. 2016). In recent experimental murine *in vivo* studies, many agents, including strontium, theaflavin-3,3′-digallate, a compound derived from black tea, dopamine, and scutellarin have been found to inhibit RANKL-mediated osteoclastogenesis (Zhu et al. 2016; Zhao et al. 2016; Yang et al. 2016; Hu et al. 2017).

2.4.8 Failed total ankle arthroplasty

2.4.8.1 Component revision

Revision of a failed total ankle replacement is challenging, and no general treatment recommendations exist. Traditionally, ankle fusion has been proposed as a salvage procedure for the failed TAR. In situations where one or both components are loose, but there is sufficient bone stock left, component revision is an alternative. There are only few studies on component revisions. A retrospective review of 35 cases of failed Agility (DePuy, Warsaw, IN, USA) implant revised with an INBONE II (Wright Medical Technology Inc, Memphis, TN, USA) implant has been published (Williams et al. 2015). Reasons for revision were mechanical loosening, osteolysis, periprosthetic fractures, and prosthesis dislocation. Although the revisions were associated with a high number of intraoperative and acute postoperative complications, as well as adjunctive procedures, the authors concluded that revision is a viable treatment option for failed TAR. In a series of 117 failed TAR revised with a Hintegra (Integra, Plainsboro, NJ, USA) implant the result of revision was comparable to the primary arthroplasty, as only 15% of the revisions required further surgery, the estimated survival with loosening of the components as end-point at nine years was 83%, and the AOFAS score improved significantly (Hintermann et al. 2013). The results from the Swedish Ankle Registry are not as encouraging. The analysis of 69 revision operations with exchange of the tibial, talar, or both components showed that the 10-year survival was only 55% and only half of the patients were satisfied with the revision prosthesis (Kamrad et al. 2015). Custom implants for revision surgery are available for some implant designs, and there are some studies on the use of the Agility (DePuy, Warsaw, IN, USA) custom talar component (Ellington et al. 2013; Alvine et al. 2016).

2.4.8.2 Salvage arthrodesis

Salvage arthrodesis after failed total ankle replacement seems to yield satisfactory results. In the Mayo Clinic 38 failed TARs were revised to fusion and an 89% fusion

rate was reported (Kitaoka et al. 1992). In smaller series, a fusion rate ranging from 61% to 100% have been reported (Hopgood et al. 2006; Culpan et al. 2007; Doets & Zurcher 2010; Deleu et al. 2014). Patients with rheumatoid arthritis seem to have inferior fusion rates compared to patients with osteoarthritis (Hopgood et al. 2006; Doets & Zurcher 2010), and blade plate and intramedullary nail fixation seem to result in a better outcome than screw fixation, especially in patients with rheumatoid arthritis (Hopgood et al. 2006; Doets & Zurcher 2010). The largest data of salvage ankle fusion after TAR is from the Swedish Ankle Registry, 118 revisions. The solid arthrodesis rate at the first attempt was 90%, but similar to the revision TAR, only less than half of the patients were satisfied and the functional scores were low (Kamrad et al. 2016). Technically, there is always a substantial gap between bones after removal of the components even after TAR implants requiring minimal bone resection. To avoid shortening of the leg, a bone block usually of allogeneic origin is needed. The use of a trabecular metal implant or titanium truss has been described (Henricson & Rydholm 2010; Wiewiorski et al. 2015; Mulhern et al. 2016). In some severe cases complicated by infection, non-union, or soft tissue problems, a below-knee amputation may be the only reasonable alternative.

3. OBJECTIVES OF THE STUDY

The general aim of this study was to investigate the long-term clinical and radiographic outcome of mobile bearing third generation total ankle replacements in Finland.

The specific aims were

To evaluate the radiographic and histological features of osteolysis around AES total ankle replacement (I)

To investigate the population-based survival of third generation total ankle replacement implants in Finland (II)

To investigate the role of the RANKL system (III) and autoinflammatory DAMP-PRR interactions (IV) in peri-implant osteolysis of AES total ankle replacements

To assess the outcome and survival of the STAR total ankle replacement in Paimio Hospital (V)

To assess the outcome and survival of the AES total ankle replacement in Paimio Hospital (VI)

4. PATIENTS, MATERIALS, AND METHODS

4.1 Patients

The first 3rd generation total ankle arthroplasty was performed in Paimio hospital in 1997. The first 34 ankles received the Scandinavian Total Ankle Replacement (STAR; Stryker GmbH, Selzach, Switzerland) implant followed by the Ankle Evolutive System (AES; Biomet, Warsaw, Indiana, USA) implant as of 2002. The change was due to more developed instrumentation. 130 AES prostheses were implanted before it was withdrawn from the market due to peri-implant osteolysis in 2008, giving the total amount of 164 ankles in 156 patients for this study. There were 68 patients with rheumatoid arthritis, 82 patients with osteoarthritis, and 6 patients with other forms of arthritis.

4.1.1 STAR group

A consecutive series of 34 TARs in 33 patients operated on or supervised by one senior orthopedic surgeon was enrolled for the study. All ankles were operated between 1997 and 2002 and reviewed retrospectively in 2016. The demographic data of the patients is shown in Table 3. Patients have been followed as outpatients clinically and radiologically six weeks, three months, six months, and one year after the operation and every second year thereafter.

Table 3. Baseline characteristics of patients in the STAR group. FU=follow-up

Diagnosis	No. of ankles (patients)	Age (years) average at operation (range of parentheses)	Age (years) average at latest FU (range of parentheses)	Male/ female
Rheumatoid arthritis	19 (18)	56.6 (29 – 78)	69.5 (45 – 85)	8/10
Osteoarthritis	14 (14)	48.4 (19 – 72)	60.1 (20 – 85)	8/6
Other	1 (1)	32	41	0/1
All diagnoses	34 (33)	52.5 (19 – 78)	64.3 (20 – 84)	16/17

4.1.2 AES group

A consecutive series of 130 TARs in 123 patients operated on or supervised by one senior orthopedic surgeon was enrolled for the study. All ankles were operated between 2002 and 2008 and reviewed retrospectively in 2016. The demographic data of the patients is shown in Table 4. Patients were followed as outpatients clinically and radiologically six weeks, three months, six months and one year after the operation and every second year thereafter.

Table 4. Baseline characteristics of patients in the AES group

Diagnosis	No. of ankles (patients)	Age (years) average (range of parentheses)	Male/ female
Rheumatoid arthritis	52 (50)	56.6 (26 – 80)	8/44
Osteoarthritis	73 (68)	56.9 (18 – 86)	40/33
Primary OA	15 (14)	67.1 (39 – 79)	7/8
Posttraumatic OA	54 (50)	54.0 (18 – 86)	32/22
Secondary OA	4 (4)	57.0 (39 – 66)	1/3
Other	5 (5)	47.2 (28 – 64)	2/3
All diagnoses	130 (123)	56.4 (18 – 86)	50/80

4.1.3 Control patients

Control samples for histologic analysis for RANKL and inflammatory markers were obtained from 10 matched patients: four patients undergoing ankle arthrodesis, two patients undergoing primary Hintegra (Integra, Plainsboro, NJ, USA) ankle prosthesis implantation for chronic osteoarthritis of the ankle, two patients undergoing primary CCI (Wright Medical Technology, Arlington, TN, USA) ankle prosthesis implantation for chronic osteoarthritis of the ankle, one patient undergoing a revision of Hintegra (Integra, Plainsboro, NJ, USA) implant for early aseptic loosening, and one patient undergoing a revision for CCI (Wright Medical Technology, Arlington, TN, USA) ankle implant for malalignment. Neither of the two latter patients had osteolysis.

Control samples for the analysis of the elements were obtained from bone bank of 4 femoral caputs from patients with no metal implants in their body.

4.2 Implants

4.2.1 STAR

STAR (Stryker GmbH, Selzach, Switzerland) is still widely used in Europe and in the US (Figure 1). It consists of three components: tibial and talar components of cobalt-chrome (Co-Cr) and an ultra-high molecular weight polyethylene (UHMWPE) gliding insert. The tibial component has a highly polished flat articulation surface and two cylindrical fixation bars, which anchor the implant to the tibia. The talar component has a ridge running anteroposterior in the middle of the gliding surface guiding the UHMWPE mobile-bearing insert. The first version of the STAR implant was fixed bearing and cemented. In 1989, cement fixation was replaced by a hydroxyapatite coating over smooth Co-Cr, and since 2000 all STAR implants outside North America have been double coated with a titanium CaP porous coating. This differs from the STAR implant used in the US market, which has a titanium plasma spray coating. In this study, the single coated implant was used in 7 ankles, and double coated (Ti + CaP) in 27 ankles.

Figure 1. Ankle Evolutive System (AES) total ankle implant (picture from Biomet Finland Oy) and Scandinavian Total Ankle Replacement (STAR) implant (picture from Stryker Finland AB).

4.2.2 AES

The AES (Biomet, Warsaw, Indiana, USA) total ankle prosthesis was originally developed from the Buechel-Pappas prosthesis (Endotec, Orange, NJ, USA) and was the most popular total ankle implant in Finland and used also widely across other parts of Europe (Figure 1). It had a three-piece, uncemented, unconstrained design with tibial and talar components of cobalt-chromium (Co-Cr). It had a front to back mobile bearing of tapered ultra-high molecular weight polyethylene (UHMWPE) between the flat tibial component and the shallow sulcus of the talar implant. The meniscus was smaller than the metallic components to protect it from overhang. In 2004, the design was changed and the hydroxyapatite (HA) coating on metal (Co-Cr) components was changed to a porous coating with pure titanium and hydroxyapatite (T40 HA). The tibial component was also changed from a modular stem to a monoblock model. In 2008, the AES implant was withdrawn from the market due to alarming findings regarding a high occurrence of peri-implant osteolysis. In this series, there were 52 ankles with the first-generation implant and 78 ankles with the dual-coated implant.

4.3 Clinical evaluation

Pain and function and ROM were assessed using the Kofoed Ankle Score (Table 5). Pain points in the Kofoed Ankle Score were also analyzed separately, as a VAS pain score was not available. Patient-reported outcome was assisted using an inhouse questionnaire shown in Table 6. Clinical ROM was assessed by measuring the maximum dorsiflexion and maximum plantar flexion of the ankle subtalar joint at a neutral position.

Table 5. Kofoed Ankle Score.

Pain (max. 50 points)					
No pain **50**	Starting pain **40**	Pain walking levels **35**	Loading pain occasionally **30**	Loading pain always **15**	Pain during test or spontaneously **0**
Function (max. 30 points)					
Toe walking **3**	Heal walking **3**	Normal cadence walking stairs **6**	One-leg standing **6**	No walking aids **6**	No orthopedic foot wear **6**
Mobility (max. 20 points)					
Extension	> 10 degrees **5**	5 – 9 degrees **3**	< 5 degrees **1**		
Flexion	> 30 degrees **5**	15 – 29 degrees **3**	< 15 degrees **1**		
Supination	> 30 degrees **3**	15 – 29 degrees **2**	< 15 degrees **1**		
Pronation	> 20 degrees **3**	10 – 19 degrees **2**	< 10 degrees **1**		
Valgus	< 5 degrees **2**	5 – 10 degrees **1**	> 10 degrees **0**		
Varus	< 3 degrees **2**	4 – 7 degrees **1**	> 7 degrees **0**		
85 – 100 Excellent, 75 – 84 Good, 70 – 74 Fair, < 70 not acceptable					

Table 6. Questionnaire for assessment of subjective outcomes for patients.

	1	**2**	**3**	**4**
Improvement in function	Worse	No change	Better	Markedly better
Satisfaction	Worse	Cannot say	Satisfied	Very satisfied

4.4 Radiology

4.4.1 Radiographs

Radiographic evaluation was done using anteroposterior (AP) and lateral radiographs (Figure 2). Standing radiographs were taken whenever possible. Two independent observers evaluated the radiographs (HK and IK). The Larsen score was chosen for defining the degree of preoperative joint destruction for both rheumatoid and osteoarthritis patients because the study was originally planned in a rheumaorthopedic unit. The mean preoperative Larsen score was 4.5 (range 2–5) in the ankles in the STAR group and 4 (range 3–5) in the ankles in the AES group. Angular and linear values were measured digitally with the Kodak Carestream PACS system (Carestream Health, Rochester, NY, USA). The coronal ankle alignment was assessed in the AP view using the Meary view, if obtainable, or by measuring the angle formed between the long axis of the tibia and a line perpendicular to the superior surface of the talus or talar implant. In case of severe bony erosion, measurement was done using the sidewalls of the talus. Overhang was considered substantial if it was ≥ 3 mm. Implant migration was assessed by

comparing immediate postoperative and follow-up radiographs for evidence of movement by visual inspection. The radiological range of motion was determined by measuring the movement between the tibial and talar implants in the lateral view at maximum dorsiflexion and plantar flexion using lines drawn along the inferior edge of the components. The tibiotalar ratio (TT-ratio) was calculated as described by Tochigi et al. (2006) (Figure 3).

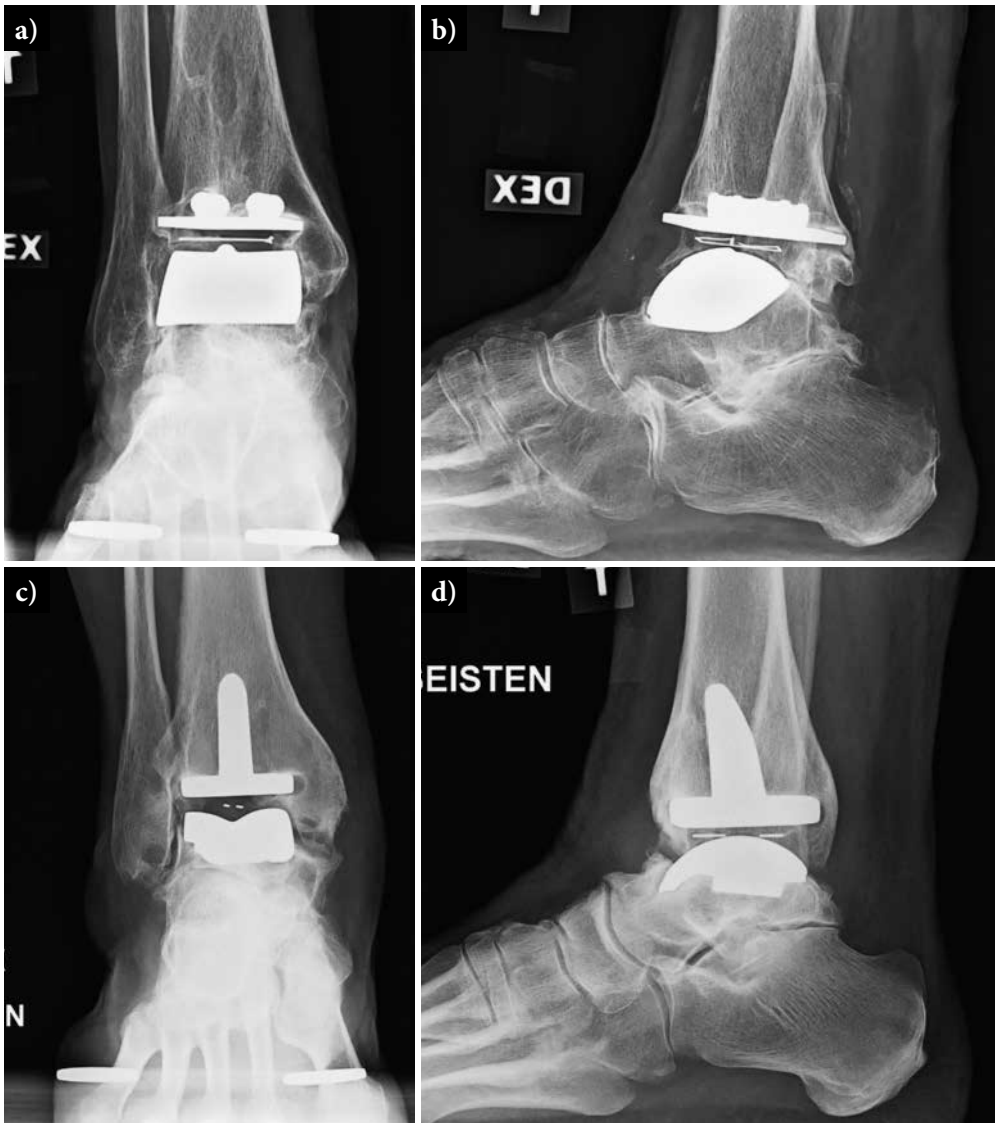

Figure 2. Radiographs of STAR (a and b) and AES prosthesis (c and d) in standing position.

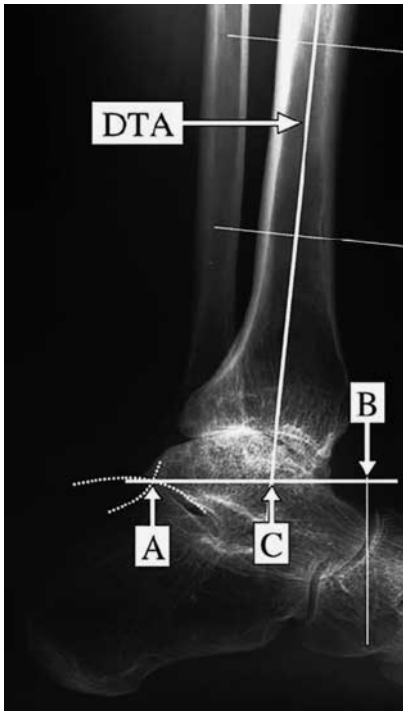

Figure 3. Calculation of tibiotalar ratio (TT-ratio). DTA=distal tibial axis. TT-ratio = AC / AB x 100. (Picture from Tochigi Y, Suh JS, Amendola A, Pedersen DR, Saltzman CL. Ankle alignment on lateral radiographs. Part 2: Reliability and validity of measures. *Foot Ankle Int* 2006;27(2)88-92, reprinted with permission of the authors)

Radiolucency was defined as a completely radiolucent line < 2 mm in width and osteolysis as discrete, well-circumscribed areas of radiolucency ≥ 2 mm in width in the periprosthetic bone. The AES components were divided into zones for describing the location of the radiolucencies and lyses as described by Besse et al. (Besse et al. 2009) and the same division was generated for STAR implants (Figure 1.). The osteolytic lesions were classified by size as shown in Table 2. Lesions ≥ 10 mm (C) were considered to be marked.

