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PhD Thesis

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Radiostereometric Analysis of Current Generations of Polyethylene in Total Hip Arthroplasty

Mid- and Long-Term Material Performance

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List of Papers

I. **13 year evaluation of highly cross-linked polyethylene articulating with either 28mm or 36mm femoral heads using radiostereometric analysis and computerized tomography.**
Nebergall AK, Greene ME, Rubash H, Malchau H, Troelsen A, Rolfson O.
Submitted manuscript

II. **Vitamin E diffused highly cross-linked polyethylene in total hip arthroplasty at 5 years: A randomized controlled trial using radiostereometric analysis.**
Nebergall AK, Greene ME, Laursen MB, Nielsen PT, Malchau H, Troelsen A.
Submitted manuscript

III. **Five year experience of vitamin E diffused highly cross-linked polyethylene wear in total hip arthroplasty assessed by radiostereometric analysis.**
Nebergall AK, Troelsen A, Rubash H, Malchau H, Rolfson O, Greene ME.
Submitted manuscript

IV. **Precision of radiostereometric analysis (RSA) of acetabular cup stability and polyethylene wear improved by adding tantalum beads to the liner.**
Nebergall AK, Rader K, Palm H, Malchau H, Greene ME.
Acta Orthopaedica. 2015;86(5):563-568.

Abbreviations

ArComXL®	Medium Cross-Linked High Molecular Weight Polyethylene (Zimmer Biomet Holdings, Inc, Warsaw, Indiana)
CT	Computerized Tomography
E1®	Vitamin E Diffused Highly Cross-Linked Ultra High Molecular Weight Polyethylene (Zimmer Biomet Holdings, Inc, Warsaw, Indiana)
EQ-5D	EuroQol 5 Dimension 3 Level Health Related Quality of Life Survey
HXLPE	Highly Cross-Linked Ultra High Molecular Weight Polyethylene
IQR	Interquartile Range
MGH	Massachusetts General Hospital
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
RSA	Radiostereometric Analysis
SEM	Standard Error of the Mean
SF-36	36-Item Short-Form Survey
THA	Total Hip Arthroplasty
UCLA	University of California, Los Angeles
UHMWPE	Ultra High Molecular Weight Polyethylene
VAS	Visual Analog Scale

Summary

English Summary

Background

Aseptic component loosening, a consequence of progressive osteolysis caused by wear of the ultra high molecular weight polyethylene (UHMWPE), has been the leading cause of failure in total hip arthroplasty (THA) since the introduction of this material for use as a bearing surface. Thus, researchers and clinicians alike have worked to improve the polyethylene articulating surface with the main goal of reducing wear. Highly cross-linked UHMWPE (HXLPE) was introduced in 1998 as a potential solution. The increased cross-link density reduced deformation that lead to wear. However, residual free radicals left the material prone to oxidation. A post-irradiation heating step eliminates free radicals, but compromises the fatigue strength of the material. Subsequently, vitamin E diffused HXLPE was developed to eliminate free radicals without reducing strength, while simultaneously maintaining the low wear observed in HXLPE. Since HXLPE and vitamin E diffused HXLPE deform and wear at dramatically reduced rates compared to UHMWPE, it is necessary to use the most sensitive and accurate tools, such as radiostereometric analysis (RSA), to monitor the performance of these materials over time.

Objective

The aim of the thesis was to use RSA to evaluate current generations of polyethylene to accurately and precisely determine their performance. Since osteolysis adversely affects THA survival, it is necessary to closely monitor wear, particularly in the mid-term and beginning stages of the long-term, to ensure that wear-related failure will not be a concern into the long-term.

Methods

In study I, the 13 year performance of HXLPE articulating with 28mm and 36mm femoral heads was assessed using RSA, plain radiographs, and computerized tomography (CT) scans. Study II was a five year randomized controlled trial comparing a medium cross-linked polyethylene (ArComXL) to a vitamin E diffused HXLPE (E1) using markerless RSA (shell only) and patient-reported outcome measures (PROMs). Study III utilized RSA and PROMs to assess the five year performance of E1 using the gold-standard RSA (shell combined with liner beads) method. Finally,

Study IV was a methodological evaluation of the three measurement methods available in marker-based RSA to monitor polyethylene wear and acetabular cup migration.

Results

The 13 year mean ± standard error of the mean (SEM) proximal femoral head penetration into the HXLPE was 0.06 ± 0.03mm, with no significant differences within the whole cohort after two years, and no significant differences between the two head sizes at any interval. No patient showed any signs of osteolysis on the plain radiographs or CT scans over the 13 years. In study II, the five year median (interquartile range [IQR]) penetration into the E1 liners was -0.04mm (-0.13 to 0) with significant differences between 6 weeks compared to three and five years ($p<0.001$ for both analyses) and between one year compared to three and five years ($p=0.005$ and $p=0.001$, respectively). The ArComXL group had 0.07mm (-0.03 to 0.16) of penetration at five years with no significant differences over time. Significant differences in penetration between E1 and ArComXL were observed at three and five years (($p=0.029$ and $p=0.019$, respectively). In study III, the mid-term mean ± SEM penetration into the E1 liners was 0.06 ± 0.01mm, with no significant differences after two years. All patient-reported outcomes in studies II and III (PROs) improved significantly from the preoperative follow-up compared to all postoperative intervals ($p<0.001$), with no differences between the two polyethylene groups in study II. Finally, study IV indicated that the shell + liner method was most desirable for measuring polyethylene wear and acetabular cup migration.

Conclusion

The current generations of polyethylene used in THA are performing safely at the mid- and long-term intervals. The medium cross-linked polyethylene, HXLPE, and vitamin E diffused HXLPE all demonstrated dramatically reduced wear compared to previously reported UHWMPE wear values. Additionally, the long-term HXLPE cohort showed no evidence of osteolysis, regardless of femoral head size. Patients in studies II and III all continued to report favorable PROs at the mid-term. The unexpected result of negative penetration values of the E1 cohort in study II could be due to the markerless RSA measurement method. The precision analysis of the three measurement methods done in study IV indicated that the shell only method was the least precise. Perhaps the negative values are a reflection of the software's attempt at measuring nearly zero penetration. Furthermore, the same material was used in study III, and the penetration was low and positive throughout the five years. Despite this discrepancy, the magnitude of all penetration values across the body of work was considerably lower than the reported wear of UHMWPE. Continued monitoring of all patients

analyzed in this work is necessary to determine if the low penetration and safety of these current generations of polyethylene is maintained into the true long-term.

Danish Summary

1 The Use of Polyethylene in THA

1.1 Ultra high molecular weight polyethylene

1.2.1 History

John Charnley developed the concept of low friction hip arthroplasty in the 1950's using polytetrafluoroethylene (PTFE, or more commonly called Teflon) as the articulating material. Teflon was chosen because of its low coefficient of friction and its low chemical reactivity[1]. The Teflon articulating surface resulted in a high revision rate due to significant wear and subsequent adverse bone reaction[2-4].

After an exhaustive search for a Teflon replacement, Charnley and his colleague, Harry Carven, fortuitously came upon ultra high molecular weight polyethylene (UHMWPE) as a suitable alternative[5]. When Charnley and Craven were first introduced to UHMWPE by a salesperson, Charnley was unimpressed[6]. Craven secretly wear-tested the material while Charnley was away and the results were quite remarkable[5,6]. Upon Charnley's return, he saw that UHMWPE had worn less than Teflon would have worn during a fraction of the time for which UHMWPE was tested[6]. Charnley first experimented with this new material *in vivo* in his own thigh and in 1962 the first total hip arthroplasty (THA) was done using UHMWPE as the articulating surface[2,7].

1.2.2 Manufacturing

The hydrocarbon, ethylene (C_2H_4), originally in the form of ethylene gas, undergoes deposition and polymerization to produce its resin powder form, polyethylene[8]. This resin powder must then be compressed into rods or sheets from which implants can constructed[8,9]. The polyethylene is then heated which produces regions of organized crystalline lamellae resulting from carbon-carbon bonds rotating about each other, mixed with disorganized amorphous regions[9] (Figure 1).

