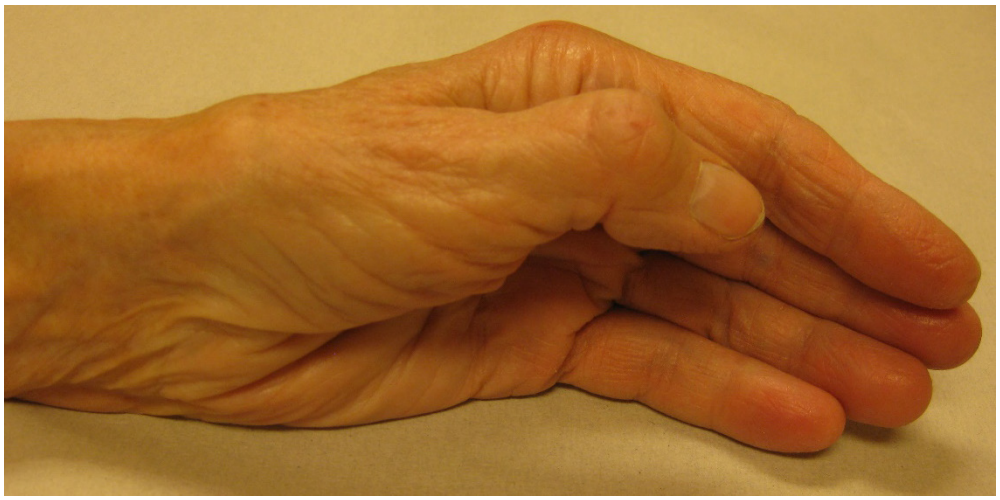
# UNCEMENTED METAL-ON-METAL ARTHROPLASTY FOR TRAPEZIOMETACARPAL OSTEOARTHRITIS

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Oslo 13.09.2019

Rasmus Dehli Thorkildsen

# Abbreviations

| | |
|---|---|
| AOL | Anterior oblique ligament |
| dAOL | Deep anterior oblique ligament |
| sAOL | Superficial anterior oblique ligament |
| AP | Adductor pollicis |
| APB | Abductor pollicis brevis |
| APL | Adductor pollicis longus |
| CAD | Computer-aided drawing |
| CMC1 | The first carpometacarpal joint (aka trapeziometacarpal joint) |
| CoC | Ceramic on ceramic |
| CoM | Ceramic on metal |
| CrN | Chrome Nitride |
| CT | Computer tomography |
| CrCoMo | Chrome Cobalt Molybdenum alloy |
| DASH | The disability of the arm, shoulder and hand score |
| DRL | Dorsoradial ligament |
| EPB | Extensor pollicis brevis |
| EPL | Extensor pollicis longus |
| EULAR | European league against rheumatism |
| FBGC | Foreign body giant cell |
| FCR | Flexor carpi radialis |
| FEA | Finite element analysis |
| FPB | Flexor pollicis brevis |
| FPL | Flexor pollicis longus |
| HA | Hydroxyapatite |
| $H_a$ | The alternative hypothesis (there is a difference) |
| $H_o$ | The null hypothesis (there is no difference) |
| ICP-OES | Inductively coupled optical emissions spectroscopy |

| | |
|---|---|
| IP | Interphalangeal (joint) |
| LA-ICP-MS | Laser ablation inductively coupled plasma mass spectrometry |
| LC1 | Load case 1 (paper 1, load applied perpendicular to trapezium surface) |
| LC2 | Load case 2 (paper 1, load applied at 30° angle) |
| LRTI | Ligament reconstruction & tendon interposition |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| MNAR | Missing, not at random |
| MHQ | Michigan hand questionnaire |
| MNGC | Multinucleate giant cell |
| MoM | Metal on metal |
| MoP | Metal on polyethylene |
| NSAIDS | Nonsteroidal anti-inflammatory drugs |
| OA | Osteoarthritis |
| OP | Opponens pollicis |
| POL | Posterior oblique ligament |
| PROM | Patent rated outcome measure |
| PRWHE | Patient rated wrist and hand evaluation |
| QDASH | The quick disability of the arm, shoulder and hand score |
| RCT | Randomised controlled trial |
| REK | Regional ethics committee |
| ROI | Region of interest |
| RSA | Radiostereometric analysis |
| SEM-EDS | Scanning electron microscopy with energy dispersive x-ray spectroscopy |
| STT | Scaphotrapeziotrapezoid (or Triscaphe) joint |
| UHMWPE | Ultra high molecular weight polyethylene |
| VAS | Visual analogue score |
| XPLE | Highly cross-linked polyethylene |

| | |
|---|---|
| 1.DI | First dorsal interosseous |
| 3D | Three dimensional |

# Thesis summary

Osteoarthritis (OA) can be thought of as a gradual failure of the joint it afflicts, causing pain and dysfunction. In the hand, OA commonly affects the carpometacarpal joint (CMC1) of the thumb (second only to the distal finger joints). In fact, OA involves the small joints of the hand more frequently than any other joint in the body. OA of the CMC1 is particularly common in females from middle age onwards. As this plays a vital role in thumb and hand function, CMC1 OA can cause considerable functional impairment and pain. The condition is one of the more common problems patients are referred to hand surgeons (and therapists) for. A large number of treatments are in use, both surgical and non surgical, but currently we do not know which, if any, are superior. Thus, there is a need for more research on this topic, and preferably randomised trials comparing methods to one another. This thesis consists of four papers that largely deal with joint replacements in the treatment of CMC1 OA, specifically their place in treatment of this condition, design issues of certain implants, ways of improving/prolonging their function and lastly, some of the problems associated with their use.

Joint replacements were first developed in the 70's. Many designs have been in use since then, mostly with ball and socket articulations. The usual solution has been to place a cup in the bone known as the trapezium, and a stem into the metacarpal bone of the thumb. Connecting the two is a third component, the head and neck of the implant, that forms the ball in the socket. The figure below shows an example of an x-ray with a joint replacement in place.

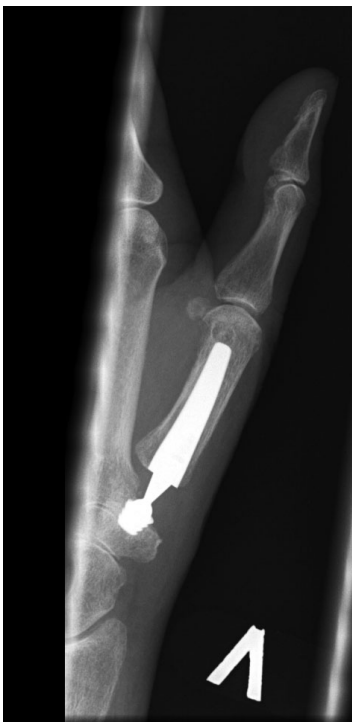

Fig 1. Lateral projection of a total joint replacement (the Elektra™) in the left CMC1 joint.

These artificial joints have generally provided good function and pain relief, but just as with development of joint replacements for other joints, there have been many problems for surgeons and engineers to deal with as these implants have evolved over the span of the last 40-50 years. The cup-side of these small joint replacements in particular has been (and still is) challenging, where good long-term fixation in the trapezium bone is the ultimate aim.

The first two papers were experimental studies; paper one considered the design features that may be advantageous for modern uncemented joint replacements. The study specifically compared two different cup designs. The second paper looks more closely at the articulation surfaces, where invariably wear products are generated. Such wear products have a detrimental effect on the artificial joint and can ultimately contribute to loosening of the implant (and necessitate repeated surgery for the patient). Thus, different joint surfaces have been developed and tested and researchers have been looking at ways of reducing the amount of wear to a minimum. A Metal on Metal (MoM) articulation was thought to hold particular merit due to low wear rates. Coating the articulation surfaces with a thin, hard coat of Chromium Nitride (CrN) has been shown to reduce wear rates further in the hip joint (in a joint simulator study). Thus, our question in paper two, was whether this technology would function equally well in smaller joint replacements such as those used in the CMC1 joint. Paper three is a randomised controlled trial (RCT) comparing an uncemented joint replacement to trapeziectomy (one of the most common procedures performed, and the procedure most other techniques are compared to). Finally, paper four is a retrieval study where we have looked closely at five trapezia removed at revision surgery after a failed joint replacement. This study gives insight into possible reasons for early loosening of the cup for the above mentioned, uncemented, MoM joint replacement.

# Articles in the thesis

**1.** Thorkildsen R, Theodorsson J, Mellgren M, Røkkum M**. Comparison of two uncemented trapezio-metacarpal cups: a finite element study.** Hand Surg. 2013;18(2):221-8.

**2.** Thorkildsen R, Reigstad O, Røkkum M. **Chrome nitride coating reduces wear of small, spherical CrCoMo metal-on-metal articulations in a joint simulator.** J Hand Surg Eur Vol. 2017 Mar;42(3):310-315.

**3.** Thorkildsen RD, Røkkum M. **Trapeziectomy with LRTI or joint replacement for CMC1 osteoarthritis, a randomised controlled trial**. J Plast Surg & Hand Surg 2019 Jul 4: 1-9.

**4.** Thorkildsen RD, Johanssson CB**,** Hogmalm J, Johansson PH, Røkkum M. **Early cup loosening after metal-on-metal total joint replacement of the trapeziometacarpal joint. A retrieval study.** Manuscript accepted 28.06.19 for publication in J Hand Surg 2019

# Introduction/background:

## Evolution:

The thumb is vital for the advanced hand function seen in humans, allowing both powerful grip and complex fine motor tasks. When comparing our thumb to that of our primate ancestors many interesting differences are found. A well known article by Marzke et al published in 2000 looked closely at these differences(Marzke and Marzke, 2000). Firstly, the thumb has become longer compared to the rest of the hand, having the largest ratio (60 %) of thumb- to index ray length compared to other primates. Secondly, the configuration of the CMC1 joint has changed, with a decrease in both the curvature of the joint surfaces and of the size of the metacarpal beak, resulting in a flatter, less stable joint that allows greater motion. Thirdly, the human thumb tip (or thumb pulp) has developed two compartments; one at the very tip of the thumb which is quite firm, and a proximal compartment that is softer and easier to deform. Fourthly, our thumbs have a powerful long flexor tendon (The Flexor Pollicis Longus, FPL). This flexor has a separate muscle not seen in primates, allowing thumb flexion independent from the other fingers as well as greater flexion strength. Lastly, the proportion of the hand's musculature that is made up by the thumb muscles is larger in the human hand (30 %) compared to that of other primates. Anatomical studies comparing the human hand and thumb of today to the fossil remains of our ancestors, argue that these developments may have bestowed a vital evolutionary advantage upon our early ancestors, allowing them the grip and function that was required for the handling of smaller objects and the production of stone tools, see Fig 2(Marzke, 1992; Marzke and Marzke, 2000).

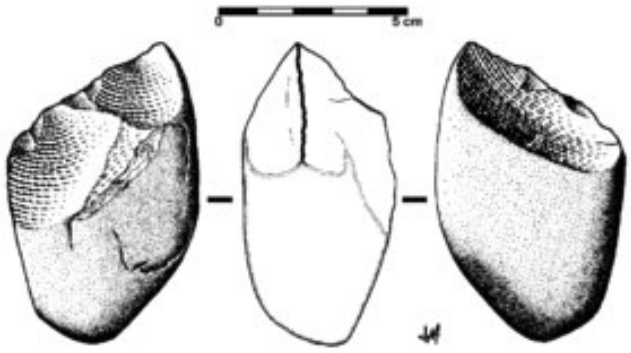


Fig 2. Oldowan (from Olduvai Gorge, Tanzania) chipping tools are thought to be the earliest stone tools made by man (*Homo habilis* or "handy man"). They were probably made by repeated strikes from another stone (the "hammerstone") held in the dominant hand, chipping away flakes until a sharp edge remained. Picture from Wikipedia

## Anatomy:

The thumb consists of three bones; two phalanges (the proximal and distal phalanx) and one metacarpal.

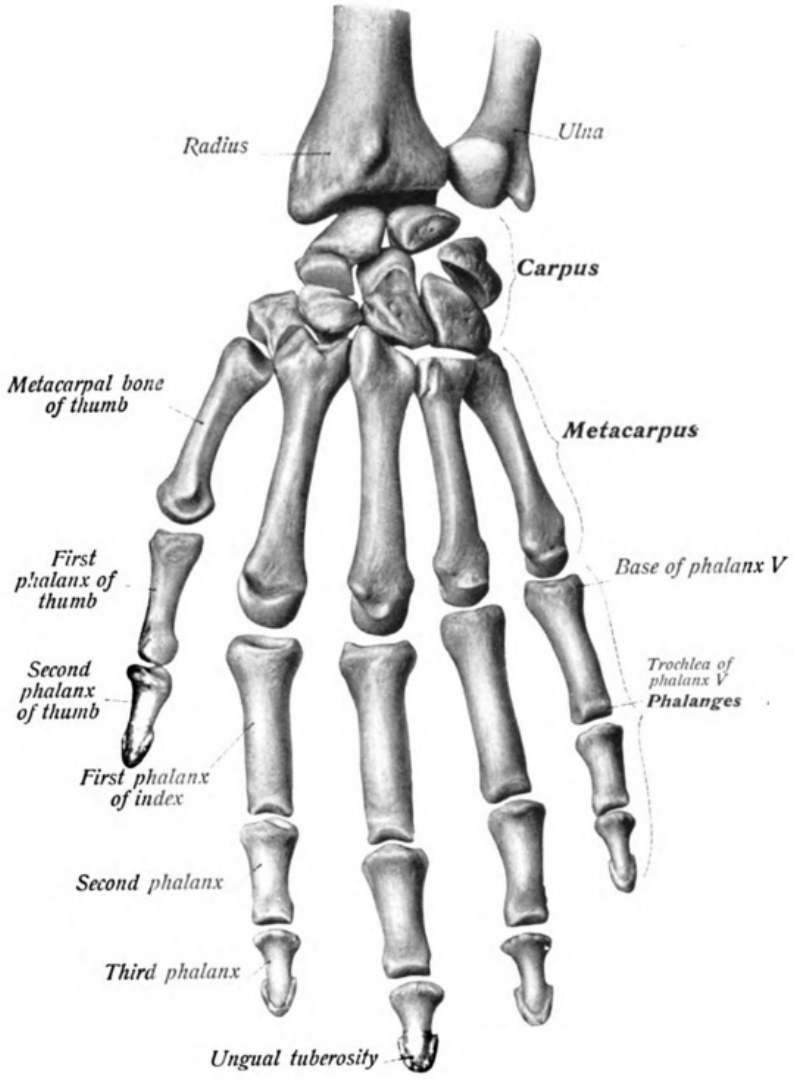


Fig 3. The bones of the human wrist, carpus and hand. Picture from Wikipedia

At the thumb base, we find the joint of particular interest for this thesis, the carpometacarpal joint of the thumb (CMC1), where the metacarpal bone articulates with the trapezium. This joint is curved in two planes, a so-called biconcave saddle joint (Fig 4.), and allows a great deal of motion.

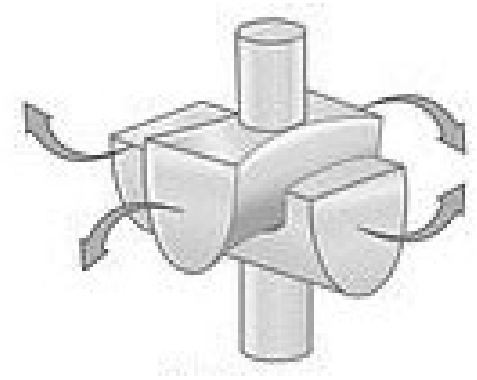

Fig 4. Schematic representation of a saddle joint. Picture from Wikipedia

It is a relatively unstable joint, highly dependent on stability from the joint ligaments (of which there are many). Bettinger et al (Bettinger et al., 1999) identified 16 ligaments, of which 14 pass from the thumb metacarpal to the trapezium. Of these, there are two sets of ligaments that are worthy of further mention; firstly, the ligaments attaching to the beak of the metacarpal. These are the superficial and deep Anterior Oblique Ligaments, sAOL and dAOL respectively. The latter also known as the beak ligament. They pass in an oblique course to the trapezium and most likely function as a pivot point for the thumb as is rotates to meet the fingers (a movement known as pronation). This ligament complex is also of interest as we later try to understand the cause, or development of osteoarthritis in the CMC1 joint. The second set of ligaments that are thought to be important for the stability and function of the CMC1 joint are the dorsal ligaments (Dorsoradial ligament, DRL and Posterior Oblique ligament, POL). These ligaments have been shown to be richly innervated by mechanoreceptors, inferring that they are important not only as stabilizers of the joint but also for joint proprioception (Hagert et al., 2012; Halilaj et al., 2015).

The trapezium bone (also known as the greater multangular bone in older literature) is an irregular shaped bone that couples the thumb to the hand (or more specifically, the carpus). It is highly constrained by ligaments, both between it and the metacarpal, as described above, but also across its other articulations in the scaphotrapeziotrapezoid (also known as the “triscaphe” or STT) joint. In addition, it has a small articular facet against the radial side of the second metacarpal. A figure of the left trapezium appears below.

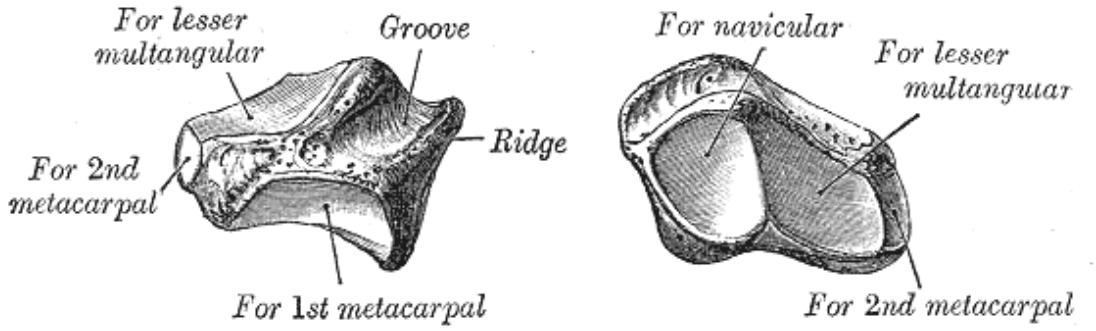


Fig 5. The left trapezium (greater multangular bone). Picture from Wikipedia

The STT joint is believed to be of great functional importance for the carpus, as the distal scaphoid is stabilized and retained by this joint, allowing the scaphoid to form a link between the two carpal rows.

On the volar surface of the trapezium, a groove (see Fig. 5) can be found where the Flexor Carpi Radialis (FCR) tendon courses tight against the bone on its way to its insertion at the base of the second metacarpal bone.

The thumb is moved by a combination of intrinsic and extrinsic muscles. The intrinsic muscles of the hand are so named because they both originate, and end (insert) within the hand. The five muscles dedicated to the thumb are the Abductur Pollicis Brevis (APB), the Flexor Pollicis Brevis (FPB), the Opponens Pollicis (OP), the Adductor Pollicis (AP) and the first dorsal interosseous (1.DI). The latter is the only one of the these muscles that is located on the dorsal side of the hand).

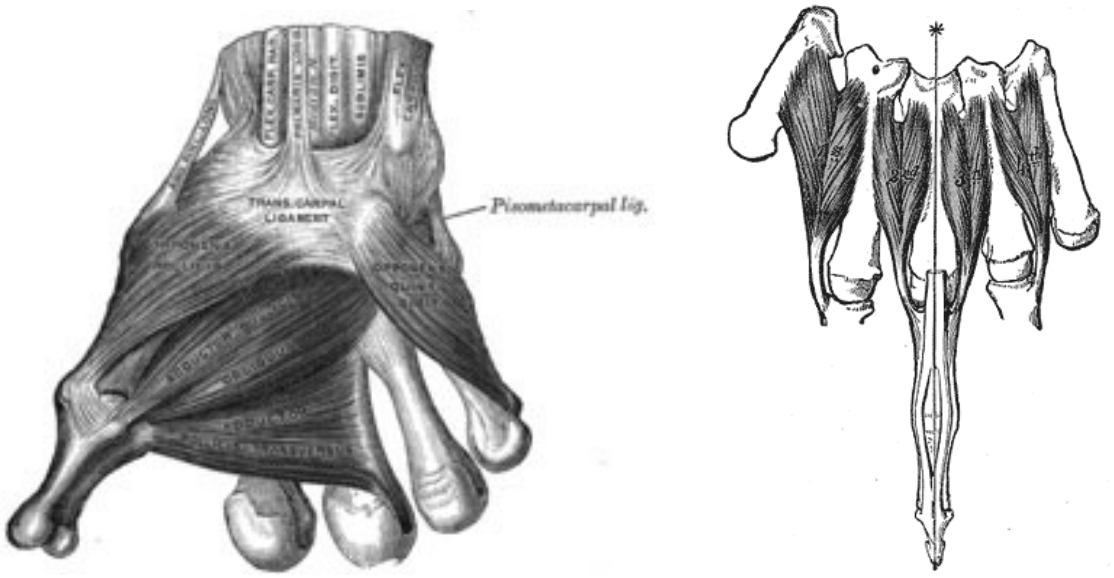


Fig 6. On the left, drawing of the intrinsic thumb musculature of the right hand shown from the palmar surface. On the right, the dorsal interossei of the left hand, where the first dorsal interosseous inserts onto the thumb's metacarpal. Collectively these muscles provide most of thumb motion and are innervated by the median- and ulnar nerves. Picture from Wikipedia

The extrinsic muscles in contrast, have their origin in the forearm and insert on the thumb via long tendons. They number four in total. There are two extensors; the Extensor Pollicis Brevis (EPB) and Extensor Pollicis Longus (EPL), one abductor; the Abductor Pollicis Longus (APL) and one flexor; the Flexor Pollicis Longus (FPL)

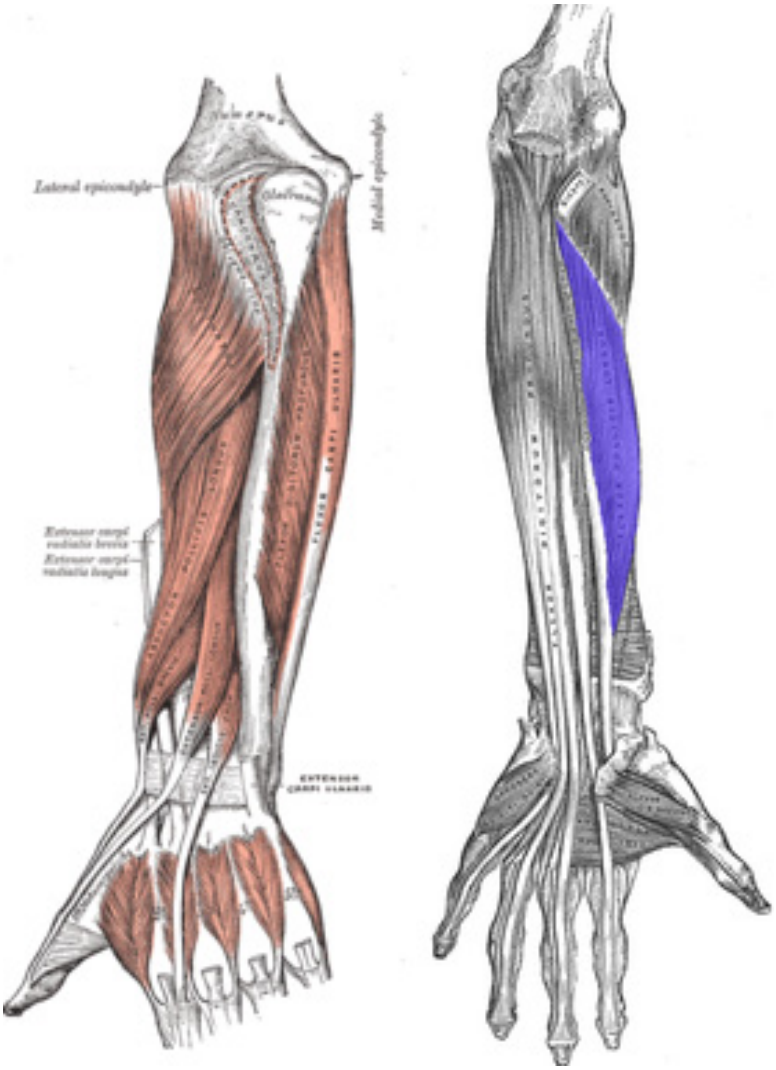

Fig 7. The extrinsic tendons of the left thumb. On the left, the dorsal side of the forearm and hand showing the long extensors and the abductor. On the right, the long flexor is marked in blue. These tendons provide extension to the thumb, some abduction and power in pinch, but contribute less to opposition and adduction. Picture from Wikipedia

## Symptoms, diagnosis and staging:

When symptomatic, patients with CMC1 OA complain of pain about the thumb base. The pain is usually aggravated by activity and relieved by rest, and may sometimes radiate out along the thumb. Most activities of daily life may cause pain, sometimes so intense that patients will involuntarily loose the objects they are handling. Grip requiring strength is panful, but also repetitive, finer motor tasks can cause pain. With progressing symptoms, the painful episodes become more frequent and the joint can ache in the evening and at night. The diagnosis of CMC1 OA is made by clinical examination, and is supported by relevant radiographs. In terms of clinical findings, there is often a dorsal subluxation of the thumb base evident on inspection, known as the “shoulder sign”. With further progression of joint destruction and basal subluxation, the thumb comes to lie against the palm and the soft tissues in the first web (the skin, fibrous tissue and musculature between the thumb and the

hand) can become contract (shortened). Gradually, the thumb ray collapses into a Z-like appearance, often readily apparent if the patient is asked to grip an object between the thumb and the index finger.

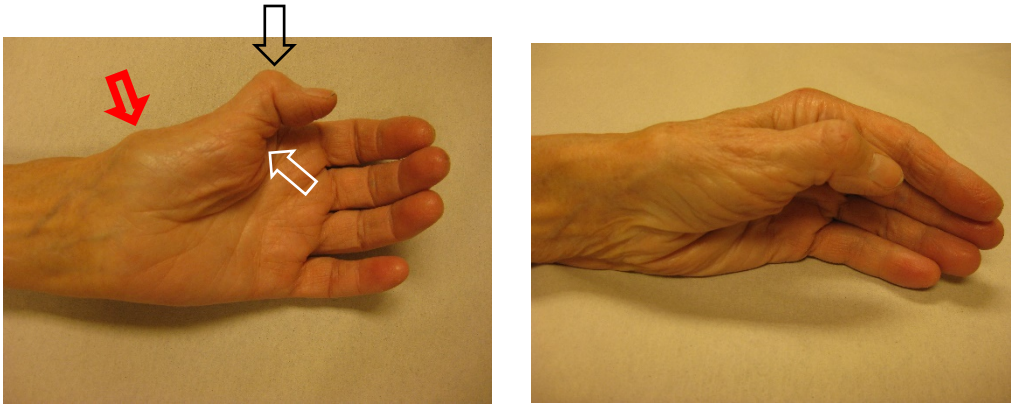

Fig 8. Photographs of advanced collapse of the left thumb secondary to CMC1 OA. The thumb base has subluxed (red arrow) with the metacarpal bone “stuck” in the palm. Furthermore, we see compensatory hyperextension in the metacarpophalangeal joint (white arrow) and flexion in the interphalangeal joint (black arrow). The changes all together are described as “Z-collapse”. Pictures RDT

The joint is usually tender to palpation and there may be some swelling about the joint (synovial effusion). Manipulation of the thumb base can be very painful, and the examiner need to be cautious of this. Different manipulations of the thumb form the basis of clinical tests that suggest or support the diagnosis when they elicit pain. The “grind test” is one such test frequently mentioned in text- books; the examiner holds the painful thumb with one hand and supports the patients wrist and hand with the other hand as compressive and rotatory forces are applied to the thumb along the axis of the metacarpal bone. Recently, two publications suggest that other clinical tests may be more sensitive for the condition (Mailey et al., 2019; Model et al., 2016). Two tests recommended by these papers are the “lever test” and the “relocation test”. The former consists of the examiner moving the metacarpal from side to side in the joint whilst the latter involves slight traction to the thumb and relocation of the thumb base against the trapezium.

The examiner should be mindful of other conditions that can cause radial-sided hand pain, but I will not go into details of this here. It is worth mentioning however that the neighbouring joints should be examined. We will further discuss the significance of this when discussing the existing knowledge gaps for this condition.