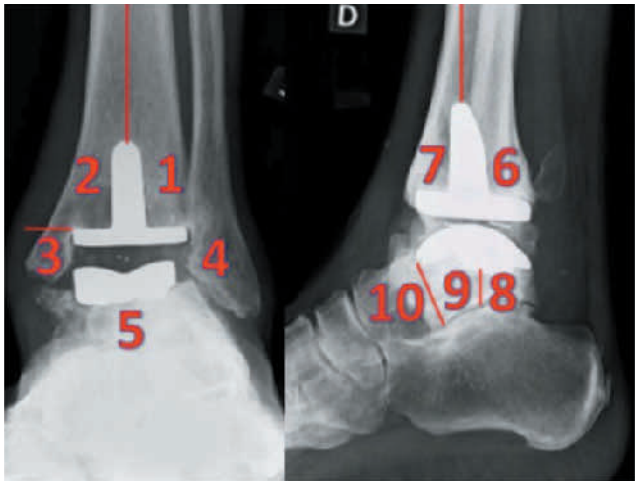

Figure 4. Protocol for X-ray analysis according to Besse et al.

Table 7. Classification of osteolytic lesions by size.

Grade	Size of osteolytic lesion (largest diameter)
N	Normal
L	Lucencies
A	Bone lysis between 0 and 0.5 cm
B	Bone lysis between 0.5 and 1 cm
C	Bone lysis between 1 and 2 cm
D	Bone lysis between 2 and 3 cm
E	Bone lysis over 3 cm

4.4.2 CT

A Siemens Somatom Sensation 64-slice CT was used (Siemens AG Healthcare Sector, Erlangen, Germany). The protocol consisted of scanning at 120 kV with a metal-artifact reduction algorithm. Automatic tube current modulation was used. The slice thickness was 0.6 mm and the reconstruction increment 0.4 mm. The scanned area included the whole implant and the peri-implant area. During scanning, the patient lay supine on a table. Coronal, sagittal, and axial images (following the tibial implant) were reformatted from the original data. Osteolytic lesions were defined as well demarcated, periprosthetic radiolucencies containing no osseous trabeculae. Measurements on CT were made using the coronal and sagittal reformatted images. Streak artifacts caused by metallic ankle prosthesis were visually appraised.

4.5 Revision surgery and samples for osteolysis

4.5.1 Revision surgery

The indications for reoperation due to osteolysis were large or continuously growing osteolytic lesions during follow-up. These patients were radiologically characterized by granulomatotic osteolytic areas, defined as discrete, well-circumscribed areas of radiolucency ≥ 2 mm wide, as seen in routine radiographs and CT images in peri-implant bone. Osteolytic lesions > 10 mm were defined as marked. Revision was performed to prevent loosening of the implant. During the revision operation, the osteolytic cavities were curetted, debrided, and filled with either autologous bone or an allogenous bone graft.

4.5.2 Samples

At revision surgery for periprosthetic osteolysis of the AES implant, samples were taken from the joint capsule, joint fluid, bone, and the contents of the cavities. Microbiological and histological analyses were performed.

4.5.2.1 Histological and microbiological analysis

For histological examination, the samples were fixed in formalin and stained with hematoxylin-eosin (HE) and the van Gieson (VG) stain. Four to ten micrometer-thick serial sections were made from paraffin-embedded specimens and studied by light and polarized-light microscopy. The microbiological analysis followed hospital routine.

4.5.2.2 Scanning electron microscope and analysis of elements

Back-scattered electron imaging of a scanning electron microscope (BEI-SEM) equipped with energy dispersive x-ray analysis (EDXA) was done from histological samples showing debris particles under light microscopy and from some removed implants. The sample surface was coated with a thin layer of carbon. EDX analysis was used for the elemental identification.

For the analysis of elements 33 common elements were investigated from 7 different samples of two patients. The samples of the periprosthetic tissue were dried to constant weight and the organic material of bone samples was destroyed with an acid mixture (nitric, sulphuric, and chloral acids). The analyses were performed with the ICP-MS technique (Thermo XSeries2 ICP-MS equipped with CRC). Scandium, germanium and platinum group metals were used as internal standards. The method is based on NIOSH 7000 series methods (Health 2003, continuous updating). The standards were made in acidified solutions and for some rare elements a semi-quantitative method was used. The detection limit for the elements analyzed was at least <0.0001 mg/g.

4.5.2.3 Samples for RANKL

Soft tissue samples were collected from multiple periprosthetic sites from ten patients undergoing revision operation of AES TAR for peri-implant osteolysis. Despite large osteolytic lesions, these revised TAR implants were intraoperatively found to be fixed to the bone, and the cavities were filled with cancellous bone. Bacterial culture was negative. None of these patients had marked ankle pain preoperatively. In contrast, all primarily operated patients of the control group had chronic osteoarthritis of the ankle joint, associated with impaired joint mobility and pain. The mean follow-up time between the primary and revision operation was 34 months (range 27–44). Patients are described in Table 8.

Immunohistochemical staining

Tissue samples were fixed in neutral formalin and embedded in paraffin. 5 µm tissue sections were used for routine histopathological evaluation after hematoxylin and eosin staining.

Table 8. Patients with reoperated ankles (study III and IV). All patients were male. Ten patients matched for age and sex with intraoperative biopsies from the peri-articular capsule functioned as controls.

Diagnosis	Age[1]	Osteolysis, detected months after operation	Osteolysis, widest diameter in CT, mm	Reoperation and the biopsy, months after operation	Medication used after operation	Notes
Primary OA, and diabetes mellitus, hypertension, hyperlipidemia	66	36	> 40	44	Aclasta®	Aclasta® infusion 3 yrs after primary operation
Seropositive RA, and I type diabetes mellitus	66	23	30	38	Insulin, Aclasta®	Aclasta® infusion 3 yrs after primary operation
Seronegative enteroarthritis, and colitis ulcerosa	52	12	27	40	Adalimumab (Humira), Fosavance®, Cholecalciferol, Aclasta®	Aclasta® infusion 2 yrs after primary operation
Seropositive RA	47	14	22	27	Remicade®, Fosamax®, Aclasta®	Aclasta® infusion 2 yrs after primary operation
Posttraumatic OA	55	51	14	53	none	Impingement revision at same time as osteolysis revision
Posttraumatic OA, and hyperlipidemia	59	25	25	33	Crestor®	Impingement revision at same time as osteolysis revision
Posttraumatic OA	45	63	15	71	Aclasta®, Prolia®	Aclasta® infusion 5 yrs after primary operation, Prolia® started 7 yrs after primary operation. Impingement revision at same time as osteolysis revision
Posttraumatic OA	60	36	24	88	Aclasta®	Aclasta® infusion 7 yrs after primary operation. Loose tibial component revised to Mobility®
Posttraumatic OA	50	71	35	72	Prolia®	Prolia® started 7 yrs after primary operation. Impingement revision at same time as osteolysis revision
Primary OA, and hypertension, hypothyreosis	58	37	27	40	Micardis®, Thyroxin®, Aclasta®	Aclasta® infusion 3 yrs after primary operation

[a] age of patient at time of operation, years

For immunohistochemical analysis, tissue sections were stained using a BondMax immunostaining robot and Bond Polymer Refine detection (Leica Microsystems, Wetzlar, Germany) using optimized protocols identified in pilot studies. All steps except dehydration and mounting were performed by the robot. Slides were deparaffinized with Dewax solution, followed by one wash in absolute ethanol. Endogenous peroxidase was quenched in Peroxide Block reagent for 5 minutes. Antigens were retrieved by using Epitope Retrieval solution 1 (Leica, Wetzlar, Germany) for 20 minutes (CD163) or Epitope Retrieval solution 2 (Leica, Wetzlar, Germany) for 10 minutes (RANK, RANKL, OPG). Sections were incubated for 60 minutes in 1:200 diluted mouse anti-human CD163 IgG_1 (clone 10D6, Novocastra, Newcastle upon Tyne, UK), 4 μg/ml mouse anti-human RANKL IgG_{2b} (clone 20725), 0.2 μg/ml mouse anti-human OPG IgG_{2a} (clone 69127) or 0.2 μg/ml mouse anti-human RANK IgG_{2a} (clone 80707) (the last three antibodies were all from R&D Systems, Minneapolis, MN, USA). Antibodies were diluted in BOND primary antibody diluent. Non-immune mouse $IgG_{1\kappa}$, IgG_{2a} or IgG_{2b} were used at the same concentrations as and instead of the primary antibodies as negative staining controls. Slides were incubated for 30 minutes in Post Primary solution followed by 30 minutes of incubation in Polymer solution, which is a combination of HRP polymer-conjugated anti-rabbit IgG and anti-mouse IgG antibodies. Color was developed using H_2O_2 substrate and diaminobenzidine (DAB) chromogen for 10 minutes. Slides were counterstained with hematoxylin for 5 minutes. Between the steps, the slides were washed in Bond Wash Solution or in distilled water after certain steps, for at least three times. Finally, the slides were dehydrated through graded ethanol series, cleared in xylene, and coverslips were mounted using Mountex (Histolab, Gothenburg, Sweden).

Microscopy and grading

Stained specimens were analyzed and photographed with a Leitz Diaplan microscope coupled to a 5MP digital Leica DFC420 camera and a semiautomatic Leica Application Suite 3.0 image processing system (Leica, Wetzler, Germany). To visualize polyethylene particles slides were observed under polarized light.

RANKL, RANK, and OPG expression

Tissue sections stained for RANKL, RANK, and OPG were analyzed under light microscopy. The total number of positive cells per sample were graded from 5 to 10 high resolution fields (400-fold magnification) using the following grades: 0 when no/or almost no immunoreactive cells; + when there were immunoreactive cells but not more than 50%; and ++ when more than 50% of the cells were immunoreactive.

4.5.2.4 Samples for inflammatory markers

Hypoxia-inducible factor-1 alpha (HIF-1α), the key transcription factor for the adaptation of cells to hypoxic conditions, was chosen as a marker for tissue hypoxia. Cells stressed by hypoxia can undergo an internal stress-related programmed cell death, which can be analyzed by staining the active effector caspase-3, which is considered to bring the process of programmed cell death to an irreversible effector state.

RAGE, TLR2, and TLR4 were selected as PRR biomarkers because they bind HMGB1.

Samples were collected from the synovial membrane and cyst contents from ten patients undergoing revision for peri-implant osteolysis of AES TAR implant. Despite marked osteolysis around the TAR implants seen in revision, all except one implant were found during surgery to be fixed to the bone. Lesions were debrided by curettage and the cavities were filled with autologous bone grafts. In one patient, the tibial component of the ankle implant was changed due to extensive osteolysis and component loosening. Samples were fixed in 10% neutral formalin and processed to paraffin blocks. Bacterial cultures were negative suggesting that all cases represented so-called aseptic loosening. The description of the patients is shown in Table 8.

Immunohistochemical staining

5 μm tissue sections were used for routine histopathology evaluation after hematoxylin and eosin staining. A two-layer horse radish peroxidase (HRP)/anti-rabbit-labelled polymer method was used for immunohistochemical staining (Bone Polymer Refine detection kit, Leica Microsystems GmbH, Wetzlar, Germany). Staining was done using the BondMax immunostaining robot and optimized protocols identified in pilot studies. All steps, except dehydration and mounting, were performed by the robot. Slides were deparaffinized with Dewax solution; washed in absolute ethanol; endogenous peroxidase was quenched with Peroxide Block reagent for 5 minutes; antigens were retrieved using Epitope Retrieval solution (Leica, Wetzlar, Germany) for 20 minutes. Sections were incubated for 60 minutes in 2 μg/ml mouse anti-human HIF-1α IgG_{2b} (or mouse anti-human HIF-1α IgG_1, Novus Biologicals, Littleton, CO, USA), 1 μg/ml monoclonal mouse anti-human HMGB1 IgG_1 (Abnova, Taipei City, Taiwan), 0.5 μg/ml rabbit anti-human cleaved caspase-3 IgG (Cell Signaling Technology, Inc., Danvers, MA, USA), 2 μg/ml diluted mouse anti-human RAGE IgG_{2a} (Millipore/Chemicon, Billerica, MA, USA) 2 μg/ml polyclonal rabbit anti-human TLR2 (Santa Cruz Biotechnology, Santa Cruz, CA, USA) or 1.3 μg/ml polyclonal rabbit anti-human TLR4 (Santa Cruz Biotechnology). Antibodies were diluted in BOND primary antibody diluent. Non-immune mouse IgG_1, IgG_{2a}, or IgG_{2b} were used at the same concentrations as and instead of the primary antibodies as negative

staining controls. Slides were incubated for 30 minutes in Post Primary solution followed by 30 minutes of incubation in Polymer solution, which is a combination of HRP polymer-conjugated anti-rabbit IgG and anti-mouse IgG antibodies. Color was developed using H_2O_2 substrate and diaminobenzidine (DAB) chromogen (Mix DAB Refine) for 10 minutes, followed by DAB enhancer $CuSO_4$. Slides were counterstained in hematoxylin for 5 minutes. Between the steps, the slides were washed in Bond Wash Solution or in distilled water after certain steps, at least three times. Finally, the slides were dehydrated through graded ethanol series, cleared in xylene, and coverslips were mounted using Mountex (Histolab, Gothenburg, Sweden).

Microscopy and grading

Stained specimens were analyzed and photographed with a Leitz Diaplan microscope coupled to a 5MP digital Leica DFC420 camera and a semiautomatic Leica Application Suite 3.0 image processing system (Leica, Wetzlar, Germany).

Evaluation of biomarker levels in tissues

Tissue sections stained for HIF-1α, caspase-3, HMGB1, RAGE, TLR2, and TLR4 were analyzed using light microscopy. The total number of positive cells per sample was graded from 5–10 high resolution fields (400-fold magnification) using the following grades: 0 point, no positive cells; 1 point, + occasional positive cells covering < 5% of the tissue examined; 2 points: some positive cells covering 5%–25% of the tissue examined; 3 points: moderate numbers of positive cells covering 25%–50% of the tissue examined; 4 points: many positive cells covering > 50% of the tissue examined.

4.6 Implant survival and failure

Failure was defined as the need for revision by exchange of a metal component or conversion to arthrodesis, and the implant survival was analyzed by using these factors as an end-point for the statistical analyses. An isolated exchange of the polyethylene insert was not considered as failure (Henricson 2010), even in cases of polyethylene breakage.

4.7 Finnish Arthroplasty Register

Study II was based on information recorded in the Finnish Arthroplasty Register (Puolakka et al. 2001) relating to patients who underwent TAR between 1982 and 2006. The coverage of the Finnish Arthroplasty Register was analyzed in 1994–1995 by comparing its data with those of the discharge registers of the participating hospitals, and was found to cover 90% of implantations and implant removals. Since

1995, the data of the register have been compared with those of the hospital discharge registers every few years. At the time of analysis, generally over 95% of all joint implantations were recorded, but coverage of total ankle implants turned out to be inferior, approximately 62% (0%–88%) for primary operations and 33% (0%–86%) for revisions (Finnish National Institute for Health and Welfare). An English translation of the form used for data collection has been published elsewhere (Paavolainen et al. 1991). Revisions were linked to the primary operation, using the unique personal identification number assigned to each resident of Finland. The register contains data on 645 TARs, each of which has been recorded individually for every operation since the beginning of the Register. Of these 645 TARs, 573 (89%) were primary operations and 72 (11%) revisions.

4.7.1 Implant-dependent trends - inclusion criteria

To assess the survival of different TAR designs, only the designs that had been used in more than 40 operations during the study period were analyzed (Havelin et al. 1995). In addition, only implants with a mean follow-up of more than 2 years, and more than 20 patients at risk at five years were included. Bilateral TARs were considered as separate cases, since bias related this procedure is likely to be minimal (Robertsson & Ranstam 2003).

4.7.2 Selected prostheses types

To meet the inclusion criteria, STAR and AES implants were selected. All the STAR prostheses were uncemented. Of the other implant designs used in Finland at the end of 2006, the Hintegra (Integra, Plainsboro, NJ, USA) was excluded due to an insufficient number of operations. The use of earlier designs was scarce and the designs have been discarded in the late 1980s. A total of 515 primary TARs were included in the study.

4.7.3 Disease-dependent trends

In Finland, most of the 515 TARs were performed due to rheumatoid arthritis (RA) of the ankle (n=252; 49%). Other indications included posttraumatic (n=111; 22%) and primary (n=99; 19%) osteoarthritis, other arthritides (n=9; 2%), and other diseases (n=44; 8%). The overall survival of TARs performed due to RA was analyzed and compared with the other indications group to assess the impact of the underlying disease.

4.7.4 Hospital-dependent trends

In Finland, 355 (69%) of the 515 TARs were performed in one foundation-based hospital and two university hospitals, each performing more than 100 TARs in 1997–

2006. Four more hospitals had performed 10 to 50 TARs, and 10 other hospitals less than 10 operations. The overall survival of TARs performed in high volume hospitals was analyzed and compared to the two low volume hospital groups together and separately to assess the impact of hospital volume.

4.8 Statistical methods

In study I, statistical evaluation was done with the SPSS software (version 16.01; SPSS Inc, Chicago, IL, USA). Survival curves for osteolysis as an endpoint were done using the Kaplan-Meier method and implants were compared with the log-rank test. Cox's proportional hazard model was used to analyze whether an implant type or any demographic factors influenced the risk of osteolytic lesions.

In study II, statistical analysis was also done with SPSS software (version 17.0; SPSS Inc, Chicago, IL, U.S.A.) The endpoint for survival was defined as revision, with either one component or the whole implant being removed or exchanged. Kaplan-Meier survival data were used to construct the survival probabilities of implants at 1, 3, 5, and 7 years. Survival data obtained in the Kaplan-Meier analysis were compared by the log-rank test. The Cox multiple-regression model was used to study differences between groups and to adjust for potential confounding factors. In all models, the confounding factors were age and gender. The factors studied with the Cox model were TAR design, and hospital type (high volume vs. low volume hospitals). All models included adjustment for differences in age and gender. The Cox regression analyses provided estimates of survival probabilities and revision risk ratios (RR) for different factors. Estimates from the Cox analyses were used to construct adjusted survival curves at mean values of the risk factors. The Wald test was applied to calculate p-values for data obtained from the Cox multiple regression analysis.