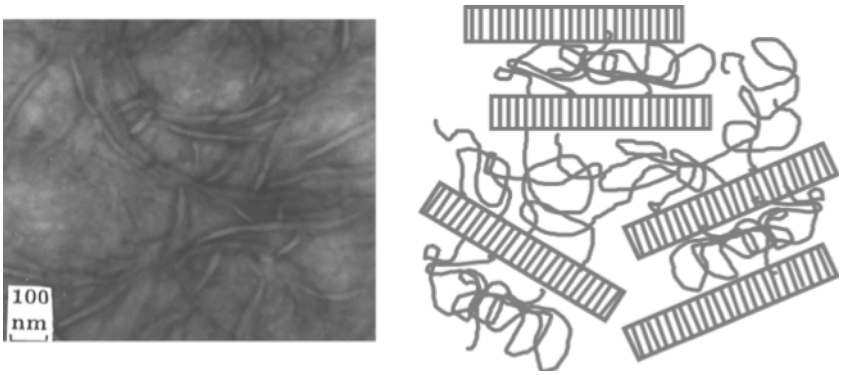


Figure 1: *UHMWPE showing the organized crystalline lamellae (regions with organized chain folds) amidst the disorganized amorphous regions (image courtesy of Orhun Muratoglu).*

The final step is sterilizing and packaging the material. Historically, gamma sterilized with 25-40 kGy and storage in air-permeable packages predominated[10,11]. However, this combination resulted in oxidation and reduced the mechanical properties of the material while it was on the shelf, which increased wear and reduced longevity *in vivo*[12-16]. Consequently, manufacturers have either focused on eliminating the exposure of gamma sterilized implants to oxygen, or used entirely different sterilization techniques, such as ethylene oxide gas sterilization, and gas plasma sterilization[11,17-21].

1.2 Osteolysis with ultra high molecular weight polyethylene

The exceedingly high wear rate of Teflon led to loosening of the implant and a catastrophic failure rate, ultimately due to osteolysis from wear particles. However, as Harris points out, particle induced osteolysis was not identified as the culprit of the negative Teflon experience, and in fact this osteolysis went on to be mistaken for sepsis in the early days of UHMWPE[22,23]. Many blamed cement particles for causing the loosening, and this led to a shift to cementless arthroplasty and the emergence of improved second generation cementing techniques[24,25]. However, the incidence of osteolysis remained[26,27]. It soon became clear that wear-induced osteolysis was a major threat to THA survival[28,29]. Osteolysis that compromises implant survival can appear as early as five years after surgery and as late as after the first decade[30,31].

It was discovered that wear rate can increase depending on activity level[24]. Wear particles are produced several ways, including reduced mechanical strength (from sterilization), increased shear stress, head sizes greater than 32mm, and third body particles such as metal, cement, and bone trapped between the articulation of the metal head and polyethylene liner[24,32-36]. The accumulation of polyethylene wear debris in the joint space induces a macrophage-charged response that phagocytize small particles (Figure 2).

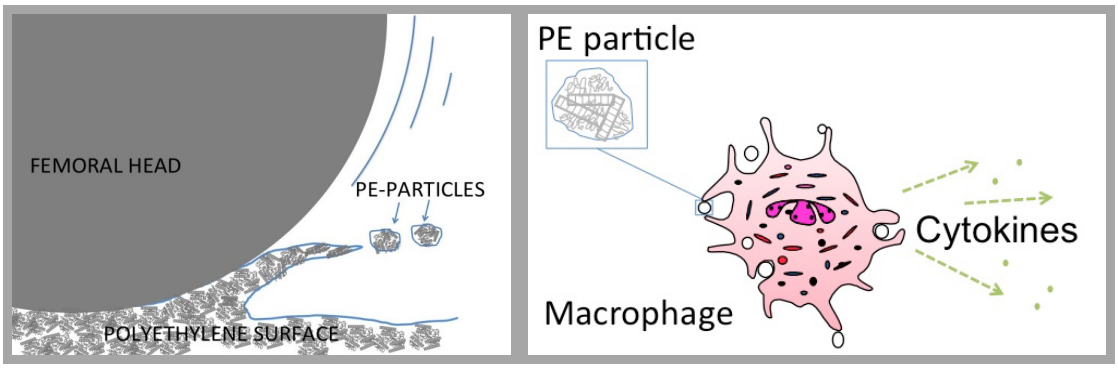


Figure 2: *Stress from the femoral head produces polyethylene wear particles which induce an inflammatory response (image courtesy of Orhun Muratoglu).*

Several reports have indicated that small particles, 0.3 to 10µm, induce the greatest inflammatory response, and that the shape and source of these particles also affects the response[37-39]. These particles move with the joint fluid throughout the joint space which allows them to have widespread affects on both the acetabular and femoral side[40]. Because of this flow of particle debris with fluid, particles pool in areas with greater space, such as screw holes[41]. The phagocytization of wear particles by macrophages induces the macrophages to release cytokines. These cytokines subsequently trigger osteoclasts to break down bone tissue[39,42,43] (Figure 3). Ultimately, this inflammatory mechanism leads to loosening of the component.

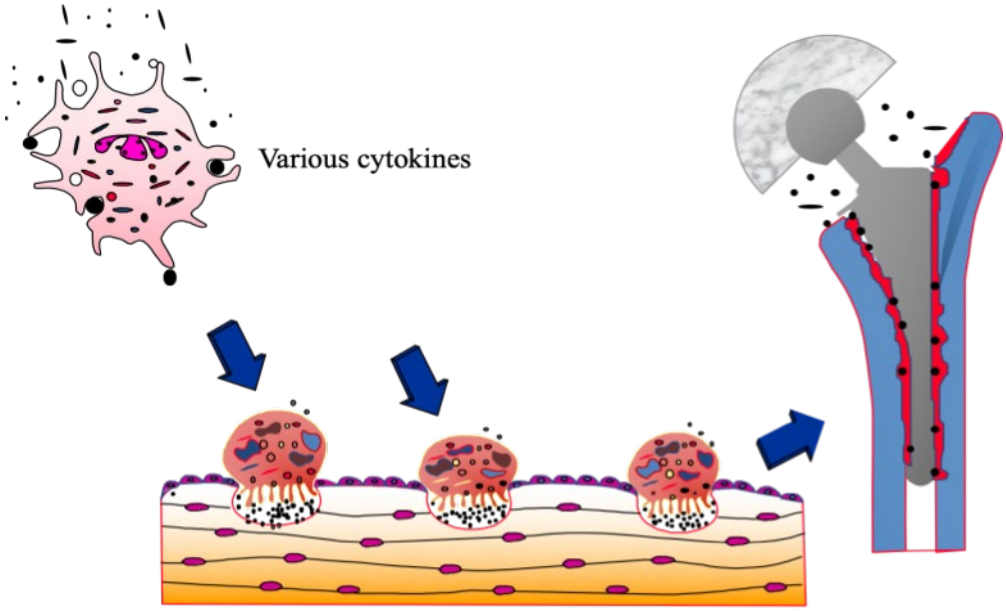


Figure 3: *The accumulation of wear particles activates an inflammatory cascade that results in accelerated bone resorption contiguous to the prosthesis, eventually leading to loosening (image courtesy of Orhun Muratoglu).*

The most obvious presentation of osteolysis on plain radiographs is a large amorphous region of reduced bone density contiguous to the femoral or acetabular component. However, progressive

radiolucent lines can also be indicative of a future loosening problem[44]. The literature is replete with reports of osteolysis resulting from polyethylene wear, with some reaching an incidence as high as 60%[30,45,46]. Dumbleton et al. reported a 90% survival of UHMWPE THA 25 years after surgery if the wear rate was less than 0.1mm/ year[47]. This group also reported that the presence of osteolysis significantly increased and the survival dropped considerably, to just 30%, if the wear rate was greater than 0.2mm/year[47]. Revision arthroplasty associated with osteolysis often has a worse outcome than the primary THA, further compounding the serious consequences of bone loss from wear[42,48]. Since the wear induced osteolysis phenomenon was identified as the sole cause of high THA failure rates, the quest continued for a bearing surface with significantly reduced wear characteristics.

1.3 Highly cross-linked ultra high molecular weight polyethylene

The mechanism of UHMWPE wear and consequential generation of polyethylene particles, is thought to be from the break-up of surface fibrils when the articulating surface crosses them[49]. Researchers soon discovered that cross-linking the material reduced the polyethylene deformation that led to the increased incidence of wear[8,50-54]. This highly cross-linked polyethylene (HXLPE) was introduced in 1998 to decrease osteolysis secondary to the accumulation of wear debris and increase the long-term survivorship of THA through dramatically reduced wear rates[55-58]. When either a gamma or electron beam, irradiates UHMWPE bonds within the hydrocarbon break, producing highly reactive free radicals. These free radicals react with each other and form cross-links in the amorphous regions of the polyethylene[59,60] (Figure 4).