Radiographs of the thumb should be a standard part of the assessment and generally include at least two views, taken perpendicular to one another. The lateral view is standard, but the frontal view can be taken either from dorsally (called a posteroanterior, or PA view) or with the arm and forearm completely pronated and the hand resting against the radiograph

plate. This latter view is called an anteroposterior or AP view, but is also known as the Robert's view or projection after the French radiologist who first described it in 1936(Ladd, 2014). Frequently all three projections are used and generally both thumbs are included side by side on the PA view allowing the clinician to compare the two sides of this frequently bilateral condition.

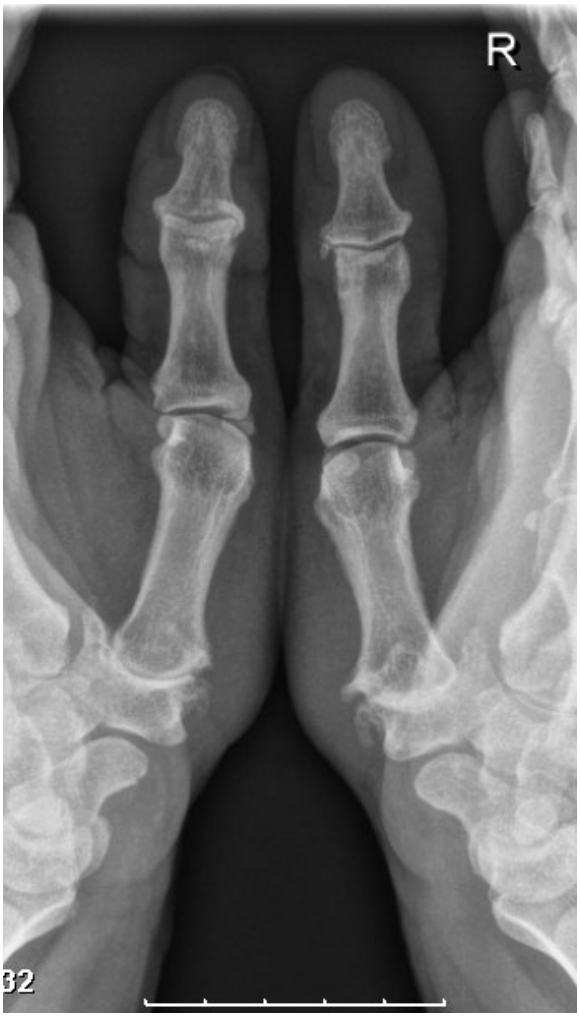


Fig 9. PA radiographs of both thumbs. The right thumb is symptomatic in this case, but both CMC1 joints show advanced OA with obliteration of joint space, subchondral sclerosis and osteophytes at the joint edges. Picture RDT

The most recognized radiographic staging system was published in 1973 by Eaton and Littler(Eaton and Littler, 1973). It was later modified in 1987 by Eaton and Glickel (Eaton and Glickel, 1987) to include the scaphotrapeziotrapezoid (also known as the triscaphe, or STT) joint. This classification system is still in use today. The authors described four stages:

Stage 1: Normal joint surfaces, some widening of the joint space (suggesting a joint effusion)

Stage 2: Slight narrowing of the joint space and minimal subchondral sclerosis. Small osteophytes and/or loose bodies in the joint (not exceeding 2 mm)

Stage 3: Increased narrowing, or obliteration of joint space. Marked subchondral sclerosis and larger osteophytes and/or loose bodies in the joint. Subchondral cysts and varying degrees of subluxation

Stage 4: Findings as in stage 3 with the addition of joint space narrowing in the STT joint

Whilst the above staging system is used in numerous publications, it has little, or no clinical significance as there is no clear correlation between increasing Eaton grade and symptoms or patient outcomes. Furthermore, a review article published in 2014 concluded that the interobserver reliability (how often two independent observers agree on the staging when assessing the same radiograph) was only poor to fair (kappa values 0.11-0.56). The intraobserver reliability (how often the same observer agrees with him/herself when assessing the radiograph at two different time points) was slightly better (kappa values 0.54-0.67)(Berger et al., 2014)

In addition to radiographs, Computed tomography (CT) scans can be a useful supplement when assessing the CMC1 joint. We have used this routinely in our RCT. The scans allow more reliable assessment of the STT joint and readily show cysts in the trapezial bone that can be overlooked on plain radiographs. This is of particular importance when considering a joint replacement, as large cysts in the trapezium may prevent adequate fixation for parts of the prosthesis (the cup, see later).

In conclusion, there is no reliable single staging or scoring system available today for this common condition that can guide surgeons when assessing patients with painful OA of the CMC1. Rather, all the above information must be taken into account, along with the patient history as well as any previous treatment given, before a decision is made to offer surgical treatment or not. Patient rated outcome measures and work status are also useful to consider, but none the less it is difficult to compare different patient cohorts and publications with respect to disease severity prior to treatment.

One recent article is worth mentioning that looked at the patients perspective when faced with the recommendation to undergo surgery for CMC1 OA; a very recent multicentre study has looked at the possible benefit of a web based decision aid. Patients were randomised 90 patients (45 patients in each arm) to receive to receive standard care (a standard brochure about CMC1 OA from the American society of hand surgery) or the decision aid. The researchers found that patients in the decision-aid group experienced significantly less decisional conflict at the conclusion of the preoperative consultation with the surgeon as measured by the study's primary outcome measure, the Decisional conflict score with scores of 9.3 (1.9) and 17 (2.0) in the intervention and standard care groups respectively. The outcome measure gives a score from 0 (no conflict) to 100 (highest decisional conflict). The group points out that this type of aid may be useful before procedures that are largely based on patient symptoms such as surgery for CMC1 OA (Wilkens et al., 2019).

## Biology of Bone:

We should briefly review this topic as much of this thesis is concerned with the interaction between bone and an orthopaedic implant (joint replacement). The ultimate success of a joint replacement is completely dependent on the integration of the implant with the host bone. For more detail, the reader is referred to a recent review article on bone biology from 2015 (Florencio-Silva et al., 2015). Briefly, bone is a living biological tissue consisting of four principal cell types; the osteoblast and the osteoclast, the osteocyte and the bone lining cell. The former two cells are involved in the formation and breakdown of bone respectively. This continuous process is believed to be regulated by the latter two cell types, se Fig. 10.

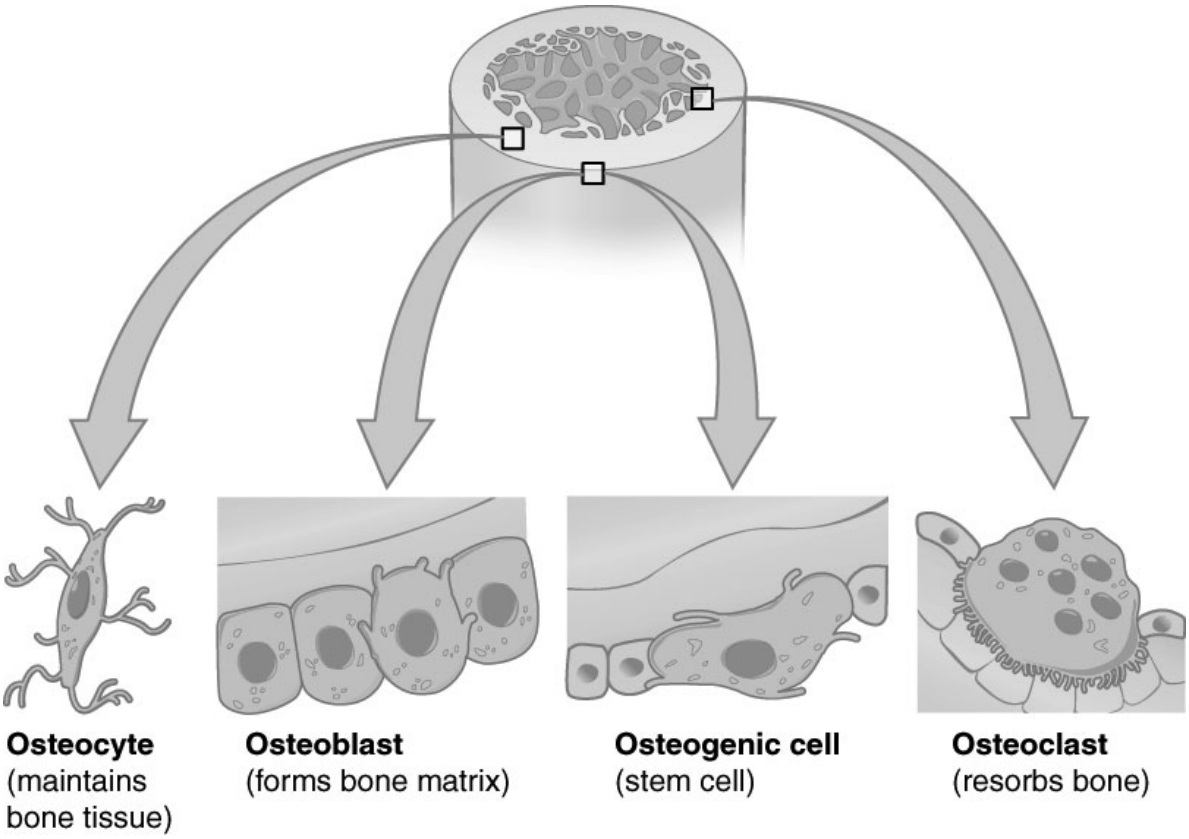


Fig 10. Cells in bone. Picture from Wikipedia

### *The osteocytes:*

Osteocytes comprise 90-95% of the total cell population in bone and are differentiated from osteoblasts. A proportion of osteoblasts differentiate into osteocytes at the end of a cycle of bone formation, the latter cell then becomes gradually encased in bone matrix, where they reside in small spaces called the lacunae. (Fig. 11)

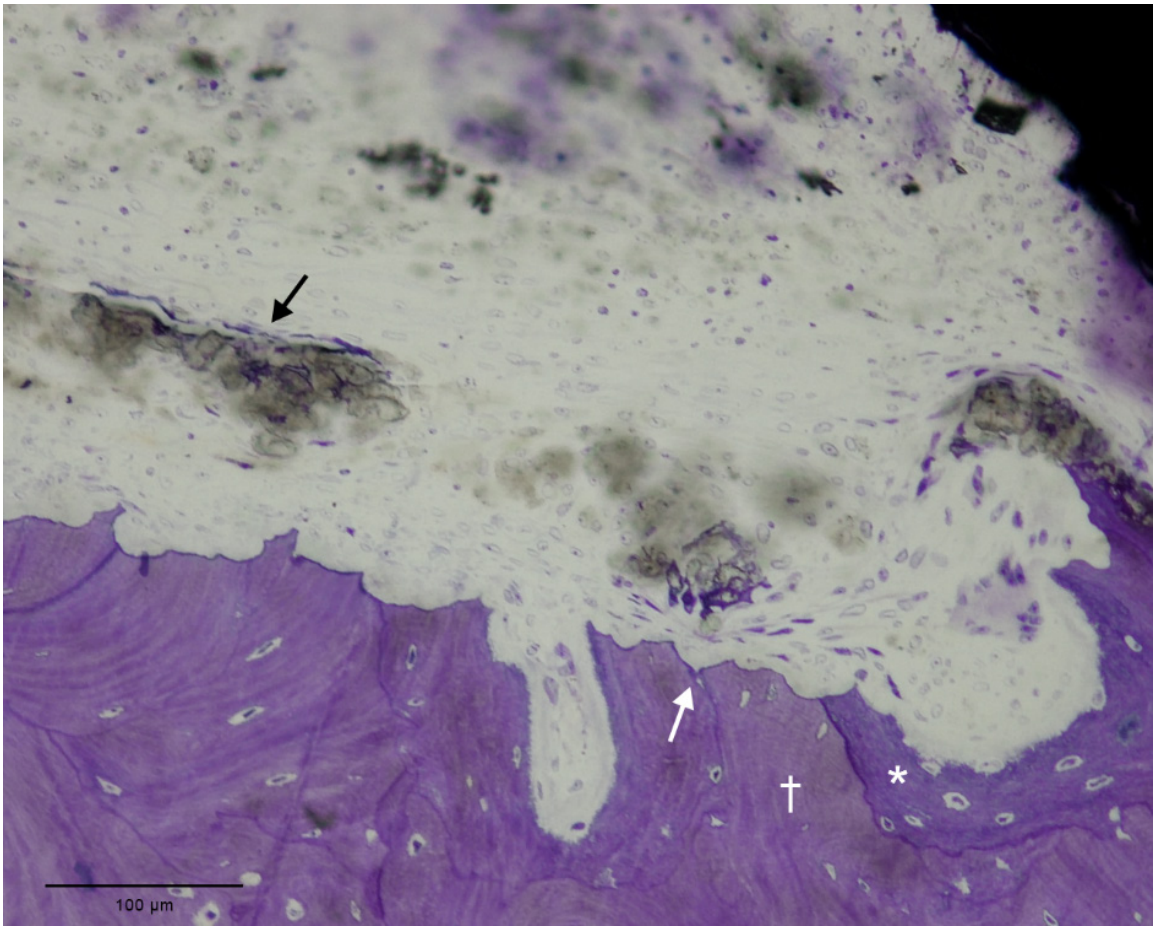


Fig. 11. Photomicrograph of trapezium with a loose cup (appearing black in the upper right corner). The bone stains blue/purple and multiple osteocytes can be seen in their lacunae. The darker staining bone on the right (*) is new, immature bone, sharply demarcated from older, mature bone (†) that stains somewhat lighter. The upper surface of the bone appears irregular. This is typical of previous osteoclastic activity (bone resorption). Vast amounts of debris can also be seen (mainly flakes of Hydroxyapatite that is used to coat the implant in order to improve the integration into the host bone). Picture RDT,CBJ,MR.

Bone matrix, where the osteocytes reside, is predominately composed of collagen and inorganic materials like calcium and phosphorous ions. The osteocytes develop tentacle- like extensions known as dendritic processes through poorly understood mechanisms. These extensions of the osteocyte are numerous in number and communicate with neighbouring osteocytes and bone lining cells via small tunnels in the bone matrix structure called the lacunocanalicular system. The above mentioned review article explains that the osteocytes act as mechanoreceptors via these connections, highly sensitive to the mechanical loading of bone. They are thought to coordinate the activities of osteoclasts and osteoblasts and help the bone to respond to changes in load by either bone formation, or breakdown.

*The osteoclasts:*

Whereas the osteoblast and the osteocyte are derived from the mesenchymal stem cell, the osteoclasts differentiate from the mononuclear cells of the haematopoietic stem cells. They are thus related to the macrophage and are multinucleated when differentiated. Osteoclast activity is regulated through complex pathways that is outside the scope of this thesis, but both the osteocytes and osteoblasts are involved.

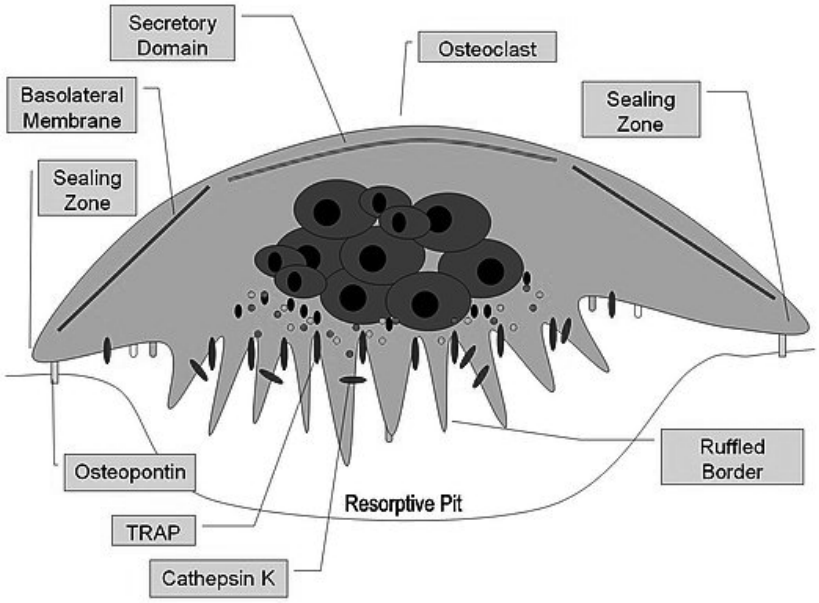


Fig. 12. Drawing of an osteoclast with its multinucleated appearance, actively resorbing bone. Picture from Wikipedia

*The osteoblasts:*

The osteoblasts comprise around 5% of the cells in bone and they are cuboidal in shape. They are located on the bone surface and specialized for protein synthesis. They produce primitive bone, known as osteoid, laying it down towards the bone matrix. When this process is complete, the osteoblasts are capable of differentiating into either bone lining cells or osteocytes.

The bone lining cells appear as inactive, flattened osteoblasts and as the name would suggest they line the bone surfaces. Their actions are not completely understood, but some of them have cellular processes extending into the bone canaliculi. In addition, connections to neighbouring bone lining cells and osteocytes have been demonstrated. They appear to be involved in regulation of osteoclast activity, perhaps by preventing their access to the bone matrix at times when bone breakdown is unwanted. They can also become activated again, reacquiring the cuboidal shape of osteoblasts as well as their secretory abilities.

## What is, and what causes osteoarthritis?

This is still an unanswered question and a thorough discussion of this is outside the scope of this thesis, but some background needs to be provided: Our joints are enclosed in a capsule that invariably is reinforced by ligaments. The inside of this capsule is lined by synovium that produces the synovial fluid found in the joint. Its principle function is to reduce friction between opposing cartilage surfaces during motion. It also provides nourishment to the same cartilage. The cartilage covers the ends of the bones and is a specialized tissue designed to absorb and distribute the load placed on the joint, whilst providing low frictional motion and resisting wear. There may also be other structures like menisci or intraarticular ligaments in a joint, but that does not apply to the CMC1 joint so we will not discuss this further here. An overview of the general anatomy of a healthy joint in shown below:

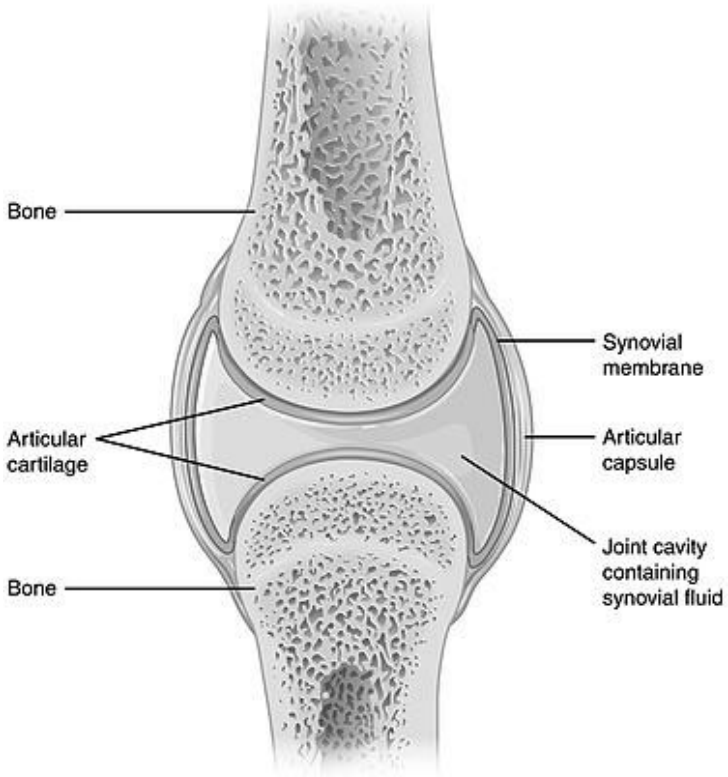


Fig. 13. Anatomy of a synovial joint, picture from Wikipedia

For an up to date review on OA, readers are referred to a recent article published in the Lancet (Hunter and Bierma-Zeinstra, 2019). The authors explain that OA is a “disease of the whole joint”, so all structures shown in the figure above are involved, in addition to the periarticular muscles. Furthermore, they state that pain is the predominant symptom (and ultimately what leads to treatment, be it surgical or non-surgical). No disease-modifying therapy is available as of yet. Registry data predicts an increase in the prevalence of OA in future years. The authors point out that age is one of the most evident risk factors for OA,

most likely as a result of exposure to various risk factors over time, in addition to biological processes (ageing of the joint), but they also explain that there may be a genetic predisposition to develop OA, particularly in the hand and hip. The understanding of pathogenesis of OA is still not complete. It is multifactorial and complex and most likely best considered as a syndrome, where the end stage (joint destruction) can be reached by many different pathways. The old mechanistic conception of wear is outdated they explain. Rather, OA is best viewed as "an active dynamic alteration arising from an imbalance between the repair and destruction of joint tissues".

Looking at the CMC1 joint specifically, the anatomy of the joint surfaces and ligamentous attenuation (particularly of the beak ligament) have been implicated as factors important in the development of OA in this joint. Surgeons have noted that joint degeneration is particularly advanced volarly, and in osteoarthritic thumbs a dorsal translocation of the metacarpal is apparent. This dorsal translocation would seem to stress the volar compartment, particularly in adduction and flexion as seen during pinch. Pellegrini et al (Pellegrini et al., 1993) published a much cited article in 1993, based on a cadaver model. They placed highly sensitive pressure films in the CMC1 joint and measured contact pressure as the joint was moved in a jig via its intrinsic- and extrinsic muscles in a previously described experimental set up. Both normal and arthritic joints were used and measurements before and after sectioning of the palmar beak ligament were performed. Twenty-three thumbs were examined, 16 of these had osteoarthritic changes with most advanced changes in the palmar/volar region of the joint. Four of these 16 thumbs had advanced disease with degeneration more widespread and absent, or greatly attenuated, beak ligaments. The remaining 7/23 were considered healthy joints with only mild changes seen. The authors found that 90 % of the thumbs without end-stage disease had changes confined to the palmar/volar part of the joint and furthermore, this was the region with the greatest contact pressure during simulated pinch. Sectioning of the beak ligament led to dorsal translation of the metacarpal on the trapezium in all "normal" joints and in 10 of 12 diseased joints. In the four with end stage disease there was an abnormal, diffuse contact pattern, unaffected by joint motion and pinch.

Another cadaver study in 1999 concluded similarly; increasing histological degeneration of the beak ligament was associated with increasingly severe cartilage disease in the joint (Doerschuk et al., 1999) and a recent cadaver study also confirmed the beak ligaments primary role in preventing the dorsal subluxation of the metacarpal (McCann et al., 2018). Indeed the ligament reconstruction and tendon interposition (LRTI) procedure performed along with removal of the trapezium (trapeziectomy) in paper 3 of this thesis, aims to reconstruct this ligament.

Other researchers remind us that the isolated focus on the beak ligament may be overly simplistic and that other ligaments also contribute significantly, particularly the dorsal ligaments (Hagert et al., 2012; Halilaj et al., 2015). Furthermore, a causality between failure of the beak ligament and development of OA has not convincingly been shown.

The anatomy of the joint surfaces has been another point of interest with respect to the pathogenesis of CMC1 OA. This interest seems to have come about after researchers observed different rates of CMC1 OA in different populations. In particular, the rate of OA in this joint is particularly low in the Asian population. Marzke at al (Marzke et al., 2012) published a cadaver study in 2012 comparing 80 different cadaver thumbs of European, Asian, African and Australian (Aboriginal) descent and found significantly lower joint curvatures in the non-European joints. The researchers suggest that the flatter joint seen especially in the Asian population may be one of the main reasons behind the observed difference in prevalence. The exact mechanism in uncertain, but they suggest that a larger, more curved beak will lead to increased pressure in this part of the joint during flexion and pinch. On the other hand, a more curved configuration would seem inherently more stable, potentially preventing dorsal dislocation of the metacarpal.

Of course, these studies do not explain the gender difference when it comes to CMC1 OA. There are conflicting reports on anatomical differences between male and female trapezia, some claiming that the articulating surfaces in females are shallower, predisposing them to OA. Marzke et al (Marzke et al., 2012), did not find this difference. Nor did a recent radiological study where 67 asymptomatic (and younger) volunteers and 87 patients with early signs of CMC1 OA were recruited. The participant's thumbs were examined by CT scans. The images were used to create 3-D bone models of the trapezia and metacarpals, which were then compared. The authors found no gender difference amongst either the asymptomatic volunteers or the patients with early CMC1 OA. There were however differences between these two patient groups; the older symptomatic group had "a higher curvature in the concave and lower curvature in the convex directions of both the trapezial and metacarpal saddles than healthy young adults". The authors argue that changes observed in previous cadaver studies where joints invariably are worn, may be secondary to the degenerative process rather than inter-gender differences (Halilaj et al., 2014). A gender difference is also seen in other joints such as the knee joint, but at present, the mechanisms behind this are poorly understood.

## Treatment:

As for osteoarthritis in other joints, one generally starts with non-surgical (often coined "conservative") measures. Surgical treatment should be reserved for patients with severe symptoms in whom conservative therapy has failed. First, we will briefly mention which conservative measures are recommended, before considering some of the surgical procedures in detail.

### *Conservative treatment of CMC1 OA:*

At present no studies comparing surgery to placebo or sham have been performed. Thus, the ultimate place for conservative therapy compared to surgical treatment is uncertain. A commonly held belief is that conservative therapy at least can post pone (if not prevent) the need for surgical treatment. A study by Berggren and colleagues(Berggren et al., 2001) explored this, offering three different conservative interventions to a group of 33 patients that were waiting for surgery for symptomatic CMC1 arthritis. All patients followed the

regimen for 7 months. One group was provided with technical assistive accessories, the other two groups had two different thumb base orthoses ( or “splints”) provided to them in addition. All three groups were advised on ways of modifying activities of daily living. The patients were followed for 7 years. After the first 7 months, 23 of them declined surgery and during the remaining follow-up only two patients had surgery. A recent Cochrane review included 7 trials comparing exercise to no exercise in the setting of hand OA (largely CMC1 OA) and concluded that there was low level evidence for the benefit of exercise with regards to improving pain, function and joint stiffness (Osteras et al., 2017). The European league against rheumatism (EULAR) first gave their recommendations for the management of hand OA based on expert opinion and existing research in 2007. (Zhang et al., 2007). These were then updated in 2018 (Kloppenburg et al., 2019). According to the EULAR, conservative management includes self- management, the use of thumb base orthoses, topical non-steroidal anti-inflammatory (NSAIDs) medications, oral NSAIDs, corticosteroids and various intraarticular therapies. Of interest for the CMC1 joint, the group concludes that there is evidence supporting the use of orthoses (long-term use) and for exercise programs. These (the exercises) should “aim at improving joint mobility, muscle strength and thumb base stability”. Furthermore, the group concludes that there is little or no research supporting the use of intraarticular steroid injections. Patients should be educated about the nature of the disease and in ergonomic principles. Assistive devices should be offered. Topical use of NSAIDs is recommended as the first pharmaceutical intervention, and oral NSAIDs, if given, should only be used for a short duration. The effect of paracetamol in hand OA was found to be uncertain based on available evidence. Interestingly, the group concludes that if conservative measures fail and surgery is to be offered, then simple trapeziectomy should be the method of choice. This was based on the fact that complication rates are higher in more complicated surgeries, and no difference in outcome has been shown for the various surgical treatments on offer. Gravås and colleagues (Gravas et al., 2019) point out that at present the majority of patients (80 %) with CMC1 OA are referred to surgeons without first having tried non operative treatment.

*Surgical treatment:*

The main indication for surgery is pain. An increasing number of operations are suggested for this condition, making it difficult for both patient and surgeon to make an informed choice. Furthermore, meta-analyses and Cochrane reviews have not been able to show that any one procedure is superior to another (Martou et al., 2004; Vermeulen et al., 2011; Wajon et al., 2015). The reviews point out that few RCT’s comparing different operations have been published and different outcome measures are used in the various studies, making comparisons difficult. It is beyond the scope of this thesis to provide a detailed review of all surgical procedures, but in broad terms four main types of operations are performed and these will be described in more detail below; trapeziectomies (or variants thereof), arthrodesis, various interposition of tissue into the CMC1 joint and joint replacements (total or hemi).