In study III, Fisher's exact text was used to calculate the differences in RANKL, RANK and OPG expression levels between patient and control samples.

In study IV, no statistical analysis was conducted.

In study V, the descriptive statistics were shown for numerical variables; means and standard deviations were reported in case a variable follows the normal distribution, otherwise median and range were presented. Kaplan-Meier curves were shown for implant survival. The failure rate and its 95% confidence interval were presented. A p-value of less than 0.05 (two-tailed) was considered statistically significant. SAS® Version 9.4 for Windows was used for statistical reporting. A hierarchical linear mixed model was used to evaluate whether there is significant mean change in Kofoed scores over the time of the study. Cox's proportional hazard model for implant survival was

also performed where gender, BMI, age at operation, and diagnosis were included in the model.

In study VI, the descriptive statistics were shown for numerical variables; means and standard deviations were reported in case a variable follows the normal distribution, otherwise median and range were presented. Kaplan-Meier curves were shown for implant survival. The failure rate and its 95% confidence interval were presented. A p-value of less than 0.05 (two-tailed) was considered statistically significant. SAS® Version 9.4 for Windows was used for statistical reporting. A hierarchical linear mixed model was used to evaluate whether there is any significant mean change in Kofoed scores over the time of the study. Cox's proportional hazard model for implant survival was also used for statistical analysis, where gender, BMI, age at operation, and diagnosis class were included in the model.

P-values less than 0.05 were considered statistically significant.

5. RESULTS

5.1 Study I – Osteolysis after AES total ankle replacement

5.1.1 Radiolucency and osteolysis

Radiolucent lines or osteolytic lesions in radiographs were found at some time point in 48 (37%) of the ankles. Only two patients had isolated radiolucent lines and all the others had osteolysis of some extension. Marked osteolytic lesions, defined as lesions ≥ 10 mm of largest diameter, were found in 27 (21%) of the ankles. The distribution of the radiographic lesions is shown in Figure 5. 26 of the 27 ankles with marked osteolysis were examined with CT. Examples of typical lesions are shown in Figure 6.

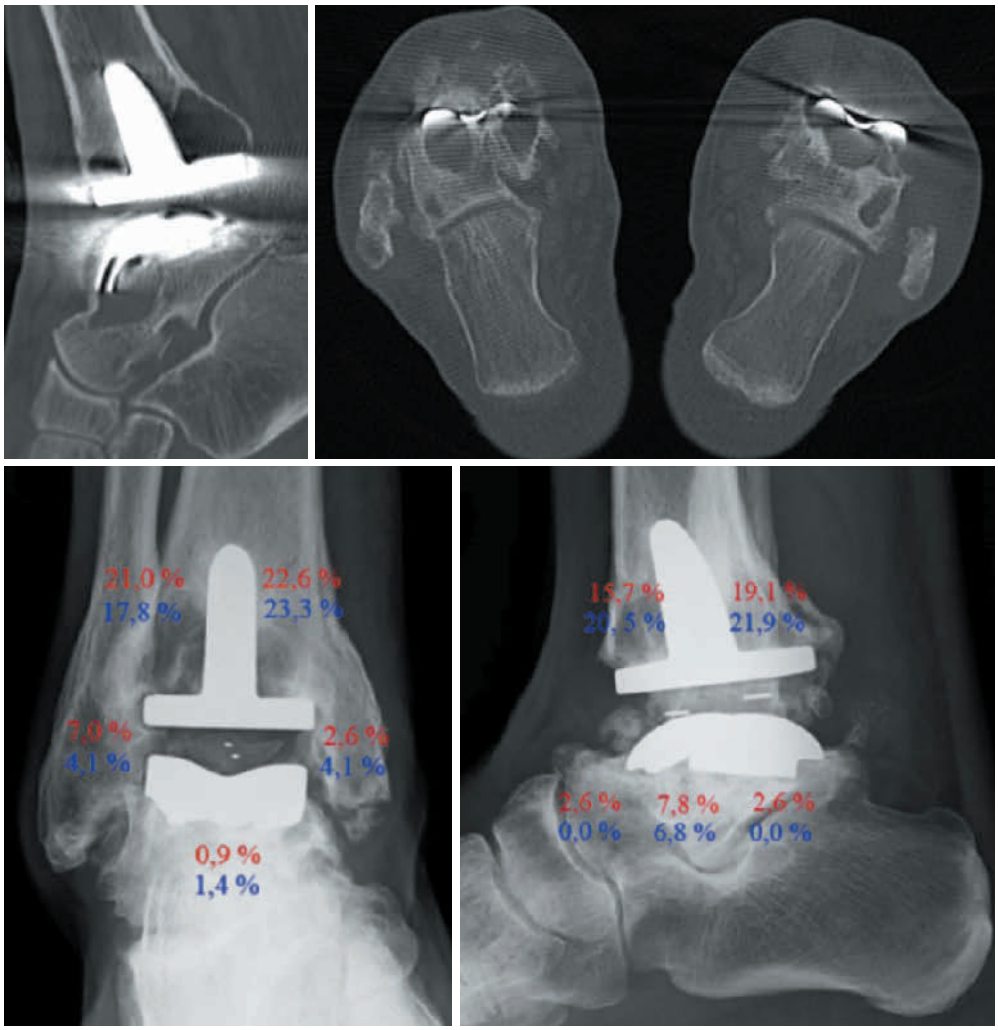

Figure 5. Examples of osteolytic lesions in CT scans and plain radiographs and distribution of lesions in plain radiographs in Study I (red: all lesions, blue: marked lesions)

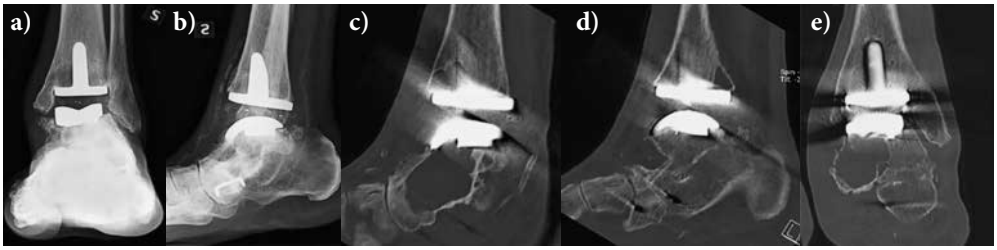

Figure 6. 67-year-old male with rheumatoid arthritis. Osteolytic lesions in distal tibia and suspicion of osteolysis also in talus on radiographs 2 years after total ankle replacement (a and b). Several osteolytic lesions in the tibia and one huge lesion with cortical disruption in the talus is seen in CT images 3 years after AES TAR (c-e)

The risk for osteolysis was 3.1 (95% confidence interval, 1.6 to 5.9) times higher with dual-coated implants compared to implants with HA-coating alone (p=0.001). The Kaplan Meier survival curves of implants with osteolysis as end-point is shown in Figure 7. Progression of the lesions in sequential radiographs occurred in sixteen (33%) ankles with osteolysis. Substantial overhang was present in altogether nine ankles three of which had osteolysis (p=0.21).

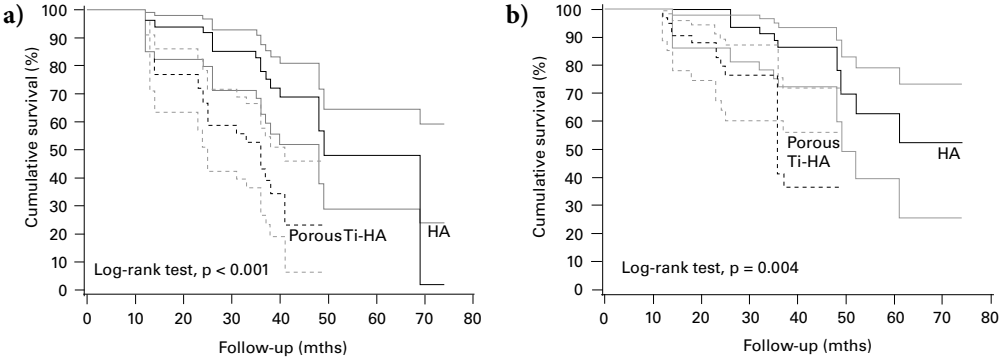

Figure 7. Kaplan-Meier survival curves of implants with osteolysis as the endpoint (Study I), a) osteolytic lesions and b) marked lesion (Ti-HA, titanium-hydroxyapatite). Grey lines indicate 95% confidence intervals.

Male patients had a 2.0-fold (95% CI, 1.13 to 3.6) risk for osteolysis (p=0.018), but none of the other demographic factors, including age (p=0.82), diagnosis (p=0.92), bisphosphonate (p=0.88), or anti-TNF therapy (p=0.44), was a significant risk factor for osteolysis.

5.1.2 Component migration

The talar component migrated in nine ankles; in two of these also the tibial components had migrated. Predisposing factors for talar component migration were present in two patients with talar necrosis, one deep infection with talar necrosis,

one neuropathic arthropathy (Charcot), and three osteolyses; in two patients, no predisposing factors were identified. One tibial component migration was minimal and associated with talar component migration of no specific reason and the other had also malalignment and osteolysis around the tibial component. Altogether three of the ankles with component migration have been fused.

5.1.3 Revisions for osteolysis

16 ankles underwent revision surgery because of osteolysis. Fifteen of these patients had marked osteolysis around the tibial and/or talar components and one had a large lesion in lateral malleolus. The implant had only HA-coating.

The revision operation of the lesion in lateral malleolus included debridement of the lesion, allogenous spongious bone grafting, and lateral gutter debridement. The initial lesion healed well, but a minor osteolytic lesion has developed around tibial stem. Bacterial samples were all negative; histological samples revealed mainly fibrosis and neither apparent foreign body reaction nor wear particles were present.

At revision surgery of the other 15 ankles there were large, lytic cavities around the components (Figure 8). Cavities contained brownish grey granulomatous necrotic material but there was no visible metallosis in the surrounding tissues. In 12 ankles both tibial and talar components were stable despite large cavities and a debridement of the lesions, and bone grafting was done in addition to exchange of the polyethylene insert. In three ankles with HA-coating both components were loose and arthrodesis was performed. All polyethylene inserts were nearly intact.

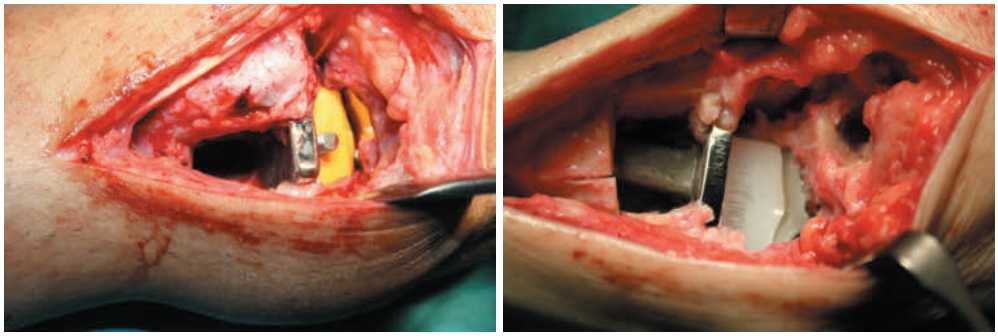

Figure 8. Examples of revision surgery showing large osteolytic lesions around stable tibial components.

5.1.4 Histology and microbiology

All bacterial cultures and stainings of samples taken from the joint capsule, joint fluid, and the contents of the cavities were negative. Most histological samples contained

large acellular, necrotic areas where the original tissue could not be identified and wear debris was absent. There was an increased amount of histiocytes with small, sharp foreign material particles, which were best visible under polarized light (Figure 9). Some giant cells were also present in these areas. The number of osteoclasts was increased compared to normal bone tissue and there were sporadic resorption lines in healthy bone. Overall, the histological findings were interpreted as foreign body reaction.

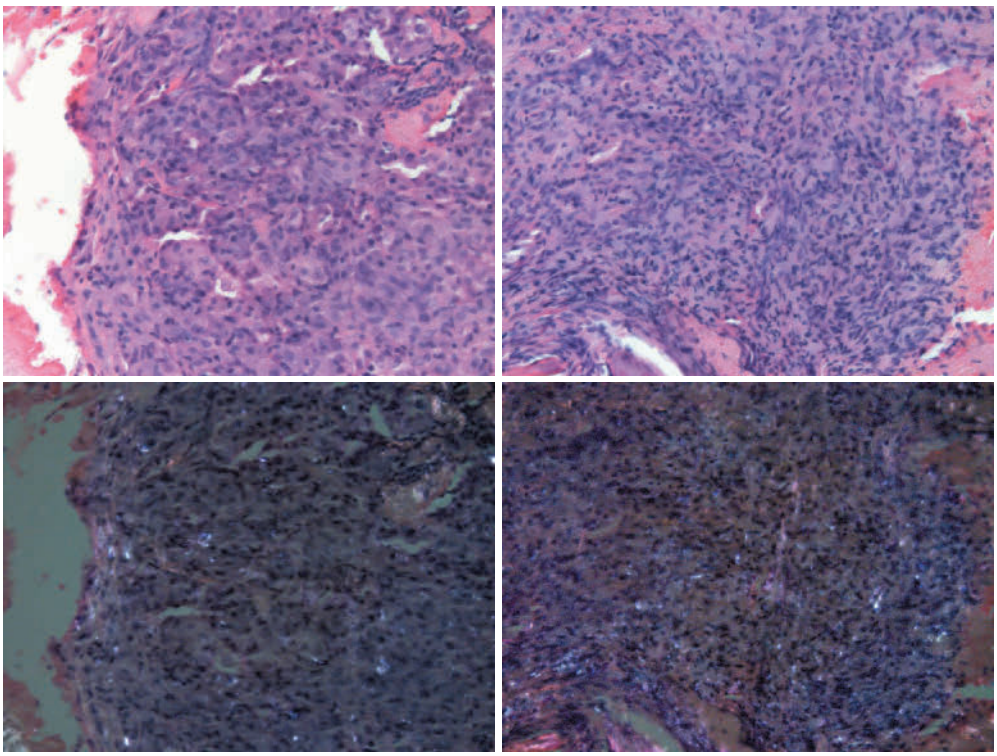

Figure 9. Examples of histology, in light microscopy, H-E staining and same samples under polarizing light.

5.1.5 Scanning electron microscopy and elemental analyses

Several particles of titanium and cobalt chromium a few micrometers in size were identified with BEI-SEM/EDX analysis of samples of Ti-HA ankles (Figure 10). PE particles, if present, could not be identified in tissue samples, since tissue digestion methods were not available. There were scratches filled with hydroxyapatite in one removed polyethylene implant (Figure 10).

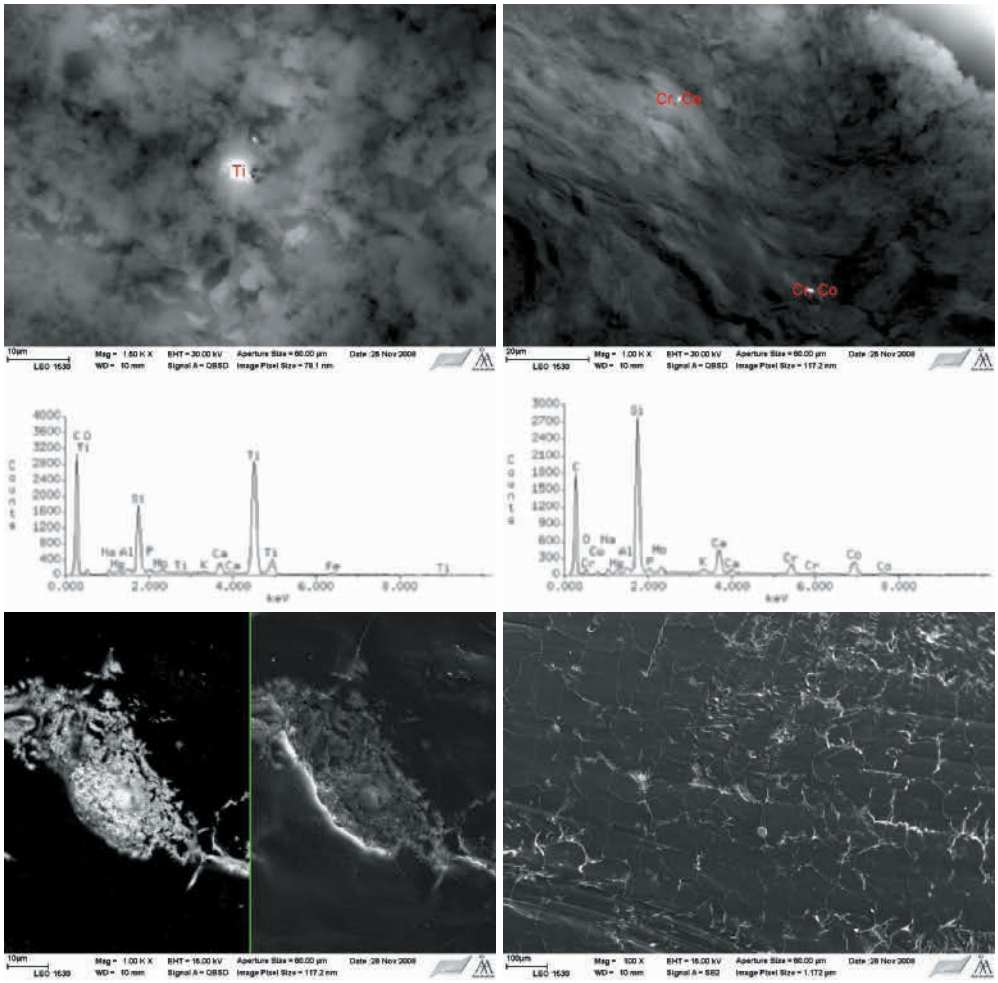

Figure 10. Examples of BEI-SEM micrograph and EDXA spectra of two histological samples showing Ti and Co-Cr particles and BEI-SEM micrograph of one removed PE insert showing scratches filled with hydroxyapatite.