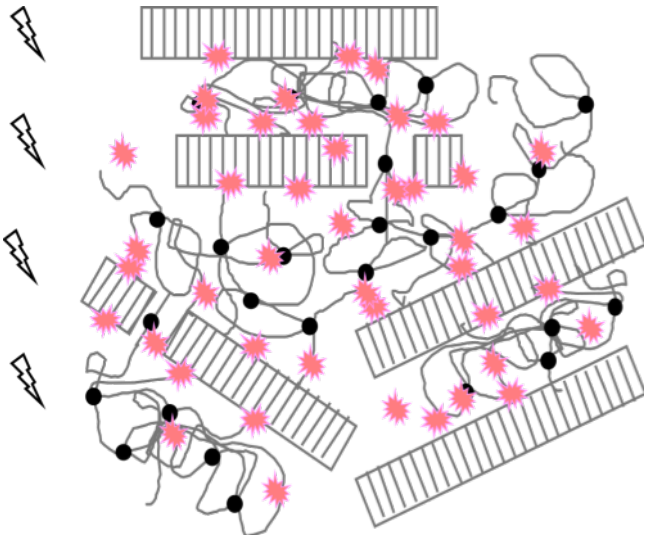


Figure 4: *The irradiation of UHMWPE produces free radicals (stars), some of which react with one another to form cross-links (circles) (image courtesy of Orhun Muratoglu).*

As the irradiation dose increases (dose ranges from 50 kGy to 100 kGy), a greater density of cross-links is generated, which increases the wear resistance of the material[50,61]. After the irradiation process, some free-radicals that did not react remain trapped within the crystalline lamellae, which can negatively react with oxygen[62]. An increased irradiation dose increases the number of residual free radicals. When oxygen reaches these residual free radicals, hydroperoxides form, which degrade and damage the polyethylene[63] (Figure 5).

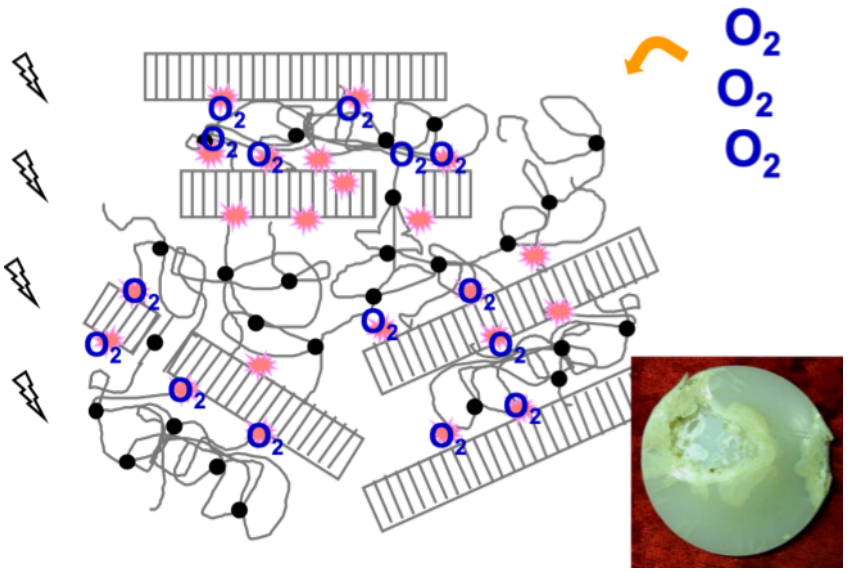


Figure 5: *Oxygen reacts with residual free radicals which causes oxidation and subsequent damage of the polyethylene liner, shown on the right (image courtesy of Orhun Muratoglu).*

Since the presence of residual free radicals could lead to oxidation that is detrimental to long-term survival, the material must either be melted or annealed, which allows the free radicals to combine and form additional cross-links[58,64]. Heating the polymer above its melting temperature allows for maximal recombination and thus elimination of free radicals (Figure 6).

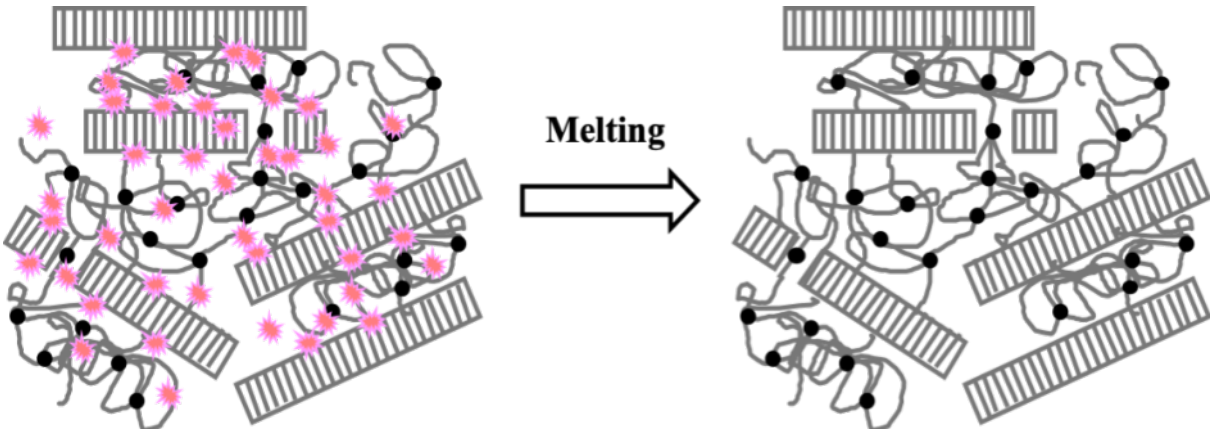


Figure 6: *Irradiated and melted UHMWPE showing elimination of free radicals after melting (image courtesy of Orhun Muratoglu).*

However, heating at this temperature reduces the crystalline lamellae, compromising the fatigue strength of material, and potentially increasing the risk for fracture in the future[62,65,66]. Decreased fatigue strength caused by melting is compounded by the preceding irradiation step, which also reduces strength in a manner that is directly proportional to irradiation dose[66,67]. There have been a few reports of rim fractures of HXLPE, particularly in large head articulations with malpositioned cups, providing evidence for the reduced fatigue strength of some formulations of HXLPE[68,69]. Alternatively, if the polymer is annealed, or heated to a temperature just below its melting point, fatigue strength is not as compromised as much as it is after melting, but free radicals remain, which may be prone to oxidation [65,70-74] (Figure 7).

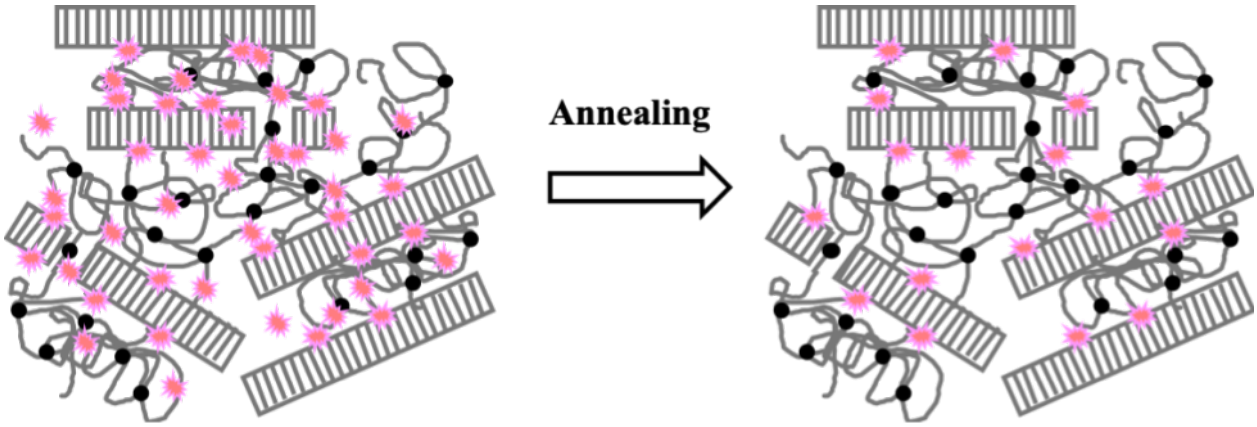


Figure 7: *Irradiated and annealed UHMWPE showing some residual free radicals after annealing (image courtesy of Orhun Muratoglu).*

Because irradiated and melted, and irradiated and annealed polyethylene formulations both have intrinsic limitations, medium cross-linked polyethylene, which is irradiated to only 50 kGy was developed to help circumnavigate these issues. With this lower irradiation dose, cross-links still form, albeit at a reduced density, but the number of residual free radicals that form is less than highly cross-linked formulations (usually irradiated with approximately 100 kGy). The material can then be annealed to eliminate remaining free radicals, since fewer existed initially, and therefore the fatigue strength is maintained.