*Trapeziectomy:*

Presently, trapeziectomy is considered the gold standard treatment (Efanov et al., 2019; Rhee and Shin, 2014; Wajon et al., 2015). Short- and long term results have been encouraging with approximately 80-90 % of patients satisfied after the procedure (Efanov et al., 2019; Lied et al., 2016; Pomares et al., 2016). Gervis is credited with first describing this procedure. In 1947 he presented his experience with two such surgeries at the proceedings of the Royal Society of Medicine (Gervis, 1947). His first patient (a female aged 53) had the procedure done bilaterally and was very satisfied, but had slight loss of power. His second patient was a man aged 48 who worked as a farmer, and Gervis noted that he "was able to start milking within a month of operation". The loss of power that Gervis mentioned was a cause for concern however, and later various procedures for suspending and supporting the thumb were recommended, aiming to prevent the shortening of the thumb ray that invariably follows after plain trapeziectomy. Burton and Pellegrini published such a technique in 1986 that later has been one of the more popular (Burton and Pellegrini, 1986). This is the method we have used in study 3. It involves splitting the FCR tendon along its length in the forearm (through two small incisions) and then passing this tendon through an oblique bone tunnel in the base of the thumb's metacarpal. The tendon is used to secure the metacarpal bone towards the base of the second metacarpal (where the FCR inserts) and the remainder of the tendon is placed as a cushion in the space left after the trapeziectomy. Thus, it aims to reconstruct the beak ligament attaching at the beak of the metacarpal and at the same time it provides a tendinous interposition (see Fig. 14).

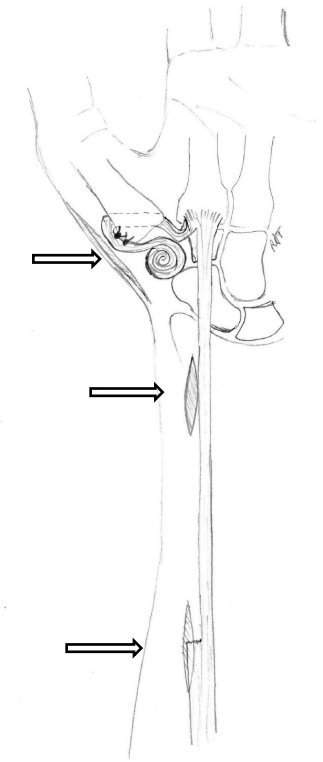

Fig. 14. Drawing of a left sided trapeziectomy with LRTI performed in study 3. The 3 incisions are indicated with black arrows.

These type of procedures were commonly performed (and still are), but in the early 2000s other surgeons questioned the importance of the ligament reconstruction and tendon interposition. Several RCTs comparing simple trapeziectomy to trapeziectomy with various LRTIs have not been able to show any significant difference in outcome both in the short and mid-term. (Davis et al., 2004; Field and Buchanan, 2007; Salem and Davis, 2012). Meta-analytical studies have found the same (that is, no difference), but also a tendency towards more complications in the ligament reconstruction groups. (Vermeulen et al., 2011; Wajon et al., 2015)

Thus, we have come full circle returning to simple trapeziectomy. However, it appears not all surgeons are convinced that the two procedures are equal. A recent survey amongst American hand surgeons show that the overwhelming majority still perform trapeziectomy with some sort of ligament reconstruction as their main surgical procedure for symptomatic CMC1 arthritis (Yuan et al., 2017). Furthermore, a synthetic alternative has become available (TightRope©), facilitating the anchoring of the thumb ray to the second metacarpal without the use of a tendon graft. So far, only short (to mid) term results have been published for this product (Yao and Cheah, 2017). Other, newer variations on the trapeziectomy are the hemitrapeziectomy performed either with open surgery or with arthroscopic technique. A review article from 2014 indicates that the results are similar (and good) in both groups and that interposition of various materials is not necessary (Adams, 2014). A recent review article looked at rates of reoperation for a large variety of surgical procedures used for CMC1 OA (Ganhewa et al., 2019). Whilst there are some weaknesses with this study (incomplete follow-up and a high drop-out rate to mention two), the general finding was that non-implant surgeries had lower failure rates. Failure was in this study defined as the need for further surgery. This was expressed as failure rates per 100 procedure-years. Trapeziectomy with LRTI (including other variants of ligament reconstructions or interpositions) had the lowest failure rate of all treatments (0.24 revisions per 100 procedure years), even slightly less than plain trapeziectomy operations at 0.49. This study concludes that failure rates (defined as reoperation) after trapeziectomies are low. This is in concordance with two other papers, where the rate of reoperation has been stipulated to be 2-3 % (Cooney et al., 2006; Megerle et al., 2011), but the article does not discuss in detail the difficulties involved in addressing failed trapeziectomies surgically. This surgery is highly challenging and the results are unpredictable with success rates quoted from 20-84 % (Cooney et al., 2006; Megerle et al., 2011; Papatheodorou et al., 2017; Sadhu et al., 2016).

*Arthrodesis:*

Arthrodesis, or fusion of the CMC1 joint has long been used as effective treatment for this condition. The procedure was first described by Muller in 1949 (Muller, 1949). However, concerns have been raised about high complication rates, including non-union, problems with metal hardware and development of osteoarthritis in the neighbouring STT joint. Non-union rates vary from 8 - 21 % according to a recent article which included a literature review (Lansinger and Lehman, 2015), although other authors cite rates of up to 50% (Jimenez-Diaz et al., 2017). However, most patients are asymptomatic after failed arthrodesis attempts. Indeed, this has been the basis for a newly described operation where the surgeon simply resects a small part of the joint, “aiming for a non-union”. This method

has surprisingly good results in one publication (Rubino et al., 2013), but these results need to be verified by others. Similar results to trapeziectomy have been shown in prospective and retrospective comparative studies, although complication rates were found to be higher in the arthrodesis groups (Hartigan et al., 2001; Hippensteel et al., 2017; Kazmers et al., 2017). An RCT comparing arthrodesis with plate and screws to trapeziectomy with LRTI was started (Vermeulen et al., 2014), but had to be abandoned due to an unacceptable complication rate in the arthrodesis group (71 % vs 29 %). On the other hand, a large (70 patients with 85 arthrodeses), single surgeon prospective series (Jimenez-Diaz et al., 2017) with mean 60 month (range 20-100) follow up, reported high patient satisfaction and union rate (95 %). Mild loss of motion was described, but the patients enjoyed improved function and significant improvement in pain. The authors did not observe any development of osteoarthritis in neighbouring joints, although this has been reported by others, and is another possible concern after CMC1 arthrodesis. As the CMC1 joint is fused, greater stress can be put on the neighbouring STT joint. Some retrospective studies have assessed this; Fulton and Stern (Fulton and Stern, 2001) reviewed 49 patients in which 59 CMC1 fusions had been performed. Of these, 32 patients (with 38 fused joints) were assessed clinically at a mean of seven years postoperatively (range 2-20 years). Twenty-seven patients (with 33 joints) had x-rays taken at final follow-up. In seven of these, the authors found that the STT arthritis had progressed. None were symptomatic. A larger study (Rizzo et al., 2009), also retrospective, assessed 114 patients with 126 CMC1 fusions at a mean 11.2 years postoperatively (range 3-28 years). The authors noted radiographic progression of STT arthritis in 39 cases, however, only 8 of these were symptomatic. So at present then, there is some evidence of progression of STT arthritis after CMC1 fusion, however, we do not know for certain that this is due to the fusion itself (rather than the natural progression of OA at the STT joint), or if it has any consequence, as most patients do not have symptoms that require further treatment.

*Interpositional procedures:*

Various procedures have been recommended, but they have largely been abandoned due to local foreign body reactions and high rates of complications (Clarke et al., 2011; Willekens et al., 2016). The use of a silicone interpositional implant (The Swanson implant) was popularized in rheumatoid patients and some good results have also been published in osteoarthritic patients (Jewell et al., 2011). However, high rates of synovitis with aggressive bone destruction have been reported (Lanzetta and Foucher, 1995) and the implant has fallen out of favour for this patient group. Another product that was popularized in the early 2000's was the Artelon® spacer (Ehrl and Erne, 2015; Smeraglia et al., 2018), a synthetic T-shaped spacer that was secured in place between the metacarpal and trapezium, or even between the scaphoid and trapezium (if used for STT arthritis). After some years of use, many publications have warned against a high rate of complications (mostly foreign body reactions) and it has also fallen out of favour. (Blount et al., 2013; Clarke et al., 2011; Richard et al., 2014)

*Joint replacements:*

Many implants have come and gone as hand surgeons have strived to develop an implant that will give long lasting function. Unfortunately, we have thus far not been able to attain the level of success seen after total joint replacement in the hip. This may of course be an unfair comparison with the many differences apparent between the two joints. A complete review of the many implants that have been developed for the CMC1 joint is beyond the scope of the present thesis, but a summary will be offered before we discuss the Elektra implant more closely. For more detail, the reader is referred to review articles by Linschield (Linscheid, 2000) and Bozentka (Bozentka, 2010). In addition, a review article that summarises published results for CMC1 joint replacements was published in 2014 (Huang et al., 2015). Linscheid mentions in his introduction that "there are factors that make it difficult to transfer large joint technology to the joints of the hand. These include the small sizes of the joints, their presence within kinetic chains, their complex soft tissue investments, and their relationships to adjacent rays". Botzenka concluded in 2010 that the ideal CMC1 joint replacement "should be strong and stable, provide full range of motion, and prevent loosening". Furthermore he continues; "Unfortunately, no current prosthesis accomplishes all of these goals". The review article published by Huang et al in 2014 concurs, stating that; "Overall the published evidence does not show that total arthroplasty is better than trapeziectomy and its variants yet there is a higher complication rate and significant extra cost of using an implant". As mentioned previously, Ganhewa et als recent review article also supports this.(Ganhewa et al., 2019)

Most joint replacements have been based on a ball and socket design, which seems sensible considering the large range of motion in multiple planes that the thumb requires. Generally, the cup has been placed in the trapezium, but the reverse had also been tried, exemplified by the Mayo prosthesis. The de la Caffinière prosthesis was introduced in 1971 and de la Caffinière and Aucouturier published the first results in 1979 (de la Caffiniere and Aucouturier, 1979). The prosthesis consisted of a CrCoMo stem and a polyethylene cup, both made for cemented fixation. They used the implant for cases of primary osteoarthritis in the CMC1, post-traumatic arthritis, rheumatoid arthritis and for joint stiffness in the thumb basal joint. The follow up was longer than 6 months for 28 of 34 joint replacements, with a maximum and mean follow up of 5 and 2 years respectively. The authors reported problems on the trapezial side with five early loosenings. In these cases, the trapezial bone was found to be abnormal, either flattened, eroded or shallow. Thus, they pointed out, there may have been problems in selecting suitable patients. Later, Chakrabarti at al published medium to long term results with the same prosthesis, reviewing 93 implants in 71 patients with a mean follow up of 11 years (range 6-16) (Chakrabarti et al., 1997). The authors presented a classification system for osteolytic lesions around the cup and stem similar to that used in the hip joint (see fig 15).

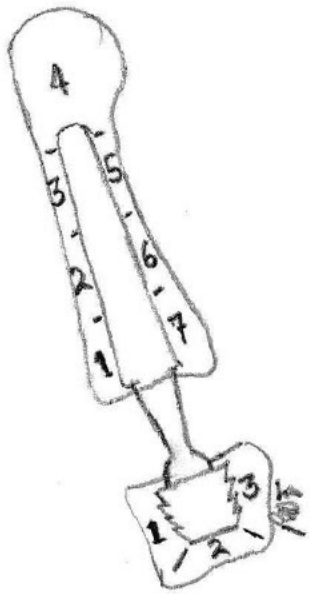


Fig. 15. Drawing by the author of the Chakrabarti classification system for zones of lucency around the cup and stem of CMC1 joint replacements . Here, depicting an Elektra™ prosthesis.

The results, even when compared to the best results currently published, were good, with a 12% revision rate (11 implants). The most common reason for revision was cup loosening. The authors reported a cumulative survival of 89% at 16 years (95% CI interval 61.2-100). However, there were an additional 10 implants that were considered to be loose radiologically. These patients were asymptomatic, but if considered with the revised cases, a rate of loosening or revision of 24% was found. Johnston et al reported on the same group of patients 10 years later with 39 implants in 26 patients available for review. The long term survival at a mean follow up of 19 years (range 16-26 years) was reported to be 73.9% at 26 years (95% CI 0.35-1.00) if only revised implants were considered. However, there were more asymptomatic loosenings at this late stage, and when included in the analysis, results deteriorated markedly to 26 % (95 % CI, 0-52.7) (Johnston et al., 2012). Whilst these results were relatively encouraging ( at least at mid-term), other authors reported higher rates of loosening and revision with the de la Caffinière implant. Wachtl et al pubished their results after 43 joint replacements with the same prosthesis. They reported revision as their end point and found a much lower survival rate than the previous authors with 66.4% of implants intact at 68 months(Wachtl et al., 1998). These articles represent the outer limits in terms of success or failure for this implant that have been published. The exact reason for the shift away from cemented to uncemented arthroplasty in the thumb is difficult to say. It may have had to do with developments in large joint arthroplasty, where a similar change was seen. Other possible reasons could be difficulties with cementation in small bones (particularly the trapezium), a belief that results could be improved upon with uncemented

implant or to preserve bone stock in the trapezium (more bone has to be removed for the mantle of cement that surrounds, and anchors a cemented cup).

Uncemented joint replacements in the CMC 1 joint rely on pressfit- or screw insertion and are dependent on bony ingrowth (often referred to as “osseointegration”) onto the prosthetic components. Several factors are known to stimulate osseointegration, including the alloy composition (titanium alloys are for example more favourable than CrCoMo (Jinno et al., 1998) and surface coating with hydroxyapatite (HA). Surface roughness is a third influential factor.

The Elektra joint replacement was developed by Regnard and he published his results in 2006 after the first 100 cases (Regnard, 2006). The average follow-up was 54 (range 36-78) months and during this period 15 cup loosenings were described. The implant consisted of a HA covered titanium alloy stem and a CrCoMo screw cup.

Fig. 16. The Elektra™ prosthesis. On the left the three components are seen; the stem, the modular neck, available in four different lengths, and the cup. On the right, the original CrCoMo screw cup. Picture courtesy of Small Bone Innovation

The latter cup design is similar to screw cups used in the hip joint such as the “Lord” prosthesis (Grant and Nordsletten, 2004), but the Elektra also utilised a MoM articulation. The merits and problems of such an articulation compared to the traditional Metal on Polyethylene (MoP) will be discussed in a separate section below. The original cup was fashioned from one piece of metal and was thus made of CrCoMo alloy. In addition to Regnard’s report, a prospective comparative study comparing this implant to trapeziectomy with LRTI demonstrated faster rehabilitation and superior function for the joint replacement group (Ulrich-Vinther et al., 2008). This study was not randomised however, and the follow up was short (1 year). Hansen and Snerum were not as optimistic, publishing “mediocre” results after 17 Elektra joint replacements in 16 patients with mean follow up of 35 (range 22-52) months (Hansen and Snerum, 2008). They revised 4 cups due to loosening (and progressive pain) and another cup was loose radiologically, but the patient was asymptomatic. The authors concluded that further studies would be necessary to confirm the promising results published by earlier authors. Further studies *were* published, and whilst some good results were reported, most publications reported unacceptably high rates of cup loosening (see Table 1) (Chug et al., 2014; Hansen and Snerum, 2008; Hansen and

Stilling, 2013; Hernandez-Cortes et al., 2012; Klahn et al., 2012; Regnard, 2006; Ulrich-Vinther et al., 2008)

Table 1

| Author(s) | Year | N | Prostheses N | Gender (male/female) | Age (years, mean, range) | Follow up (months, mean, range) | Lost to follow up | Cup loosening or revision (%) |
|---|---|---|---|---|---|---|---|---|
| **Regnard** | 2006 | 100 | 100 | 15/85 | 59 (38-81) | 4,5 (3-6.5) | 0 | 16 (16)[1] |
| **Ulrich-Vinter et al** | 2008 | 42 | 42 | 5/37 | 58 | 1 | 6 | 1/36 (3)[2] |
| **Hansen & Snerum** | 2008 | 16 | 17 | 1/15 | 54 (40-70) | 2,9 (1.8-4.3) | 0 | 7/17 (41) [3] |
| **Klahn et al** | 2012 | 37 | 39 | 5/32 | 56.6 (46-71) | 4 (0.25-7.6) | 1 | 17/38 (45) [4] |
| **Hernandez-Cortes et al** | 2012 | 19 | 19 | 0/19 | 57 (45-76) | 2,4 (2-3) | 0 | 9/19 (47) [5] |
| **Hansen & Stilling** | 2013 | 13 | 13 | 1/12 | 60 (44-77) | 2 | 2 | 2/11 (18) [6] |
| **Chug et al** | 2014 | 16 | 16 | 4/12 | 70 (54-85) | 2,2 (1-3,.2) | 0 | 1 (6) [7] |

[1] Published results for the Elektra™ total joint replacement; [1] 16 cups revised (14 aseptic loosening, 2 other. [2] 1 revision (early loosening). [3] 6 cups revised (4 aseptic loosening, 2 other), 1 loosening radiologically, asymptomatic.[4] 17 prostheses revised (13 aseptic loosening, 4 other). [5] 3 cups revised (1 with stem revision) and 6 cups loose radiologically.[6] 1 early trapezium fracture, revised. 1 loosening radiologically. [7] 1 cup revision (non union of peroperative trapezium fracture)

A second generation biomaterial cup was developed consisting of a HA covered titanium alloy screw with a CrCoMo articulation welded into the outer titanium scew. No results have been published for this cup however.

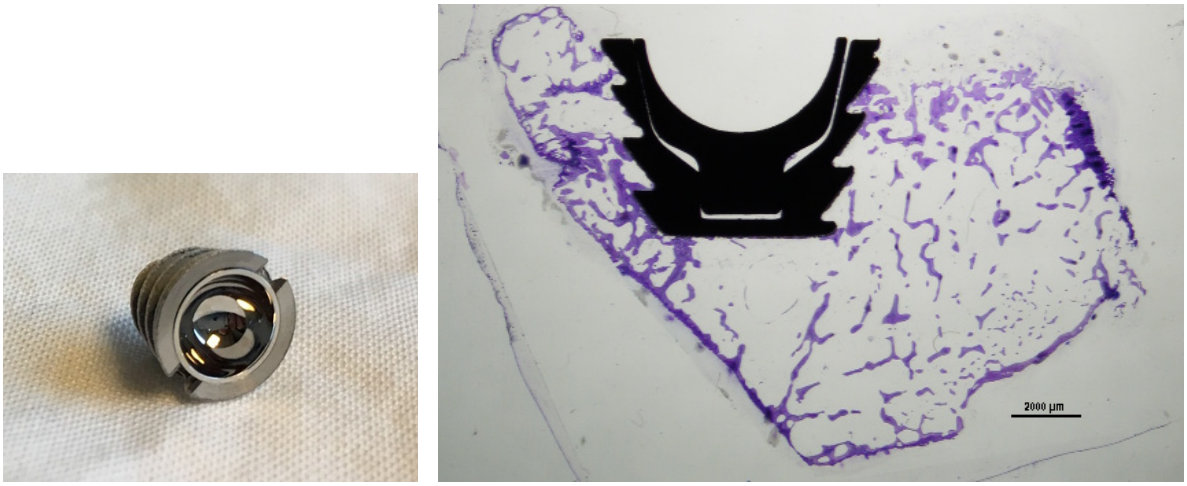


Fig. 17. On the left; Photograph of the bi-material Elektra screw cup consisting of a HA coated, titanium alloy screw. Photo RDT. On the right; photomicrograph of a central section through the trapezium with such a cup implanted. Trapeziectomy in this instance performed due to repeated dislocations. Note marked paucity of trabecular bone structure in this trapezium. Picture RT/MR/CJ

In 2013, Hansen and Stilling published a RCT which was the first to report on the use of Radiostereometric analysis (RSA) in the CMC1 joint(Hansen and Stilling, 2013). They compared Elektra implants with the conventional screw cup against the same implant with a cemented polyethylene cup. Sixteen patients were recruited to each arm of the study. The authors also reported a technical modification whereby the cup was inserted without prior threading of the bone. This was based on previous work in a pig bone model (Hansen et al., 2011) where threading the bone (as recommended by the manufacturer) was shown to weaken the primary fixation. With this method, a low rate of cup revision was reported at 2 years, two cup loosenings were seen, the second one occurred after a fall with a concomitant trapezium fracture.

The implant is now no longer in use and the other CMC1 joint replacement relying on a MoM articulations (The Motec® thumb) has also been removed from the marked.

Currently, the two uncemented joint replacements with good mid- to long term published results are the IVORY® and the ARPE. Both use cups inserted with press-fit technique, rather than screw insertion as utilised with the Elektra. The Ivory cup is made from CrCoMo, but has an exchangeable Polyethylene insert, whereas the ARPE cup is made from a Titanium alloy with a permanent (non-exchangeable) polyethylene insert. For the Ivory, 95% 5 year survival has been published for 22 implants (Goubau et al., 2013), whilst for the ARPE implant promising results have recently been published with a 10 year survival of 93.9% (95% CI, 82.3-97.9) with revision of the prosthetic cup or components as endpoint (Martin-Ferrero, 2014). This latter study was based on 69 implants in 64 patients identified retrospectively. There were 60 implants available for follow up. Five implants had been revised, two due to symptomatic cup loosening, and one due to loosening of both stem and cup. A further two were revised due to instability. In addition to these 5 revisions, 9 cups

showed subsidence into the trapezium or stable (or unchanging) osteolytic changes at the side of the cup. These patients were asymptomatic and were not included in the survival analysis. This is also one of the problems in assessing the published results, there does not seem to be a clear consensus as to what constitutes failure of an implant. In the future, the RSA technique may help us with this problem.

## Finite Element Analysis (FEA)

A brief explanation of FEA is offered here as this technique forms the basis for the first paper. As it pertains to orthopaedic research, a FEA is a mathematical model that allows us to study the behaviour of bones, methods of fixation and implants under given conditions. It consists of a highly complex "mesh" or grid, made up of several thousand elements. Example of three dimensional elements used in this mesh are the tetrahedron or the square based pyramid.

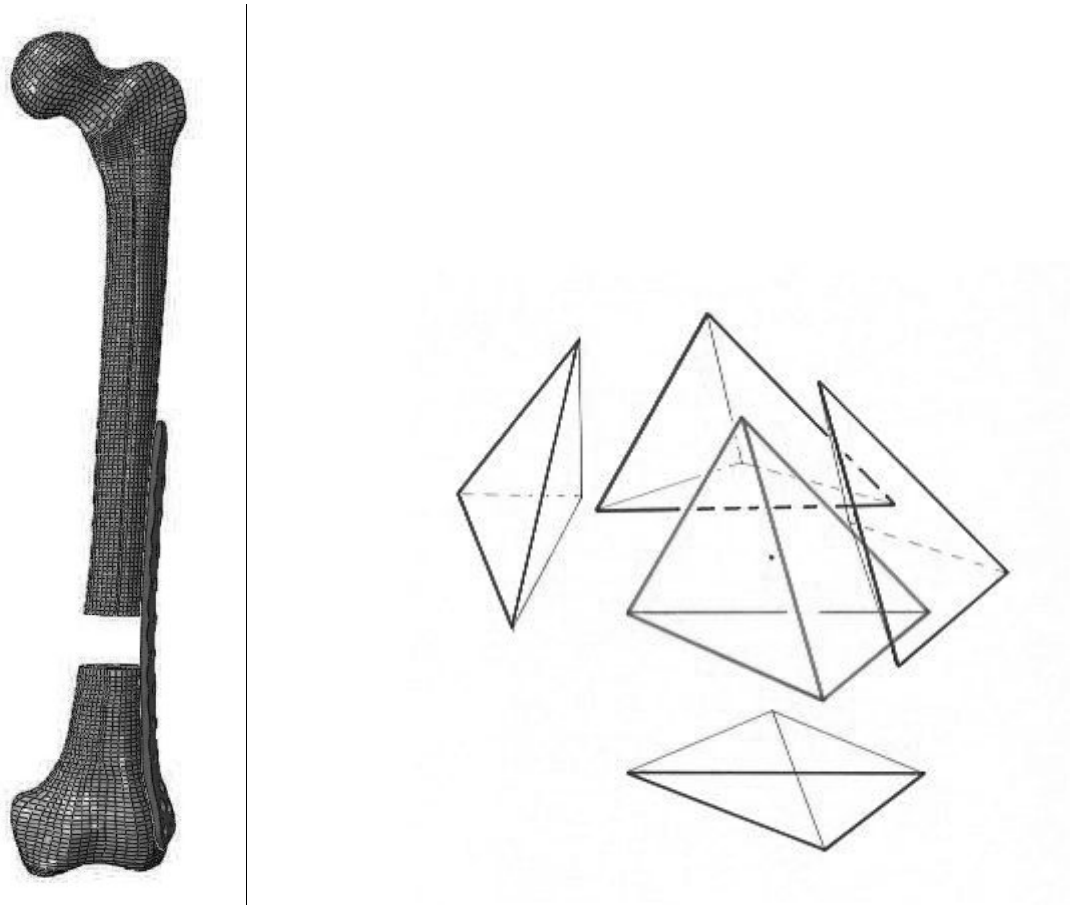

Fig. 18. On the left; a finite element mesh of the left femur with a segmental defects and a bridging plate (in green). Picture from Kluess et al, IntechOpen 2010, creative commons licence. On the right drawing of a tetrahedron, one of the common element forms used in FEA.

Once the so-called boundary conditions have been entered into the model (such as the magnitude and direction of forces acting, the strength and elastic modulus of implant and bone), calculations of loads at the interacting corners (known as nodes) between elements are made and these are in turn all incorporated in the final analysis. The more elements the mesh consists of, the more accurate the analysis will be as it attempts to approximate reality, and FEAs are continuously becoming more complex. However, increasing the complexity of the mesh requires more time and computational power for the analysis and ultimately, is also a matter of cost.

One of the pioneers of this field (the use of FEA in the study of orthopaedic implants), Rik Huiskes and his colleague Chao published a paper in 1983 that sums up the experiences from the first decade after the introduction of FEA in 1972, where relatively simple models were used for complex clinical problems(Huiskes and Chao, 1983). They state that "scientific progress in this area requires a sound understanding of engineering mechanics on the one hand and a profound appreciation of the complex reality on the other."

This method has frequently been used in the study of hip, knee and shoulder implants, but in the hand, it has not been used to a great extent. This may partly be due to the volume of implant surgery in the hand (being lower than in the aforementioned joints), and partly due to the complicated anatomy of the wrist and carpus. FEA studies have been published for wrist implants (Bajuri et al., 2013; Gislason et al., 2017) and for silicone implants in the metacarpophalangeal (MCP) joints(Podnos et al., 2006). In the CMC1 joint, two FEA studies have studied joint replacements, not including paper one in this thesis. Naidu et al studied a titanium metacarpal hemiprosthesis(Naidu et al., 2006). This was a more simplistic 2-dimensional model however. Later (in 2016), a finite element analysis of the Elektra™ prosthesis was published (Completo et al., 2016). This article consisted of a joint simulator study using novel synthetic bones and a FEA study of the trapezium and cup.

As the technique has developed and imaging has become more advanced, researchers are now able to make complex 3-dimensional (3D) models mapped from 3D CT scans of the relevant bone or joint of interest and Computer-aided drawing (CAD) models of the implant(s) being tested. The CT scans not only ensure an exact replica of the anatomy, they also convey information (such as density) of the bone that can be incorporated directly into the FEA model, rather than basing the same information on assumptions or previous studies. For an overview of more contemporary FEA the reader is referred to Kluess et al (Kluess et al., 2010).