Elemental analysis revealed measurable amounts of titanium, chromium, cobalt, aluminum, and molybdenum in Ti-HA samples. The concentration of titanium was 230 micrograms per gram of dry tissue and of chromium 18, cobalt 11, aluminum 1.7, and molybdenum 1.2 micrograms per gram of dry tissue. Compared to the control samples, the average concentration of titanium was approximately 60 % greater in the patient samples.

5.2 Study II – Finnish Arthroplasty Register

The annual incidence of TAR was 1.5 per 10^5 inhabitants. The 5-year overall implant survivorship for the whole TAR cohort was 0.83 (95% CI: 0.81–0.86).

The most frequent reasons for revision were aseptic loosening of one or both prosthesis components (39%) and instability (39%). There was no difference in survival rate between the STAR and AES designs, and age, gender, diagnosis, and hospital volume (< 10 vs. > 100 replacements in each of 17 hospitals) did not affect TAR survival. The revision rate was 11%.

5.3 Study III – RANKL and osteolysis of AES total ankle replacements

5.3.1 Routine histology

The samples contained three different types of histological areas. Coagulative soft tissue necrosis covered usually 5–15% of the tissue section area (Figure 11A). The capsule of the implant consisted of relatively dense irregular connective tissue containing a variable number of fibroblasts, mast cells, and some histiocytes, and was vascularized by microvessels. In some samples the periprosthetic dense connective tissue was not homogenous, but formed separate, compact, unidirectional fibroblast layers rich in extracellular matrix, and contained some infiltrating inflammatory cells encircled with microscopic cell-free holes of variable form and size containing extracellular matrix ground substance. In some samples a synovial lining-like layer was also observed. The two last mentioned tissues contained often pieces of necrotic bone embedded in a soft connective tissue matrix, but evident metallosis was absent. Polarized light microscopy revealed only some singular birefringent polyethylene particles. Despite this, the implant capsule and the synovial-lining like interface membrane were heavily infiltrated by macrophage-like cells and cells typical of foreign body reactions. Biopsies from the control group showed a synovial membrane and capsule, which was slightly infiltrated by chronic mononuclear inflammatory cells.

5.3.2 Immunohistopathology

5.3.2.1 Macrophages

The part of the capsule facing necrotic masses was bordered by $CD163^+$ macrophages (Figure 11A) but only occasionally by singular polymorphonuclear neutrophilic leukocytes (not shown).

Although histopathological analysis of the periprosthetic tissues obtained at implant revision revealed hardly any implant-derived wear debris, the connective tissue matrix of the implant capsule and the synovial lining-like interface membrane was heavily infiltrated by $CD163^+$ macrophages (Figure 11B), often in a close spatial relation to necrotic tissue and bone fragments (Figure 11C). CD163+ multinuclear foreign body giant cells were seen in many such active areas (Figure 11D).

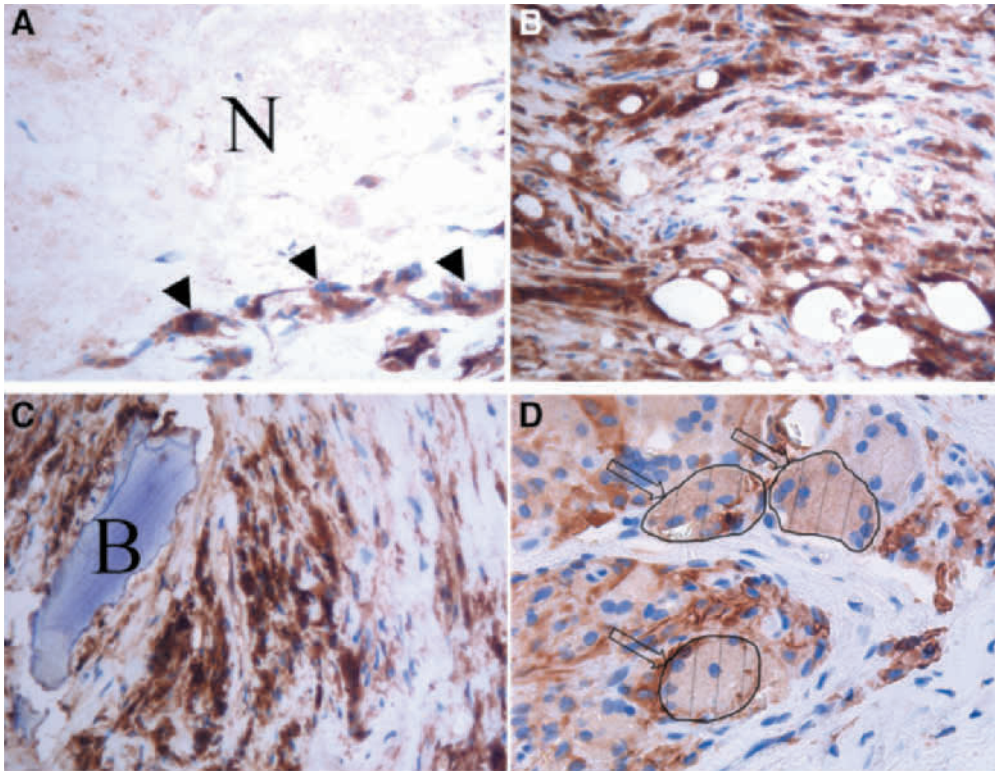

Figure 11. CD163-positive cells in the periprosthetic tissue of the ankle. Counterstained with hematoxylin. (A): Macrophages (arrowheads) facing necrotic masses (N). (B): Heavy macrophage infiltration in the implant capsule. (C): bone debris (B) surrounded with macrophages. (D): CD163-positive multinuclear foreign body giant cells (empty arrows) in the implant capsule. Original magnification ×400.

5.3.2.2 RANK and RANKL

RANKL$^+$ fibroblast-like mesenchymal cells were seen in the same microscopic fields as CD163$^+$ macrophages (Figure 12A). In some bone fragments embedded in connective tissue matrix, some of the osteocytes were RANKL-positive (Figure 12A). Its cellular receptor RANK was seen in the synovial-like lining, probably in the macrophage-like type A lining cells, and in macrophage-like cells of the connective tissue stroma (Figure 12B). RANK immunoreactivity was also seen in vascular endothelial cells (Figure 12B). RANK$^+$ cells were particularly frequent close to foreign bodies composed of dead bone fragments embedded in the implant capsule and/or interface membrane, and was also found in multinuclear foreign body giant cells (Figure 12C). OPG staining was restricted to vascular endothelial cells (Figure 12D), and was not observed in the interstitial tissue, where RANKL- and RANK-positive cells were located. The specificity of immunohistochemical staining was confirmed by negative staining controls (Figure 12D).

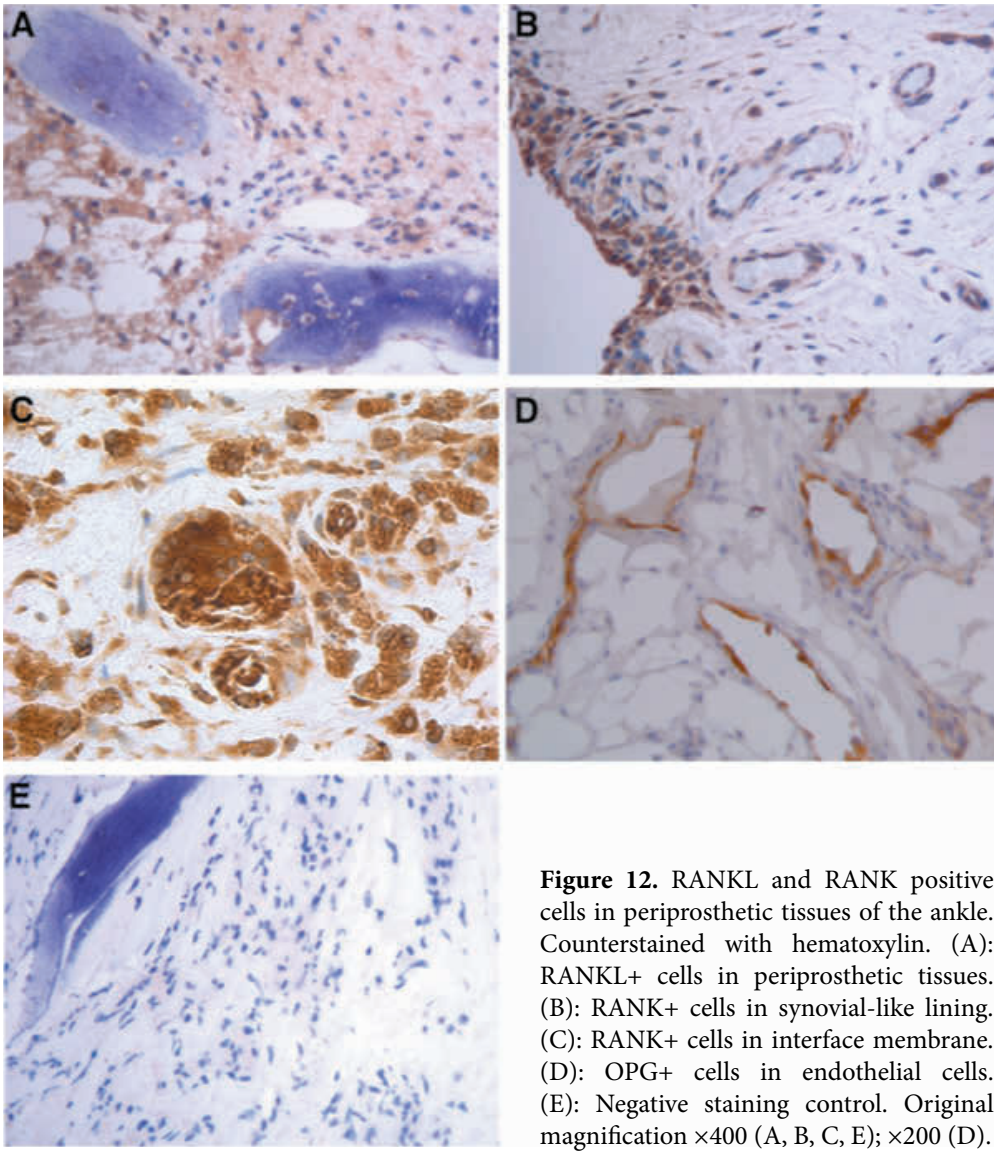

Figure 12. RANKL and RANK positive cells in periprosthetic tissues of the ankle. Counterstained with hematoxylin. (A): RANKL+ cells in periprosthetic tissues. (B): RANK+ cells in synovial-like lining. (C): RANK+ cells in interface membrane. (D): OPG+ cells in endothelial cells. (E): Negative staining control. Original magnification ×400 (A, B, C, E); ×200 (D).

In the control group, biopsies showed some chronically inflamed synovial membranes but no bone fragments or tissue necrosis containing foreign body giant cells in the matrix. In patient samples, RANKL expression and RANK expression were significantly increased ($p=0.020$ and $p=0.023$, respectively) compared to control samples. OPG expression was lower in patient samples than in control samples, but this difference was not statistically significant ($p=0.070$) (Figure 13).

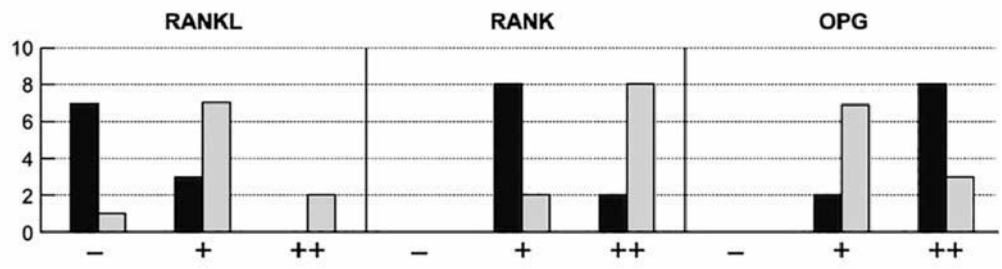

Figure 13. Comparison of immunohistochemically stained receptor activator of nuclear factor kappa B ligand (RANKL, p=0.020), receptor activator of nuclear factor kappa B (RANK, p=0.023), and osteoprotegerin (OPG, p=0.070) in control samples (n=10) and periprosthetic tissues (n=10). Relative number of positive cells per sample is scored as: absent (0), medium (+), and high number of positive cells (++). Number of control samples is denoted by black bars and number of patient samples is denoted by gray bars. Fisher's exact test.

5.4 Study IV – Autoinflammation around AES total ankle replacements

5.4.1 Routine histology

The findings of routine histology were similar as in study III (5.3.1).

5.4.2 Immunohistopathology

The part of capsule facing necrotic masses was bordered by macrophages and only occasionally by singular polymorphonuclear neutrophilic leukocytes.

Histopathological analysis of the periprosthetic tissues obtained at implant revision revealed hardly any implant-derived wear debris. Still, the connective tissue matrix of the implant capsule as well as the synovial lining-like interface membrane was heavily infiltrated by macrophages, often in close spatial relation to necrotic tissue and occasional bone fragments.

In the control group, biopsies showed a slightly chronically inflamed synovial membrane but no bone fragments or tissue necrosis containing foreign body giant cells in the matrix.

A summary of the results of immunohistochemical staining of tissues from the primary operation and after revision are shown in Table 9.

Table 9. Score value of immunoperoxidase staining of peri-prosthetic tissues.

Revision samples

		HIF-1alpha	Caspase3	HMGB1	RAGE	TLR2	TLR4
N	Valid	10	10	10	10	10	10
	Missing	0	0	0	0	0	0
Mean		3.0000	2.2000	2.0000	1.7000	3.0000	3.3000
Median		3.0000	2.0000	2.0000	2.0000	3.0000	3.5000

Control samples

		HIF-1alpha	HMGB1	Caspase3	RAGE	TLR2	TLR4
N	Valid	3	3	3	3	3	3
	Missing	0	0	0	0	0	0
Mean		3.0000	1.0000	1.3333	1.0000	2.0000	2.0000
Median		3.0000	1.0000	1.0000	1.0000	2.0000	2.0000

5.4.2.1 HIF-1alpha

In both primary and revision surgery tissue samples many cells expressed HIF-1α activity. There was no difference between two groups. Immunostaining was found in fibroblasts forming the carcass of the capsule and in inflammatory infiltrating cells (Figure 14).

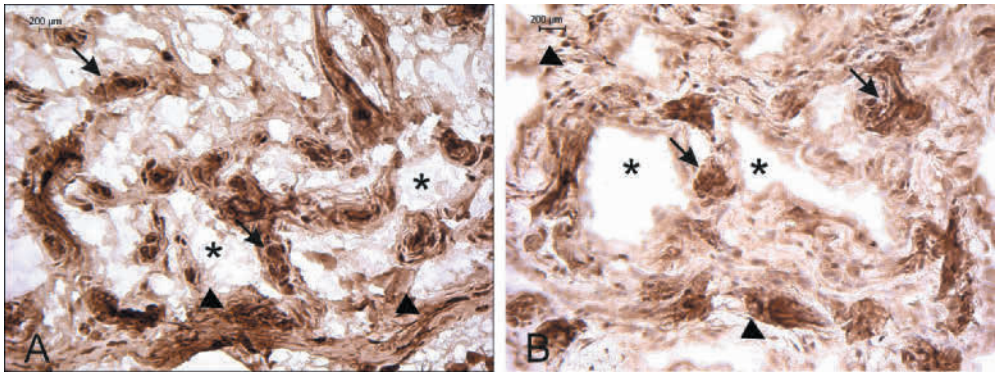

Figure 14. HIF-1α expression in tissue sample taken during primary (A) and revision operation (B). HIF-1α is highly expressed in most cells of the capsule and peri-implant tissue. Fibroblasts are indicated with arrowheads, inflammatory cell infiltration with arrows, and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

5.4.2.2 Active caspase-3

Immunoperoxidase staining for active caspase-3 as an indicator of incipient apoptosis showed that some cells of control samples had a dramatic deficiency of oxygen, which heralded apoptosis. Some clusters of fibroblasts and perivascular cells were caspase-3 positive. There were especially many fibroblasts in the periprosthetic tissue retrieved

from revision operations that became apoptotic compared to control samples (Figure 15).

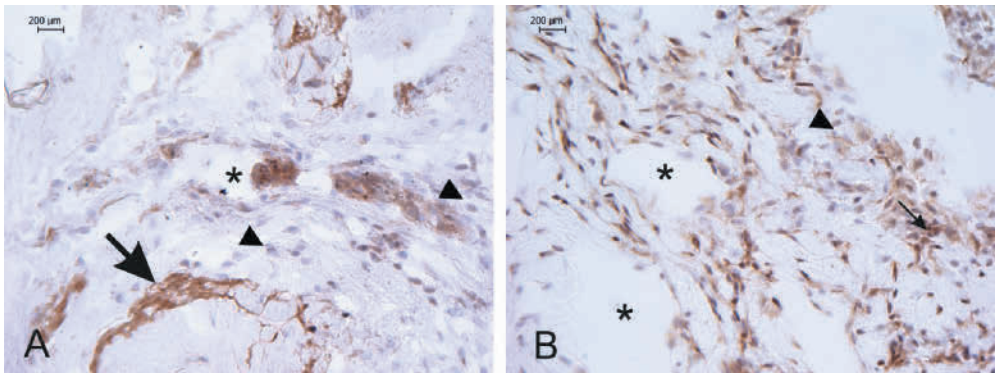

Figure 15. Active caspase-3 expression in tissue sample taken during primary (A) and revision operation (B). Active caspase-3 is expressed in many cells. Cluster of perivascular cells (thick arrow), inflammatory cells infiltration (thin arrows), fibroblasts in the process of apoptosis (arrow heads), and cell-free holes (asterisks). Immunoperoxidase staining, counterstaining with hematoxylin.

5.4.2.3 HMGB1

Some covering cells of the pseudo synovial membrane exhibited nuclear expression of HMGB1 in specimens from primary operations. HMGB1 was expressed in the cytoplasm of some inflammatory infiltrating cells (Figure 16A). The number of HMGB1-positive cells throughout the capsule of the tissue samples from revision operations was about double than of the controls. HMGB1-activity occurred mostly in the cell cytoplasm (Figure 16B).