1.4 Highly cross-linked polyethylene ultra high molecular weight polyethylene with larger head sizes

Another challenge to the survival of THA is recurrent dislocation, often ameliorated through the use of larger femoral head sizes. Greater stability in larger heads arises from an increase in the head to neck ratio and a larger jump distance, which therefore offers a broader angle of motion prior to

impingement with the acetabular cup[75-77]. In the 1950's, Charnley pioneered the use of larger diameter femoral heads but soon promoted significantly smaller head sizes after discovering that large heads induce an unfavorable amount of torque on the articulating surface, leading to loosening[4,78,79]. As bearing surfaces improved, the use of larger head sizes became prevalent again[80,81]. But, larger head sizes caused greater wear of UHMWPE compared to the wear of their smaller diameter counterparts[34,82]. The preponderance of larger head sizes seen in the most recent years results from *in vitro* studies using hip simulators and clinical studies that have indicated that HXLPE has the ability to maintain its dramatically reduced wear rates compared to conventional UHMWPE, irrespective of head size[83-86].

While the reduced wear of HXLPE compared to conventional UHMWPE, coupled with its ability to withstand larger femoral head sizes, was certainly encouraging, both of the post irradiation heating treatments (melting and annealing) possess intrinsic limitations. Therefore, the search continued for a material that was concurrently resistant to wear and oxidation without compromising fatigue strength.

1.4 Vitamin E diffused highly cross-linked ultra high molecular weight polyethylene

Vitamin E (α-tocopherol) stabilized HXLPE was introduced for clinical application in 2007 to address some of the shortcomings of HXLPE; namely to eliminate oxidation prone free radicals without compromising the mechanical strength by melting the material, while maintaining the low wear properties of HXLPE[87-90]. The added vitamin E stabiles the residual free radicals by hindering the oxidative chain reactions of primary and secondary free radicals, thereby eliminating the need for melting, which subsequently preserves the material's strength[65,91] (Figure 8).

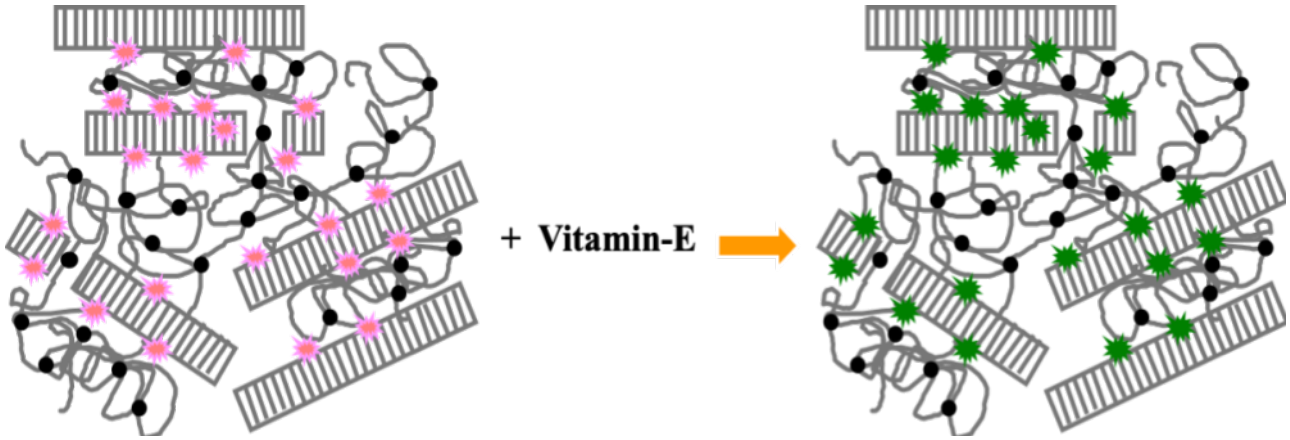


Figure 8: *The added vitamin E quenches and stabilizes the residual free radicals of HXLPE without a post irradiation heating step (image courtesy of Orhun Muratoglu).*

The vitamin E can either be blended into the UHMWPE powder before the consolidation and irradiation steps, or it can be diffused into the material post-irradiation. It has been shown that blending the vitamin E hinders the cross-linking when the material is subjected to irradiation, which reduces the overall cross-link density[92-94]. If the vitamin is diffused, cross-linking is not affected since the introduction of the vitamin occurs after irradiation[8,87,90].

Retrieval and accelerated aging studies on HXLPE showed that oxidation does occur, particularly in formulations that were annealed after irradiation, the long-term outcome of HXLPE is uncertain[71,72]. *In vitro* evaluations of vitamin E diffused HXLPE have shown that the anti-oxidative properties of vitamin E eliminate free radicals while maintaining strength, even when tested under adverse loading conditions such as a steep cup inclination angle with large head articulations[65]. Similarly, it has been shown that the oxidative stability of vitamin E diffused HXLPE was not influenced by the accelerated aging process, which further substantiates the promise of vitamin E diffused HXLPE as an improvement over HXLPE[65]. *In vivo* studies have reported very low wear of vitamin E diffused HXLPE compared to non-antioxidant stabilized HXLPE[95-97].

2 Measuring polyethylene wear

2.1 Plain radiographic assessment of wear

Since Charnley's first low friction arthroplasty design, loosening secondary to wear induced osteolysis is the most common reason for THA failure. Therefore, detection of such wear is crucial to assess whether a patient may be at risk for failure[98-100]. Before the advent of HXLPE, wear of conventional UHMWPE could be measured manually on plain radiographs, as yearly wear rates were significantly greater than what is now observed with current generations of UHMWPE[61,101,102]. Charnley first measured wear on plain radiographs by inserting a metal wire into one of the grooves on the backside of the polyethylene, and subsequently measured the smallest distance between the femoral head and this implanted wire[102,103]. The mean wear observed in Charnley's series was 1.18mm[102].

Charnley's technique of performing wear measurements was met with mixed criticism, as some concluded that the method was too inaccurate[104]. In 1990, Livermore et al. introduced a new method utilizing plain radiographs to manually assess wear without relying on a metal wire, but rather the bone-cement interface, to compare to the femoral head[34]. Finally, in 1997, Martell and Berdia developed a computer-assisted wear measurement technique that demonstrated greater accuracy and reproducibility than the Livermore method[105]. Martell's method uses automated edge detection of the backshell and femoral head to determine femoral head penetration over time. The only information the reader must input is femoral head size, and manual selection of the femoral head, backshell, and ellipse opening, thus making this method easy, inexpensive, and widely applicable to any patient who has had standard radiographs of the hip taken.

2.2 The use of radiostereometric analysis in THA

In 1972, Göran Selvik invented the method of RSA in Lund, Sweden, for measuring the relative motion of prostheses with respect to fixed bone[40,106,107]. Implant loosening, predominantly due to polyethylene wear, remains the most common reason for failure of THA and therefore detection of early migration of these implants is of paramount importance[107]. As materials and methodologies of arthroplasty improve through *in vitro* research, there is a continued demand for prospective *in vivo* investigation with sensitive measures that will avoid an unnecessary burden on patients by identifying inferior outcomes earlier and with greater accuracy[107,108]. The use of RSA to monitor

new technologies puts the fewest patients at risk and allows for safe examination of migration without sacrificing statistical power[108]. As a result, it is not necessary to wait for late-term failures to identify problems with new technologies should they arise.

New technology, such as the metal-on-metal bearing, often promises to improve long-term outcomes and infiltrates the market without sufficient preclinical testing, leaving clinicians and patients with the devastating result of a very high failure rate[109-112]. This is a contemporary demonstration of the need for thorough preclinical testing, followed by clinical testing with very sensitive and accurate measures so that the least number of patients are exposed to the new technology; Malchau's method of a stepwise introduction of technology must be utilized to avoid situations such as the metal-on-metal disaster[113]. *In vivo* and *in vitro* RSA is a uniquely qualified technique for vetting implant technology to assess long-term outcomes, while not posing a risk to a large number of patients[114]. RSA is also exceedingly important in monitoring known technologies with small migration patterns, such as HXLPE, since previous generations of this material have caused catastrophic failure of THA. Given the amount of insight gained, in addition to the low radiation exposure compared to plain radiographs, RSA is both an effective and safe tool for closely monitoring wear[108,115,116].