### Tribiology and osteoimmunology:

Since the second and fourth papers (and partly the third) are concerned with the choice of articulation surface, it seems relevant to mention the field of tribiology (the study and engineering of surfaces in motion) as it pertains to joint replacements. Since the design of the first joint replacements, engineers and orthopaedic surgeons have strived to develop the ultimate articulation, providing long lasting and reliable function with low friction and low rates of wear. Furthermore, potential wear particles should ideally be biologically inert. It is

outside the scope of the thesis to describe the field in detail, but an overview of the mechanisms behind implant wear can be found in an article by the American academy of Orthopaedic surgeons (AAOS, 2001) “What are the wear mechanisms and what controls them”). For a review of the various articulation surfaces in use for total joint replacements (in the lower limb) the reader is referred to a most recent review article (Merola and Affatato, 2019). The authors describe the evolution of the modern hip replacement, also discussing the history of polyethylene used in joint replacements. Sir John Charnley developed his very successful hip arthroplasty based on an articulation of a 22 mm CrCoMo head against a cemented ultra high molecular weight polyethylene (UHMWPE) cup. A more recent advance is that of highly cross-linked polyethylene (XLPE), where through irradiation and heat treatment “cross-linking” or bonds between the polymer chains in the polyethylene are produced. Comparative studies in the hip joint have been promising with yearly wear rates of 0.003mm reported for XPLE liners compared to 0.051mm for UHMWPE (McCalden et al., 2009). Whilst XPLE seems to generate less wear, a recent article summarising the state of current bearing surfaces in the hip joint raised concern about higher rates of osteolysis from XPLE particle wear compared to that seen with UHMWPE (Rajpura et al., 2014). The authors suggest that this is due to smaller wear particles inciting a stronger immune response, as well as a lower resistance to third body wear for XPLE. Thus they conclude “ the superior wear properties of XPLE may be somewhat offset by the greater osteolytic potential of the wear products”.

Harder articulating surfaces may be advantageous, potentially reducing wear. Examples are Metal on Metal (MoM) and Ceramic on Ceramic (CoC) or hybrid solutions (Ceramic on Metal, CoM). Both above mentioned papers also discuss the relative merits of metal on metal articulations (low wear rates, but local toxicity and loosening) and ceramic surfaces. The latter is harder than metal and has inert wear products, but there have been problems with fractures of the ceramic heads in the hip as well as squeaking from the articulation. The problems of ceramic fracture seems largely to have been solved with the latest generation of heads. The publications also mention the promising CoM hybrid articulations (Merola and Affatato, 2019; Rajpura et al., 2014). Indeed, wear 100- fold lower than MoM articulations in a hip simulator study has been demonstrated for such an articulation (Firkins et al., 2001). A more recent simulator study has also demonstrated a significant difference under “adverse conditions” such as one might see with some malalignment of components(Williams et al., 2013).

Metal on metal articulations were introduced as an alternative to MoP articulations where orthopaedic surgeons where faced with problems related to polyethylene wear. Their use increased as hip resurfacing became popularized in the early 2000’s. Dramatically reduced rates of wear were demonstrated in hip joint simulator studies. Wear is generally reported as volumetric wear per year in $mm^3$/ million cycles in these studies and rates from 0.2 – 2.5 $mm^3$/ million cycles have been published for 28mm MoM bearings compared to 32.8 and 9 $mm^3$/ million cycles for metal on UHMWPE and XPLE respectively(Clarke et al., 1997; Isaac et al., 2006; Rajpura et al., 2014). Early results were promising, but local and systemic reactions to metal debris were reported with increasing frequency and the use of MoM articulations in the hip joint have dwindled dramatically(Perry and MacDonald, 2015). Retrieval studies

revealed foreign body reactions with white blood cells, macrophages and granulomas. In addition, concerns were raised about increased serum and blood levels of chrome and cobalt. In the upper extremity, loads are low in comparison and joint replacements are much smaller due to strict size constraints. MoM technology allowed the manufacturing of small components and has up until now been used in some wrist and hand implants (the CMC1 joint and the wrist). They have not been studied as extensively as the hip joint. A Danish group presented results of serum Cr and Co levels after MoM joint replacements in the CMC 1 joint, showing "slightly elevated" serum levels in 10/50 patients. They also presented results after MoP articulations in the same joint for 23 patients, where only 1 patient (4 %) showed similar elevated serum levels. In all cases however, levels were well below those seen after MoM hip replacements, and below the minimum safety levels that have been set by the authorities(Hansen et al., 2013).

In this thesis, paper two and four in particular contribute to the body of knowledge regarding MoM articulations in the small joints of the hand. Paper two was a simulator study, but unfortunately our results are difficult to compare directly with those published by colleagues working with hip simulators. The reasons for this is discussed later under the discussion section. The study did however allow us to compare the merits of surface-coating for smaller spherical articulations like those used in the CMC1 joint. Paper four in this thesis raises serious concerns about the use of MoM articulations in the CMC1 joint and illustrates a similar development to that seen in large joint MoM arthroplasty. Whilst the rate of wear in a MoM articulation may be much reduced compared that of a MoP articulation, other researchers have showed that the particles produced from such an articulation are smaller and potentially more toxic (Prokopovich, 2014). Furthermore, whilst the volumetric wear may be lower, the number of particles produced is actually higher in absolute terms (Doorn et al., 1998; Firkins et al., 2001). The relative toxicity Cr and Co have been the focus of many papers (Ingham and Fisher, 2000; Maloney et al., 1993; Prokopovich, 2014). Both are toxic to multiple cell lines, Co in particular. In addition, their presence in the periarticular tissues incite an aggressive immune response where the macrophages seem to be a main contributor.

On the cellular level a new field of research known as osteoimmunology is largely concerned with the interaction between the cells of the immune system and bone, as well as the complex situation involved in the interaction between these two and an implant. In this field, several specialities have a common interest. Dental implants for example, face similar challenges to those orthopaedic implants are faced with, although the latter have additional tribiological concerns. Both dental/oral- and orthopaedic/hand surgeons are concerned with long lasting integration of their implants in the host bone. Our collaboration with the team of professor Johansson at the institute of Odontology is an example of this common interest, allowing us to draw on their many years of experience with bone-implant interface research.

Miron and Bosshardt, leading the oral cell biology and oral histology units at the university of Bern published a review article in 2016 where they point out that in the past the majority of dental and orthopaedic implant research has focused on the osteoblasts, very little has been done to better understand the macrophage(Miron and Bosshardt, 2016). They state that "

immune cells play a pivotal role in determining the in vivo fate of bone biomaterials by facilitating  new bone formation around bone-implanted devices, but have also been associated with creating an inflammatory fibrous tissue encapsulation." Furthermore, they go on to say that "the macrophages are the major effector cells in immune reactions to biomaterials". The macrophage (See figure below) was also the dominant cell type we identified in paper 4 and a quick overview of the macrophage and its functions follows.

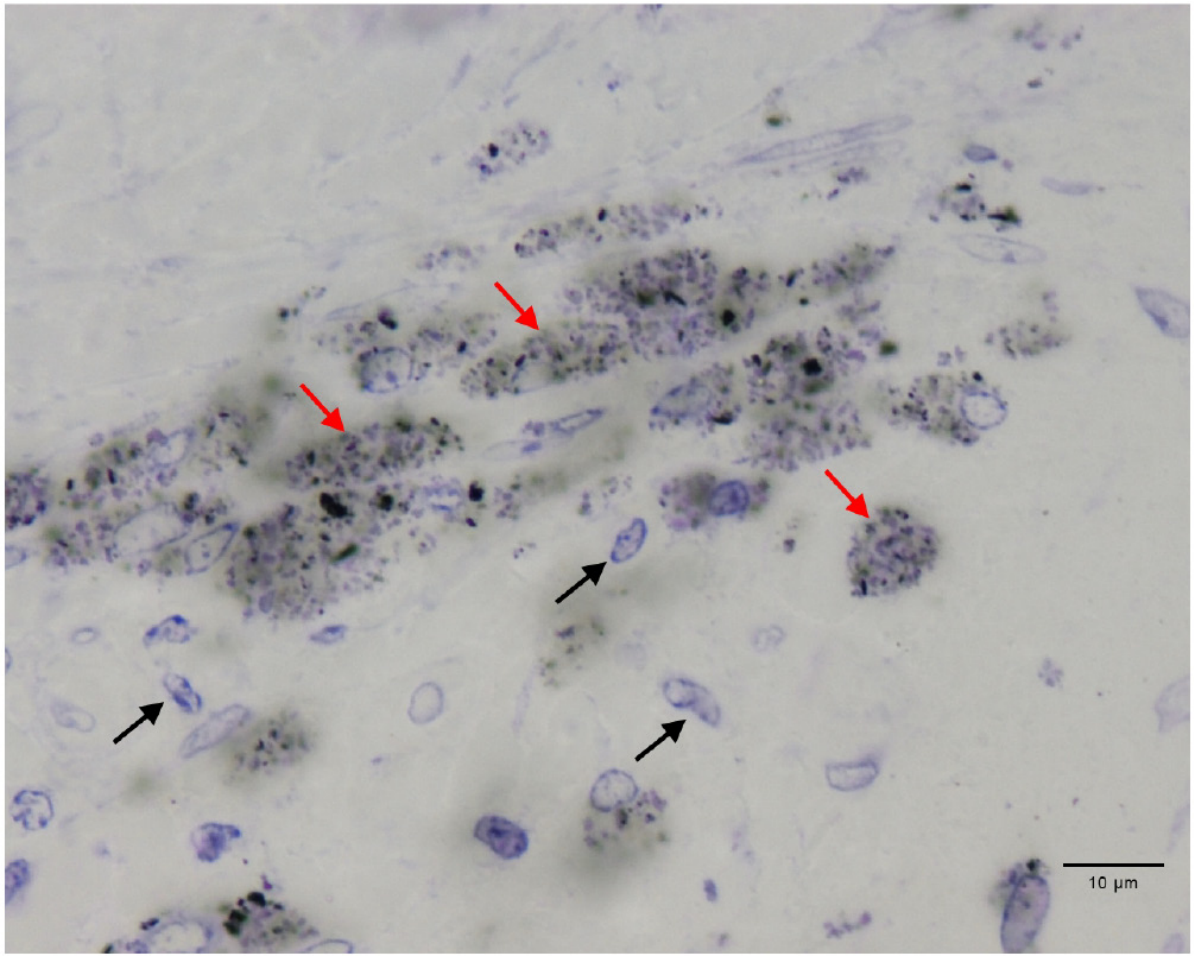


Fig. 19. Photomicrograph of periprosthetic tissues in a osteolytic cyst beneath a CrCoMo Elektra™ cup. Macrophages in various stages of differentiation are seen. The black markers show large multinucleated macrophages (MNGCs) without intracellular content. Even larger macrophages are shown by the red arrows, laden with intracellular content. These would be called Foreign Body Giant Cells (FBGCs). Picture RDT,CBJ,MR

## The macrophage and its role at the bone-implant interface:

A complete review of macrophage function is also outside the scope of this thesis. The reader is referred to two recent review articles (Gu et al., 2017; Miron and Bosshardt, 2016) that cover this topic in detail with a particular reference to that of bone metabolism and biomaterial/implant research. To give a quick summary, the macrophage (from greek; Macro- "Large"; Phage – "to eat") has traditionally been depicted as a scavenger cell

devouring foreign material, bacteria and dead cells (the process of phagocytosis). The two review articles point out that research over the past two decades has uncovered more complex functions.

The macrophage is part of the monocyte cell line. They exist either as locally residing macrophages in the tissues, or circulating in the bloodstream. In bone, local macrophages have been named “Osteomacs” by a team of Australian researchers led by Allison Pettit (Batoon et al., 2017; Miron and Bosshardt, 2016). These Osteomacs make up about one sixth of all cells in the bone marrow. When macrophages come into contact with biomaterials, traditional teaching has been that they fuse into multinucleate giant cells (MNGCs) and are associated with implant rejection. This however is an oversimplification. Various names have been given to these larger multinucleated macrophages historically, depending on their perceived function at the time, for example, Foreign Body Giant Cells (FBGCs) that seem to result as macrophages encounter larger foreign pathogens or biomaterials than they are capable of phagocytosing alone. Miron and Bosshardt explain in a recent article concerned with the MNGC and its various functions that “it is important to note that these cells are phenotypically derived from the same precursor cells and often confused in terminology”(Miron and Bosshardt, 2018). Whilst the purpose of fusion of these cells may be degradation or removal of foreign material, other MNGCs are found around bone grafts and implants and seem incapable of resorbing bone. The above mentioned reviews by Miron/Bosshardt and Gu also explain that the macrophage is much more sophisticated, capable of differentiation into many different phenotypes. The MNGC is one, but they can also differentiate into osteoclasts, as has been briefly mentioned previously. Furthermore, two subsets of macrophages have been identified, the M1 (also known as classically activated macrophages) that has a proinflammatory effect, and the M2 subset (also known as alternatively activated macrophages), which is involved in bone formation. The articles point out that there is still much to learn about the pathways of differentiation, but it seems that different in-vivo situations and different characteristics of the biomaterial (or implant) the macrophages interact with, can lead to different responses. Macrophages (and especially the M2 subset), have been found in abundance around bone grafts and implants where bone healing and new bone formation has been observed. This, of course, would seem to be a desired, or beneficial response to a new implant. The same subset of macrophages have been implicated in calcified plaques in arteries (a pathological state) where their presence and activity is less desirable.

A third review article on this topic by Sridharan et al explains that “historically, biomaterials were designed to be inert to minimize the host response”(Sridharan et al., 2015). In the article they point out that in light of the above mentioned research into macrophage biology, tissue engineering and regenerative medicine, in the future we may be choosing implants that result in a favourable host response in order to improve implant survival. One example the authors mention that already is in use, is that of surface modification of titanium implants. Changes to the surface topography leads to improved attachment of bone forming cells (the osteoblasts), but it is also one way of inducing a more favourable macrophage response to the implant, with a larger proportion of M2 macrophages. The researchers explain that “current research in this area focuses on varying surface chemistries

and roughness to modulate the macrophage response toward an M2 phenotype, which will in turn secrete pro-healing and anti-inflammatory factors to mitigate the formation of fibrous tissue". As pointed out in paper four, other research has shown that factors like Cr and Co from metal wear, tip this balance in the other direction with a larger proportion of M1, proinflammatory macrophages(Chen et al., 2015). In this situation, an unfavourable response is seen, with recruitment of more macrophages, activation of osteoclasts and bone breakdown around the implant. In summary, osteoimmunology seems to hold great promise in many fields including orthopaedics, but there are still many questions here that remain unanswered.

### Knowledge gap:

What then are the unsolved puzzles when it comes to the treatment of CMC1 arthritis? Unfortunately, there are many, and probably too many to mention in this thesis, but I will focus (and only briefly for the two first points) on the following:

1) Natural history
2) The role for conservative treatment
3) The choice of surgical treatment
4) The role of the metacarpophalangeal joint (MCP joint, and in particular hyperextension of this joint)
5) The role of the STT joint (coexistent arthritis of)

1) What do we know about the natural history of CMC1 OA? Several epidemiological studies have studied patients seeking health care after sustaining distal radius fractures where a radiograph of the affected hand is invariably taken. As a fracture of the distal radius is the most common of all fractures(Nylenna et al., 2013), and particularly common in the age group where CMC1 OA is seen, assessing a large amount of wrist radiographs has given researchers insight into the prevalence of radiographic CMC1 OA at various ages. Sodha et al suggested a simple radiographic classification of CMC1 OA with 3 grades; little or no arthrosis (grade 1), obvious arthrosis (grade 2) and a totally destroyed joint (grade 3). They also demonstrated an adequate inter- and intraobserver reliability for this grading system. An excess of 600 radiographs were assessed in this study (Sodha et al., 2005). Becker at al performed a similar study, but included over 2300 radiographs (Becker et al., 2013). Both studies were performed in western countries and reported an increasing prevalence of CMC1 OA with age, rising to around 90 % for patients above 80. Women had more frequent and severe changes than men. Very few patients (0.1%) in the latter study had radiographic evidence of previous CMC1 surgery. The authors concluded that CMC1 OA generally causes few symptoms. Rather, they suggest it should be considered a natural part of aging.

Armstrong et al performed a similar study (radiographs of 143 wrists in women aged 45 to 70 years), but also asked the participants if they had experienced pain at the thumb base prior to their wrist injury(Armstrong et al., 1994). They found a lower prevalence of CMC1 OA, reporting 25 % in this patient group. In the cohort of women with radiographic evidence

of OA (as classified by the Eaton classification into stage 2, 3 and 4) 28 % complained of pain around the thumb base. This study would indicate that approximately 1/3 of women with radiographic findings of CMC1 OA are symptomatic. Of course, there are a number of weaknesses with these studies, but they all indicate that CMC1 arthritis, as assessed by radiographs, is exceedingly common in the aging western population. This is something surgeons need to bear in mind as they advise their patients. Surgeons, on the other hand, may well argue that by the time patients present to them, they have quite severe symptoms that by no means can be managed with a wait and see approach. As we already have discussed in the introduction, at present there is no consensus as to what constitutes an indication for surgery either- we lack a universal scoring system like the Harris hip score for the hip joint where patients who score above a certain level are referred to surgery although as mentioned previously, a decision aid may be useful for patients when they are considering surgery (Wilkens et al., 2019).

2) With the above in mind, it would seem prudent to refer patients to handtherapists for exercises and the fitting of orthotics and helping aids. The various nonoperative treatments offered have been mentioned previously, but to reiterate, no randomised trial has compared conservative to operative treatment. It seems likely that many patients can postpone (perhaps indefinitely) surgery if they are offered this type of assistance. Indeed, one study suggests this (Berggren et al., 2001). At present, another multicentre study is underway which may help clarify this in the future.

3) When surgery seems appropriate, surgeons have little evidence-based research to guide them in their choice of the most appropriate method of treatment. At present, most evidence is rated level 3 or 4 (case series or case control studies). Furthermore, different outcome measures have been used, and a multitude of different treatments are offered. The few RCTs that have been published regarding surgical treatment of CMC1 OA have mainly compared various forms of trapeziectomies and have aimed to resolve whether ligament reconstruction or tendon interposition improves the results when compared with trapeziectomy alone (Belcher and Nicholl, 2000; Davis et al., 2004; Field and Buchanan, 2007; Salem and Davis, 2012). The studies conclude that trapeziectomy alone gives results equal to that of trapeziectomy with the additional procedures. Meta-analysis of these studies have in addition suggested that complication rates are slightly higher in the latter procedures compared to simple trapeziectomy, as previously mentioned.

A few other RCTs have been published comparing trapeziectomy (with or without ligament reconstruction) to other procedures: Tägil and Kopylov compared trapeziectomy with LRTI with trapeziectomy with the interposition of a silicone spacer (Tagil and Kopylov, 2002), concluding that results at mean 43 months were the same for both groups. However, the groups were small (13 patients in each) and silicone spacers may give problems with synovitis and osteolysis in the long term. Marks et al used trapeziectomy with an allograft (a “human dermal collagen template”) wrapped around the FCR tendon functioning as a spacer between the scaphoid and the metacarpal. This was compared with trapeziectomy with LRTI using the Michigan Hand Questionnaire as the primary outcome measure. For this study, 60 patients were recruited. There was no significant difference in outcomes, but there were

more complications (and reoperations) in the allograft group, the authors abandoning the use of the allograft as first line treatment at their institution thereafter (Marks et al., 2017). Arthrodesis has been compared with trapeziectomy with LRTI in a RCT, but the trial was stopped prematurely due to a high rate of complications in the former group. After about half of the estimated sample size had been included, there were "significantly more moderate and severe complications following arthrodesis compared to trapeziectomy with ligament reconstruction and tendon interposition" (Vermeulen et al., 2014). Seventy-one percent of patients experienced some kind of complication in the arthrodesis group compared to 29% in the trapeziectomy group. The main complications in the arthrodesis group were related to the surgical scar (tenderness and sensory disturbances) as well as delayed- and non-union. 5 years after trial commencement, the authors reviewed the patients that had been operated prior to trail cessation (17 trapeziectomies with LRTI and 21 arthrodeses). During that time there had been a further two complications in the arthrodesis group and they hypothesized that there may be a significant difference in outcome (the PRWHE was the primary outcome measure) at the late follow-up (mean of 5 years postoperatively), despite there not having been a difference at 12 months in the original study. They found significantly  better results in the trapeziectomy group as assessed by their primary outcome measure and other PROMS (the DASH and MHQ). Strength measurements had increased for both groups between 1 and 5 years, but were not significantly different between groups. At present then, this is the closest to a randomised comparative study between trapeziectomy with LRTI and arthrodesis and the evidence at present would seem to favour trapeziectomy with LRTI. Lastly, Hansen and Stilling published the results of their RCT in 2013, comparing 16 cemented polyethylene cups to 16 uncemented Electra screw cups as mentioned previously (Hansen and Stilling, 2013).

Review articles and a Cochrane review (Martou et al., 2004; Vermeulen et al., 2011; Wajon et al., 2015) have also been unable to conclude on the subject. The conclusion that they agree on, is that further comparative studies are needed. Our RCT is thus one more piece for the puzzle, but many more are required.

4) The range of motion at the thumb MCP joint is highly variable between individuals. In 100 thumb-healthy participants, Barakat et al measured a mean flexion of 60° and extension of 8.1° with a range of 43-70° and 0-15° respectively (Barakat et al., 2013). Ebata et al published their measurements from 150 healthy Japanese volunteers (75 of each gender, mean age 36.2) in 2016 (Ebata et al., 2016). They reported an average flexion of 59.1°, but the range was from 16-90°. Extension was 7.9°. Their range was also larger than the previous authors with -32 to 58°. The former would seem to constitute a flexion deformity, and the latter quite marked hyperextension. Interestingly, the authors found only small differences when measuring the other thumb, with an average difference in flexion and extension of 4.8 and 6.4°. The ranges for these measurements were 0-28° and 0-38° respectively, but they conclude that these differences are small enough to make range of motion on the contralateral side a useful indicator of the original motion in the affected joint. These differences may also be found in the patient population with CMC1 OA. As the joint degeneration develops, the metacarpal base subluxates dorsally and the metacarpal is drawn into flexion and adduction. The gradual elongation and failure of the beak ligament

has been proposed to be a cause of the subluxation (Doerschuk et al., 1999; McCann et al., 2018; Pellegrini et al., 1993), and various theories have been proposed for the adduction contracture including spasm or contracture of the adductor pollicis muscle, shortening or fibrosis of the overlying fascia, or secondary changes in the joint itself (Armbruster and Tan, 2008). The traditional view has been that this position of the metacarpal favours, or necessitates, hyperextension at the MCP joint in order to grasp and the resulting hyperextension of the MCP joint is a secondary phenomenon. Indeed, a fairly predictable sequence of collapse of the thumb ray can be seen in advanced CMC1 OA (see fig 8.).

Another theory is that the forces at the MCP joint, particularly in a joint that allows hyperextension, is the primary force driving the metacarpal into the palm. At present, we do not know which is correct (or indeed if both mechanisms contribute), but the consequence of this "Z-collapse" is poor opening for grasp, and a weak pinch. From a mechanical view-point, further shortening of the thumb ray will make matters worse. This is the important point for surgeons to consider when assessing patients. Unfortunately, we do still not know the significance of MCP hyperextension. It has not been widely studied, but the general opinion in the surgical literature is that hyperextension above 20-30 degrees should be "addressed" during surgery for CMC1 OA (Armbruster and Tan, 2008; Klinefelter, 2011; Poulter and Davis, 2011; Qadir et al., 2014; Tonkin et al., 1995). Various procedures have been proposed. These can be divided into:

Soft tissue procedures; tenodesis of the short thumb extensor tendon to the distal metacarpal eliminating its pull on the basal phalanx, or shortening of the volar joint capsule, so called capsulodesis.

Bony/joint procedures, ranging from temporary pinning to fusing the sesamoid bones to the distal metacarpal, or full arthrodesis of the MCP joint.

Many of the procedures have a high failure rate in common, resulting in recurrence. Fusion of the MCP joint is favoured by some authors in this setting, particularly in the more severe cases as it has a high rate of success and permanently addresses the problem (Armbruster and Tan, 2008; Lourie, 2001).

Two studies have looked retrospectively at the consequence of untreated MCP hyperextension after trapeziectomy with LRTI (Brogan et al., 2017; Poulter and Davis, 2011). The degree of hyperextension was mild (≤ 30°) in both studies, including 157 and 36 patients respectively (Brogan et al included only patients with mild hyperextension, Poulter and Davis had only 8 patients with untreated hyperextension above 35°). Thus, there were too few subjects to make any comment about appropriate treatment for more severe cases. Both studies conclude that there was no difference in the clinical result (judged by strength measurements and range of thumb motion). It is worth noting that the mild degree of hyperextension quoted in these studies is almost within the range of extension considered as normal in the previously mentioned studies by Barakat et al and Ebata et al.

Restoring thumb length would seem logical in order to maintain the correct balance between the long extensors and flexor tendon, as well as the intrinsic thenar musculature. There is some evidence to suggest that patients with CMC1 OA and hyperextension of the

MCP joint may be better treated by joint replacement. Robles et al performed a retrospective comparative study comparing the ARPE prosthesis (n=31) with trapeziectomy with LRTI (n= 34) (Robles-Molina et al., 2017). The two groups had comparative and mild hyperextension preoperatively (4.5 +/-9.7° and 6 +/- 10.9°), but whilst this improved marginally after the joint replacement (3.5 +/- 7.7°), it increased significantly in the trapeziectomy group postoperatively (mean 4.8 year follow up) to 17.9 +/- 15.4°. The study also found significantly improved pinch strength for the joint replacements compared to the trapeziectomies, but whether this is due to the joint replacement or the prevention of hyperextension of the MCP joint (or a combination of both) is not known. Degeorge et al reported similar findings in 2018 (Degeorge et al., 2018).

Unfortunately, in our clinical study (paper 3) we did not routinely measure the hyperextension at the MCP joint at follow-up so we do not know how this may have affected our results. In future studies on CMC1 OA, this would seem a highly relevant parameter to include. In particular, we need to find out how the patients with hyperextension above 30° fare after various surgical procedures.

5 ) Lastly, the STT joint deserves mention. Lying in close proximity to the CMC1 joint, it can be difficult for the clinician to differentiate symptoms coming from one or the other (or both) joints (Tomaino et al., 1999). Unaddressed, arthritis in this joint is thought to be one possible cause for persistent symptoms (pain) after trapeziectomy.

There is some discrepancy with regards to the frequency of STT joint involvement in patients with CMC1 arthritis. In the radiological study of patients with distal radius fracture mentioned previously (Armstrong et al., 1994), the prevalence of concomitant radiological CMC1 and STT osteoarthritis was 8 %. Of these, about half had pain around the thumb base. Other authors have pointed out that STT arthritis is difficult to assess on standard radiographs. Tomaino et al published a rate of radiologically evident STT OA (in a patient population with symptomatic CMC1 OA) of 32 % (12 of their 37 patients). Intraoperatively the surgeon routinely assessed the STT joint (after removing the trapezium, the surgeon can easily look into the remaining joint between the scaphoid and the trapezoid assessing visually the cartilage and joint surfaces) and found the “true prevalence” to be twice as high (62 %). Furthermore, they calculated the sensitivity and specificity for radiographs (identifying STT arthritis) to be 44 and 86 % respectively (Tomaino et al., 1999). This study did not address the problem of what to do for patients who have OA in both joints.

If performing a trapeziectomy, one suggestion has been to remove a sliver of the trapezoid bone, effectively off-loading the joint between it and the scaphoid. The surgeon must remove enough bone to prevent contact between the two bones as the wrist is moved into radial deviation (which is often a position most painful for patients with STT OA). Usually about 3-4mm of bone needs to be removed. This effectively releases the distal pole of the scaphoid (and prevents contact between the two bones) that normally is tightly bound to the trapezium and the trapezoid. This may be problematic as this link is thought to be of great importance for the carpus, the scaphoid connecting the proximal and distal carpal rows. Anecdotal rapports in the literature would suggest that the carpus can become unstable after such resections (Rectenwald et al., 2005; Yuan et al., 2009). Other authors do

not support this view; a recently published cadaver study assessed carpal kinematics (specifically at the scapholunate and lunocapitate joints) to address this question. The group first assessed the hand in the normal state in eight fresh frozen cadavers. Then trapezictomy was performed. Thereafter, 2mm of the proximal trapezoid was removed followed by a further 2mm sliver of boner (for a total of 4 mm). The wrists were analysed after each step of the above sequence. The authors found that these procedures had negligible effect on the scapholunate or lunocapitate joint relationships as the wrists were moved through flexion-extension and radial- to ulnar deviation (Alolabi et al., 2019). At present, the long term clinical significance of this remains unclear.