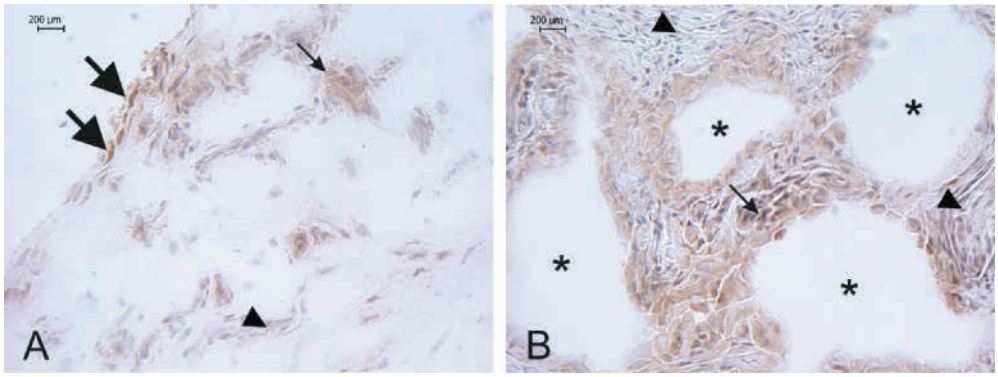

Figure 16. HMGB1 expression in tissue sample taken during primary (A) and revision operation (B). HMGB1 is expressed in some synovial-like cells (thick arrows) and many inflammatory cells infiltration (thin arrows). Fibroblasts are indicated with arrow heads and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

5.4.2.4 RAGE

Only some cells – mostly fibroblasts – in the primary operation tissue samples were RAGE-positive (Figure 17A). The number of RAGE$^+$ cells was considerably higher in the samples from revision operations compared to control samples, and the activity resided in fibroblasts and inflammatory infiltrating cells (Figure 17B).

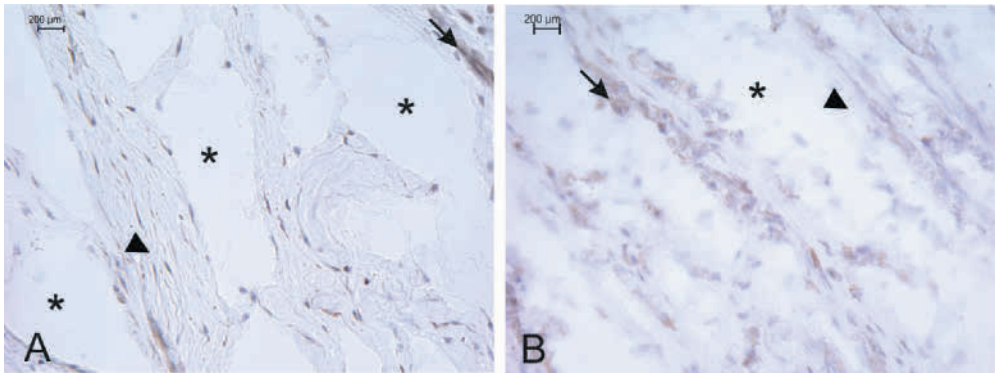

Figure 17. RAGE expression in tissue sample taken during primary (A) and revision operation (B). RAGE+ cells are more numerous in periprosthetic tissue from the revision operation than from the primary operation. Fibroblasts are indicated with arrow heads, inflammatory cell infiltration with arrows, and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

5.4.2.5 TLR2

Many cells of mesenchymal origin in specimens from primary operation stained positively for TLR2 (Figure 18A). Their number was increased for about one-third in the peri-implant samples taken during revision operation compared to control samples (Figure 18B).

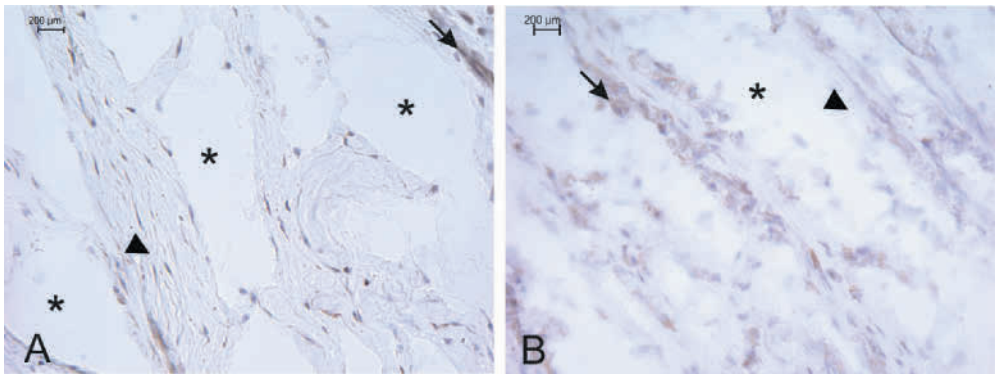

Figure 18. TLR2 expression in tissue sample taken during primary (A) and revision operation (B). TLR2 is expressed in many cells. Fibroblasts are indicated with arrow heads, inflammatory cell infiltration with arrows, and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

5.4.2.6 TLR4

TLR4 was expressed in many cells in tissue samples of the primary operation (Figure 19A). The number of TLR4-positive cells was markedly increased in the samples from peri-prosthetic tissue in revision operation compared to the control samples (Figure 19B).

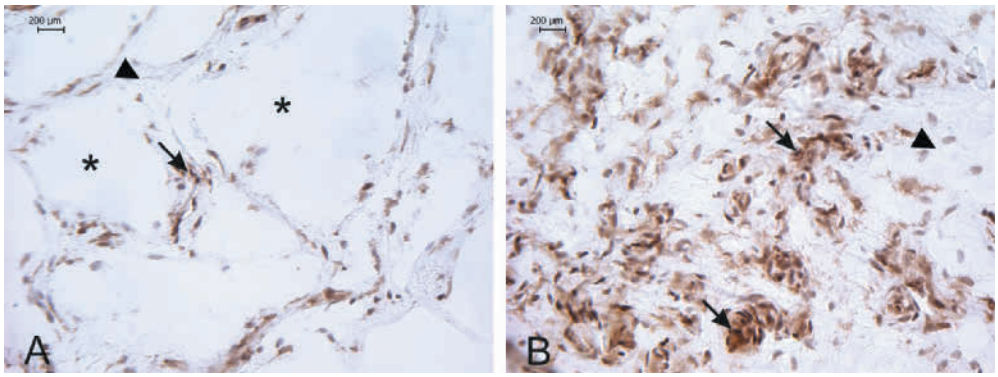

Figure 19. TLR4 expression in tissue sample taken during primary (A) and revision operation (B). TLR4 is expressed in many cells especially in tissue taken during revision operation. Fibroblasts are indicated with arrow heads, inflammatory cell infiltration with arrows, and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

The specificity of the immunohistochemical staining was confirmed by negative staining controls. (Figure 20).

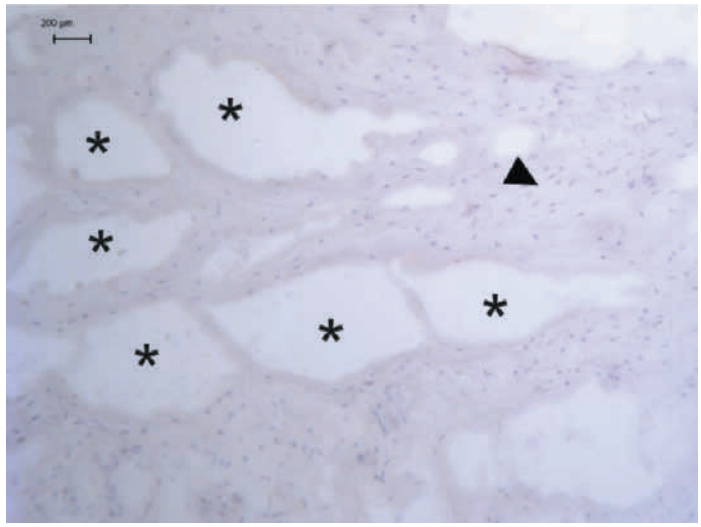

Figure 20. Negative control of immunoperoxidase staining. The sample is taken from peri-prosthetic tissue. Fibroblasts are indicated with arrow heads, and cell-free holes with asterisks. Immunoperoxidase staining, counterstaining with hematoxylin.

5.5 Study V – Outcome and survival of the STAR total ankle replacement

During the study period, one patient was lost to follow-up, and five patients had died due to causes unrelated to ankle replacement. The median follow-up time was 159 months (13.3 years; range 13–202).

5.5.1 Clinical outcome

The median preoperative Kofoed score was 42 points (range 9–80, n=32). The median postoperative Kofoed score was 88 points (range 24–99, n=29) at one year, 82 points (range 34–96, n=31) at five years, 81.5 points (range 38–93, n=20) at ten years, and 79.5 points (range 48–94, n=10) at 15 years postoperatively. The improvement of the Kofoed score was statistically significant at every postoperative evaluation point compared to preoperative value (all $p<0.0001$), although the average score was classified as excellent only at one year.

The median preoperative Kofoed score pain points was 15 (range 0–35). The median Kofoed score pain points was 40 (range 0–50) at the latest follow-up. The improvement of the Kofoed score pain points was statistically significant at every postoperative evaluation point compared to preoperative value (all $p<0.0001$).

The subjective score was available for all ankles and the mean latest score for function was 3.62 (range 1–4) and for satisfaction 3.68 (range 1–4).

The mean preoperative clinical ROM was 24 degrees (range 4–53, n=30). The mean postoperative clinical ROM at one year was 34 degrees (range 15–55, n=30) and at the latest follow-up 28 degrees (range 10–50, n=34).

5.5.2 Radiological outcome

CT was available for 16 ankles. Radiolucency at the interphase between implant and bone or frank osteolytic lesions were seen on plain radiographs in 17 (50%) ankles, and osteolytic lesions were found on plain radiographs or CT images in 13 (38%) ankles, ten (29%) of these lesions were considered to be marked. The median time for detection of osteolysis was 7 years (range 2–12 years), and for marked osteolysis 9.5 years (range 2–12 years).

Preoperatively, there was varus alignment in 15 ankles (mean 10.1; range, 3–19 degrees), and valgus alignment in 19 ankles (mean 3.8; range, 0–12 degrees). Postoperatively, the alignment was varus in 14 ankles (mean 7.8; range, 0–27 degrees), and valgus in 20 ankles (mean 5.6; range, 0–36 degrees). Seven ankles had a preoperative varus alignment greater than 10 (range 12–19) degrees. Of these ankles, the varus alignment

worsened postoperatively in 2 ankles, but in 5 ankles it was successfully restored to neutral. In one ankle, the preoperative valgus alignment was 12 degrees, but it was restored to neutral. Of the preoperatively well-aligned ankles there were 3 ankles with postoperative valgus alignment over 10 degrees (14, 20, and 36 degrees), and 2 ankles with postoperative varus alignment over 10 degrees (13 and 16 degrees). One of the ankles with postoperative malalignment failed, and was converted to arthrodesis 72 months postoperatively.

The mean preoperative tibiotalar ratio was 33% (range 7–50%). The mean postoperative ratio was 34% at three months (range 7–52%), and 35% at the latest visit (range 9–56%).

The mean radiological ROM at one year was 24 degrees (range 12–45, n=33).

Migration was detected in nine talar and seven tibial components. Of the migrated talar components, two were due to osteolysis, two due to varus or valgus malalignment, one due to component loosening, and four of unspecified reasons. Of the migrated tibial components, two were due to varus or valgus malalignment, one due to component loosening, and in four cases no specific reason could be determined. Two migrated tibial components were revised to Ankle Evolutive System (AES) (Transystème, Nîmes, distributed by Biomet, Valence, France) tibia component early after implantation.

5.5.3 Revisions and complications

Perioperatively, there were two fractures of the medial malleolus, which were fixed with screws. There were two fractures of the lateral malleolus, one was fixed with a plate and the other was not fixed. All fractures healed without complications.

Postoperatively, there were one stress fracture of the medial malleolus, and two stress fractures of the distal tibia. One fracture of the tibia was operated two times with bone grafting and plating, and it was associated with wound healing problems, whereas the other fracture healed conservatively without complications.

There were three wound complications (8.8%). One patient had superficial wound necrosis, which healed without complications. The second had wound necrosis with a stress fracture of the tibia and required several operations, the last of which was a latissimus dorsi flap. The third patient had multiple revisions due to wound necrosis, followed by a deep infection with fistulation and a need for permanent antibiotic prophylaxis. All these patients had rheumatoid arthritis.

There were two deep infections in these series (5.9%). One was described above. The other patient who had a hematogenic *Streptococcus* infection at 53 months postoperatively had rheumatoid arthritis and multiple comorbidities, including severe

arteriosclerosis. At last follow-up at 158 months postop, this implant was apparently loose, but due to comorbidities revision was not possible.

There were four insert fractures at 24, 40, 88, and 141 months postoperatively, which were treated by exchange of the insert. There were two insert dislocations. One was due to valgus malalignment at 72 months postoperatively, which was converted to fusion, and one at 164 months postoperatively, which was treated by exchange of the insert. The insert fracture at 40 months postoperatively and dislocation at 72 months postoperatively occurred with the same patient with valgus malalignment, which required conversion to fusion.

There were three component revisions. Two were revised due to migration of the tibial component and were treated with conversion to AES tibia component at 5 and 24 months postoperatively. One revision was done at 208 months postoperatively due to loosening of both metal components and polyethylene wear to TMTA ankle implant (Tantal Metal Total Ankle, Zimmer, Warsaw, IN, USA).

There were two conversions to arthrodesis. One was due to marked osteolysis around both components at 109 months postoperatively. The other was due to valgus malalignment, which caused first a fracture and exchange of the insert, and then dislocation of the insert and arthrodesis 72 months postoperatively.

There were five revisions due to osteolysis. The indication for revision was one or more peri-implant osteolytic cavities exceeding 10 mm diameter or progression of lesions on CT imaging. The revisions were done by curettage and bone grafting at 98, 99, 110, 120, and 149 months postoperatively (range 98–149, median 110 months). All revised implants have been followed by CT and none of them has required a second revision or conversion to arthrodesis so far.

There were no nerve or tendon injuries in this series.

The complications are shown in Table 10.

Table 10. Overall outcome of patients with STAR implants, including complications and reasons for further surgery. If there were several operations on one ankle, only the last operation was included.

	No further surgery	Intra-operative corrective surgery	Further corrective surgery	Revised by fusion	Revised by exchange	Revised with autologous bone graft
Major delay of wound healing	1		2			
Deep infection	1		1			
Intraoperative fracture of medial malleolus		2				
Intraoperative fracture of lateral malleolus	1	1				
Stress fracture of medial malleolus	1					
Stress fracture of tibia	1		1			
Broken polyethylene insert					3	
Polyethylene insert luxation					1	
Osteolysis	7			1		5
Aseptic loosening					1	
Component migration	14				2	
Varus malalignment (> 10°)			4			
Valgus malalignment (> 10°)				1		

5.5.4 Additional procedures

There were 12 additional procedures in 10 ankles. Preoperatively, there were five triple fusions and one subtalar fusion. One subtalar fusion was done perioperatively. Postoperatively, there were three triple fusions. A reoperation for impingement was done in one ankle and removal of hardware in one ankle. There were no osteotomies, ligament balancing procedures, or Achilles tendon lengthenings in this series. Revision for osteolysis was performed in five ankles as described above.

5.5.5 Implant survival

Of the 34 ankles, 23 were followed to the end of follow-up without failure, death, or loss to follow-up. The implant survival rate was 93.8% (95% CI 77.5% to 98.4%) at five years, and 87.2% (95% CI 69.4% to 95.0%) at ten and at fifteen years (Figure 21).

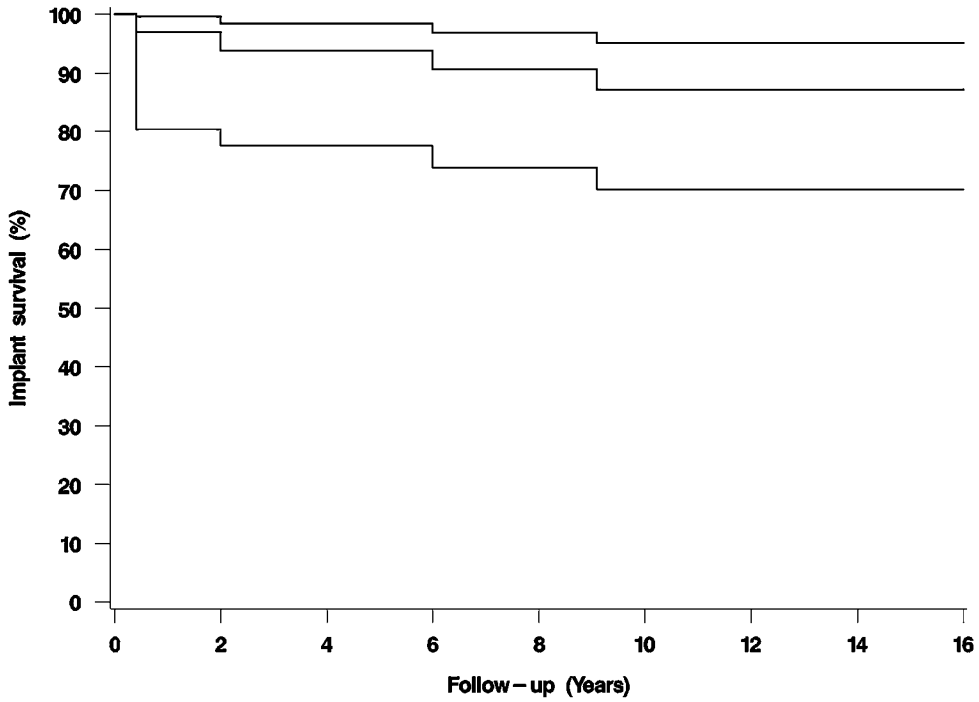

Figure 21. Kaplan-Meier survival curve with 95% confidence intervals for STAR total ankle replacement with failure defined as the need for revision by exchange of a metal component or conversion to arthrodesis as an end-point.