RSA is widely accepted as the most accurate and precise method for the early assessment and measurement of femoral head penetration (wear) and acetabular shell and femoral stem stability[54,107,117-122]. Due to RSA's sensitivity in measuring progressive micromotion (up to 10 microns), indications of implant failure, and wear that could lead to failure, are detectable much sooner than otherwise would be possible on plain radiographs, making RSA a valuable instrument for predicting long-term patient outcomes[108,117,122-126]. Malchau et al. determined that the detection limit of stem migration on plain radiographs is approximately 4mm[127]. However, the risk threshold for failure is far below what can be detected on plain radiographs[124]. Therefore, if plain radiographs are the only method of assessment, patients with an increased risk for revision or failure may go entirely undetected. RSA also captures migration in all 3 orthogonal planes, providing more information than what one could gather on a plain two-dimensional radiograph[106,108].

2.3 Modalities of radiostereometric analysis

2.3.1 Marker-based radiostereometric analysis

The traditional method of RSA employs several tantalum beads (usually 0.8mm or 1mm in diameter) that are implanted into the bone surrounding the implant, as well as implantation into the implant

itself, to define anatomical and prosthetic segments[107]. RSA studies have been conducted in Europe for several decades and no bead related adverse events have been reported[117]. During surgery, the surgeon inserts patient bone beads using a specialized gun inserter. Due to the malleability of the polyethylene liner, tantalum beads can also be press-fitted into the liner during surgery by an assistant in the operating room. A minimum of three beads within a particular anatomical or implant segment must be visible to produce a kinematic analysis. A maximum of nine points can be used to define any one segment. Therefore, the surgeon typically implants greater than nine beads in a region of bone in order to account for the fact that some beads will be obstructed by the implant, or poor resolution of a particular bead. To achieve maximal definition of the segment in question, beads should be implanted in a dispersed fashion around the implant, to utilize as much radiographic information as possible (Figure 9).

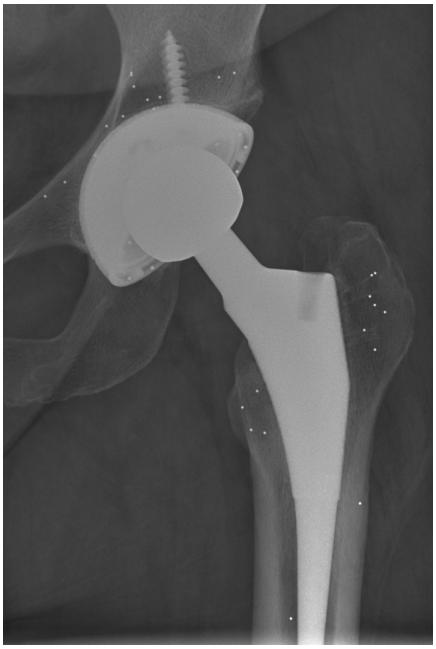


Figure 9: *Plain radiograph of a hip showing tantalum makers implanted into the acetabulum, femoral bone, and polyethylene liner in a dispersed manner. All beads were implanted during surgery.*

While RSA has remained the most accurate method to assess migrations between skeletal and implant segments (or implant point), there are some inherent characteristics of the method that limit its generalizability[107,121]. First, beads must be attached to the implant in order to obtain the most precise kinematic analyses by increasing the number of points defining the implant segment[128]. While polyethylene beads can be inserted during surgery, beads on the stem (to measure stem stability) and acetabular cup (to measure cup stability) must be attached at the time of manufacturing. This is often costly, time-consuming, and logistically difficult as government regulations

surrounding the alternation of components constrains manufacturers[107,129,130]. The marker-based system also adds time to the surgical procedure and requires extra operating room personnel (unless polyethylene beads are inserted at time of manufacturing). During the analyses of marker-based patient films, beads can either be obscured from view due to the implant or another nearby bead, or visible, but not adequately defined for use in the analysis due to obstruction from a nearby component. This can reduce the number of beads taken into consideration in the analysis, which may affect the precision.

2.3.2 Model-based radiostereometric analysis

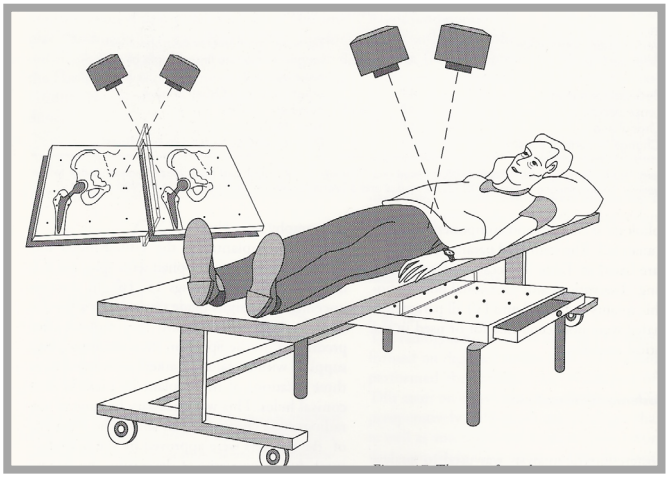
In 2001, a group from Leiden, The Netherlands, developed a model-based RSA system to side-step many of the intrinsic difficulties associated with traditional marker-based RSA[130-132]. This technique utilizes the concept of attempting to match the two-dimensional projection of the implant and maps this projection onto a computer aided design (CAD) model image. Thus, by matching the actual image with a model image, the software is able to estimate the position of the implant[132]. *In vitro* and *in vivo* studies have shown similar accuracy and precision with model and marker-based RSA[133-135]. This system has also been validated for use in total knee arthroplasty[136]. Using the marker-based system in the knee is difficult due to large amounts of bead obstruction from the metal of the knee components. For this reason, the marker-based system has predominantly been applied to the hip, making an additional opportunity for the markerless system in knee settings. Despite these positive aspects of the model-based system, several users of the marker-based system argue that a model cannot exactly match all degrees of freedom seen *in vivo.* Furthermore, there are some concerns that this technique is not yet applicable to all implant systems[134]. Several modifications continue to improve the system leading to a growing popularity.

3 Outcome assessment

3.1 Radiostereometric analysis

Prior to 2006, RSA films in this body of work were taken in the standing position using one portable and one fixed x-ray source, which required the operator to time the capture of the radiographs simultaneous. In this orientation, the uniplanar calibration cage (cage 43, RSA Biomedical, Umeå, Sweden), with two digital cassettes, was placed behind the standing patient and two bi-planar radiographs were taken simultaneously. The calibration cage served as a reference for all measurements. By moving the patient to a supine position, two fixed x-ray sources could be used thus allowing for automated capture of both films. It has been shown that there is no difference between standing and supine RSA films[137]. For study I, RSA films for the postoperative through five year follow-up were taken in the standing position. All other RSA films for the other studies were taken with the patient in the supine position.

All RSA radiographs obtained after 2006 were taken with the patient in the supine position with the calibration cage placed beneath the patient's operative hip. Each patient was oriented with their hip and implant centered within the calibration cage in both foci, such that the long axis of the femur was parallel to the y-axis. Bi-planar digital radiographs of the patient's operated hip were captured simultaneously using two ceiling-mounted x-ray sources positioned at 40° with respect to each other, and 60 inches above the calibration cage (before the tubes are angled toward one another). With this positioning, the two x-ray beams intersect at the exact location of the femoral head, which is 12



inches above the control points, and equally centers the implant within both foci (Figure 10).

Figure 10: *The calibration cage placed beneath the operative hip. Both fiducial (shown on the flat portion of the cage) and control markers (shown on the raised center piece of the cage) served as the reference for all subsequent image comparisons (image courtesy of Henrik Malchau).*

The control points are defined by the points in the cage on the arm perpendicular to the ground and the x-ray beam, which calibrates the angle of the foci with respect to each other[138]. In addition, the fiducial points within the calibration cage are defined by the fixed points on the plane of the cage parallel to the ground, which create reference points for the two-dimensional projection of the hip onto each of the foci[138]. The coordinate system defined by the fiducial and control points embedded in the calibration cage enable the creation of a three-dimensional reconstruction of the various segments within each anatomical area of the patient[117].

All analyses utilized the UmRSA 6.0 software (RSA Biomedical, Umeå, Sweden). This system relies on tantalum beads (0.8mm or 1mm in diameter) implanted in a dispersed fashion into the bone surrounding the prosthesis and the prosthesis itself, such as the polyethylene liner (Figure 11).