The effect of removing the proximal part of the trapezoid on patient symptoms (pain) has not been thoroughly studied either. Davey and Belcher performed a retrospective review of 87 trapeziectomies (68 simple and 19 with LRTI) in 77 patients. In none of the cases was the STT joint addressed. Degenerative changes in the STT joint apparent on plain radiographs (with the inherent weaknesses this involves, see above) was staged into 3 grades (0 = no changes, 1 = loss of joint space and sclerosis, 2 = obliteration of joint space and spurs). They found 42 patients with no STT changes on radiographs, 37 with stage 1, and 8 with stage 2. Comparing pain before, and after surgery (VAS scale), patient satisfaction, range of motion and strength measurements, the authors found no difference between the groups. They concluded that routine resection of the trapezoid should not be done. Rather, surgeons may consider it if the clinical examination preoperatively suggests that the patient has substantial symptoms from this joint(Davey and Belcher, 2004).

The other common treatment for symptomatic STT arthritis is fusion of the joint, but this is seldom performed if faced with concomitant CMC1 OA . STT fusion can be performed in conjunction with joint replacement at the CMC1 joint, however have not been able to find any reports on this in the literature. Surgeons may shy away from joint replacement at the CMC1 in the setting of advanced degenerative change in one of the neighbouring joints (MCP or STT) as this may put undue stress on the prosthetic joint. However, there are no studies to support either side of this argument. STT fusion and arthrodesis at the CMC1 is not a viable first option as it leaves the patient with a very stiff thumb. Fusion of the STT joint carries with it a set of complications of its own (non-union, loss of wrist motion and accelerated radiocarpal joint degeneration to mention the main ones) (Wolf, 2008)

In summary we can see that there are still many unanswered questions about the role of the STT joint in patients with CMC1 OA.

## Thesis Aims:

i) To compare the cup design of the newly developed Motec® Thumb joint replacement with that of the Elektra™ in a three-dimensional finite element model.

ii) To assess whether coating the components of a 6 mm spherical CrCoMo metal-on-metal articulation with a thin layer of Chrome Nitride can reduce the rate of wear in a joint simulator.

iii) To compare uncemented Elektra™ joint replacement with trapeziectomy with ligament reconstruction and tendon interposition in a randomised controlled trial with two years follow up.

iv) To study histologically the mechanisms behind early cup loosening after the uncemented Elektra™ metal-on-metal trapeziometacarpal joint replacement.

## Synopsis of papers:

Paper 1:

A finite element analysis model was used to compare two trapezial cups made for uncemented use ( the Motec® Thumb and the Elektra™). The cups were tested in a simplified model trapezium consisting of a softer centre and a hard outer shell, simulating the cancellous and cortical bone respectively. Two test conditions were applied to simulate normal and osteoporotic bone, and the cups where loaded with a force of 100 Newtons (which is equivalent to about 10 kg of force) both axially and at an angle (30°) in these two bone models.

We found that the Elektra cup performed less favourably under axial load in both test situations. The axial deformation (in mm), the contact pressure and the von Mises Stress values (both in MPa) in the model were all greater for the Elektra cup. Whilst the contact pressure gives an indication of the force acting against the bone surface, the von Mises Stress value is a sum of all stresses at a given node in the model. Here, shear forces are also included. Another finding was that the Elektra™ loaded the trapezial bone unevenly compared to its counterpart, loading in particular the cortical bone rim. Whilst all the above findings favour the Motec® design, its design was potentially problematic due to two main features: Firstly, it was designed with a collar, which could act as a lever arm against the surface of the trapezium. Secondly, the centre of rotation was raised from the trapezial surface due to the modular design of the trapezial component (designed as a screw with an exchangeable cup fitting into the screw with a traditional taper, see fig. 20).

Fig. 20. Picture of the Motec® CMC1 joint replacement with its four components. The $Ti_6Al_4V$ screw-cup had a collar and a modular CrCoMo articulation. Picture courtesy of Swemac

The consequence of this was seen when the articulations were loaded at a 30° angle. The relative increase in load was higher for the Motec® design, although the load in absolute terms was still higher for the Elektra™. We concluded that the study uncovered potential weaknesses in both designs; the larger change in load to the trapezial bone when loaded from an angle may be a problem for the Motec® cup, whilst the higher total load of the trapezial bone is a concern for the Elektra™cup.

Paper 2:

In a joint simulator we compared six ordinary Motec® thumb 6mm metal-on-metal articulations with six identical articulations that had been coated with a layer of Chrome Nitride (CrN). The main aim of the study was to compare the amount of wear produced by the two different sets of articulations. A previous publication from the hip joint had shown that coating the articulating surfaces in this manner could reduce the amount of wear (Fisher et al., 2002). The main mechanism is thought to be by increasing the surface hardness of the coated surfaces (Black, 2006; Yan et al., 2006). Thus, we wanted to see if these results could be replicated in a smaller articulation, in this case an articulation used in a total joint replacement for the trapeziometacarpal joint. The work was done at the SP technical Research Institute in Borås, Sweden.

Fig. 21. On the left; the Motec thumb 6mm CrCoMo articulation used for testing. Picture courtesy of Swemac. On the right, picture of an articulation loaded in the jig. Picture courtesy of Benny Lyvén, SP technical Research Institute, Borås, Sweden

The simulator set up involved testing through 512 000 cycles where six articulations could be tested in series. Each articulation (cup above, head below) was loaded with 5 kg as the jig moved uni-directionally with a frequency of 1 Hz out to an angle of 45° each way from the neutral axis. Wear was assessed in two main ways; firstly by weighing the components before and after testing. This gave us the weight loss of each component and the components combined. From this, the volumetric loss of metal from the components could also be calculated. We found a significant reduction in both component weight-loss and the volumetric wear in favour of the coated components, the latter by a factor of approximately 10. Secondly, we assessed the wear products left behind in the bellows. The wear products

were retrieved, processed, dried and weighed. In addition, inductively coupled plasma optical emissions spectroscopy (ICP-OES) was used to assess the amount of Chrome, Cobalt and Molybdenum in the particulate and soluble form present in the bellows. Again the coated articulations produced significantly less wear, the total amount of Chrome, Cobalt and Molybdenum reduced by more than a factor of 10 compared to the standard articulations. Our findings support previous experimental work from the hip joint and it is relevant in the ongoing discussion about Metal on Metal articulations. If we are able to reduce wear as shown in this study, then one would expect less problems with wear-related osteolysis and implant loosening. At this stage however, the clinical implication is unknown.

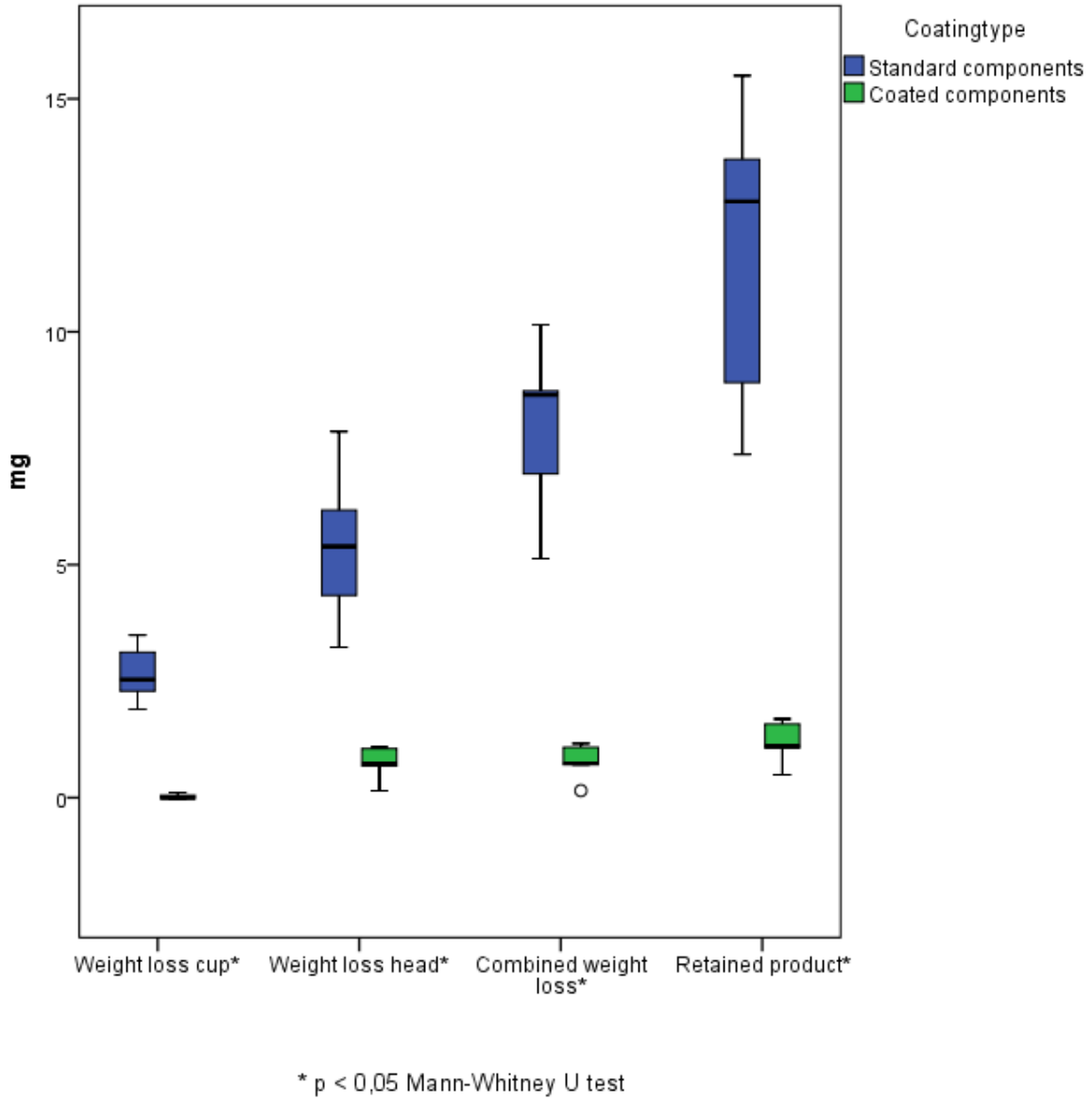


Fig. 22. The different ways of assessing wear in the two sets of CrCoMo articulations. In green, the CrN coated articulations, in blue the standard components. Graph RDT

Paper 3:

The third study was a randomised controlled trial comparing trapeziectomy with LRTI with an uncemented joint replacement (the Elektra™). Forty patients with symptomatic CMC1 OA were recruited from the hand surgical outpatient clinic and randomised to receive one of the two above treatments with 20 patients in each group. Adult patients with good general health and symptomatic CMC1 OA were eligible for inclusion. Exclusion criteria were; advanced degenerative arthritis of the STT joint or large cysts in the trapezium (both assessed on CT scans), other injuries in the thumb or carpus, language problems preventing participation and pregnancy. Patients were followed for 2 years and the primary outcome measure was the quick DASH (Norwegian version)(Finsen, 2008) at final follow up. Secondary outcome measures were the Nelson score (translated to Norwegian), strength-measurements (grip strength, key- and tip pinch), range of opposition (assessed by the Kapandji score) and range of abduction and extension (measured with goniometer). Assessments at 1 and 2 years were performed by a blinded assessor (a physiotherapist not involved in the patients' care). In addition, complications were registered for both groups.

We found that the joint replacement group recovered faster after surgery with significantly better subjective and objective assessments of hand function at 3 and 6 months. From 1 year on, the only difference between the two groups was the range of thumb abduction and extension, significantly better in the joint replacement group at the final 2 year follow up. Patient satisfaction was high in both groups, but the rate of complications was higher after joint replacement. Revision surgery, necessitating removal of part, or all of the implant, was necessary in about ¼ of the patients.

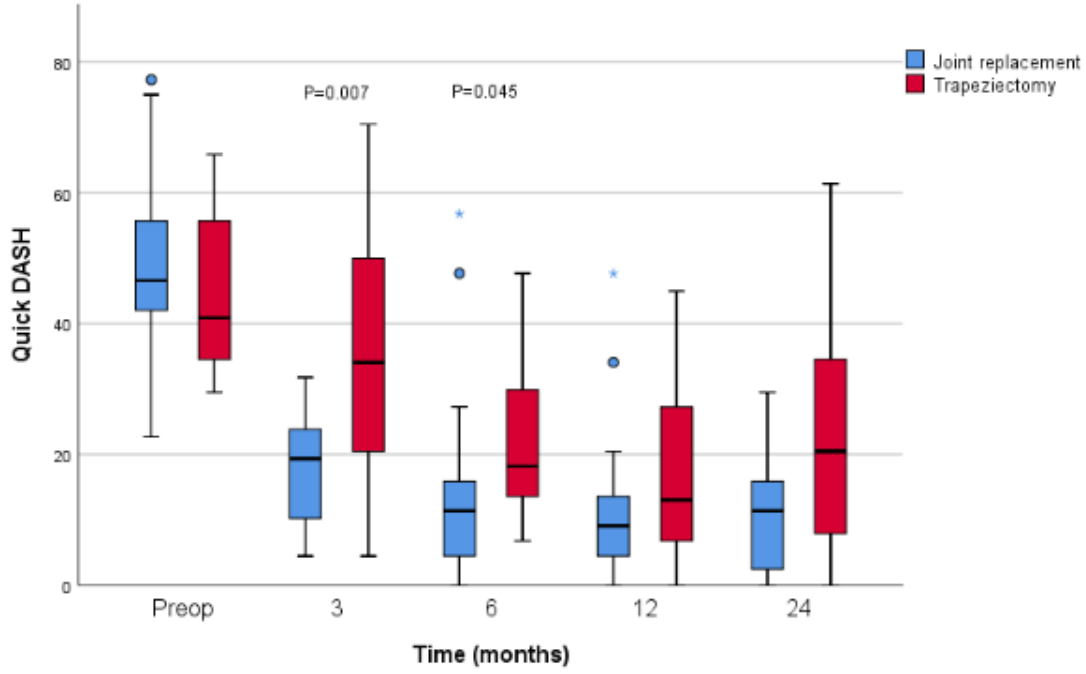


Fig. 23. Box plot of the primary outcome measure, the Quick DASH. The joint replacements performed significantly better at 3 and 6 months.

Paper 4:

This was a retrieval study performed in cooperation with the Institute of Odontology at the University of Gothenburg. Various rates of revision for the Elektra™ joint replacements have been published as shown in previous table (Table 1). Concern has been raised about the high rate of cup loosening for the first generation Elektra™ cup. The process leading to loosening was poorly understood and our aim was to study this in detail using a histological model. Removal of the trapezium (trapeziectomy) is a recognized and recommended method of revision in the setting of implant failure after joint replacement in the CMC1 joint(Hansen and Homilius, 2010; Kaszap et al., 2013; Lenoir et al., 2016). During this procedure, the trapezium can be removed in one piece (rather than in 2-4 pieces which is more commonly performed) with the cup component retained.

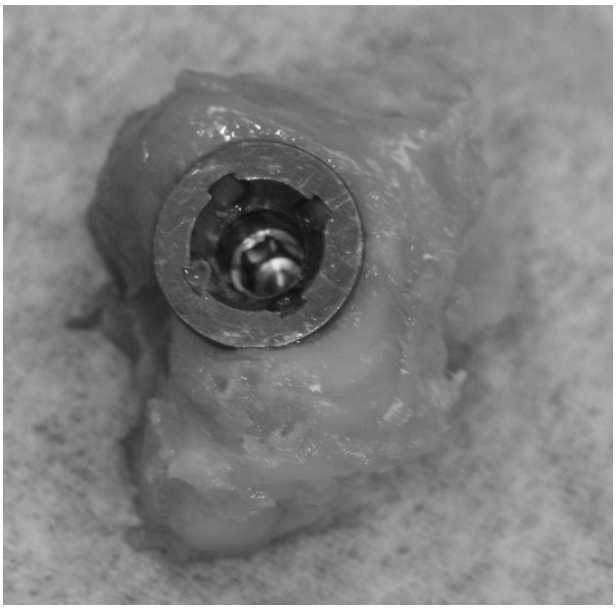

Fig. 24. Trapezium with cup (a Motec® cup in this case) in situ. Picture RDT

The surgeon then removes the neck component from the implant and the stem can usually be left in place in the metacarpal bone. Usually, some sort of ligamentous reconstruction is performed to complete the procedure.

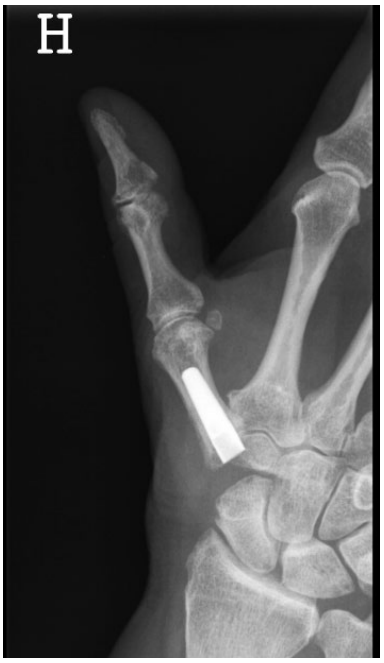


Fig. 25. Lateral radiograph 5 months after revision to trapeziectomy with LRTI. The joint replacement was revised due to early instability.

Indications for trapeziectomy as a revision procedure include cup-loosening and instability (recurring dislocations not amendable to surgical stabilization).

We performed trapeziectomies for these two indications in five female patients (3 due to cup loosening, 2 with instability) at median 22 months after primary joint replacements with the Elektra™. The trapezia were preserved in formaldehyde and processed (the process involved dehydration of the specimen in concentrated ethanol, embedding in resin, curing in UV light prior to sectioning and grinding to a suitable thickness for study under the light microscope (20-30µm).

We found large amounts of dark staining material as well as hydroxyapatite remnants in the tissues surrounding the cups. The former material appeared like metal under polarized light and was to a large extent contained in macrophages in various stages of differentiation.

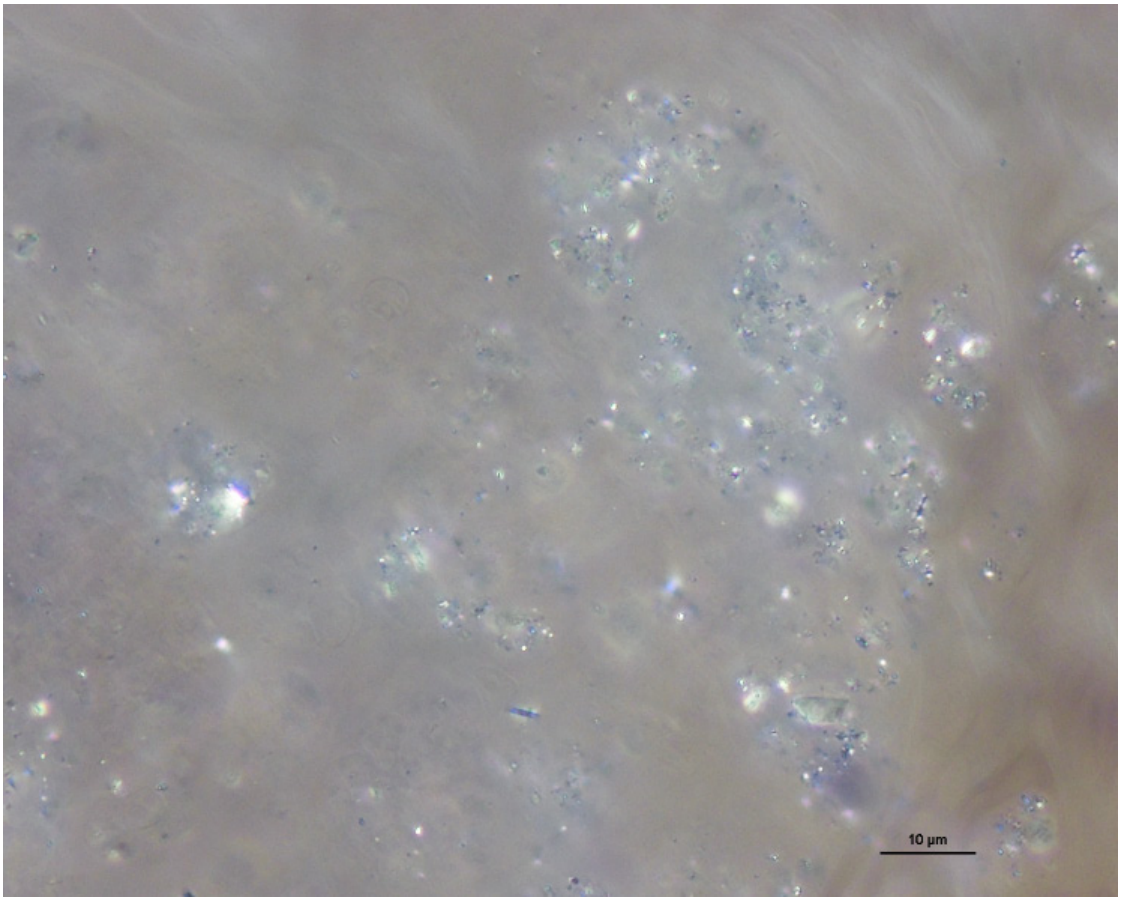


Fig. 26. Photomicrograph under polarized light of an area with FBGCs with intracellular content underneath a loose cup. The intraarticular particles light up. Picture RDT,CBJ,MR

The bone around the cups was largely destroyed by osteolytic lesions. These were especially advanced underneath the cups, thus undermining the support that the cups initially would have had on implantation. Furthermore, osteolysis was apparent at the cortical surface of the trapezia at the cup edges.

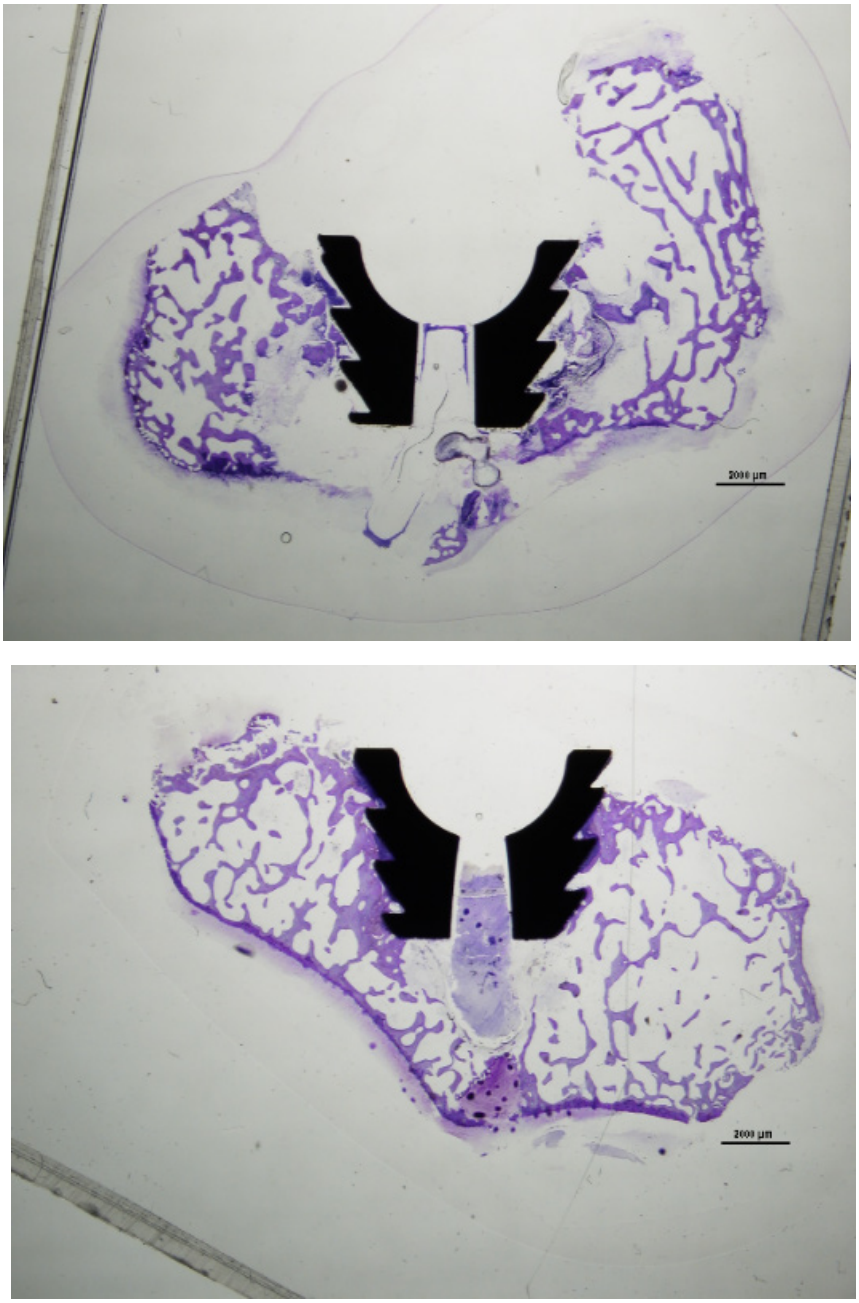

Fig. 27. Photomicrographs of central stained sections of two trapezia. Above, a loose cup with osteolytic areas at the cup surface and undermining the cup. Below, the cup is still fixed, but a large osteolytic cyst is apparent under the cup (filled with blue-staining debris in the cannulation canal and into the cyst). Picture RDT,CBJ,MR

In addition, we found early and advanced breakdown of hydroxyapatite (HA) with 4/5 cups almost, or completely, devoid of HA

Through further collaboration with the department of Earth sciences (Gothenburg University), additional studies (Laser Ablation Inductively Coupled Plasma Mass Spectrometry, LA-ICP-MS and Scanning Electron Microscopy with Energy Dispersive X-ray Spectroscopy, SEM-EDS) were performed on two of the samples (one loose and one fixed

cup). Both techniques verified, as we suspected, the presence of Chrome and Cobalt in the periprosthetic soft tissues amongst other elements such as those seen in the hydroxyapatite (HA) coat that these implants were supplied with.

The study is important in that it clearly demonstrates wear-related problems with MoM articulations in the small basal joint of the thumb. The finding are similar to those described from large joint arthroplasty, and it should have implications for the choice of future articulations.

# General discussion:

## Methods:

Paper 1:

This was an experimental study utilizing a finite element analysis (FEA). One of the obvious advantages of FEA is that researchers can quickly assess advantages and flaws in implant design. Thus, it is frequently used in product development. At the time this study was performed, there had been encouraging short- to mid-term results published for the Elektra™ (Regnard, 2006; Ulrich-Vinther et al., 2008). The Motec® Thumb was a more recent development without published results. The two implants share many common features including the use of uncemented screw cups. Thus, a FEA study comparing the newcomer to the more established implant seemed appropriate. In addition to the above mentioned aspect of time, FEA does not involve the use of human subjects. Comparing the two implants in a clinical trial would have been a large and difficult undertaking. Furthermore, such a study would not necessarily allow us to look at the cups in isolation. The lack of published results for one of the implants was also an issue with regards to its clinical use.

The method behind FEA has already been described in the introduction, along with some of the assumptions inherent to the technique. We will therefore now look specifically at the method behind the specific FEA used for this study.