There was no statistically significant association between implant survival and patient age (p=0.95), sex (p=0.94), BMI (p=0.56), or diagnosis (p=0.76). Perioperative fracture or postoperative stress fracture of the medial malleolus had no effect on implant survival (data not shown). The overall rate of revisions was 44% (15/34), which includes all postoperative revisions for osteolysis, component and insert exchanges, and conversions to arthrodesis. There were altogether 5 failures defined as a need for revision by exchange of metal component or conversion to arthrodesis. Osteolysis was the reason for revision in five of the 15 cases (33%), and for failure in one of the five cases (20%). Insert fracture or luxation was the reason for revision in five of the 15 cases (33%), and for failure in one case (20%), in this case there was also valgus malalignment. The other reasons for failure were component migration and aseptic loosening, which caused three of the five failures (60%).

5.6 Study VI – Outcome and survival of the AES total ankle replacement

Thirteen patients had died during follow-up to causes not related to ankle replacement, and one patient was lost to follow-up. The median follow-up time was 96 months (range 2 to 161 months).

5.6.1 Clinical outcome

The Kofoed Ankle Score was available for 127 ankles preoperatively and 129 ankles postoperatively. The median preoperative Kofoed Ankle Score was 44 points (range 10–82, n=127). The median postoperative score was 80.5 points (range 8–98, n=120) at one year, 79 points (range 12–97, n=73) at five years and 68 points (range 16–99, n=29) at ten years. The median latest postoperative score at any time point was 73 (range 8–99, n=129). The improvement of the Kofoed score was statistically significant at every postoperative evaluation point compared to preoperative value (all $p<0.0001$), although the average score was classified as good at one year, and decreased to only fair after that.

The median Kofoed Ankle score for pain was 15 points (n=129, range 0–40) preoperatively, and 35 points (n=127, range 0–50) postoperatively. The improvement in the Kofoed score for pain was statistically significant at every postoperative evaluation point compared to preoperative value (all $p<0.0001$).

The subjective scores were available of 129 ankles and the mean latest score for function was 3.4 (range 1–4) and for satisfaction 3.4 (range 1–4).

The mean preoperative ROM was 31 (n=125, range 0–60) and mean postoperative ROM at the latest visit was 30 (n=129, range 5–65) degrees.

5.6.2 Radiological outcome

CT was available for 96 of the 130 ankles. Osteolytic lesions were detected on plain radiographs or CT scans in 91 (70%) of the ankles, in 78 (60%) ankles it was marked. CT was not available for 22 of the 39 ankles where osteolysis was not seen on plain radiographs. There was no statistically significant difference in the number of osteolytic lesions between the implants with different coatings ($p=0.15$).

The median time to detection of osteolysis in all ankles was 3 years (range 1–11 years), and of marked osteolysis 4 years (range 1–11 years). When divided into groups with different coatings, the median time for detection of osteolysis in the ankles with single-coated implants was 4.5 years (range 1–11 years), and of marked osteolysis 6 years (range 1–11 years), compared to 2 years (range 1–8 years) for all lesions, and 3 years (range 1–8 years) for marked osteolysis for the ankles with dual-coated implants. There was a statistically highly significant difference in the time to identification of osteolysis between the implants with different coatings ($p<0.0001$). Male sex predicted earlier development of osteolysis ($p=0.016$), but there was no difference in the number of all osteolytic lesions between male and female patients. Malalignment ($p=0.17$), stress fracture of the medial malleolus ($p=0.84$), or the tibiotalar ratio preoperatively ($p=0.58$) or postoperatively ($p=0.84$) had no association with osteolysis.

Preoperatively, there was varus alignment in 53 ankles (mean 10; range 1–25 degrees), and valgus alignment in 77 ankles (mean 4; range 0–32 degrees). Postoperatively, the alignment was varus in 35 ankles (mean 5; range 1–27 degrees), and valgus in 95 ankles (mean 5; range 0–36 degrees). The preoperative varus deformity was reduced better than the valgus deformity, since 5 of the 14 ankles with a preoperative valgus deformity over 10 degrees were reduced to neutral, compared to 22 of the 27 ankles with a varus deformity. There were eight ankles with postoperative varus alignment over 10 degrees, two of which needed corrective surgery, two ended up in component revision, and two in fusion due to malalignment. There were 25 ankles with postoperative valgus alignment over 10 degrees, two which had corrective surgery, and three ended up in fusion due to malalignment, none had component revision. Postoperative varus ≥10 degrees was associated with poorer implant survival than neutral or valgus alignment (p=0.0005).

The mean preoperative tibiotalar ratio was 38% (n=120, range 27–51%), the mean postoperative ratio at three months was 38% (n=127, range 19–53%), and at the latest visit 39% (n=122, range 14–54%). The missing values are due to cases of preoperative triple arthrodesis, which in some patients prevented accurate measurements.

Migration occurred in 24 talar and one tibial component. Of the migrated talar components, 15 were due to osteolysis, four due to suspected talar necrosis, two due valgus malalignment, and one due to early aseptic loosening. The specific reason for the migrated tibial component could not be determined.

The mean postoperative radiologic ROM was 26 (n=74, range 3–45) degrees.

5.6.3 Complications

Eight ankles (6%) in eight patients had delayed wound healing leading to further surgery in five of these patients. In two ankles (1.5%) skin grafting was sufficient and in two ankles (2%) a reconstructive flap was required. One led to deep infection, which required a two-staged revision and later conversion to fusion. This was one of the two deep infections in this series.

Twenty-two ankles (17%) sustained an intra-operative fracture of the medial malleolus, which were internally fixed in all but two ankles. All fixed fractures healed without complications, one of the non-fixed healed well, but the other required two re-operations due to non-union. Two ankles (1.5%) sustained an iatrogenic fracture of the lateral malleolus, which were internal fixed during surgery and healed well without complications.

Twenty-two ankles (17%) sustained a postoperative stress fracture of the medial malleolus, which occurred after revision operation for osteolysis in two ankles. The stress fracture was associated with over ten degrees of varus malalignment in three, and over ten degrees of valgus malalignment in six ankles. Of these 22 ankles, six were managed with internal fixation and four ankles ended up in a conversion to fusion. Four ankles (3%) had osteopathic changes of the tibia above the stem characterized as a stress fracture, which in one ankle lead to fusion due to valgus alignment, the rest healed without further surgery. Five ankles (4%) sustained a postoperative stress fracture of the lateral malleolus, which in all ankles healed with immobilization. In one ankle, there was a stress fracture of the lateral malleolus preoperatively due to valgus alignment and the ankle was converted to arthrodesis 10 months postoperatively.

There was a polyethylene insert dislocation in seven ankles (5%) but no polyethylene fractures. The dislocation was associated with varus or valgus malalignment over 10 degrees in four ankles. Of these seven ankles with insert dislocation, two required component revision due to varus malalignment and three were converted to fusion, two of which due to varus malalignment.

There were perioperative lesions of the superficial peroneal or sural nerve in 5 (4%) ankles, but none of flexor hallucis longus tendons.

5.6.4 Additional procedures

There were five subtalar and 30 triple fusions preoperatively and one subtalar and one triple fusion postoperatively. Subtalar fusion was done in two ankles and triple fusion in one ankle perioperatively. A reoperation for medial or lateral impingement was done in three ankles and removal of hardware in six ankles. A medial malleolar osteotomy was done in five, lateral malleolar osteotomy in four, calcaneal osteotomy in eight, and midtarsal osteotomy in two ankles. A lateral ligament reconstruction was done in five and medial release in two ankles. Achilles tendon lengthening was done in one ankle. There were nine reoperations in seven ankles for medial malleolar stress fracture, two of which were later converted to fusion as mentioned above.

5.6.5 Revisions for osteolysis

A reoperation for marked osteolysis had been performed in 50 (38%) ankles by the end of follow-up. The indications for revision were large or continuously growing periprosthetic lesions. In 44 ankles, the implant was stable and revision was carried out by debridement of the lesions and filling the cavities with bone graft. The polyethylene inlay was exchanged whenever the joint was opened during operation. In one ankle, the tibial component was loose and it was revised with the Mobility® tibial component (DePuy Synthes, Warsaw, IN, USA). In five ankles, a conversion to fusion

was necessary due to large lesions and unstable components at the first reoperation. Seven of the ankles, where debridement and filling of the lesions had been performed once, ended up in fusion later. Thus, altogether 12 ankles were converted to fusion due to osteolysis. One of the revised ankles developed a deep infection after revision for osteolysis and ended up in fusion. Thus, there were altogether two deep infections in this series (1.5%).

All complications are shown in Table 11.

Table 11. Overall outcome of the patients with AES implant, including complications and reasons for further surgery. If there were several operations on one ankle, it appears only in column of the last operation, but the same case may appear on several rows

	No further surgery	Intra-operative corrective surgery	Further corrective surgery	Revised by fusion	Revised by exchange	Revised with bone graft
Major delay of wound healing	3		4	1		
Deep infection				2		
Intraoperative fracture of medial malleolus	2	20				
Intraoperative fracture of lateral malleolus		2				
Stress fracture of medial malleolus	12		6	4		
Stress fracture of distal tibia	3			1		
Stress fracture of lateral malleolus	4			1		
Polyethylene insert luxation			2	3	2	
Osteolysis	41			12	1	37
Nerve injury	5					
Aseptic loosening					1	
Talar osteonecrosis				3		

5.6.6 Other revisions

There were altogether six (5%) component revisions, of which one was due to loosening of the talar component, one due to osteolysis and loosening of the tibial component, three due to varus malalignment and one due to infection. All the other ankles with component revision are still in follow-up, but the one with infection had later a conversion to fusion.

There were altogether 24 (18%) conversions to fusion, 12 of which were due to osteolysis. Of the remaining 12 fusions, four were done due to varus malalignment, five due to valgus malalignment, and three due to talar osteonecrosis.

5.6.7 Implant survival

Of the 130 ankles, 86 were followed up to the end of follow-up without failure, death, or loss to follow-up. The five-year survival was 87.3% (95% CI 80.0% to 92.0%), and the ten-year survival 74.9% (95% CI 65.4% to 82.2%) (Figure 22).

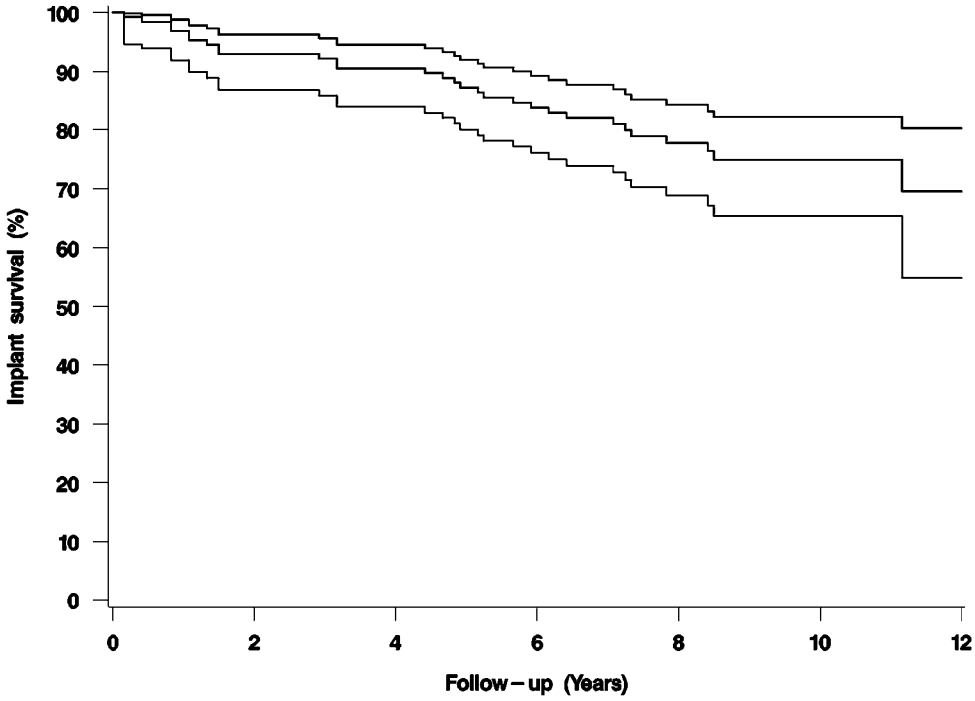

Figure 22. Kaplan-Meier survival curve with the 95% confidence intervals for the AES total ankle replacement with failure defined as the need for revision by exchange of a metal component or conversion to arthrodesis as an end-point.

There was no statistically significant correlation between implant survival and patient age (p=0.62), gender (p=0.38), diagnosis (p=0.18), or BMI (p=0.82). The presence of a perioperative fracture or postoperative stress fracture of the medial malleolus had no effect on implant survival, although there was a trend towards stress fractures predicting poorer survival (p=0.29 and p=0.062, respectively). Postoperative alignment of 10 or more degrees of varus predicted a poorer outcome and was statistically significant for implant survival (p=0.0005).

The overall revision rate was 57% including all postoperative revisions for osteolysis, component exchanges, and conversions to arthrodesis. There were altogether 30 failures defined as a need for revision by exchange of metal components or conversion to arthrodesis. Osteolysis was the reason for revision in 57 of 74 cases (77%), and for failure in 13 of 30 cases (43%). The other main reason for failure was postoperative

malalignment, which caused 12 of the 30 failures (40%). The reasons for failure are shown in Figure 23.

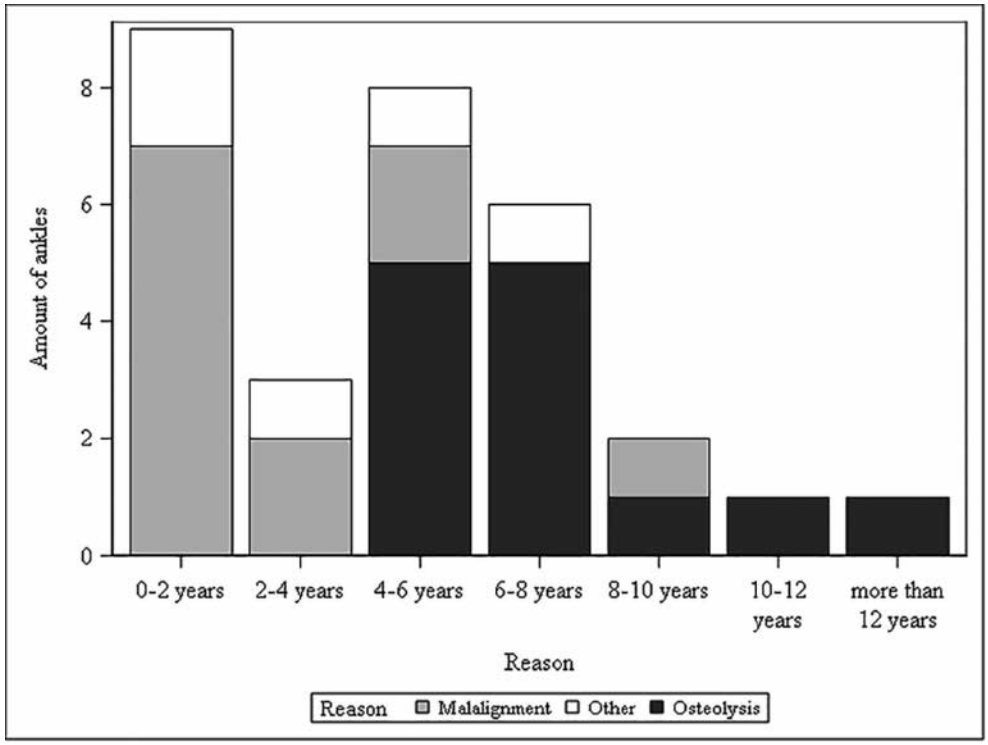

Figure 23. Causes for failure and incidence at different timepoints (Study VI).

6. DISCUSSION

6.1 General methodological considerations

The main limitations of the clinical studies are that they are retrospective. In studies V and VI all measurements were not available at the exact same time points for every patient, and some values were missing due the retrospective clinical nature of the studies. In addition, in study V two different versions of the STAR implant were included, and because of a small study population and only few end-points, it was not possible to determine the potential effect of all parameters on implant survival. On the other hand, clinical studies V and VI represent true life with structured follow-up and long follow-up times. The 34 ankles in study V are the first third generation total ankle replacements operated on in Finland and our institute, and the long learning curve known to be related to TAR operations must certainly have had an impact on the results (Henricson et al. 2007; Myerson & Mroczek 2003; Saltzman et al. 2003; Haskell & Mann 2004; Schubert et al. 2006; Lee et al. 2008; Schimmel et al. 2014). In study VI, the study population was large and homogenous, and the median follow-up time is the longest published on AES implant.

The limitations of the register study (Study II) are the lack of radiological and clinical follow-up data. It was not possible to report any subjective outcome measurements, *e.g.,* ankle performance scores or disease-specific quality of life measurements. Register coverage was not absolute and all complications were not recorded. For example, wound complications are managed by plastic surgeons and therefore not usually reported to the register. A failed TAR is often converted to an arthrodesis, and some of the procedures are done by orthopedic surgeons who are not familiar with reporting to the register, which may result in under-reporting of failures despite instructions.

The weakness of studies III and IV are that the results rely on histological analysis using immunostaining and that they are not confirmed by quantitative analysis, such as real-time PCR. In addition, due to relatively small sample size, it was not possible to fully exclude the effect of the primary diagnosis or medication on the measured factors. On the other hand, the immunohistopathological results were similar in all samples and comparable to previous results regarding total hip and ankle replacement.

6.2 Discussion of the main results of Studies I–VI

6.2.1 Clinical aspects

Patients who have undergone total ankle replacement and ankle fusion have reported good satisfaction in many studies. Nunley et al. found that STAR total ankle replacement

was associated with pain relief and improvement of function and quality of life (Nunley et al. 2012), and Daniels et al. concluded that the medium term patient-reported outcomes were good after TAR (Daniels et al. 2015). Likewise, in both Studies V and VI patient satisfaction was excellent, despite several complications and revisions, especially in Study VI. The self-reported scores of satisfaction were high and the Kofoed Ankle score improved statistically significantly at every postoperative evaluation point compared to the preoperative value. It is noteworthy that the Kofoed Ankle Score could be relatively low although the self-reported scores were good and the patients were very satisfied with their ankles. The Kofoed score points for function could be close to zero especially among elderly patients and rheumatoid patients due to problems in other joints or comorbidities, and this is probably why the result for TAR was poor. Therefore, PROM is recommendable when evaluating the outcome of TAR.