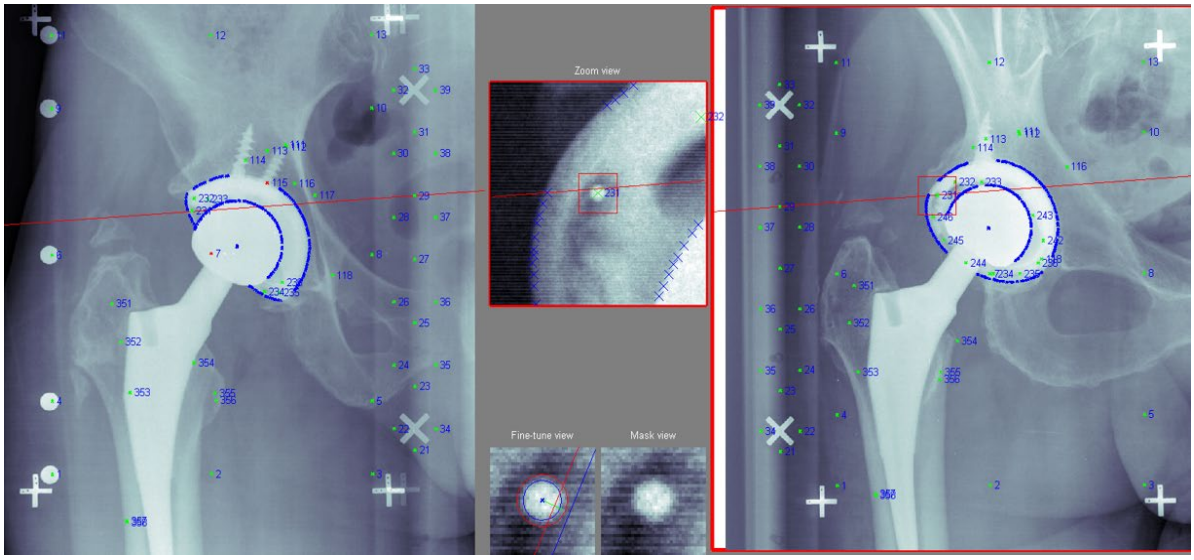


Figure 11: *A film pair displayed in the UmRSA software depicting the fiducial and control markers of the cage, tantalum markers implanted in the acetabulum, the polyethylene liner, and the femoral bone, and the automated points of the backshell, cup opening, and femoral head.*

Occasionally beads are inserted onto the acetabular cup and femoral stem at the time of manufacturing, however regulations surrounding the alteration of implants makes this difficult to achieve, and thus was not done in the studies in this thesis. These beads define certain anatomical and implant segments such that the relative positions of their contrived three-dimensional reconstructions can be compared over time to determine polyethylene wear and implant migration. The user manually selects the position of each patient and implant bead. Each bead is assigned a

unique number relative to its segment. All bead numbers are 3 digits; the first two define the segment, and the last number defines the bead within that segment. The user must select the beads so that the numbering is maintained for each patient throughout the study. The software then applies an algorithm based on pixels surrounding the selected bead in order to accurately determine its center. The software atomically assigns the fiducial and control markers imbedded within the cage. After manual selection of five points on the periphery of the femoral head by the user, the software automatically assigns points to the edge of the head to determine its center. A similar process is used to assign points to the acetabular backshell to define the cup segment. The user deletes automated points from visible breaks in the edge of backshell, due to screw holes or a flattened top, as such breaks reduce the reliability of the edge detection algorithm[128].

A maximum of nine and a minimum of three points, visible in both foci must be selected and validated (adequate definition of their centers) to define one segment. The position of a fixed reference segment and a mobile segment (or a single point, such as the femoral head) from one film pair is compared to the relative position of these same two segments (or segment and point) from another film pair to produce a kinematic analysis. These kinematics show migration that has taken place between the two segments within the time frame of the two film pairs. When two segments are compared one another, the software calculates translations and rotations in the three orthogonal planes (medial/ lateral, proximal/ distal, and anterior/ posterior) of the position of the mobile segment compared to the fixed segment between two films pairs. When comparing one mobile point, such as the center of the femoral head, to a fixed reference segment, the software calculates migration in the three orthogonal planes, but not rotation. Both types of analyses produce a three-dimensional migration and maximum total point motion, respectively, which describes the total migration of the segment or point across all planes. Furthermore, both analyses produce a condition number, which describes the quality of the dispersion of beads within a segment, and a mean error, which represents the stability of the beads (rigid body fitting) from one time point to the next using an algorithm that determines the difference in respective distances of the beads over time. Low numbers are desirable for both parameters, and thus a cut off of 110 for condition number and 0.25mm for mean error is recommended to preserve the integrity and reliability of RSA analyses[129]. Two sets of RSA images (double examinations) are performed at least once per patient at the same visit to establish the precision.

3.1.1 Measuring femoral head penetration using markerless UmRSA

Femoral head penetration can be measured by utilizing point motion to compare the position of the center of the femoral head to the fixed cup segment, both of which are defined by points assigned by the software rather than implanted beads. Automated edge detection after manual selection of five points evenly spaced about its periphery, and one point at the center of the head, derives the center of the head. Points on the backshell and cup opening characterize the cup segment (Figure 12). Five points assigned by the software using edge detection defines the cup segment: one at the north pole, one at the south pole, one anterior point, one posterior point, and the center of the sphere. The software calculates such points based on edge detection after the user manually selects five points along the periphery of the backshell and one at the center of its ellipse, in addition to six points on the periphery of the cup opening (three on either side of the femoral neck)[128].

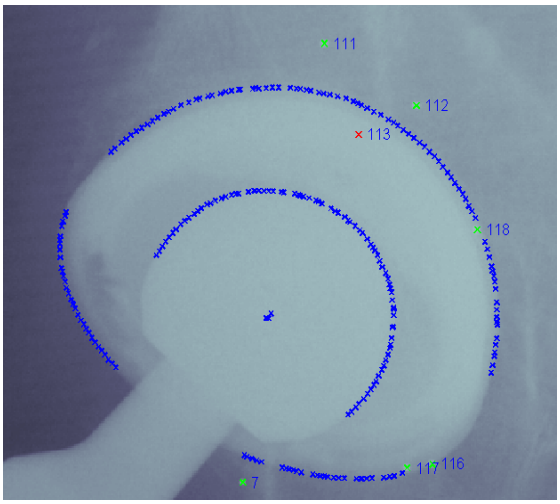


Figure 12: *Automated edge detection of the femoral head and acetabular cup, allowing for the utilization of markerless UmRSA. The software populates points on the edge of the head, backshell, and cup opening after manual selection on the radiograph.*

3.1.2 Measuring femoral head penetration using gold-standard UmRSA

If beads are implanted into the liner, these beads can be combined with the points automatically assigned to the backshell to provide a broader definition of the cup segment to compare to the mobile femoral head (Figure 13). Previous studies have indicated that a combined segment provides optimal precision[128]. Up to six beads labeled in the polyethylene and three points from the backshell (the anterior and posterior points are eliminated) can be used to define the shell + liner segment. During surgery, 12-14 beads are implanted into the polyethylene using a specialized gun inserter. Obstruction from the femoral head and neck prohibits the visualization of all implanted beads on postoperative radiographs. Therefore, the user chooses the six points most consistently visible in both foci over time, and those with the most optimal definition, to define the polyethylene liner

segment. The user then relegates other visible polyethylene beads to a separate (unused) segment. Combining the polyethylene beads and backshell points permits the use of up to nine points to define the cup segment, rather than five utilized in the markerless method. These added points expand the dispersion of points defining the segment, thus more information from the radiograph contributes to the characterization of the cup segment, yielding a more reliable result[120,128,139].

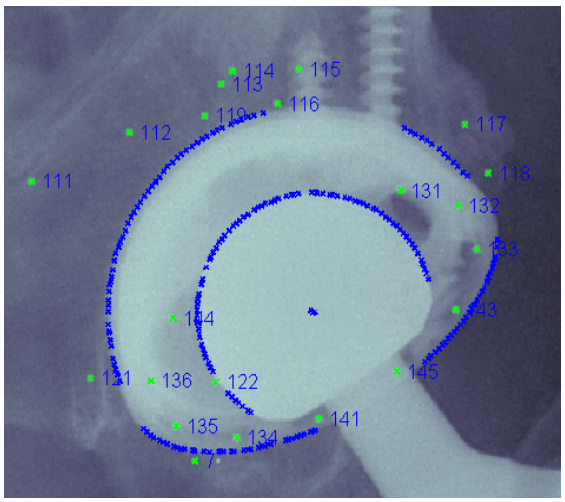


Figure 13: *The definition of the cup segment utilizing the backshell points from automated edge detection combined with the polyethylene beads.*

3.2 Plain radiographs

Plain radiographs are minimally invasive and widely applicable tools for monitoring implant performance over time. Radiolucent lines at the bone-implant interface may be indicative of loosening[140-142]. However, radiolucency width and length, as well as its progression over time, must be assessed to determine the pathology[143]. Osteolysis is identified by progressive bone destruction or amorphous regions of reduced bone density contiguous to the implant, which often leads to loosening[144]. DeLee and Charnley delineated three zones around the acetabular cup and Gruen et al. delineated seven zones around the stem to characterize the location and extent of radiolucencies and bone remodeling of the acetabular and femoral bones, respectively[145,146].