If we first consider the complex shape of the trapezium bone, our model trapezium bone was simplified with a cylindrical form with a flat surface where the cups were “implanted”

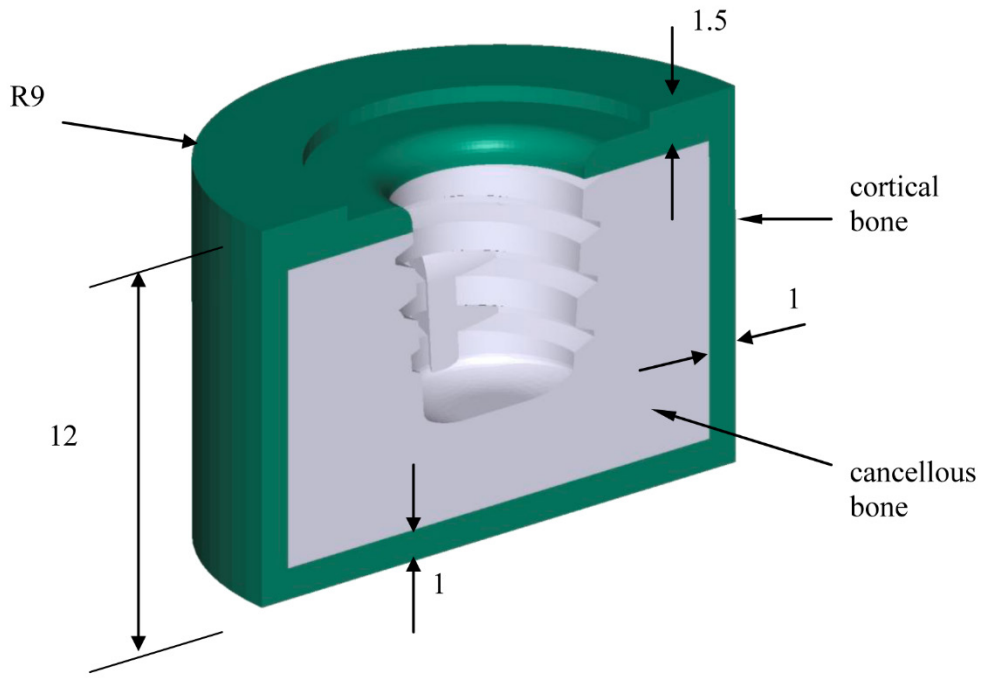


Fig. 28. CAD drawing of the model trapezium bone. Picture RDT

In the clinical situation, the cups do not rest completely flush on the bone surface as the concave trapezial surface usually is eccentrically worn. Using a 3D CT scan model would have allowed us to more closely mimic the real scenario that these cups are used in, but in this case, we felt the simpler model was sufficient for the testing that we were interested in. Such a CT scan model would have also given us a radiographic assessment of the density of the cancellous and cortical bone. Instead, we based the values in this model on previously reported values (Mow, 1997). This work however, was in the femur, not the hand, so this may have had some bearing on our results, at least the specific magnitudes we found.

Our model trapezium was fashioned with a denser outer shell with a thickness of 1.5mm representing the cortical bone. This is consistent with assumptions made in another FEA involving the carpal bones (Guo et al., 2009). This study did not however, consider osteoarthritic bones. One hallmark of osteoarthritis is that of subchondral sclerosis of the involved joint surfaces, which in this case would render the trapezial surface thicker than normal. Nufer et al described this phenomenon after micro CT scans of osteoarthritic trapezia where osteoarthritic trapezia, removed at trapeziectomy, had a 50% thicker subchondral sclerotic bone layer than unaffected healthy cadaver trapezia (Nufer et al., 2008). From our findings, the Elektra cup in particular would stand to gain from a thicker cortical surface as it primarily distributes load to this part of the trapezium.

Huiskes and Chao point out that FEA studies do not take into account the biology of bone (Huiskes and Chao, 1983). Bone, being a living tissue, adapts to loads imparted to it by an implant as described by Wolff's law (Julius Wolff, 1836-1902). This is also the case for the present study, and would seem very difficult to include in a FEA. Of course, other biological processes (such as the host tissues response to wear debris) are not considered either.

Further assumptions about the trapezium were that it was fixed (the so-called boundary conditions in the model). This seems a reasonable assumption however, considering the multiple and sturdy ligaments stabilising the trapezium. We also simplified the bone-implant interface with friction-less contact between the two. In the clinical situation there should be no movement of course, the implant solidly anchored to the bone. Completo et al included a friction coefficient between bone and implant, more closely mimicking reality, in their FEA study(Completo et al., 2016). In our model, rotational forces on the implant could result during loading. This was prevented by the collar of the Motec cup (resting against the cortical bone) and for the Elektra cup, solid bone notches were modelled gripping the cup surface and preventing such movement.

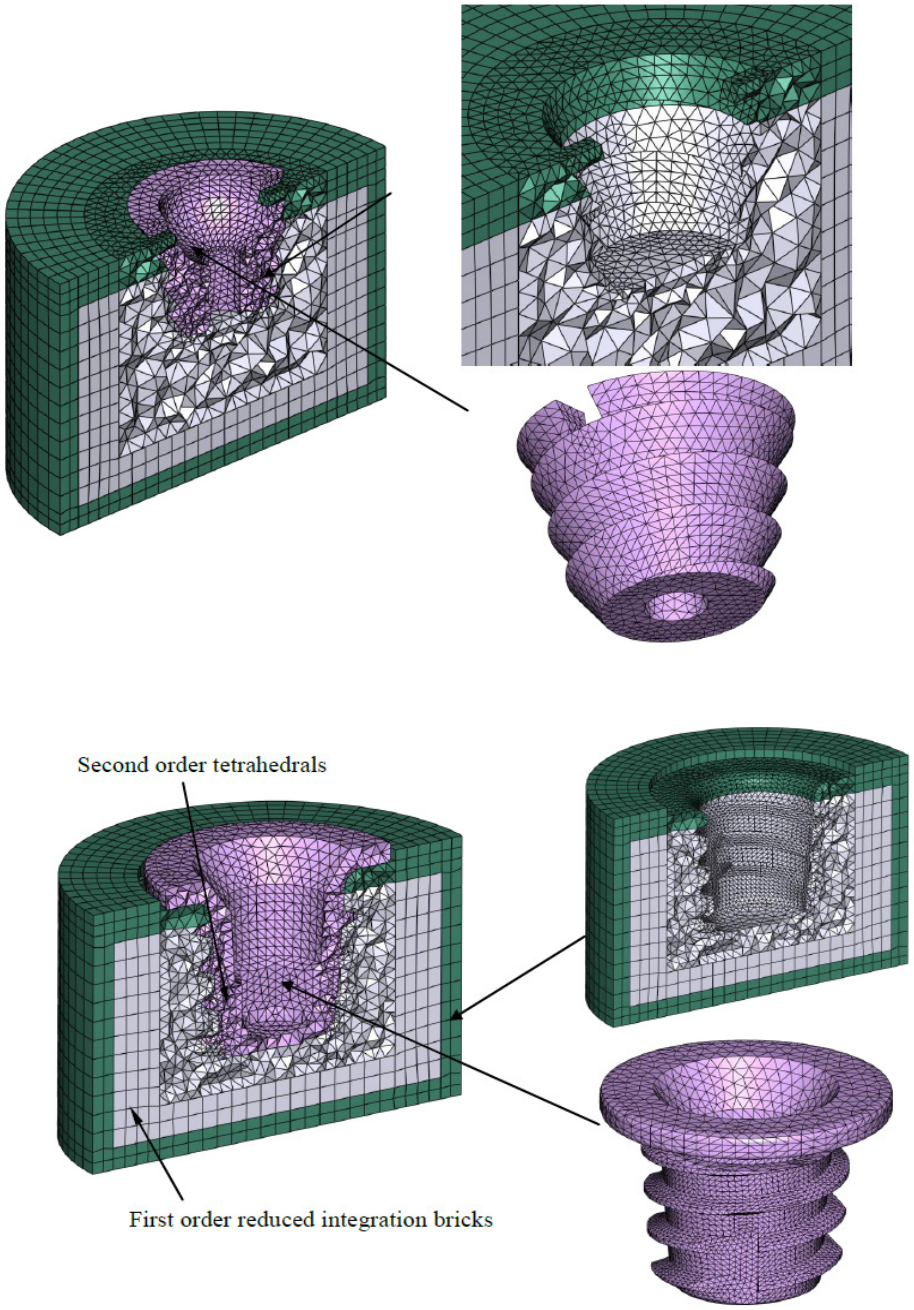


Fig. 29. CAD drawings of the messh for the Elektra™ (above) and the Motec® (below). A bone notch was included in the Elektra model to prevent rotations of the cup. Picture RDT

The complexity of the mesh is another issue in FEA, the higher the number of elements, the more accurate a model will be. In our case, the Elektra- and the Motec mesh consisted of 70.000 and 120.000 elements respectively, considerably more than that later used by Completo et al (60.000 elements for the entire mesh including the metacarpal bone and prosthetic component in addition to the trapezium and cup).

The implants were loaded axially and at 30°, the latter representing the maximum excursion of the CMC joint from the neutral position (Kapandji, 1986). A motion capture study of

thumb pinch (key pinch and tip pinch) showed that the CMC joint moves about half of this angle (12.9° for key pinch and 16° for tip inch) during the two types of pinch which are the situations where the thumb is maximally loaded in daily life (Jahn et al., 2013). Thus, one could argue that we should have used a smaller angle, but we do not think the exact angle is of great importance in this study. The main aim was to study the behaviour of the two cups when loaded from an angle, rather than drawing conclusions from the specific values obtained from the model.

The load we applied (100 N, or 10kg) was another simplification of the clinical situation. A much sited biomechanical study by Cooney and Chao (Cooney and Chao, 1977) showed through vector calculations that the force transmitted though the interphalangeal (IP), MCP and CMC joint of the thumb are a magnitude of 3, 5.4 and 12 times respectively that applied to the thumb tip during pinch. Adult female patients (that most often have surgery for CMC1 arthritis) commonly apply about 5-6 kg of force in key pinch after successful joint replacement surgery, which would result in approximately 600 N at the CMC1 joint. This represents forces 5-6 times greater than what we have tested with in our study. In addition, the force applied will not be constant in the clinical situation as it was in this study. With respect to the magnitude of force applied, we would argue that the exact amount is not so important. Certainly, it should be in the vicinity of loads applied to normal joints, but a study of this nature is only an approximation of reality and the trends of what is occurring was the main point of interest. More intermittent and varying loads would have been interesting to include as this could potentially give sharp increases in load transferred to the bone, a condition that would be considered unfavourable for implant longevity. This was however not possible in the present static model.

The load transfer to the bone was assessed by the axial deformation and contact pressure, both giving an estimation of the forces acting perpendicularly to the trapezial surface. The von Mises stress values were also calculated. These give us a sum of all the forces acting at a particular node in the model, but can be difficult to interpret. This is a general problem with FEA, also seen in our study where very high loads are seen in parts of the mesh. Here we run into the problem of singularities. The forces at some nodes may approach the infinite at sharp angles and transitional zones where many nodes meet, and this phenomenon is known as a singularity. In areas with these extreme values, we therefore considered the average values from the surrounding bone instead in order to aid interpretation.

Table 2

| (Mpa) | Normal bone, LC1 | Normal bone, LC2 | Osteoporotic bone, LC1 | Osteoporotic bone, LC2 |
|---|---|---|---|---|
| **Motec** | 2-3 | 20-25 | 7 | 40 |
| **Elektra** | 20 | 20 | 30 | 60 |

Average von Mises stress values from bone surrounding unnaturally high peak values (so-called singularities). Load case 1 (LC1) was along the long axis of the cup, load case 2 (LC2) was at 30° to this axis. The Elektra has higher values in all cases, but the relative increase on changing to angular load is less than for the Motec design

Paper 2:

This was also an experimental study, comparing two different articulations in a joint simulator. In terms of methodology, a clinical study could have been considered as the coating-technology is available for clinical use ( Medthin™ 30, IHI Ionbond, Zürich, Switzerland), but for the question we were asking, a simulator study seemed most appropriate. There is a long tradition for similar studies in the hip joint when one wishes to preliminary test different articulations. Simulator studies afford us the advantage of studying new developments without involving human subjects, which of course is sensible from an ethical perspective. In addition, other confounders frequently experienced in clinical studies, can be avoided. Whilst the choice of a simulator study seemed to be sensible, there were some methodological challenges with the internal set up of the study.

Developing joint simulators and running simulations with in vivo-like conditions is expensive. The smaller field of implant surgery in the hand does not have access to the kind of resources available to researchers of hip implants where hips simulators are increasingly advanced. We had to make some simplifications to the experimental set-up, however every effort was made to make the conditions for the two sets of articulations equal so that any experimental short comings should have affected the two sets equally.

If we compare our study to the "gold standard" of the field (recent hip simulator studies), then the main methodological problems with our study were: i) the short study time, ii) the lack of a joint simulator capable of simulating the complex movements of the CMC1 joint and iii) the study conditions (quality and temperature of the joint fluid). Ideally, we also should have performed surface analysis of all articulating surfaces (with scanning electron microscopy) before and after the simulation to look for irregularities in the surface, a factor that can increase wear dramatically (Lancaster et al., 2000).

i) Of the three above mentioned problems, the short study time is probably the most important. MoM articulations have been shown to have a "bedding in" phase where wear initially is high before settling to a lower steady state. This phase has been shown to last for the first 1-2 million cycles (in the hip) (Khan et al., 2007; Lancaster et al., 2000). The consequence of the short test time for our study is two fold; first, we have stopped testing whilst still in the early, high wear phase and second, we have not assessed the longevity of the coat. With regards to the first issue, it is in our opinion not so important- the main finding in our study remains the same – the rate of wear was significantly lower in the coated group tested under the same conditions as the controls. The second point is however more important – if the coat in fact wears off early, then the technology is of little interest clinically, only inferring a short term advantage to the articulation. The present study cannot answer this question unfortunately, and I have not been able to find other publications that have assessed it either.

ii) With respect to the simulator itself, it was a fairly simplistic design. It provided motion in one plane stopping at 45° from neutral in each direction at a frequency of 1 Hz and allowed testing of 6 parallel articulations at a time.

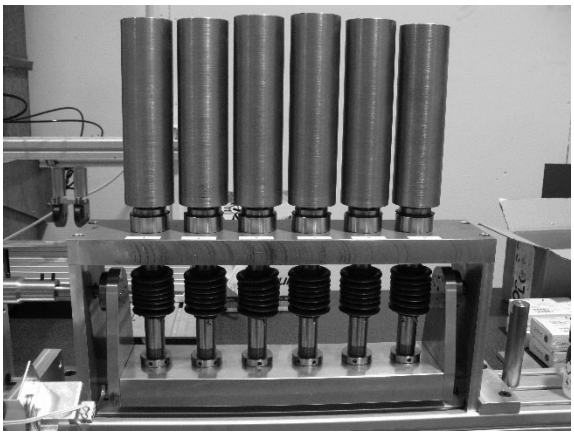

Fig. 30. The experimental set up; 6 articulations each in their own bellow and loaded with a continuous weight from above. The Jig moved as a pendulum around the axis of rotation for the joints, 45° each way. Picture courtesy of Benny Lyvén, SP technical Research Institute, Borås, Sweden

Thus, each set took a little under one week to test. The articulations were loaded with the equivalent of 50N force continuously throughout the testing (which as discussed in paper 1 is a relatively low load for the CMC1). To avoid mixing the articulations (that look exactly the same), we tested the controls first, and then reset the jig with the coated components. The CMC1 joint moves in 4 planes with different combinations and rotatory as well as shear movements in addition. To capture this in a simulator is challenging, but the closer to the natural movement and load pattern a simulator can get, the more relevant the findings will be. In the future more work and development needs to be done in this field.

iii) The conditions in the joint chamber (the rubber bellow in this case) should also mimic the conditions in the joint as closely as possible. This involves a much more complex (and expensive) set up and was therefore not feasible, but to briefly explain; bovine serum is recommended to more closely mimic the properties of joint fluid. Furthermore, the serum needs to be exchanged at set intervals as well as monitored for temperature keeping it at 37° throughout the duration of testing which in more advanced set ups must last for 3-4 weeks (assuming the same frequency of 1 Hz and 2 million cycles). In our case, the experiment ran at room temperature with Ringers solution in the bellows. This simplification has most likely affected the absolute values we have obtained, but should not have affected the difference between the two sets.

Finally, in the analysis of the study, we wanted to quantify the amount of wear. This was somewhat problematic as mentioned in the paper, but we have used three different methods:

i) Weighing of the components before and after testing. Some of the CrCoMo debris may have been left on the jig or iron from the jig may have contaminated the solution in the bellows. We specifically looked for iron in

the products from the bellows without finding any, so the latter event does not appear to have taken place.

ii) Drying and weighing of the particulate matter on the filter paper. In retrospect the pores in the paper were not fine enough to collect the smallest particles of metal wear (which are in the order of 100 nm (Fisher and Ingham, 2000; Khan et al., 2007; Prokopovich, 2014) and there may have been rubber contaminants (from the bellows) contributing to the weight.

iii) The solutions as well as the material on the filter paper was dissolved in acid and assessed with Inductively Coupled Plasma Optical Emissions Spectroscopy (ICP-OES) allowing the quantification of various elements. In this case, we were particularly interested in Chrome, Cobalt, Molybdenum and Iron (the latter as a potential contaminant).

So, as set out above, there were some potential sources of error associated with all three methods, but the results from all three show the same tendency with significantly reduced wear in the coated articulations.

Paper 3:

This is a randomised controlled trial to compare two surgical treatments for CMC1 arthritis. It can be (and was) challenging to conduct such a trial, but this method is considered to be the gold standard in the scientific hierarchy. No RCT comparing these two treatments had (or has, until now) been published, but they are in high demand as the scientific community strives to advance the knowledge in the field of CMC 1 arthritis management. Thus, the choice of method seemed appropriate. Ideally, such a randomised study should be blinded (both surgeon and patient, as well as the assessor of results), but this was not possible to achieve.

The surgeries were performed as day surgery and potentially two patients could be operated on the same day. For logistical purposes, we therefore needed to know in advance what treatment the patient was going to receive. The decision was also made to inform the patient when they had their preoperative consultation with the surgeon on the day of surgery so that better, and more appropriate information could be conveyed to the patient. The patients unanimously accepted the treatment they were allocated to and no patients requested cross over.

There is of course a chance that patient expectations may have influenced their subjective outcome measures during follow up ( if they had any preconceived expectations for one or the other treatment), but the only way to avoid this would have been blinding the patients for the treatment throughout the two year follow up. This did not seem feasible and would also have required sham incisions on the forearms of the patients with joint replacements (all trapeziectomy patients had two wounds here from the harvest of the FCR tendon).

The treating surgeon saw the patients at follow up, but we included scoring by blinded physiotherapists at the 1 and 2 year follow up in order to at least partly address the issue of

blinding. The issue of concealment is also important in a RCT. Ideally, randomisation should be performed with computer programming, particularly for larger studies (Suresh, 2011). This is done to ensure completely random allocation and concealment of the randomisation process from the person(s) performing the inclusion. In our study, this was ensured by a third party selecting the next numbered envelope each time. The 40 envelopes were randomly shuffled before the inclusion process started. Whilst this could have been done differently (for example random number tables), in our opinion this simpler method was sufficient.

The main other shortcomings with the methodology of the study were the sample size and the long inclusion period. In addition, it seems relevant to discuss the outcome measures chosen for this study. I will discuss these three points in turn below.

An appropriate sample size is one of the main factors that will provide results that can be assumed to be correct. If the sample size is too small, there is a higher chance of performing a type 2 error, whereby a false null hypothesis ($H_o$) is accepted to be true. In this case $H_o$ was that there would be no difference in the results as measured by the primary outcome measure (The QDASH) at the final follow up. If in fact there was a difference (for example if the joint replacements provide better function) and the study failed to show this due to an insufficient number of participants, then a type 2 error has been made.

When planning this single centre study we also had to be realistic with regards to the number of participants we could hope to include. A sample size of 40 seemed manageable and at the same time consistent with the lower range of estimates for sample size according to Altman's nomogram. Being experimental in nature, researchers are also obliged not to include too many participants in studies, although this rarely seems to be a problem. In retrospect, we can see that our sample size should have been larger (perhaps 60-70 patients, with 30-35 in each group) to account for the unexpected problems that occur, not only in trials, but in general, when treating patients (patient drop out, cross-over, missing values, and complications). Our small dataset is vulnerable for these factors and this may have prevented us from finding an existing difference.

As it turned out, including 40 patients was more difficult than we expected. Based on experience and estimations from previous years, and the fact that CMC1 arthritis is such a common condition, we originally thought that inclusion would take two years. With two years follow up, the study would ideally have been finished four years after the first inclusion. In retrospect, more time should have been spent going over the number of cases treated in previous years and we could perhaps have anticipated more problems in the inclusion phase. Of the 57 patients that were excluded, almost half were due to the patients declining inclusion. In five cases, the patients had already had surgery on the contralateral side and were happy with their results. Understandably, they were reluctant to be included, risking an unfamiliar treatment for the second thumb. This problem also led us to abandon the idea of including two thumbs from one participant in this trial. Others had preconceived notions about what treatment they wanted and some simply did not like the idea of their treatment being randomly assigned. Arthritis of the joints between the scaphoid, trapezium and trapezoid, (the STT joint) was an exclusion criterion and was the second most common

reason for exclusion. As discussed under “knowledge gap” in the introduction the consequence of coexistent STT arthritis is uncertain when performing trapeziectomy. However, performing a joint replacement in the CMC1, leaving behind an arthritic, and potentially symptomatic STT joint does not seem sensible and this was the rationale for excluding these patients from the trial. Other unexpected problems also hampered the inclusion, including a turbulent merging of hospitals in Oslo.

We chose the QDASH as our main outcome, being well known and widely used in various upper extremity conditions. However, it is a general outcome measure, not specific for the hand or thumb. Other aches and pains in the same extremity may thus “pollute” the results using this measure alone, and it may not be sensitive enough to catch small changes in function. The “floor effect” illustrates this problem. If the subjects being studied score 0 (the lowest score for the QDASH), then there is a chance that the outcome measure simply cannot discern the small changes taking place. If one considers the difference in biomechanics between a ball and socket articulation, providing not only smooth and efficient motion, but also full length of the thumb ray, to that of a trapeziectomy with LRTI, where the base of the thumb is stabilized by scar tissue in a shortened position, then the most appropriate outcome measure can be difficult to choose. PROMs have become an important part of orthopaedic research but one can question whether the first six questions (asking about hand function during daily activities) in the QDASH will be able to distinguish differences in this type of function. We also included the Nelson score, consisting of 10 questions, where the last 6 ask the patient about finer motor tasks, for example buttoning a shirt, and turning the pages of a book. These types of questions may be more useful in assessing thumb function rather than functions requiring power grip or involving heavier hand use (that the QDASH focuses on). The Michigan Hand Outcome Questionnaire (Nolte et al., 2017) or the Patient Rated Wrist and Hand Evaluation (Reigstad et al., 2013) could have been other alternatives, but they are lengthy and both include few finer motor tasks. The Sollerman hand function test, published in 1995 (Sollerman and Ejeskar, 1995) mainly for the assessment of tetraplegic patients, could have been an alternative way of scoring these patients. The test has high reliability and reproducibility and includes 20 common tasks that are scored from 0 (unable to do it) to 4 (performed with normal hand grip quality, without difficulty and within 20 seconds). The majority of the tests are fine motor tasks and test the various forms of grip and pinch in the hand. According to the authors, the test takes about 20 minutes to perform by trained therapists. Thus, it is not feasible in a busy surgical practice, but it could be an interesting research tool. If joint replacements have significant better fine motor function, then that would be an interesting and important finding. In fact, one recent study by Hippensteel and colleagues used this outcome measure in a prospective comparative cohort study comparing arthrodesis (with a mini plate) to trapeziectomy with LRTI. In this case, there was no significant difference in this outcome measure at the final follow up (12 months post operatively)(Hippensteel et al., 2017).

Paper 4:

This study was conceived as a spin-off study from the use of the Elektra™ at our department (in use since 2006) and designed as a retrieval study. Trapeziectomy is ideal for this kind of study as the bone normally is discarded as medical waste after this procedure.

We had 5 trapezia, 3 with loose cups and 2 with intact fixed cups. It would have been interesting to have had a larger number to study, but as we started work with these 5 trapezia, it became clear that the changes we saw were almost uniform and we decided to proceed with the 5 trapezia that we had.

The method we used was based on previous work published in the Journal of Oral pathology in 1982 by Donath and Breuner. It was called the Säge-Schliff Technique (or "sawing-grinding technique) as was first used to perform histological evaluation of bone with dental implants in situ (Donath and Breuner, 1982). Our colleagues at the Institute of Odontology have been using this method for many years (Johansson and Morberg, 1995; Johansson and Morberg, 1995) and it has also proven very useful for the study of orthopaedic implants in bone (Reigstad et al., 2011; Rokkum et al., 2003). The process is described in more detail in the article, but in brief it involved embedding the trapezium (and cup) in resin and cutting out a central section with a width of approximately 200 µm. This was then ground to a thickness of 20-30 µm, and stained for examination under the light microscope. As the method is well known and much used I will not discussed this part of the methodology any further here.

The examinations were both qualitative and quantitative, the former was the most challenging to describe in a scientific journal; we looked at the general structure of the trapezium, the tissue surrounding the cup and ascertained whether the cup was loose or still fixed. At higher magnification, we looked at the cells present, as well as wear debris and zones of lucency. Quantitative measurements were performed as set out in the paper, where we aimed to measure the outer perimeter for the cup, the amount of hydroxyapatite- and/or bone covering the cup, the thickness of HA and width of the gap between implant and bone (if present). A potential flaw with this technique is that it is performed in one plane of section, and may not be representative for the rest of the implant or trapezium bone. Whilst we accept this, the findings were quite similar for the five samples and the trapezium is a small bone where large osteolytic regions, like the ones we observed, would have to have been quite widespread in the bone to reach the size apparent in these sections. Thus, we argue that the measurements we have made describe a trend of the process occurring around the cups in these trapezia.

There may also be some uncertainty as to when the cup loosening took place; in vivo prior to revision, during the trapeziectomy itself, or during the preparation of the sections as the bone is fixed in resin and cut and polished into the thin sections mentioned above. The operating surgeon verified loosening at the time of surgery, small movements of the cup being readily apparent to the naked eye (and even more so under loupe magnification). In addition, it was apparent on preoperative radiographs in some of the cases.

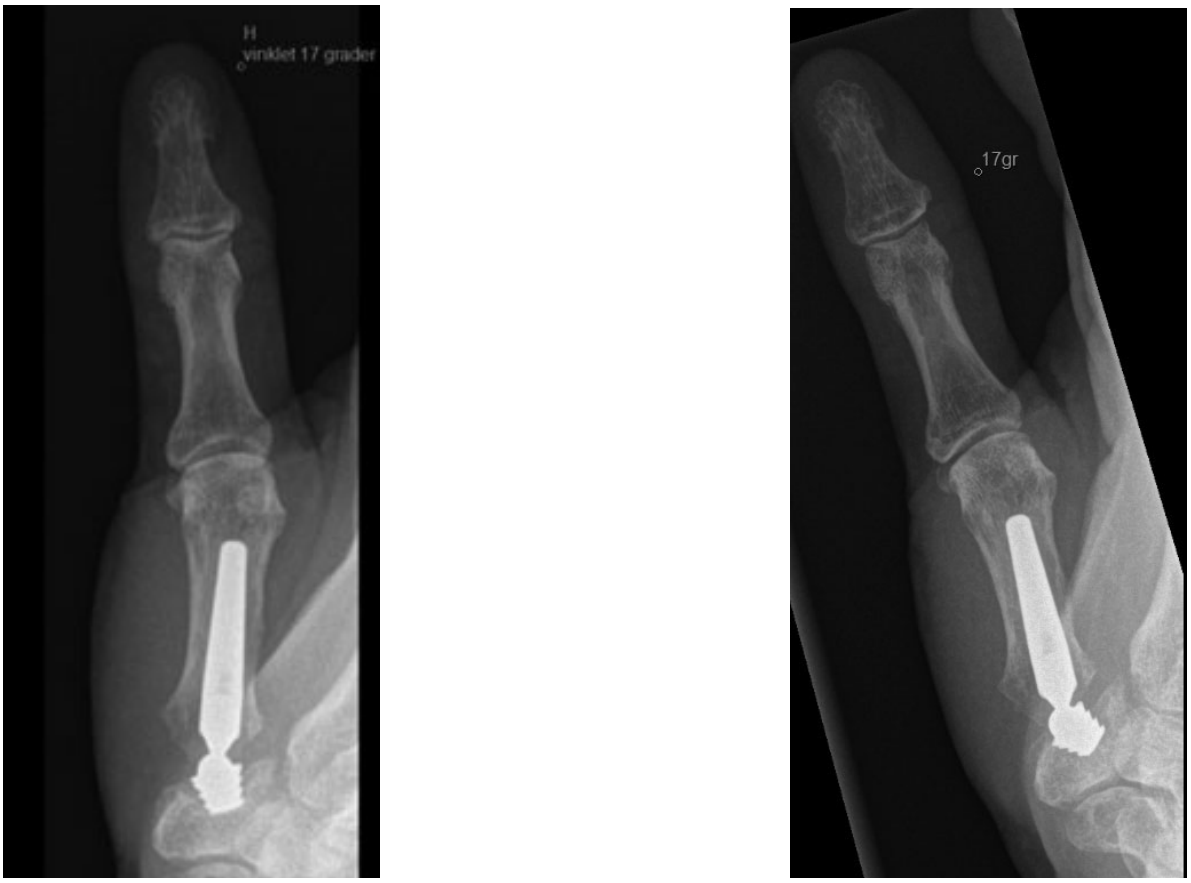


Fig. 31. Roberts view of the left thumb with an Elektra joint replacement (with 2nd generation cup) at 3,5 years on the left. The patient had increasing pain on use. At this stage there was no obvious change of cup position, but some osteolysis at cup margins. On the right, three months later, symptoms unchanged, the cup has tilted into abduction and is clearly loose.