In studies V and VI, the amount of clinical ROM did not change significantly after ankle replacement, but it was preserved or slightly improved. This is in accordance with previous studies (Coetzee & Castro 2004; Wood & Deakin 2003; Wood et al. 2008; Brigido et al. 2015). After total ankle replacement, the overall sagittal range of movement of the ankle consists of both tibiotalar and talonavicular movements (Pedowitz et al. 2016). In the present studies, the radiologic ROM was less than the clinical ROM and in some ankles the radiologic ROM was minimal while the clinical ROM was acceptable.

Compared to other joint replacements, it is generally more acceptable to do revision procedures after total ankle replacement than for example after hip or knee replacement. Some of the revisions are considered benign, as they usually do not threaten the survival of the implant, *e.g.*, surgery for impingement caused by heterotopic ossification. However, there are inconsistencies in reporting the revisions and complications associated with TAR (Mercer et al. 2016). Several suggestions have been put forward for a uniform coding system for complications and revisions related to TAR, but none has yet proven to be entirely reliable (Glazebrook et al. 2009; Gadd et al. 2014; Younger et al. 2016).

Besides osteolysis, there were many other complications and revisions in Study VI. The most common intra-operative complication was fracture of the medial malleolus; the rate of the fracture (17%) was similar or slightly higher compared to previous reports (McGarvey et al. 2004; Stengel et al. 2005; Wood et al. 2007; Jung et al 2015). In comparison, there were only 6% intra-operative medial malleolar fractures in Study V, although they were the first TAR implants used in this institution. The safe amount of resection at this area is an interesting question. In these series, the fractures resolved with no further problems when fixed during surgery. Based on this experience, it would probably be beneficial to apply internal fixation of these fractures during the initial operation. However, there are opposite suggestions and good results have

been reported on using a medial malleolar lengthening osteotomy for correction of a preoperative varus deformity with no internal fixation (Doets et al. 2008).

The number of stress fractures of the medial malleolus in Study VI was also quite high. However, usually there were only minor osteopathic changes probably due to resection of strong medial subchondral bone at the superomedial corner of the joint, which was compulsory. This resolved with conservative treatment, usually by limiting weight bearing. More difficult cases were strongly associated with malalignment, which was the cause for many complications. All but one stress fracture of the distal tibia were reversible osteopathic changes just proximal to the stem or rods of the tibial component (Studies V and VI).

The number of the polyethylene insert exchanges was higher in Study V than Study VI, 14.7% vs. 5.4%. Interestingly, there were no insert fractures in Study VI, but this may have been due to a shorter follow-up time. However, the amount of insert exchanges in Study V was comparable with previous results of STAR implants with 18% insert exchange (Daniels et al. 2015).

The percentages of wound healing complications and deep infection in Studies V an VI were similar compared to previous reports, and slightly lower in Study VI than Study V, possibly due to a learning curve affect in Study V. Learning is exemplified by the fact that during the study period the use of tourniquet was discontinued after the first cases of wound healing problems.

6.2.2 Radiology

Like other total joint replacements, patients with total ankle replacements are traditionally followed up by plain radiographs. After the problem of peri-implant osteolysis became evident, more precise imaging of the implants became necessary. Hanna et al. studied the use of CT for imaging of peri-implant osteolysis, and found that CT detected osteolytic lesions of the tibia better than plain radiographs (Hanna et al. 2007). Therefore, CT was added to the routine follow-up of total ankle replacements in our institution.

During the study period, a coincident study on imaging of osteolysis around TAR implants was conducted. It was found that CT detected osteolytic lesions better than radiographs, especially under the talar component, where even large lesions might not be visible at all in plain radiographs (Kohonen et al. 2013a). The optimal imaging parameters and positioning for CT was also evaluated (Kohonen et al. 2013b).

The revision rate after TAR increases when preoperative varus deformity is present (Henricson et al. 2007). However, more recent studies show that preoperative

malalignment does not affect the result of TAR if alignment is reduced to normal (Kim et al. 2009; Shock et al. 2011; Queen et al. 2013). In addition to osteolysis, the other main reason for the poor outcome in Study VI was postoperative malalignment: a postoperative varus deformity of 10 degrees or more predicted poor implant survival. In addition, both varus and valgus malalignment were often associated with complications and were the fundamental indication for many revision operations. Malalignment could be considered a technical failure. The enthusiasm favoring rather new surgery with better instrumentation may have accounted for broadening of the indications, and this may have resulted in the increased rate of postoperative deformity in Study VI with the AES implants compared to Study V with the STAR implants. In Study IV, there was also an obvious statistical trend towards preoperative malalignment predicting a poor result, although the study population was too small to allow for significance. Valgus malalignment seemed especially prone to proceed to stress fracture, and insert dislocation or fracture, and both studies V and VI imply that the flatfoot deformity is not compatible with ankle implant survival unless the anatomy of the foot is restored before or during the operation.

Although there were considerable problems with varus malalignment in Study VI, the coronal plane deformity and the resulting overhang between the components potentially leading to postoperative edge loading and implant failure was not associated with implant survival neither in Study V nor Study VI. Marked overhang in the coronal plane was nonetheless present in 11 AES ankles and 11 STAR ankles. In addition to the coronal plane, sagittal alignment is also considered to be an important factor, since anterior translation of the talus is thought to be one of the causes of TAR implant failure due to lift-off of the polyethylene bearing (Tochigi et al. 2006). However, there were no significant differences between the tibiotalar ratio before and after surgery, and the postoperative tibiotalar ratio was not associated with implant survival in these series.

Component migration occurred in both STAR and AES ankles. Although the relative number of ankles with component migration was less for AES than STAR, AES migration was usually caused by osteolysis, whereas the reasons for migration in the STAR group were more diverse and could not always be determined. Early migration of TAR components has been detected in RSA studies, which have shown rapid initial migration of up to 0.9 mm until 6 months postoperatively, after which the situation stabilizes (Carlsson et al. 2005; Nelissen et al. 2006). Continuous migration has, however, been reported for up to 2 years postoperatively, 2.28 mm at most (Dunbar et al. 2012). Osteolysis-related migration in AES ankles (Study VI) occurred later after surgery, was progressive, and required ultimately often revision of the implant. However, since the radiological measurements relied on visual estimation and RSA was not used, it is not possible to draw conclusions about early implant migration.

6.2.3 Osteolysis

Study I is the first published report on the high rate of peri-implant osteolysis related to AES TAR, soon to be followed by others (Besse et al. 2009; Rodriguez et al. 2010, Kokkonen et al. 2011). Most of the severe cases of osteolysis in Study I took place after 2004, when there was a change in the component design and the study showed a 3.1-fold risk for osteolysis with the double-coated implant compared to single-coated implant. Male gender was also associated with a double risk for osteolysis compared to female gender. In a study by Kokkonen et al. (Kokkonen et al. 2011) osteolytic lesions were found in 50% of the ankles and cyst-like and large lesions were related to the dual-coated implant. In Study VI with a longer-term follow-up (average 8 years) with survival analysis, the high rate of osteolysis resulted in poor implant survival and a high rate of revisions.

In Study I, osteolytic lesions were found in 37% and marked lesions in 27% of the ankles by plain radiography. At that time, 15 ankles (11.5%) had been revised, 12 by debridement and filling of the cavities with bone graft, and three by conversion to arthrodesis indicated by loosening of the components. When the results between Study I and Study VI are compared, the amount of all osteolytic lesions increased from 37% to 70%, and the of marked lesions from 27% to 60%. At the same time, the proportion of the marked lesions of all lesions increased slightly. The number of revisions for osteolysis rose to 50 ankles (38%). Interestingly, the difference in the number of osteolyses between implants with different coatings in Study I had disappeared in Study VI, but osteolysis did emerge earlier with the dual-coated implants. Thus, the difference between the coatings may even out, as the amount of osteolysis in this population increases. Furthermore, male gender was not related to an overall increased risk of osteolysis in Study VI, but the lesions appeared earlier in male patients than female patients. In the light of current findings, the dual-coating and male gender seem to be associated with early osteolysis, but over time some degree of peri-implant osteolysis will develop in nearly all AES implants.

Although the AES implant has had the worst performance regarding osteolysis, the problem is common with almost every modern total ankle replacement implant. The highest occurrence of peri-implant osteolysis has been reported for the Hintegra TAR, up to 48% (Yoon et al. 2014; Deleu et al. 2015). Study V, addressing the outome and survival of the STAR implant, shows that osteolysis to any extent was present in 38% of the implants. However, the median time to detection of osteolysis for the STAR implant was 7 years for all lesions and over 9 for the marked lesions, compared to the 3 years and 4 years AES implants, respectively. Only 5 of the STAR osteolyses needed revision, done on average nearly a decade after the primary operation. At follow-up, all ankles revised due to osteolysis have been without complications. Our findings

suggest that peri-implant osteolysis in STAR implants is a more benign phenomenon than in the AES. There might also be some association between the different coatings of the STAR and osteolysis; Wood and Deakin reported that osteolytic cavitation was 7.5 times more frequent in single-coated STAR implants than double coated (Wood & Deakin 2003). The number of ankles in Study V was too low to allow a closer look at the possible connection between different coatings and osteolysis. In any case, the osteolytic lesions were distributed almost equally between single-coated and double-coated implants.

The exact pathophysiological mechanisms that lead to osteolysis remain unclear, but in addition to wear debris particles, several other factors may contribute: local damage to blood supply, fluid pressure, and mechanical factors (Sukur 2016). Studies I and VI show that there were problems with the coating of the AES implant, and it has been suggested that the coating may lead to delamination by fretting and generation of metal particles by detachment of particles from the coating by shear stress (Cottrino et al. 2016). Although the AES implant was withdrawn from the market, it would be beneficial to establish the mechanisms producing this phenomenon to avoid problems when new total ankle joint implant designs and implantation methods are developed in the future.

The main finding of Study III was identification of a possible role of the RANKL system in the periprosthetic tissues: $RANKL^+$ mesenchymal cells were observed more frequently in peri-implant tissues than in control tissues. Recently, RANKL and OPG have been shown to play a key role in initiating osteolytic lesions (Bitar et Parvizi 2015; Sukur et al. 2016). An imbalance in the RANKL/OPG ratio (Mandelin et al. 2003; Mandelin et al. 2005) has been described in both aggressive granulomatosis (Konttinen et al. 2005; Goodman et al. 2009) and aseptic loosening of the hip. In hip arthroplasty, the implants can be stable despite large aggressive granulomatous lesions around them and according to some authors these lesions and aseptic loosening should be considered different conditions (Santavirta et al. 1990a,b). Previous findings (Wood & Deakin 2003; Knecht et al. 2004; Valderrabano et al. 2004; Dalat et al. 2013; van Wijngaarden et al. 2015; Singh et al. 2016) and the results of the current studies support this theory also regarding ankle arthroplasty. RSA studies have shown micromotion of the TAR implants in up to two years postoperatively – thus, although the implant is clinically stable, there is probably motion in the bone-implant interface.

During mobilization and cyclic loading of the joint and upon expansion of the effective joint space, the fibrous implant capsule encounters pseudo-synovial fluid formed in the synovial-like lining of the prosthetic joint (Mandelin et al. 2003; Mandelin et al. 2005). Staining of consecutive tissue sections in Study III suggests that $RANKL^+$ mesenchymal cells come often in close contact with $RANK^+$ mononuclear

cells, and it seems that RANKL drives cellular fusion between RANK+ mononuclear cells and multikaryons. The microenvironment might be important for the terminal differentiation of such cells. OPG capable of preventing the RANKL action was mostly located in the endothelial cells, away from the RANKL-RANK interaction area, which indicates that the control tissues were better vascularized than the peri-prosthetic tissues. Biomechanical loading may play an important role in stimulating RANKL expression, as micromotion at the bone-implant interface upregulates RANKL expression and downregulates OPG expression creating a bone resorption response in human bone (Stadelmann et al. 2008). Fluid pressure and flow, induced even in the absence of microinstability, might contribute to osteolysis in otherwise securely fixed ankle implants via unknown pathways, perhaps, in part, via shear and hydrostatic pressure, finally involving RANKL signaling.

It was somewhat surprising (Studies I, III, and IV) to find relatively extensive soft tissue necrosis and frequent occurrence of detached and necrotic pieces of bone embedded in peri-implant tissues in routine histology, which has not been seen earlier even in aggressive granulomatous loosening of total hip replacement implants (Santavirta et al. 1990a,b). The histological presence of extensive necrotic tissue in Study III raised the working hypothesis for Study IV according to which circulatory failure together with mechanical stress would reduce tissue oxygen tension leading to ischemia and ischemic necrosis. Therefore, hypoxia-inducible factor-1 alpha (HIF-1α), the key transcription factor for the adaptation of cells to hypoxic conditions, was chosen as a marker for tissue hypoxia. Necrotic and dying cells alarm close-by cells by releasing damage-associated molecular patterns (DAMPs), danger signals also known as alarmins (Bianchi et al. 2007), via a broad spectrum of danger signal receptors known as pattern recognizing receptors (PRRs) (Bianchi et al. 2007). Thus, the key alarmin HMGB1 and the main receptors TLR2, TLR4 and RAGE were measured in Study IV. To analyze internal stress-related programmed cell death caused by hypoxia, the active effector caspase-3, considered to bring the process of programmed cell death to an irreversible effector state, was also chosen as a marker.

As hypothesized, the HIF-1α score was found to be quite high in tissues surrounding revision TAR implants indicating tissue hypoxia. Surprisingly, however, also control tissues collected from primary TAR operations had similarly high HIF-1α scores. This may relate to previous reports that overexpression of HIF-1α occurs in many types of human cancer (Jubb et al. 2004) and that inflammatory cytokines induce RANK dependent expression of the HIF-1α gene even under normoxic conditions. HIF-1α is thus active and stable in hypoxia as well as in inflammation (Frede et al. 2006; Rius et al. 2008). High HIF-1α activity might be related to chronic inflammation of the tissues present also in control samples. The main finding of Study IV was that peri-implant tissues contain increased levels of both DAMPs and PRRs, which could cause autoinflammation. The

findings suggest quite effective, albeit variable overall mobilization of HMGB1. RAGE and, in particular, TLR2 and TLR4 were up regulated in peri-implant tissues, suggesting that these tissues are very responsive to HMGB1 and to their other ligands. In tissue surrounding failed TAR implants caspase-3 positive cells and tissue and cell necrosis were common, which may represent more severely affected areas of the failure process.

The necrosis of peri-implant tissues could also be explained by toxic effects of high concentrations of implant-derived metal particles and ions (Huk et al. 2004; Mahendra et al. 2009), analogously with metal-on-metal (MoM) implants, which produce numerous nanoparticles (Brown et al. 2007), which are effectively subjected to electrochemical corrosion. However, direct toxic effects are an unlikely cause for peri-implant tissue necrosis in AES TAR, since the peri-implant tissues were not characterized by metallosis typical for MoM implants. In contrast, a tiny amount of allergen can cause a massive hypersensitivity response, but the role of metal ion-induced delayed hypersensitivity reaction was excluded by the absence of typical perivascular T lymphocyte infiltrates and other features of "aseptic lymphocyte-dominated vascular associated lesions" (ALVAL) (Willert et al. 2005). Nor was there evidence of T lymphocytes, B lymphocytes, plasma cells, or eosinophils typical for pseudotumors in MoM patients (Pandit et al. 2008).

Our studies show that osteolysis related to AES implants is not caused by polyethylene wear particles. This claim is based on the following findings: Osteolysis was initiated soon after implantation, the removed polyethylene inlays were not significantly damaged, and the number of birefringent particles interpreted as polyethylene in histological analysis was low. More likely, osteolysis was induced by nanoparticles and soluble ions, probably titanium and hydroxyapatite released from the implant coating. The amount of titanium in the analysis of elements was high compared to the control samples and to the amounts of other metals. In addition, there were several titanium as well as cobalt chromium particles in the periprosthetic tissue according to BEI-SEM/EDX analysis. Although titanium and its alloys are widely used in total joint replacements due to their biocompatibility, high corrosion resistance, and non-allergenic nature, titanium is a soft material and wear may generate debris (Brunski 1996). *In vitro*, submicron particles of titanium stimulate the release of proinflammatory mediators of macrophages even more effectively than polyethylene particles (Lee et al. 1997; Nakashima et al. 1999; Rader et al 1999; Jacobsen et al. 2007; Kaufman et al. 2008; Tamaki et al. 2008) and enhance the osteolytic potential of monocyte/macrophage cells (Tamaki et al. 2008). In addition, titanium and soluble ions of cobalt and chromium interfere with the functions of human osteoblast-like cells and stimulate fibroblasts to support osteoclastogenesis, presumably via the RANK/RANKL/OPG pathway (Maloney et al. 1993; Yao et al. 1995; Shanbhag et al. 1997; Wang et al. 1997; Yao et al. 1997; Zambonin et al. 1998; Vermes et al. 2000; Vermes et al. 2001; Pioletti et al. 2002; Wang et al. 2002; Sakai et al. 2002; Wang et al. 2003; Bukata

et al. 2004; Wei et al. 2005; Koreny et al. 2006; Ramachandran et al. 2006). Both titanium and cobalt-chromium release proinflammatory cytokines and have a negative impact on bone matrix formation (Jonitz-Heincke et al. 2016), and titanium particles inhibit the actions of the antiosteoclastogenetic cytokines (Rakshit et al. 2006). The findings in studies III and IV confirmed the role of the RANKL system for osteolysis in connection with AES implants and the responsiveness of the peri-implant tissue to inflammatory markers, which could be a consequence of particles released from the coating. These findings are also in accordance with a study on the wear of retrieved AES total ankle implants, where aluminum particles caused by a defective sand blasting phase during industrial production of the implant might have weakened the mechanical properties of the coating and caused premature wear to the titanium coating because of interference of the aluminum particles (Cottrino et al. 2016). A poor of the titanium and of the coating of the AES total ankle implant could cause particles to loosen from the surface of the implant and lead to aggressive and large granulomatous osteolyses.