3.3 Computerized tomography

Wear induced periprosthetic osteolysis leads to devastating consequences for the survivorship of THA. Plain radiographs may fail to identify the extent of osteolysis present, due to pelvic positioning, patient characteristics such as body mass index, the radiographic view, and the area where the osteolysis is present[147,148]. The inability to accurately and precisely detect bone remodeling on plain radiographs may inadvertently attenuate the clinician's concern for loosening

and subsequent failure, when such outcomes could be imminent. CT scans allow for a thorough examination of the bone contiguous to the acetabular and femoral components to assess bone resorption that may not be evident on plain radiographs[149,150]. For the detection of osteolysis specifically, CT is more sensitive than plain radiographs in identifying the location and volumetric size of the lytic region, as well as specifying lytic regions that were entirely invisible on plain radiographs[147,151]. While CT scans provide detailed information on bone remodeling, the cost and radiation levels likely prohibit their widespread use.

3.4 Patient-reported outcome measures

Clinicians and researchers often measure the success or failure of THA objectively by monitoring migration, revisions, complications, and radiolucencies and more extensive bone remodeling such as osteolysis[152-154]. However, assessing the outcome in multiple dimensions, including the patient's perception of their intervention through the use of patient-reported outcome measures (PROMs), provides valuable information, which is unattainable through many of the aforementioned outcome metrics[154]. PROMs contribute critical information given that patients who are doing well by all traditional outcome metrics may continue to experience poor functional status, satisfaction, and general health-related quality of life. PROMs allow clinicians to quickly and easily compare several patient and disease specific dimensions from before surgery to those after surgery to make a determination on the overall effectiveness of the intervention. Due to the considerable increase in demand for total hip arthroplasty as a result of an aging population, evaluating the outcome of THA through reliable and cost-effective metrics such as PROMs, has gained substantial momentum in recent years[152,155].

3.4.1 Harris hip score

Dr. William H. Harris of the Massachusetts General Hospital (MGH), Boston, Massachusetts, created the Harris hip score in 1969 as a disease-specific survey (Appendix A). Two fundamental factors, pain and function, which provide crucial information for assessing indications for and outcomes after THA, carry the most points in the survey[156]. The scale contains four dimensions each with a varying number of questions and maximal point allotments, to yield a total maximum score of 100. The dimensions are pain (44 points), function (47 points), range of motion (5 points), and absence of deformity (4 points). Since its introduction, the Harris hip score remains one of the most universally adopted outcome measures for the assessment of THA both before and after surgery[157]. This score is self-reported by the patient[158].

3.4.2 Pain VAS

The pain visual analog scale (VAS) is a horizontal scale ranging from 0 to 10 where 0 corresponds to very little pain and 10 corresponds to the worst imaginable pain, with several intermediate anchors (Appendix A). The patient self-reports the average pain they have experienced in the last month, associated with their operative hip, on this scale.

3.4.3 Satisfaction VAS

The satisfaction VAS is another horizontal scale where the patient self-reports their recent satisfaction with the outcome from surgery. The scale ranges from 0 to 10 where 0 corresponds to very satisfied, and 10 corresponds to dissatisfied (Appendix A).

3.4.4 EQ-5D-3L

The EuroQol Group developed the EQ-5D-3L in 1987 as a tool to assess self-reported general health-related quality of life[159,160]. The EQ-5D-3L has two components, the first of which produces a weighted index score (range -0.109 to 1.000, where -0.109 coincides with a health-state worse than death, 0 is death, and 1 is a perfect health-state) based on questions pertaining to five dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression[159-161]. Each dimension has three levels of answer choices, leading to 243 possible health states that are translated into a weighted index (EQ-5D index)[161]. The second component is a VAS (EQ VAS), which allows the patient to self-report their health-related quality of life based on a visual scale that ranges from "worst imaginable health state" (0) to "best imaginable heath state" (100)[161].

3.4.5 UCLA activity scale

Physical activity level is an important outcome metric considering the implications associated with lack of activity on general health. The University of California, Los Angeles (UCLA) activity scale has good reliability and validity in assessing physical activity after THA, with minimal floor and ceiling effects[162]. The survey asks the patient to self-report one activity level that most closely correlates with their current physical abilities. There are 10 activity levels which range from 1 (wholly inactive; dependent on others; cannot leave residence) to 10 (regularly participate in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor, or backpacking)[163] (Appendix A).

3.4.6 SF-36

The Medical Outcome Study 36-item short-form survey is a general health survey consisting of eight dimensions: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions[164]. Each dimension contains a different number of questions with varying levels of responses pertaining to each question. The survey was designed to accommodate self-reporting, staff-administration over the telephone, or staff-administration in the clinic[164]. All patients included in the studies of this thesis self-reported this survey.

4 Aims

Osteolysis, a once prevailing bone disease secondary to the accumulation of wear debris in the joint space from conventional UHMWPE, was the leading cause of failure of THA. The advent of second generation UHMWPE, HXLPE, revolutionized THA by significantly decreasing wear and osteolysis, and therefore drastically improving the survival of THA. Vitamin E diffused HXLPE was introduced shortly thereafter, in 2007, to address the deficiencies of HXPLE. These second-generation polyethylene materials wear an amount imperceptible by most measurement techniques. Therefore, the objective of this thesis was to use the most sensitive wear measurement method of RSA to determine if current generations of polyethylene have low wear and thus no risk of osteolysis and subsequent failure at the mid- and long-term stages *in vivo.*

4.1 Aim of the thesis

The aim of the thesis was to use RSA to evaluate current generations of polyethylene to accurately and precisely determine their performance and safety at various stages *in vivo*. Since osteolysis is a direct result of wear particles, it is necessary to closely monitor wear, particularly in the mid-term and beginning stages of the long-term, to ensure that wear-related failure will not be a concern into the long-term.

4.2 Aim of the studies

4.2.1 Study I: Long-term evaluation of HXLPE using RSA and CT

The objective of this study was (1) to assess the long-term *in vivo* penetration of the femoral head into the HXLPE and the long-term true wear of the HXLPE articulating with either 28mm or 36mm femoral heads, using radiostereometric analysis (RSA), and (2) to assess plain radiographs and CT scans for the presence of any bone remodeling and/or osteolysis.

4.2.2 Study II: Mid-term evaluation of vitamin E diffused HXLPE using markerless RSA

The objective of this five year prospective, blinded, randomized controlled trial was to monitor and compare femoral head penetration into vitamin E diffused polyethylene acetabular liners with the penetration into medium cross-linked polyethylene control acetabular liners using markerless RSA. PROMs were used to assess the patients' perception of their clinical outcome from surgery.

4.2.3 Study III: Mid-term evaluation of vitamin E diffused HXLPE using gold-standard RSA

The purpose of this prospective clinical study was to evaluate femoral head penetration into the vitamin E diffused HXLPE liners up to five years postoperatively. Gold-standard RSA was used to accurately measure relative displacement of the center of the femoral head compared to the polyethylene liner over time. Patient-reported outcomes (PROs) were evaluated at each follow-up interval to determine the patient's perception of their outcome at five years.

4.2.4 Study IV: Precision of RSA of acetabular cup stability and polyethylene wear

The purpose of this study was determine if the *in vivo* precision of RSA measurements of acetabular cup stability and femoral head penetration into the polyethylene differed among three measurement methods: (1) combining the shell and liner as one segment; (2) using the shell segment alone; and (3) using the liner segment alone.

5 Subjects and methods

5.1 Study design, patients, material, and ethical considerations

5.1.1 Study I: Long-term evaluation of HXLPE using RSA and CT

5.1.1.1 Study design

This study was originally designed as a ten year single center, prospective, RSA, and plain radiograph study to determine the *in vivo* performance and safety of HXLPE with two femoral head sizes. However, all patients were asked to return for 13 year follow-up, which included a CT scan of the hip, in order to obtain longer-term penetration and steady state wear data and to understand if late-term osteolysis is a concern with this new material, as it was in the first generation UHMWPE.