Under the microscope, loosening due to the handling of the trapezium by the surgeon or loosening occurring shortly before trapeziectomy is associated with certain changes: Firstly, red blood cells may be visible between the implant and the bone. Secondly, the bone edges should be sharp (as in a fresh fracture) next to the thread of the implant. In the three cases where cups were loose, we observed some biological (blue-staining) material with cells present between the bone and the implant, but no red blood cells. In addition, the bone edges were worn consistent with micro-motion over some time (consistent with earlier loosening). Thus, we are confident that loosening in these cases has occurred in vivo, some time prior to surgery. The time at which pain was reported by the patients (in this case ranging from one to four months prior to trapeziectomy) may give us some indication, however cup-loosening does not necessarily cause pain and dysfunction.

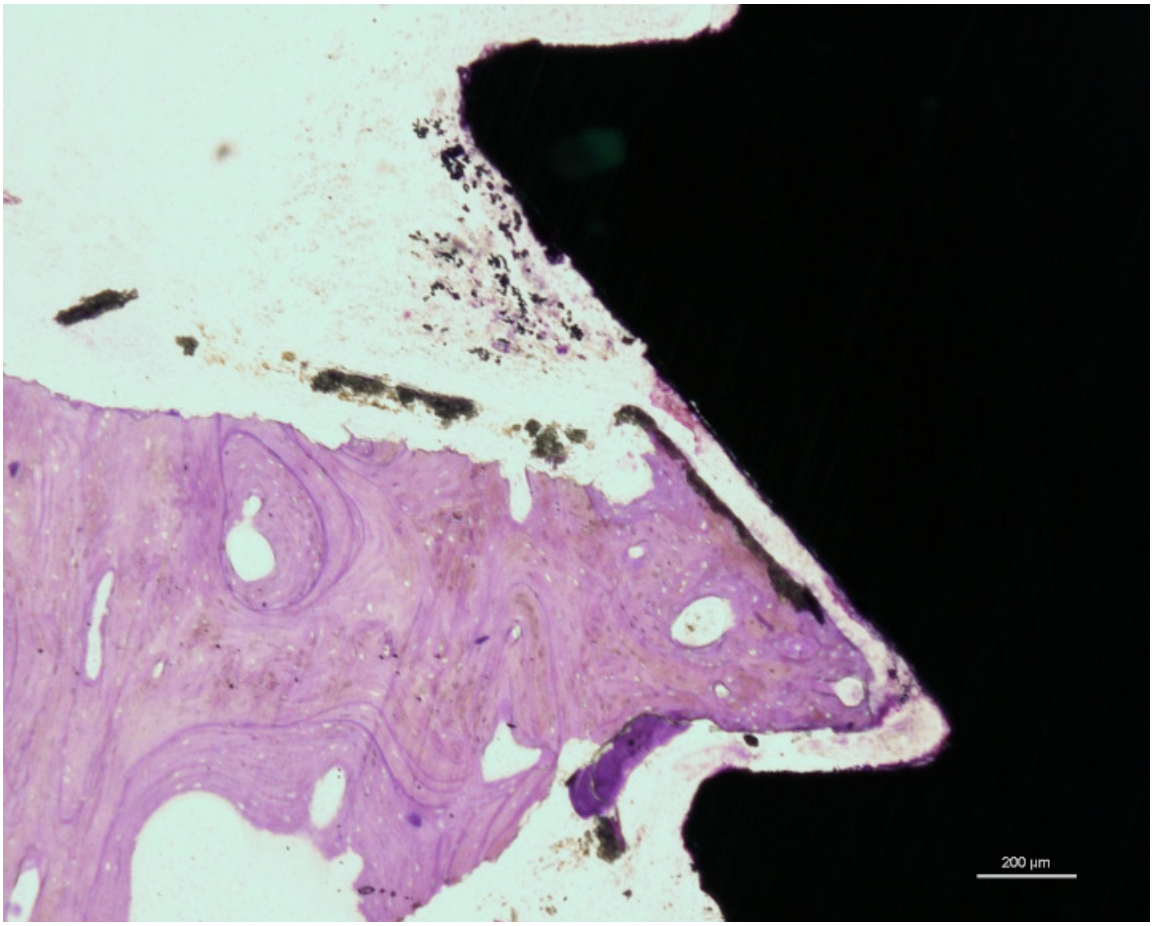


Fig. 32. Photomicrograph of a loose cup with loose HA flakes in the soft tissues. Some HA is still incorporated in the bone that displays rounded corners in the thread angles consistent with earlier, in vivo loosening. Picture RDT,CBJ,MR

In the second part of the study, we performed additional studies on two of the samples. This involved new sections being taken from the trapezia (as the ones used for histology were stained and unsuitable for these examinations). These new sections were approximately four times thicker (at approximately 120µm) and they were both assessed with LA-ICP-MS and SEM-EDS. For this work, we relied on our co-author at the department of Earth Sciences, so I will only mention these two methods briefly here. They are both well recognised techniques for detecting the presence of various elements in different types of biological tissues (Newbury and Ritchie, 2013; Qin et al., 2011). LA-ICP-MS makes laser ablation tracks in the tissue being studied, displaying all elements identified along the entire laser track. To ensure we sampled in areas of interest, we first identified these on light microscopy and verified afterwards that the tracks had passed through the right area(s)

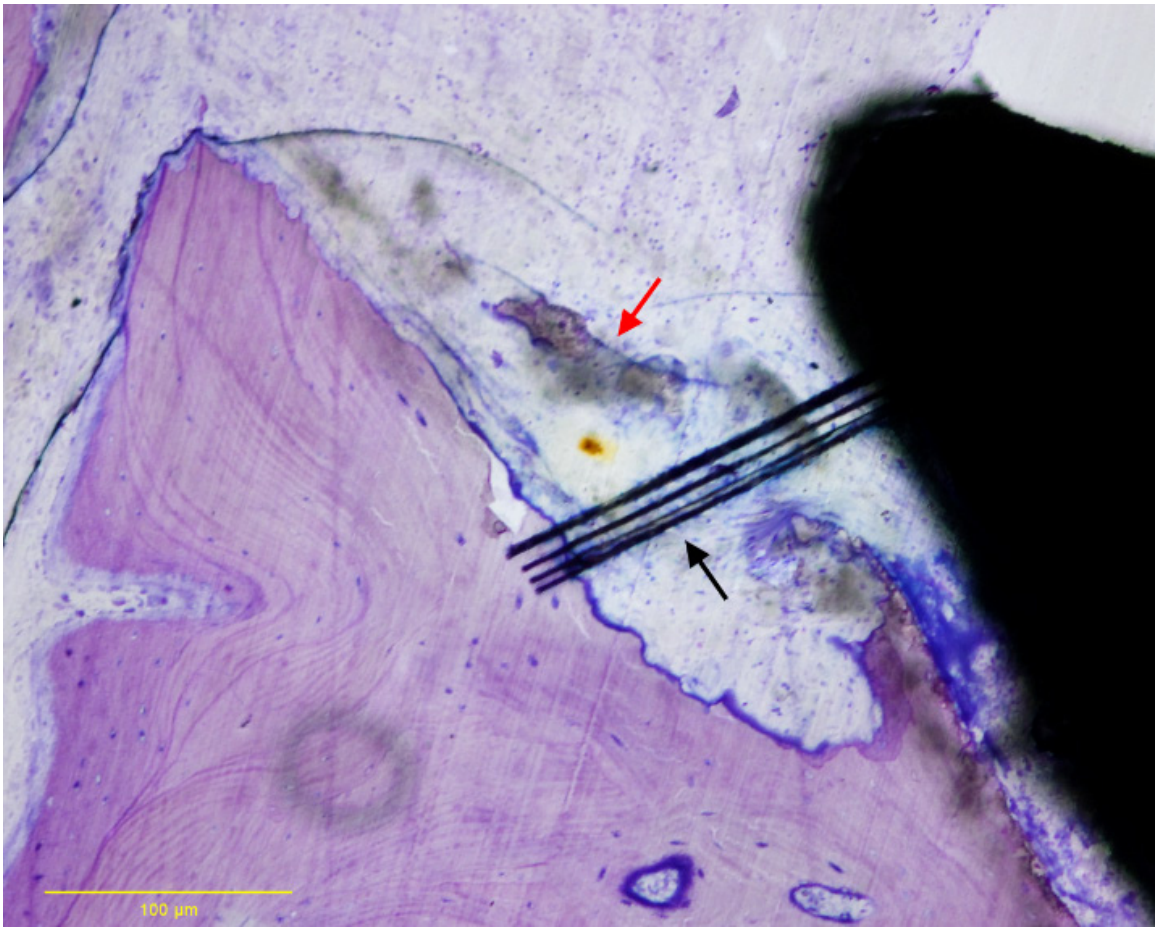


Fig. 33. Photomicrograph after LA-ICP-MS, the laser tracks apparent (black arrow). We could thus make sure the tracks had passed through the areas we were interested in. A loose HA flake is also apparent (red arrow). Picture RDT,CBJ,MR

SEM-EDS however gives a quantification at a point in the tissue and we could thus focus on particular regions of interest (ROI). Light microscopy was again used to find, and verify, that the right ROIs were sampled. Prior to, and after each examination, ROIs were identified under the light microscope to identify areas where we could see large quantities of cells with wear debris seemingly internalised, allowing us to target these areas specifically.

## Statistical considerations:

Paper 1 and 4 did not include statistical analysis due to the nature of these studies (an experimental finite element analysis and a descriptive histological study of 5 trapezia, thus they are not mentioned further here.

Paper 2: We compared two sets of six articulations in a joint simulator. The experimental set up had some limitations, as discussed below, but in our opinion, these were the same for both sets of articulations. Thus, it seemed appropriate to compare statistically the results that we found. We had two unrelated samples, but the number of articulations in each set was low, we therefore used a non-parametric analysis. It is not meaningful to speak of a "normal distribution" with the low number of "participants" in this analysis. Parametric tests (for example the t-test) base their validity on this assumption, whereas non-parametric tests do not. In this case, we were comparing four different measurements with continuous variables (different weights, in mg). The Mann-Whitney U test (according to many) is a test of the difference in median values for two independent samples, but it also assesses the spread of values (the range or the shape of the distribution curve), thus this is necessary information to interpret the test in a meaningful way (Hart, 2001). The results have already been discussed, they are summarised in the box plot below with significant findings highlighted (by an *). The Cr/Co ratio was also assessed, but one can argue that the significance of a statistical assessment of this ratio is difficult to interpret. It was higher in the coated articulations and this we believe was due to the CrN coat contributing more Chromium to the wear products.

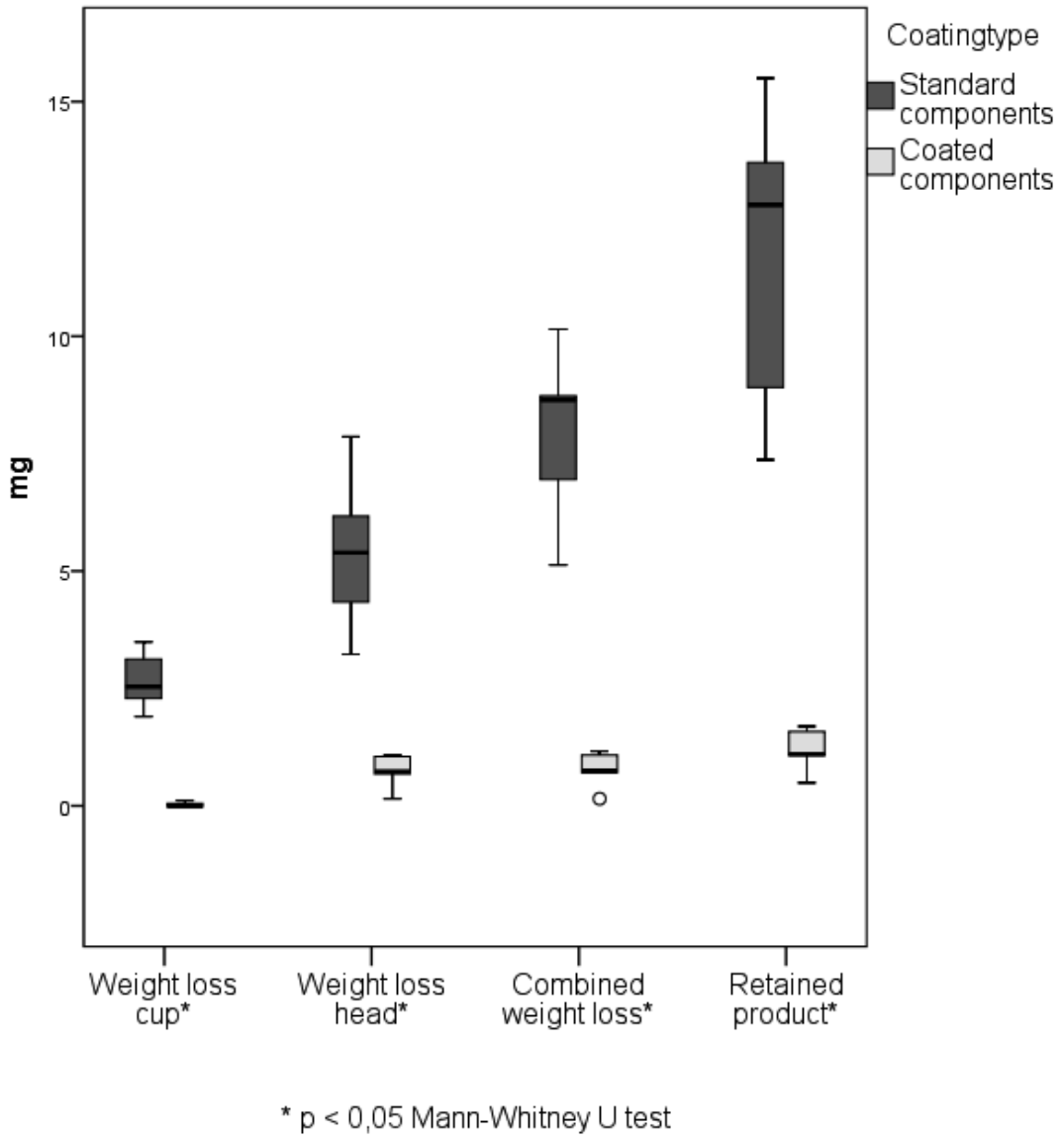


Fig. 34. Box plots displaying median and range for weight loss of cup, head and combined articulation, as well as the amount of product retained after testing. Coated articulations in light grey with significantly lower quantities

Paper 3: The RCT involved the most statistical calculations and advice from a statistician was sought as we analysed the results. The calculation of the sample size is discussed under methodological considerations so I will not go into that here. In this trial we were considering continuous variables for somewhat larger groups (N=20 in each arm), both within groups (that is, related samples- looking for a change from one observational point to another) and between groups (that is, unrelated samples). When looking at the outcome measures, most were skewed, as shown here by the distributional curve for the primary outcome measure at base line and at 6 and 12 months:

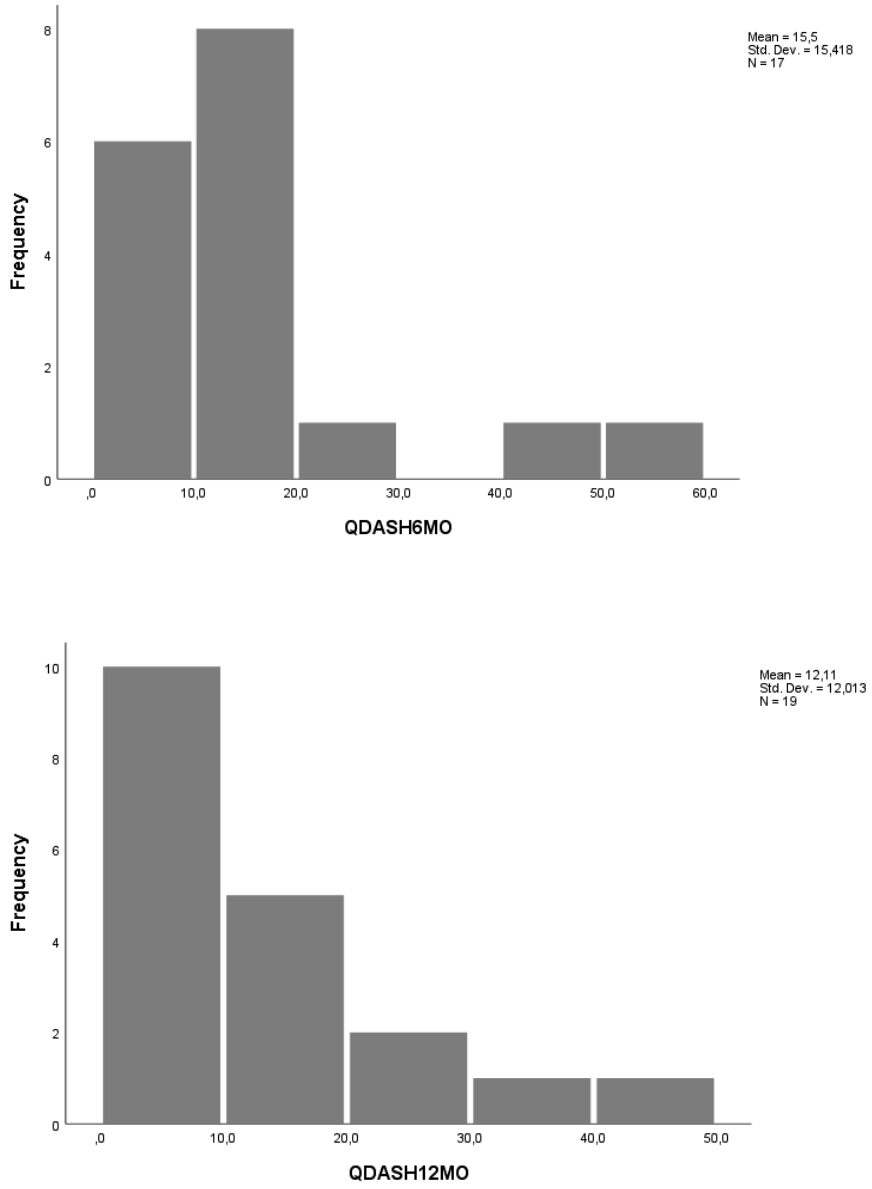


Fig. 35. Histogram displaying the QDASH 6 and 12 months, the data is skewed to the left.

In addition, 20 participants in each group is a relatively low number when considering if the data is normally distributed. Thus, non parametric tests where used with data presented as median and range. Wilcoxon Signed Rank test was used to assess changes within groups compared to baseline and we used the Mann-Whitney U test to assess differences between groups at the various time points.

Missing data was a problem we discussed with the statistician. Missing data comes in three main categories; missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). In the case of this study, the latter applies. There are more missing observations in one arm of the study (the joint replacement group) and some of

these are due to complications from the treatment. We have accounted for the missing data in the flow chart for the study, summarised again below:

| Analysed (trapeziectomy, N=20) : | Analysed (joint replacement, N=20) : |
|---|---|
| 3 months: 17 (3 U.t.a[4]) | 3 months: 17 (2 U.t.a[4] , 1 C.R[5]) |
| 6 months: 19 (1 U.t.a[4]) | 6 months: 18 (1 U.t.a[4] ,1 Rev[6]) |
| 12 months: 20 | 12 months: 19 (1 Rev[6]) |
| 24 months: 19 (1 U.t.a[4]) | 24 months: 17 (1 U.t.a[4], 2 Rev[6]) |

We can see that five patients were unable to attend (U.t.a) in the trapeziectomy group whilst in the joint replacement groups there were four. These omissions were due to patient related factors only, and are evenly distributed. In the joint replacement group, there were five additional time points with missing data. These were due to a closed reduction of a dislocated prosthesis (C.R) and four revision surgeries (Rev). We discussed the problem with missing values with the statistician. A useful overview of the topic is also given in an article on the topic from 2013(Dong and Peng, 2013). The default method in most statistical programs is that of list-wise deletion; if data is missing from any one observation then the data from that participant is entirely excluded from the analysis. Depending on the distribution of missing data, this can lead to a drastic fall in the number of participants in the analysis and consequently reduce the validity of the findings, unless the study is sufficiently powered to handle this. Indeed, sufficient power is one of the prerequisite conditions required in order to use list-wise deletion. The other is that the missing data needs to be of the MCAR type (where the mechanism or reason for the missing data is completely unrelated to any of the variables or the treatment given in which case the analysis will be the same regardless if the observations are excluded). In our case, neither of these two conditions were satisfied and list-wise deletion was not used. There are complex ways of dealing with Missing not at random (MNAR) data. One solution involves imputational methods where estimations of the missing value are made and used in the data set to make it complete before analysis. I have not studied this further however, as our statistician felt this was not appropriate for our relatively small dataset. Rather, we performed an analysis of all available observations at each time point. This is consistent with the intention to treat principle but does affect the dataset in its own way. We concluded that if anything, this method would be unfavourable for the joint replacement group (as observations made after revision surgery were bound to be worse than for a functional implant. But, in the setting of a superiority study this is appropriate. It would not be correct to exclude list-wise the patients that had complications from the analysis, only including the patients with uncomplicated joint replacements giving a more positive result than what we in reality observed.

Finally, we carried out a survival analysis (Kaplan- Meier analysis). The Kaplan Meier method of survival analysis is regarded as the gold standard method of estimating joint replacement survival (Ranstam and Robertsson, 2010). In this case, the data set is small and the observation time short. In addition, there were no revisions in the trapeziectomy group, so the revisions that were performed are fairly easy to assess. However, a Kaplan-Meier analysis is often requested by readers interested in joint replacements, and it allows readers a quick overview of the revisions. Therefore, we opted to include it.

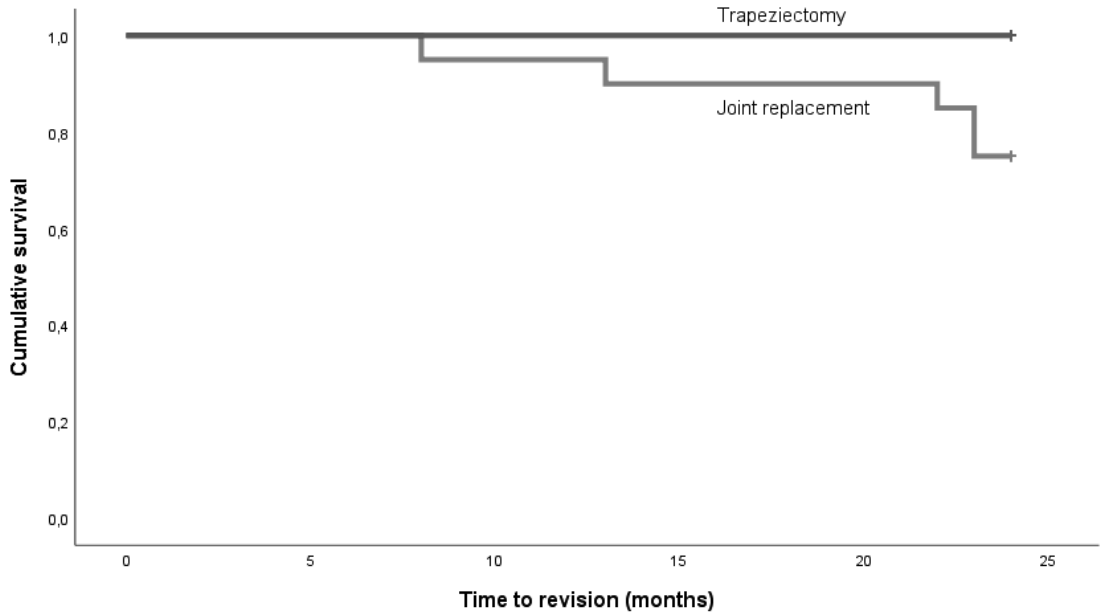


Fig. 36. Kaplan-Meier cumulative survival for both arms of the study, “revision” defined below. Picture RDT

In order to perform the analysis we had to define the event “revision”. For the trapeziectomies, this was easy- there was no revision surgery in this group. Our definition of revision surgery for this group was “repeated surgery to stabilize the thumb due to ongoing pain”. For the joint replacements however, the issue of competing events may be an issue. The above mentioned review of statistical analysis of register data explains that for joint replacements, revision of one component (for example the cup) is considered a competing event with respect to revision of the other component (the stem in this example). When a total revision is performed due to failure of one component, then this excludes the possibility of the other component becoming a cause for revision. Failing to correct for this introduces bias when interpreting the results (for example a falsely low rate of stem revisions). In the present study, two total revisions were performed due to inflammatory reactions in the joint. There have been very few problems with the stem for this implant and it would require longer observation to assess this. Had stem revision been an end point of interest for the analysis then more complex statistical methods would have been necessary (Regression methods to calculate the probability of each competing event). In the present

study, we defined “revision of either cup or stem” as the revision event for the survival analysis and this captured all cases of cup revision in the study.

## Results:

Keeping in mind that a finite element study involves some inherent assumptions (and limitations, see below), we did make some interesting observations none the less. The Elektra™ design was particularly dependent on support from the upper cortical bone layer. We used a thickness of 1.5mm for this layer. Other FEA studies of the carpus have used either 1mm, as in a study of scaphoid fracture by Ezquerro et al (Ezquerro et al., 2007) or 1.5mm (Guo et al., 2009), the latter a study of the entire carpus and the transverse carpal ligament. In the clinical situation of CMC1 OA, with dense sclerotic bone the cortical bone layer may be thicker. Nufer et al found a 50% increase in the thickness of the subchondral bone layer compared to normal trapezia(Nufer et al., 2008). In light of this, the Elektra cup may have better support from this layer in the clinical situation. When we compare these findings to the observations we made in paper 4 (trapezial histology), we found that the cancellous bone was more affected by the osteolytic process and that the two cups that were still fixed, primarily had their support from the sclerotic, upper cortical bone layer.

The Elektra design transmits more stress (when loaded) to the trapezial bone (and more so than the Motec counterpart in all conditions we tested with). Ideally, these sharp increases in stress under loading should be avoided and we can speculate as to whether this is part of the explanation behind the early loosening that many surgeons have reported. Of course, this ignores the other main reason for aseptic loosening of implants; that of wear-induced osteolysis. Our findings in paper four indicate that this is probably a more important contributor to the early loosening of the Elektra cup.

The Motec thumb design with its collar and raised centre of rotation (due to not only the collar, but also its modular design) appeared promising based on the stress values in the surrounding bone and the comparatively higher values for the Elektra design. However, the relative increase in stress to the periprosthetic bone when changing from axial to angular load was greater for this implant, the Von Mises Stress values increasing by a magnitude of 7 and 10 times (for the average, and maximum values respectively) compared to the Elektra design where the stress values are more constant- in the normal bone model, there is hardly any change, in the osteoporotic model the load approximately doubles.