Dalat et al. (2013) made a histologic study of periprosthetic osteolytic lesions after AES total ankle replacement and reported a foreign-body reaction with large and small PE and metal particles. They also identified a brownish pigment, which was neither hemosiderin nor formalin. Routine staining with hematoxylin and eosin did not disclose information to explain the pathomechanism of the lesions, but the authors concluded that the process is probably related to primary fixation of the implant and involves the cancellous bone and the coating of the implant (Dalat et al. 2013). The chronic inflammation and the high amount of tissue necrosis as a reaction to the foreign body might be explained by the local scavenging capacity of the phagocytic cells becoming overwhelmed, as is known from other conditions (Mackiewitz et al. 2005). The inflammatory fluid in the osteolysis-associated cysts may arise from strongly irritated synovial fibroblasts in the interphase between tissue and implant material. Irritation could be caused by small crystals capable of stimulating the fibroblasts due to their shape and dimensions. The crystals could arise from the friction surface of the Ti-HA coated implant and act as irritants causing the fibroblasts to change their phenotype epigenetically into rheumatoid arthritis-like aggressive synovial fibroblasts. Once the cysts are formed, they augment, merge, and start exerting hydraulic pressure on the surrounding soft tissue and bone vasculature and cause irritation to the surrounding tissues. This irritation leads to inflammation, hypoxia, and, finally, necrosis and bone fragment sequestration. The reduced oxygen level creates an acidic environment in the cyst, which stabilizes into an inflammatory state. Mechanical stress may deform blood vessels favoring ischemia. Hypoxic conditions in some tissues generate lipofuscin pigment from oxidation of unsaturated fatty acids, which could explain the unidentified brownish pigment seen by Dalat et al. and further support the hypothesis of local hypoxia around the implants. The

molecules released from necrotic cells and tissues might maintain autoinflammation and support and enhance the adverse peri-implant host response.

The theory of the development of osteolysis around AES total ankle implants is illustrated in Figure 24.

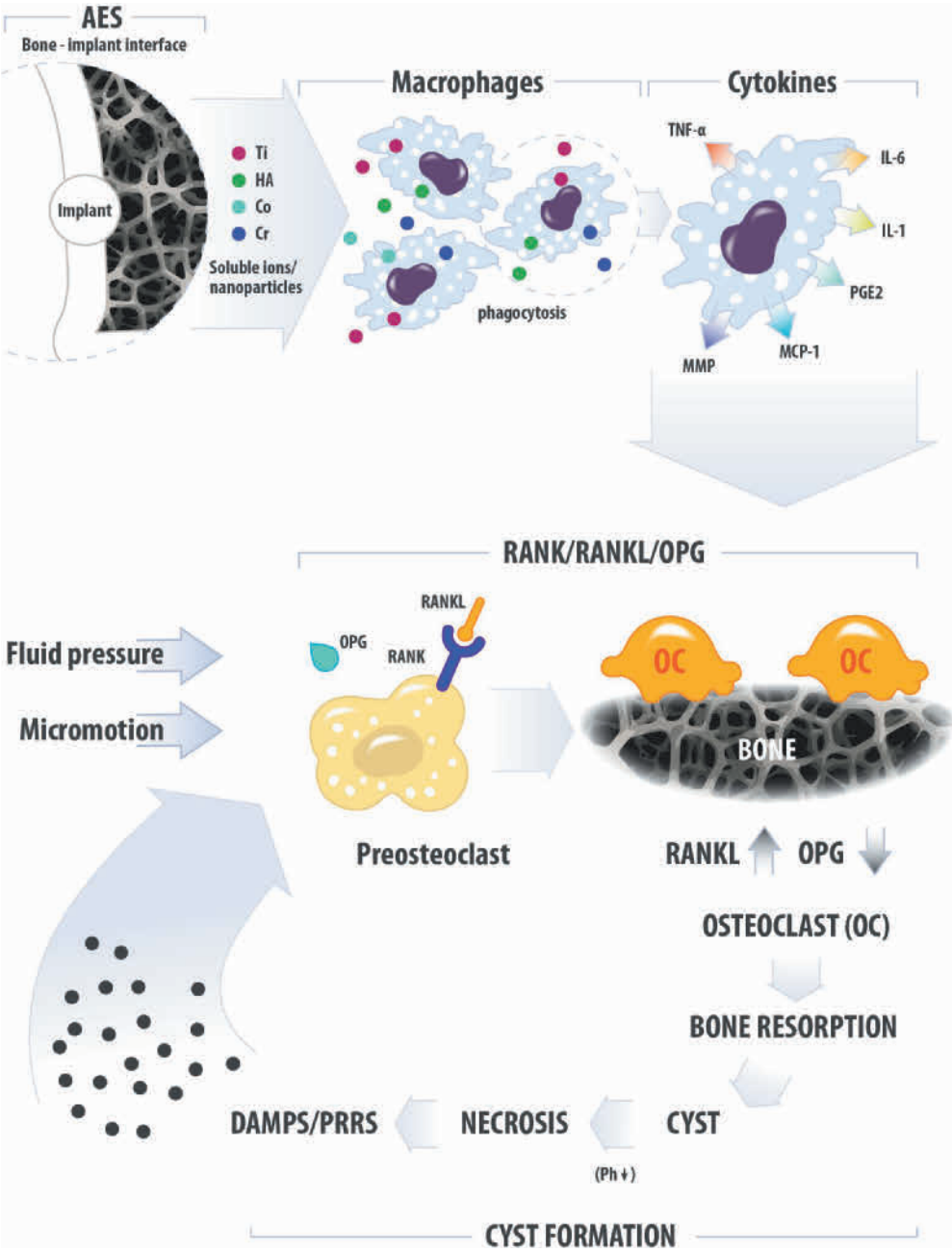

Figure 24. Illustration of the theory of the development of osteolysis around AES total ankle implants (figure Sauli Laine)

There are no established treatment protocols for osteolytic lesions of the ankle. Some authors recommend grafting of the major lesions, especially when there is progression of the lesions (Gupta et al. 2010; Rodriguez et al. 2010; Prissel & Roukis 2014; Roukis et al. 2015; Gross et al. 2016c). However, some authors suggest only follow-up, since the results of bone grafting have been poor (Besse et al. 2013). Generally, the follow-up should include CT, since plain radiographs underestimate the lesions (Rodriguez et al. 2010; Hanna et al. 2007; Kohonen et al. 2013, Viste et al. 2015). Curettage and bone grafting in cases of large or continuously growing lesions to prevent implant subsidence and loosening increased the need for revision operations in Study VI, and a recent follow-up study on the grafted lesions of the same ankles as in Study V and VI indicates that the osteolytic process tends to continue in most cases (Kohonen et al. 2017). Nevertheless, grafting of the lesions might be useful for some patients, since it may prolong the time to implant removal and fusion, and make the fusion technically easier because of better bone stock.

6.2.4 Implant survival

Study VI was the first long-term study on the outcome and survival of the AES TAR. Previously, there have been only some reports on the survival of the AES implant and the follow-up time has been much shorter (Henricson et al. 2010; Morgan et al. 2010; Rodriguez et al. 2010; Besse et al. 2010; Kokkonen et al. 2011), and studies with a short follow-up have failed to identify the impact of osteolysis (Henricson et al. 2010; Morgan et al. 2010). The five- and ten-year survival and the revision rate of the AES implant in Study VI were inferior to what has previously been reported. On the other hand, the long-term survival of the STAR total ankle replacement was similar level as in several long-term survival studies (Andersson et al. 2003; Wood & Deakin 2003; Valderrabano et al. 2004; Schutte & Louwerens 2008; Wood et al. 2008; Henricson et al. 2007; Henricson et al. 2011b; Mann et al. 2011; Nunley et al. 2012; Brunner et al. 2013; Jastifer & Coughlin 2015; Daniels et al. 2015; Henricsson & Carlsson 2015; Kerkhoff et al. 2016), although the STAR implant was the first ankle replacement to be used in our institution and the result has certainly been affected by the learning curve, as has been shown for TAR operations in general (Myerson & Mroczek 2003; Saltzman et al. 2003; Haskell&Mann 2004; Schuberth et al. 2006; Henricson et al. 2007; Lee et al. 2008; Schimmel et al. 2014).

The results of component revisions of total ankle replacement have been variable (Hintermann et al. 2013; Kamrad et al. 2015; Williams et al. 2015). All component revisions in Study V were technically easy, regardless of whether the revision was performed very early or late after implantation. In turn, in most revision cases in Study VI the implants were unstable and there was not enough bone stock left to perform a component exchange even with revision implants. In cases of aseptic

loosening without osteolysis the use of revision implants might be recommendable, but if there are osteolytic lesions, this very likely results in conversion to fusion.

In Study II, overall device survival of 83% at 5 years after any revision or 95% after revision for aseptic loosening are comparable studies from Swedish and Norwegian national registers (Fevang et al. 2007; Henricson et al. 2007; Henricson et al. 2011b; Henricson & Carlsson 2015). Aseptic loosening was the reason for revision in 39% of the cases; this rate is similar to what has been reported in other register studies (31–48%) (Fevang et al. 2007; Henricson et al. 2007). In the present study, there was no difference in survival rates between the STAR and AES designs, but the data on total ankle replacements originated from 1998–2006, at a time when the impact of peri-implant osteolysis related to the AES implant was not yet observed.

Coverage of registry data on total ankle implants was lower than expected when compared to data in the discharge registers of the participating hospitals after conducting the Study II. Interestingly, the proportion of rheumatoid patients has decreased over the years. In Study II and study V most patients had rheumatoid arthritis, whereas in Study VI most had osteoarthritis.

Previous studies have shown an effect of surgical volume on implant survival, but this was not the case in Study II, and there were no differences between TAR survival between high-volume and low-volume institutions. This finding may be due to two circumstances. First, many of the low-volume institutions are private clinics where the surgeon comes from a high-volume hospital to perform the operation. Second, as the total annual number of TARs in Finland is small, very few surgeons ever reach and maintain their skill level at the top of the learning curve. Instability was a common reason for revision, and instability could be considered to be a technical failure, since is probably largely the result of postoperative malalignment.

6.3 Future focus

As overall survival of total ankle replacement is continuously improving, the main future challenges for developers of new total ankle joint implant designs and better implantation methods are to prevent osteolysis and aseptic loosening. Care is needed when introducing new implants into clinical practice. The differences between total joint implant designs, materials, and manufacturing procedures are small, but may result in massive problems. Factors related to implant design and material, as well as surgical techniques, are important considerations for decreasing wear particles and mechanical stresses. The exact mechanisms that cause peri-implant osteolysis must be identified and, for this, the first step should be to determine the key mechanisms

of tissue protection underlying the way how the host accommodates to prosthetic particles and biomechanical stresses.

The optimal treatment of large peri-implant osteolytic lesions remains unclear and deserves more attention. The patients seem generally to remain symptomless despite even massive lesions. More follow-up studies of are needed to determine whether the osteolytic process continues or if grafting is beneficial to salvage the implant, at least for some patients.

The registry studies are shown to give reliable information on the survival of total joint implants, and therefore it is important to improve the coverage of the Finnish Arthroplasty Registry also of ankle implants. The registry has already been updated for the hip and knee implants, and improvement for other implants is in the making. In addition to maximum coverage, an important feature of a functional registry is real time operation, so that all potential complications are noted as soon as possible.

In the light of current knowledge, the ideal patient for total ankle replacement is a non-smoking, middle-aged or older patient of normal weight and no significant comorbidities and whose ankle is well aligned, of good bone stock and a good range of motion preoperatively. Since the beginning of the third-generation total ankle replacements, most operations are now performed because of osteoarthritis rather than rheumatoid arthritis, and the average age of the patients for total ankle replacement may decline because of the increased overall incidence of ankle trauma.

Although no effect of a rising learning curve was shown in these studies, many of the failures were, in fact, related to technical failures. The very high number of technical errors in primary TARs suggests that this field of implant arthroplasty, performed at low volumes, should be centralized and kept in the hands of orthopedic surgeons familiar with the procedure and with the special features of the foot and ankle. With the Finnish population of 5.4 million, enough centers for TAR would be 2–3 with 2 surgeons operating together at each unit. This would yield at least 25 TARs annually for each operating or assisting surgeon. Since the treatment of failed total ankle replacement is always challenging and the results are rather unsatisfactory, patient selection for primary treatment with either replacement or fusion is crucial and should be done by a surgeon familiar with both procedures.

7. CONCLUSIONS

Study I

There was an alarming percentage of early-onset and rapidly progressing periprosthetic osteolyses around the AES total ankle implants. The risk of osteolysis was 3.1 times higher with the double-coated implant compared to single-coated implant. The amount of titanium was substantial, and BEI-SEM/EDX analysis revealed several titanium and cobalt chromium particles in the periprosthetic tissues. These observations suggest that the inferior quality of titanium and defects in implant coating technique of the AES total ankle implant may have caused particles to loosen from the surface of the implant and caused aggressive, granulomatous, large osteolyses.

Study II

The overall survival of total ankle replacement in the Finnish Arthroplasty Registry was consistent with other registry studies. It was not possible to identify any prosthesis as being superior to any other.

Study III

TARs revised for osteolysis were characterized by quite extensive soft and bone tissue necrosis. Osteoclasts and multinuclear foreign body giant cells contributed to peri-implant osteolysis in the proximity of AES total ankle implants via the RANK/RANKL-pathway.

Study IV

Histology disclosed quite extensive tissue and cell necrosis around failed TAR implants, which was not only of ischemic origin. Several biomarkers associated with cellular stress and damage were used to show that archetypical danger signals were mobilized. Tissues surrounding failing TAR implants seem to be very responsive to such signals, because they contain high levels of at least three different pattern-recognizing molecules. Autoinflammatory DAMP-PRR interactions may drive the inflammatory process in tissues surrounding failed TAR implants, with the cyst and its physiology itself probably being crucial for the process.

Study V

The STAR total ankle implant survival and patient outcome results are satisfactory in the long-term regardless of several additional procedures and revision procedures.

Although STAR is not free from periprosthetic osteolysis, it seems to be a benign phenomenon occurring late in the lifespan of the implant. STAR seems to produce reliable results, which may further be improved with better instrumentation, better patient selection, and more experienced surgeons.

Study VI

Reduction of malalignment of the ankle and restoration of a neutral foot and ankle position is crucial for best possible total ankle implant survival. Substantial peri-implant osteolysis related to the AES TAR, if present, increases over time and affects implant survival and outcome significantly.

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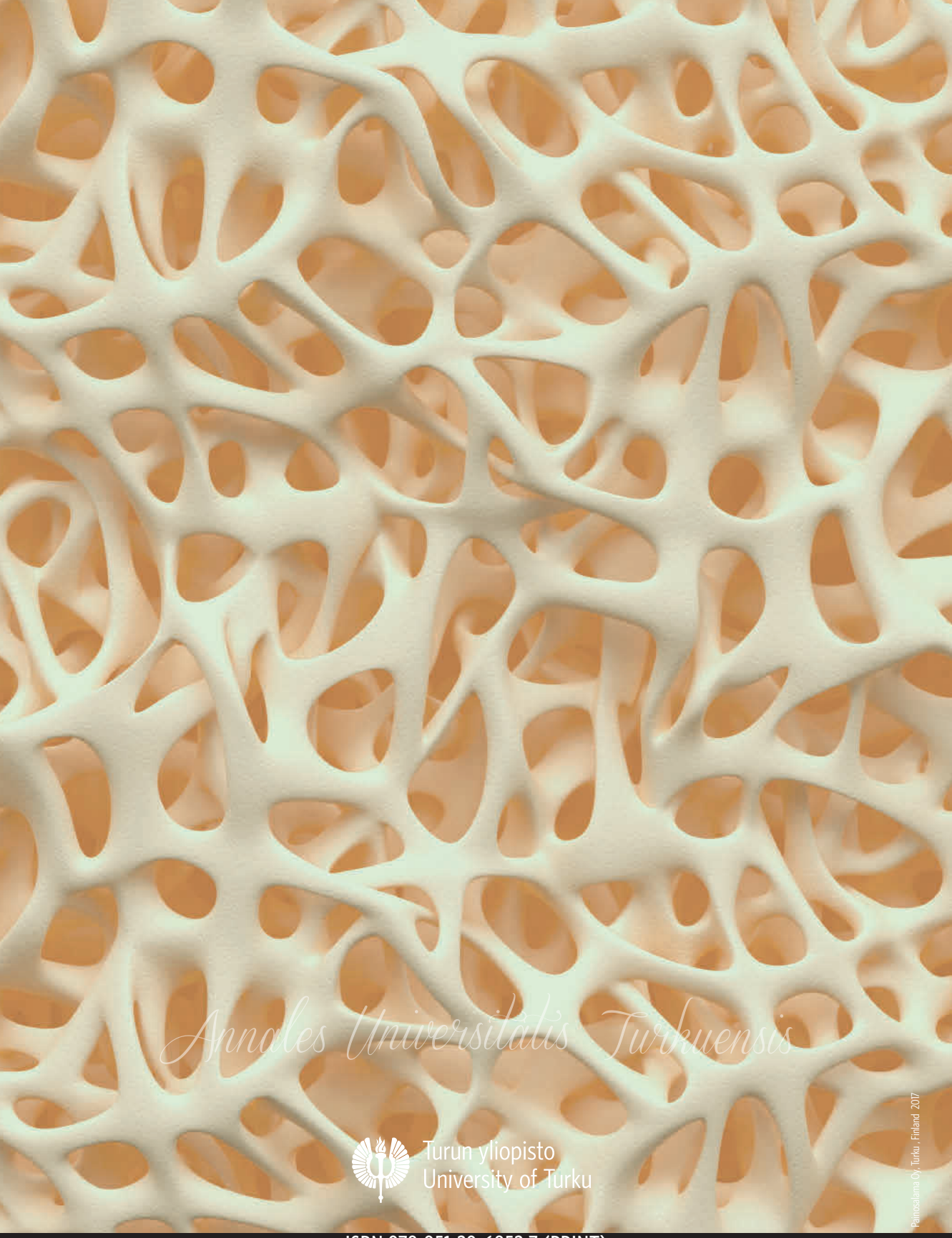

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