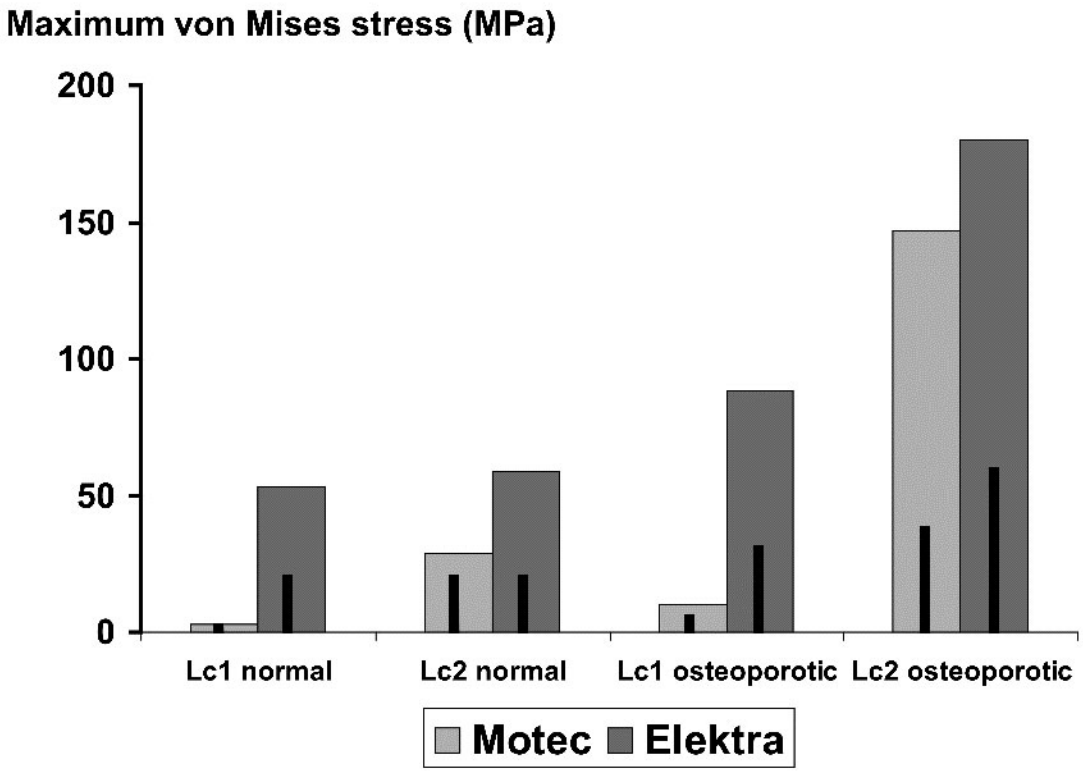


Fig. 37. Histogram of the Von Mises Stress values in the periprosthetic bone in load case (Lc) 1 (axial load) and 2 (angular loading) for the two implants in both normal and osteoporotic bone. The bars show the maximum values, with average values shown in the black, central lines. Picture RDT

This sharp rise in stress under angular loading is also problematic and may be part of the explanation for the early failures described for the Motec implant. The Motec® Thumb also utilised a MoM articulation and the authors of the largest series (42 implants in 40 patients) with this prosthesis reported a cumulative revision rate of 42% at 2 years (Thillemann et al., 2016). Whilst the article does not particularly mention the macroscopic appearance of the CMC1 joint at revision surgery, 28% of patients had elevated serum chrome and cobalt levels, and the potential contribution of wear-induced osteolysis needs to be borne in mind also for this implant.

The production of wear products was the focus of the second paper, looking at ways of reducing wear rates in a small spherical MoM articulation like those used in the CMC1 joint. Thus, it addresses the other main cause of implant-loosening the finite element analysis could not account for. Coating the articulation with CrN, enabled us to reduce the amount of wear significaantly. Assuming this reduction is long lasting, this should be of interest clinically, where osteolysis induced by metallic wear products (and other wear products for that matter) is still one of the main hurdles preventing longer implant life-spans.

The consequence of wear from a small MoM articulation become clearer when looking at the results of the last two papers, particularly paper four that showed early, advanced osteolytic lesions around five Elektra cups, three of them loose. Large amounts of dark staining material was seen in these lesions, much of it contained in macrophages.

Of particular interest was the recurring pattern seen in these five samples; the most advanced osteolytic regions were below the cups, and in this particular design, the metal wear has free access via the cup's cannulation canal. These osteolytic lesions seem to have quickly undermined the basal support for the cup, whilst at the same time osteolytic processes where visible at the joint surface weakening the support from the cortical bone.

This study, in contrast to published case cohorts, gives insight into the mechanism behind early loosening after this implant. Paper 3 is the first published RCT comparing a total joint replacement to the trapeziectomy with LRTI. The study failed to show a difference in the primary outcome measure (QDASH at two years), but did show a significant difference in favour of the joint replacement at early follow-up. One can only speculate whether the joint replacement in fact would have been superior at all time points if there had been less complications, but that will have to be studied in later trails with a different (and better) implant. There are no other RCTs with which to compare our findings, but recently two studies comparing cohorts of patients have been published, one prospective (Cebrian-Gomez et al., 2018) and one retrospective (Robles-Molina et al., 2017). Both compared uncemented joint replacements with trapeziectomi with LRTI, but used different implants from ours, the Ivory and the ARPE respectively. These have a comparable ball and socket design, but make use of a MoP articulation. The studies have a mean follow up of 4 and 4.7 years respectively and show significantly better thumb pinch-strength throughout the study period, including at final follow up. Interestingly, there was no significant difference in the QDASH in the latter study. As we have discussed previously, there may be different reasons for this. These studies had a lower complication rate than we did, thus, they presumable have had a higher proportion of well-functioning joint replacements throughout all assessments. Cebrian-Gomez et al reported three revision surgeries due to instability (two patients, in which one had a loose cup) and a third case with cup loosening at 23 months postoperatively) Their joint replacement cohort consisted of 84 patients. Robles-Molina et al reported no cup loosening, but instability and dislocations necessitating revision to trapeziectomy in 3/31 patients.

Whilst the results after the Elektra™ have not been satisfactory, some encouraging long term (10 years) results have recently been published for another uncemented joint replacement ( the ARPE) with over 90% of implants (a total of 65 implants followed) retained and still functional at 10 years(Martin-Ferrero, 2014). However, radiologically there was subsidence of the cup in 16%, indicating that the problem on the cup side still does not appear to be solved. The high rate of complications we saw after the joint replacements in the RCT seems to tie in with the findings from both paper 1 and 4 in the thesis. Whilst the rate of cup loosening was not alarmingly high in our study, other authors have raised concerns about this, and the two most serious complications in our study were most likely due to metal wear.

Lastly, we observed only minor problems with the 20 trapeziectomies and no reoperations. If a joint replacement is to be a viable alternative to trapeziectomy, it needs to demonstrate reliable long-term function. Other potential advantages of joint replacement (such as faster rehabilitation, improved strength and motion and potentially correction of MCP hyperextension) will also need to be taken into account in the comparison.

## Limitations:

### Paper 1:

The main limitation of this paper is its experimental design utilizing a FEA. As discussed previously, such a study is an experimental approximation of the real situation and results must be interpreted with caution and considered in context of clinical experience and studies. We also made some simplifications and assumptions that have been elaborated upon in the methods section that can have affected our results, however we would argue that the trends we observed in the model are relevant none the less. In fact, in the years after this study both these designs have been taken off the marked due to high rates of cup loosening. We cannot be certain as to the exact causes, but paper 4 sheds new light on the mechanism behind cup-loosening after the Elektra™ that most likely apply to the Motec® as well (due to the MoM articulation).

### Paper 2:

As mentioned briefly under methods, it was not feasible to conduct a simulator study under equivalently stringent conditions as described for the hip joint. Some simplifications had to be made, and this invariably leads to limitations when analysing results. These have been discussed previously. The main limitation with joint simulator studies in general is that of transferability. To what extent do findings in a joint simulator study allow us to predict what will happen when an implant is used in vivo? This is not so important for our study as our main aim was to see if there was a difference in wear rates between the two different articulations, but in the field of hip simulator studies (that are technically more advanced), simulator studies are becoming increasingly accurate and relevant in term of predicting in-vivo implant function(Medley, 2016).

### Paper 3:

The major limitation for this study is the long inclusion period. In this case, it was a little more than 7 years, during which time the surgeries were done by the same surgeon (RDT) in the same uniform way. Of course, there is a learning curve in all surgeries, and we cannot rule out that the surgeon became more skilled over these years (we hope so!), which may have led to some bias in the material. The second problem with a long inclusion period is that the results may not be as interesting, or relevant, when they finally are published. This is, unfortunately, somewhat relevant to this study. As our trial was concluding follow-up, other researchers had published problems with the Elektra™ and the original distributor was taken over by a larger developer of orthopaedic implants (Stryker, Kalamazoo, Michigan, USA). The joint replacement for the trapeziometacarpal joint was relaunched, keeping the stem unchanged, but completely changing the articulation and cup design (to a polyethylene

dual-mobility, HA-coated CrCoMo cup), under the new name of MOOVIS. Thus, the Elektra™ is no longer available for use, and the interest for, and relevance of the trial may be somewhat reduced. Trapeziectomy, on the other hand, is still considered to be the reference procedure that other methods are compared against. There is a trend in some centres now to omit the ligament reconstruction and tendon interposition part of the procedure, but there is no evidence to suggest that trapeziectomy alone is superior to trapeziectomy with LRTI. There may be a slightly higher rate of complications after the latter procedure, but that was not a problem in our trial and should therefore not have had any bearing on the results.

Another problem with a long inclusion period is that there may be changes to protocol as new developments occur. An example of this was the development of a new version of the cup used for the Elektra™. The old version made from CrCoMo was still available, but a new, titanium cup was developed which theoretically would allow better (in the long term) osseointegration. The new cup still retained the same MoM articulation, but had no documented results. We therefore opted to continue using the original cup, and our protocol was unchanged.

As mentioned already, there may be a ceiling effect for the QDASH or a roof effect for the Nelson score implying that the PROMs may not be sensitive enough to detect small changes.

The clinical significance of the increased range of motion at final follow-up, measured by goniometry is uncertain. The median difference between groups in our study was small, 5° and 7° difference for extension and abduction. One needs to keep in mind the measurement error for goniometry. Ellis and Burton showed that therapists measure to an accuracy within 4-5° in 95% of measurements, whereas the accuracy between different therapists is within 7-9° (Ellis and Bruton, 2002)

Finally, as pointed out in statistics, there were missing values and these were unevenly distributed between groups due to the higher number of complications in the joint replacement group. The study was not sufficiently powered to account for this unfortunately and most likely this has affected the results.

Paper 4:

This retrieval study was only based on the histological examinations of five trapezia. Thus, one can question whether the findings we have made truly are generalizable. At the outset, we were uncertain as to what we would find, and it would have been interesting to have studied more trapezia. None the less, we saw that the findings were very similar for all 5 specimens. The in-vivo exposure time is short, but the specimens with the longest exposure times had the most severe changes. Furthermore, similar changes have been described from large joint metal-on-metal arthroplasty. Thus, we argue that our findings give compelling evidence of metal-wear induced osteolysis.

Another limitation pertains to the source of the wear debris; our study does not allow us to conclude as to the source or the mechanism behind its formation. The distribution of the osteolytic lesions (under the cup and at the cup perimeter) would support the articulation

being the primary source, but the taper between the metacarpal stem and the head/neck component is another possibility. The issue of taper wear is well known and described, at least in larger articulations like the hip joint (Osman et al., 2016). It does not seem to have been a large contributor to the wear process we observed in this study however; the taper on the neck component did not show signs of wear (as examined under loupe magnification). Titanium used in the stem component, being a softer metal should have been identified in the LA-ICP-MS and SEM-EDS studies. We did not observe its presence. The mechanism behind articulation wear cannot be ascertained from our study. One possible mechanism (that our study would support) is that of third body wear- as large amounts of HA was seen in the periprosthetic tissues. As mentioned previously, irregularities of the MoM surfaces can cause marked acceleration of wear. To assess this, we should ideally have examined the articulating surfaces under the scanning electron microscope.

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## Ethical considerations:

Paper 1 and 2 were experimental in nature, thus there were few ethical considerations.

The finite element analysis was partly funded by Swemac who at that time marketed the Motec® Thumb joint replacement. Swemac had no involvement in the study itself that was performed by a third party (the Swedish branch of XDIN, an American engineering company). The company had experience with the FEA technique and two of the engineers were also involved in the interpretation of the results with us. Their contribution was invaluable as we assessed the results from both engineering/technical and surgical viewpoints, and the two are co-authors on this paper.

The biomechanical study (paper two) was also performed in Sweden, at the SP technical research institute in Borås. This work was funded by the Sofies Minde Research Foundation in Norway. Swemac provided the 6mm articulations (12 in total). The coating supplied on half of the articulations is available technology manufactured by another company (Ionbond, Switzerland) not involved in the study. This work was also done by a third party without any commercial interest in the results. Benny Lyvén at SP provided invaluable assistance with the technical set up and oversaw the conduction of the experiment. As such, he is credited in the article.

Paper 3:

This was a large and time-consuming undertaking, involving the participation of 40 patients. Prior to the commencement of the study, permissions were sought and granted from both the regional ethics committee, REK South Eastern Norway (276-08457c dated 18.08.08) and the local institutional ethics committee at Oslo University hospital (Personvernombudet, 07/3561, dated 19.6.08). Unfortunately, the trial took much longer than anticipated to complete. A second application was thus sent to REK (and granted, number 2015/1965/REK Sør-øst C) to prolong the study time (as well as adding a further radiographic assessment for a subgroup of patients, unpublished material at this stage). The REK permissions are shown below (fig. 38 and 39). At the outset of the study, I was not aware of any requirements for registration at a central trial registry. Indeed, Clinical Trials.gov first released their database in September of 2008, at which stage our study was planned and had commenced inclusion. It took some time before this was brought to my attention at one of the yearly departmental research meetings. An application to Clinical Trials.gov was then prepared and sent, and the trial was approved (NCT02556515). Patients gave written consent after receiving verbal and written information.

**UNIVERSITETET I OSLO**
**DET MEDISINSKE FAKULTET**

Lege Rasmus Thorkildsen
Hånd- og mikrokirurgiseksjon
Ortopedisk avd.
Rikshospitalet
0027 Oslo

**Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst C (REK Sør-Øst C)**
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 228 44 667
Telefaks: 228 44 661
E-post: i.s.nyquist@medisin.uio.no
Nettadresse: www.etikkom.no

**Dato: 18.06.2008**
**Deres ref.:**
**Vår ref.: 276-08457c**

**Protese eller reseksjonsplastikk ved artrose i tommelens rotledd?**

Komiteen behandlet søknaden 09.06.2008. Prosjektet er vurdert etter lov om behandling av etikk og redelighet i forskning av 30. juni 2006, jfr. Kunnskapsdepartementets forskrift av 8. juni 2007 og retningslinjer av 27. juni 2007 for de regionale komiteer for medisinsk og helsefaglig forskningsetikk.

Vedtak:
Komiteen godkjenner at prosjektet blir gjennomført.

Med vennlig hilsen

Arvid Heiberg
Professor dr.med.
Leder

Ida Nyquist
Sekretær

Kopi: Seksjonsoverlege Magne Røkkum, Hånd- og mikrokirurgisk seksjon, Ortopedisk avd. Rikshospitalet

Fig. 38. Ethical approval for the Randomised controlled trial from REK South Eastern Norway

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

| Region: | Saksbehandler: | Telefon: | Vår dato: | Vår referanse: |
|---|---|---|---|---|
| REK sør-øst | Tor Even Svanes | 22845521 | 11.11.2015 | 2015/1965/REK sør-øst C |
| | | | Deres dato: | Deres referanse: |
| | | | 13.10.2015 | |

Vår referanse må oppgis ved alle henvendelser

Rasmus Thorkildsen
Oslo universitetssykehus
Postboks 4950 Nydalen
0424 Oslo

**2015/1965 Protese eller reseksjonsplastikk ved artrose i tommelens rotledd?**

**Forskningsansvarlig:** Oslo universitetssykehus HF
**Prosjektleder:** Rasmus Thorkildsen

Vi viser til søknad om prosjektendring datert 13.10.2015 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst C på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringen består i at man ønsker å legge til en tilleggsundersøkelse, beskrevet slik av søker: *En del av studien innebærer at vi tar 4 ekstra røntgenbilder av hendene for å kunne bedre måle bevegeligheten av tomlene før, og etter operasjon. Dette er søkt om, godkjent og iverksatt allerede.*

*I ettertid har vi sett at det er viktig å kvalitetssikre metoden ved at disse røntgenbildene taes to ganger av forskjellige radiografer på noen av pasientene. Dette for å bekrefte at ikke det er større feilmargin i undersøkelsesmetoden, dvs at den er reliabel. Vi tenker å gjøre denne dobbeltundersøkelsen hos 10 vilkårlige prosjektpasienter når de kommer til en av kontrollene i studien (dvs en gang med 4 ekstra bilder for hver av de 10 pasientene ved en av kontrollene).*

Det søkes videre om å utvide prosjektperioden, til og med 2017.

**Vedtak**
Endringssøknaden godkjennes.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2017. Av dokumentasjonshensyn skal prosjektopplysningene likevel bevares inntil 31.12.2022. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren.*

*Klageadgang*
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/


Fig. 39. Permission for extended time for the RCT approved by REK

As mentioned above, this trial proved challenging to finish. This led us to have some discussions during the almost 8 year long inclusion period. One problem when trial results are delayed, is that the scientific impact of the work may decrease as already mentioned above (see limitations chapter). We were adamant that this would not affect the study and its publication. It is still the first RCT to be published, comparing a joint replacement to trapeziectomy. In our opinion, interesting and relevant findings were made, and the trial should also be useful in the planning of future studies that will be needed.

In our trial, we saw more complications in the joint replacement group and this was monitored during the trial period. Under these conditions, researchers need to consider whether to continue the trial or whether to stop (on ethical grounds). A high frequency of complications can be one such reason. In considering this, we discussed the complications we were seeing. Cup-loosening, the main complications other authors have warned against occurred less frequently in our patient cohort. We did see some problems with instability, two requiring repeated surgery, and one treated by closed reduction. This last patient has been very happy with the joint replacement, recently having attended the 10 year follow-up, pain free and still highly satisfied. The two most serious complications occurred after the inclusion period was finished. In total, the number of complications were high, but they were of three different types and the two latter would seem to be a consequence of the MoM articulation (which was the focus of paper 4). These considerations need to be weighed against the obligation to publish research results. There is still a problem with "skewed publications", were only positive findings or findings that concur with the original hypothesis stated are published. Because of this, many important findings are not brought to the attention of the scientific community (McGauran et al., 2010). After considering these factors, we decided to complete the work and publish our findings. Despite the higher frequency of complications in the joint replacement group, there was no difference in patient satisfaction in the two groups, nor in the final clinical result.

Other issues to consider for this study was the sample size. As mentioned previously, it is probably on the lower side of the sample size required to show a difference if it in fact is present. This also has ethical implications, as clinical research is dependent on patients participating. If patients are recruited to underpowered studies, then there is a chance that the findings are not valid and that their participation was in vain. This has to be balanced against certain practical limitations- such as time constraints and the number of patients that one realistically can hope to include, and the logistical problems of multicentre studies. The sample size has been discussed under methodological considerations, as well as the intention to treat principle and the need to adhere to this under the interpretation/analysis of results, but this also has ethical ramifications;  If unfavourable results are excluded, the alternative treatment may be proven superior, when it in fact was not. Another aspect of the same discussion is that complications also occur in all surgical practices (that is, not in the context of a clinical trial) and this then is highly relevant when comparing results between groups and important to report.

Paper 4:

When some of our patients experienced problems with the joint replacement (the cup more specifically), a revision to trapeziectomy was the usual revision procedure, consistent with the finding from published papers on revisions after CMC1 joint replacements as mentioned previously. Normally the trapezium is discarded after this procedure. The senior author's previous experience with retrieval studies in the hip and other histological studies on bone-implant interface led us to question whether closer study of these trapezia might be useful to understand the process behind cup loosening after this joint replacement. Our department has previously collaborated with the department of Prosthodontics/Dental materials science at the University of Gothenburg, and this was planned again for this work. This study of the trapezia was of no consequence for the patients in terms of the treatment they received. Both intact cup (revised due to instability and repeated dislocations) and loose cups were thought to be of interest. At first we were not certain what we would find, thus permission to use the trapezium for further study (rather than discarding it) was sought. All patients approved. The trapezia were kept on formalin and we applied for ethical approval to study these further, (see fig 40).

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

| Region: | Saksbehandler: | Telefon: | Vår dato: | Vår referanse: |
|---|---|---|---|---|
| REK sør-øst | Hege Holde Andersson | 22845514 | 10.06.2013 | 2013/799<br>REK sør-øst B |
| | | | **Deres dato:** | **Deres referanse:** |
| | | | 23.04.2013 | |

Vår referanse må oppgis ved alle henvendelser

Til Rasmus Thorkildsen

**2013/799b Histologisk undersøkelse av proteser fra tommelens rotledd**

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 15.05.2013. Vurderingen er gjort med hjemmel i helseforskningsloven § 10, jf. forskningsetikklovens § 4.

**Forskningsansvarlig:** Oslo universitetssykehus HF
**Prosjektleder:** Rasmus Thorkildsen

**Prosjektomtale**
*Hensikten med denne studien er å undersøke årsakene til løsning av tommelprotese som tidligere er blitt operert inn. Når slik løsning forekommer og gir opphav til smerter vil det ofte bli nødvendig med en ny operasjon. Trapeziumbenet hvor protesekoppen har vært festet blir da fjernet som en del av inngrepet. Inngrepet som planlegges for forsøksdeltakerne vil bli foretatt akkurat som før ved Håndkirurgisk seksjon på Rikshospitalet og foregår på samme vis som tidligere. Den kirurgiske behandlingen ved løsning av protesen innebærer som regel en operasjon som kalles reseksjonsplastikk. Man fjerner da trapezium-benet og lager en senepute mellom tommelroten og resten av hånden. Tommelen gipses så i 5-6 uker før opptreningen starter. I stedet for at trapeziumbenet blir kastet og destruert ønsker man å se nærmere på det under mikroskopet. Behandlingen for pasienten blir den samme om vedkommende er med i prosjektet eller ikke.*

**Vurdering**
Formålet med studien er å undersøke årsakene til at tommelproteser som tidligere er blitt operert inn løsner. På denne måten håper man bedre å forstå årsaker til slik løsning.

Etter komiteens vurdering er studien en kvalitetssikring av eget arbeid og ikke en studie som er fremleggelsespliktig. For å gjennomføre prosjekter av denne typen trenges det ingen særskilt godkjenning fra REK. Det er institusjonens ansvar å sørge for på vanlig måte at tiltaket følger gjeldende reguleringer for behandling av helseopplysninger.

Ettersom prosjektet forutsettes gjennomført i samsvar med gjeldende reguleringer vil det ikke være noe til hinder for at resultatene kan publiseres.

**Vedtak**
Prosjektet faller utenfor komiteens mandat, jf. helseforskningsloven § 2. Prosjektet kan gjennomføres uten godkjenning av REK.

**Besøksadresse:**
Gullhaugveien 1-3, 0484 Oslo

**Telefon:** 22845511
**E-post:** post@helseforskning.etikkom.no
**Web:** http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee REK sør-øst, not to individual staff

*Klageadgang*
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst B. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Komiteens avgjørelse var enstemmig.

Med vennlig hilsen

Stein Opjordsmoen Ilner
professor dr. med.
leder REK sør-øst B

Hege Holde Andersson
Komitésekretær

**Kopi til:** magne.rokkum@ous-hf.no; oushfdlgodkjenning@ous-hf.no

Fig. 40. Reply from the reginal ethics committee of South Eastern Norway, regarding paper 4.

Approval was at the same time sought from the institutional ethics committee at Oslo University hospital (Personvernombudet) and the departmental research committee (Forskningsutvalget). The project was approved and allocated project number 13-5018.

# Conclusions:

1. The maximum stress transmited to the trapezial bone is lower for the Motec® trapeziometacarpal cup compared to the Elektra™ cup, both in normal and osteoporotic bone models.
2. The Elektra™ cup primarily loads the upper cortical bone layer in the model trapezium, whereas the Motec® design transmits stress more evenly to both the cortical and the cancellous bone.
3. The Motec® design is more vulnerable to angular load than the Elektra™.
4. Chrome Nitride coating of 6 mm spherical CrCoMo articulations reduces the rate of wear significantly after 512,000 cycles with a unidirectional load of 5 kg in Ringer's solution in a joint simulator.
5. There is no difference in patient-rated outcomes when comparing the uncemented Elektra™ metal-on-metal joint replacement and trapeziectomy with ligament reconstruction and tendon interposition after two years follow up.
6. The Elektra™ group exhibited better patient-rated scores than the trapeziectomy group at 3 and 6 months for QDASH and at 3 months for the Nelson score.
7. The strength of thumb key-pinch was significantly better in the Elektra™ group at 3 and 6 months. Tip-pinch was significantly better at 3 months.
8. Joint replacement surgery was associated with more complications than trapeziectomy. These were dislocations, cup-loosening and osteolysis.
9. Osteolytic lesions were seen around most of the Elektra™ prostheses, most commonly appearing at 1 year postoperatively. In the trapezium, the lytic regions were apparent at the cup margin and beneath the cup. Metacarpal osteolysis was seen adjacent to the joint, seldom in the diaphysis.
10. Trapeziometacarpal metal-on-metal articulations may lead to accumulation of metal wear products (Chrome, Cobalt and Molybdenum) in the joint and periprosthetic soft tissues associated with osteolysis and early cup loosening.
11. Osteoclast-mediated osteolysis was evident in the surrounding bone with large amounts of particular waste, much of it internalised in macrophages.
12. The macrophage, in various stages of differentiation, was the most abundant cell type and seems to play a central role in the osteolytic process.
13. The CrCoMo cups displayed early and marked loss of hydroxyapatite coating.
14. A cannulated cup design can give the metal wear products access to the subprosthetic bone leading to osteolytic breakdown of bone underneath the cup.

## Implications for future research:

With regards to point 1,2 and 3 above, the main implications of this work would be for the development of new implants. It seems important to keep the centre of rotation low in order to avoid sharp increases in load to the periprosthetic bone. The contribution of a collar to a cup design may also in itself act at a lever arm for the cup when angular loads are applied.

The fourth point has clear relevance within the field of tribiology, particularly if MoM articulations are to be used. This technology should however be studied further to ascertain the longevity of the coating and it may be interesting to see if it can reduce wear in MoP articulations as well.

With respect to point 5,6 and 7, the first RCT comparing these two methods is now published. Hopefully it will lead to more RCTs being performed for this common condition where a plethora of treatment options exist. We did not find a difference in our study and taking the costs of joint replacement and the potential for complications into account, such treatment needs to be not only comparable, but superior, for it to be recommended on a larger scale. The non-randomised comparative studies we have referred to previously have shown a significant difference in favour of joint replacement (uncemented with MoP articulation) and promising medium to long term results have recently been published for one of these joint replacements. The problem itself should lend itself well to an RCT, but a large volume of patients is necessary to get an adequate sample size and to complete such a study on time. Other outcome measures such as the Sollerman test could be interesting to include in addition to a hand-specific PROM and functional assessments. Sick-leave and work status could also be interesting to compare, but most patients operated for CMC1 OA are at the end of their working career. This was our experience, too few patients were working to make useful comparisons between groups. The MCP joint (hyperextension) should also be considered both pre-and postoperatively.

Point 8 and 9 have important implications; for joint replacements to be a viable alternative in the treatment of CMC1 OA the rate of complications needs to be low. One question is that of cup loosening where cohort studies have indicated that trapeziectomy (as revision procedure) gives a results equivalent to a primary trapeziectomy. This is certainly interesting, but at this stage the evidence we have is from fairly small cohorts (10-15 patients) so this should be studied in further detail. The major revisions that two patients experienced are particularly unfortunate and challenging to treat, requiring surgery in two stages. The solution to this problem we think lies in the articulation (that is, finding ways to reduce wear)

With regards to points 10-14, these pertain to paper 4, which was perhaps the most interesting in our opinion, as the marked and early osteolysis we were able to demonstrate in all five trapezia show that metal wear is definitely a problem even in the smaller, non-weight-bearing joints of the hand. MoM articulations are hardly used in the hip anymore, and with the exit of the Motec Thumb and Elektra joint replacements they are no longer

available for use in the CMC1. The paper also points out a recurring pattern where the hand surgical community seems to have made many of the same trials and errors our orthopaedic colleagues have made in the treatment of hip OA 1-2 decades prior. Of course, there are many differences in the anatomy and loading of these two joints, but in retrospect, we may have been able to avoid some of the mistakes made in the treatment of CMC1 OA (with joint replacements) if we had paid more heed to their experiences. On the other hand, it is important to remember that there was a reason for the change form MoP to MoM artculations, polyethylene as discussed previously is not without problems. At present, the work with highly crosslinked polyethylene is of great interest in the hip joint. This is a technology that has not yet been embraced by the hand surgical community but should warrant further study, as should the technique of RSA, recently developed and demonstrated for the CMC 1 joint as it may provide us with more objective documentation of the real rate of loosening of these joint replacements. A cannulated system seems inappropriate, at least for metal or ceramic articulations where there is no polyethylene liner in the articulation. Lastly, it would be interesting for hand surgeons to contribute to the field of osteoimmunology, as research within this field may give us important clues on how to increase the life span of joint replacements.

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