5.1.1.2 Patients

Twenty-nine patients (18 males and 11 females) from the arthroplasty clinic at MGH consented to participate Inclusion criteria were patients with a diagnosis of osteoarthritis between 20-75 years of age, who required primary THA. Any patient that had difficulty comprehending the protocol, a limited lifespan, complex disease entities that would significantly increase the risk for complication during or after surgery, or patients who could not tolerate a 28mm or 36mm femoral head, were excluded. The average (range) age at the time of surgery was 53 years (37-71 years). Four arthroplasty surgeons from MGH performed all surgeries between November 2001 and December 2003.

Due to the addition of the CT scan at 13 years and thus the slight alteration of the study protocol from 10 to 13 years, all patients were asked for their consent to participate in the 13 year visit. Twenty-four, of the 29 originally enrolled, were eligible for participation at 13 years as two patients were deceased, one patient withdrew consent before ten years, and two patients were revised for recurrent posterior dislocation and a femoral fracture during the immediate postoperative period. Of the 24 eligible patients, 12 (eight males and four females; and six patients in each head size group) agreed to return for 13 year follow-up and only those 12 patients were included in the analysis. Eight patients were unwilling to return, however, it was confirmed during the phone interview that these patients' arthroplasty had not been revised. The remaining four patients could not be contacted as their phone numbers were no longer in service.

5.1.1.3 Material

Each patient received uncemented arthroplasty with an HXLPE liner (Longevity®, Zimmer Biomet Holdings, Inc, Warsaw, Indiana), a titanium acetabular shell (Triology®, Zimmer Biomet Holdings, Inc), a tapered femoral stem of the surgeon's choosing (either VerSys®, Zimmer Biomet Holdings, Inc or Natural Hip System, Sulzer Orthopaedics), and either a 28mm or 36mm cobalt-chromium femoral head. Sixteen patients received a 28mm head and 13 patients received a 36mm head. Stock UHMWPE rods were irradiated to 100kGy to allow for the formation of cross-links. The irradiated polymer was then subjected to a melting step (above the melt point of the polymer) in order to allow residual free radicals from the irradiation step to recombine and form additional cross-links. Finally, the liners were machined and sterilized using gas plasma. Either 12-14 (depending on the size of the acetabular shell) tantalum beads were inserted into the rim of the polyethylene intraoperatively to allow for measurement of femoral head penetration over time using RSA. Before one year, all femoral head penetration was considered bedding-in, due to settling. Thus, femoral head penetration was defined by comparing the baseline postoperative film to all subsequent follow-up images, and steady state wear (true wear, not including the one year bedding-in period) was defined by using the one year films as the baseline for all image comparisons.

Standard plain radiographs were obtained at each follow-up interval: an anterior/ posterior (A/P) pelvis, and A/P hip, a shoot-through lateral hip, and a frog lateral hip. Acetabular and femoral radiolucencies were assessed on the 1 and 13 year films according to Charnely and DeLee, and Gruen, respectively[145,146]. RSA and plain radiographs were obtained immediate postoperatively, at 6 months, 1-5, 10, and 13 years after surgery.

The 13 year metal artifact CT scans without contrast were used to determine if osteolysis was present. If areas of bone with lesser density were observed, the volume was measured, and the preoperative as well as all available postoperative plain radiographs (and other CT scans, if available) were assessed to determine if the reduced density was new or if it had changed over time.

5.1.1.4 Ethical considerations

All patients gave informed consent to participate and were educated about the new formulation of polyethylene for use as an articulating surface in THA. A control polyethylene group was not enrolled in this study as all surgeons agreed that the risks associated with first generation UHMWPE were beyond minimal.

5.1.2 Study II: Mid-term evaluation of vitamin E diffused HXLPE using markerless RSA

5.1.2.1 Study design

This was a blinded, randomized controlled trial with patients randomized to receive either a vitamin E diffused HXLPE liner polyethylene liner or a medium cross-linked polyethylene liner.

5.1.2.2 Patients

Eighty-two patients from the arthroplasty clinic at Aalborg University Hospital, Aalborg, Denmark, all with a diagnosis of primary osteoarthritis, agreed to participate in this five year study. Patients with the proper diagnosis of primary osteoarthritis, requiring an uncemented primary THA, an age within 20-75 years, ability to withstand a 32mm diameter femoral head, and ability to return for follow-up were asked to participate. Patients with a limited lifespan, complex disease entities that would greatly increase their risk of complication during surgery, or those who required special surgical techniques that deviated from the norm were not included. The median (range) age of the E1 cohort was 67 years (43-76 years) and 65 years (40-73 years) for the ArComXL cohort. All surgeries were performed by six surgeons at Aalborg University Hospital, Aalborg, Denmark, between January of 2009 and March of 2011.

5.1.2.3 Material

All patients received an uncemented THA with a highly porous titanium acetabular cup (Regenerex®), a modular titanium alloy femoral stem (Bi-Metric®), a 32mm ceramic femoral head, and were randomized with pre-assigned sealed envelopes to either receive a Vitamin E diffused HXLPE liner (E1®) or a medium cross-linked liner (ArComXL®). Both the E1 and ArComXL liners were constructed from stock compression molded GUR 1050 UHMWPE rods. For the production of the E1 material, the rods were first gamma irradiated to a 100 kGy dose to produce cross-links. The rods were then machined and diffused with vitamin E to stabilize residual free radicals. The liners were then heated to 130°C to allow the vitamin E to completely diffuse into the polymer and finally gamma sterilized with 30 kGy for a total irradiated dose of 130 kGy. The ArComXL liner production first involved gamma irradiating stock compression molded GUR1050 UHMWPE rods with a 50 kGy dose and subsequently heating the rods to 130°C, which is below the melting point for the polymer in order to preserve the mechanical properties. The polymer was then put through solid-state deformation to quench the residual free radicals and annealed at 130°C to recover the original

dimensions and reduce thermal stress. Finally, the polymer was machined into implant shape, packaged, and was sterilized using gas plasma[165]. Because the irradiation dose of the ArComXL was 50 kGy, which is half the dose of several other formulations of HXLPE (approximate dose of 100kGy), this material is henceforth termed medium cross-linked polyethylene. All components were from Zimmer Biomet Holdings, Inc, Warsaw, Indiana. RSA films and PROMs (Harris hip score, EQ-5D-3L, UCLA activity scale, SF-36, and pain and satisfaction VAS) were collected preoperatively (PROMs only), immediately postoperatively (RSA only), 6 weeks, 1, 3, and 5 years following surgery.

Markerless UmRSA was used for all analyses. The position of the center of the femoral head relative to that of the shell was compared back to the postoperative film, which defined femoral head penetration. Steady state wear was defined by comparing the three and five year films to the one year film, which served as the post bedding-in baseline.

5.1.2.4 Ethical considerations

The institutional review board approved this study and all patients gave informed consent to participate. Patients were informed that the control ArComXL has performed safely in patients for over ten years, and that the E1 showed increased fatigue strength and comparable low wear to HXLPE during *in vitro* and early clinical outcome studies.

5.1.3 Study III: Mid-term evaluation of vitamin E diffused HXLPE using gold-standard RSA

5.1.3.1 Study design

This was a single center, prospective, RSA, and clinical outcome efficacy study monitoring the *in vivo* performance and safety of vitamin E diffused HXLPE.

5.1.3.2 Patients

Forty-seven patients (32 males and 15 females) from the arthroplasty clinic at MGH, with osteoarthritis, consented to participate. Four patients had both hips enrolled in the study for a total of 51 hips. Inclusion criteria and exclusion criteria were the same as study I, except patients had to tolerate a 32mm femoral head. The mean (range) age at time of surgery was 59 years (26-75 years). Four arthroplasty surgeons from MGH performed all surgeries between November 2007 and February 2011.

5.1.3.3 Material

All patients underwent an uncemented THA and received the same polyethylene liner (E1®) and acetabular shell (Regenerex®) that was used in study II. Additionally, patients received a lateralized, proximally porous coated femoral stem (Taperloc®) and a 32mm cobalt-chromium femoral head. All components were from Zimmer Biomet Holdings, Inc, Warsaw, Indiana. Screws were inserted according to surgeon preference and either the posterior or anterior approach, with the patient in the lateral position, was used for all cases. Tantalum beads (1.0mm) were inserted into the rim of the polyethylene liner (12-14 depending on cup size) during surgery to measure femoral head penetration into the polyethylene using the gold-standard method of UmRSA.

Femoral head penetration and steady state wear in this study were defined the same way as in study I. RSA and PROMs (same PROMs as Study II) were obtained preoperatively (PROMs only), immediately postoperatively (RSA only), and at 6 months, 1, 2, 3, and 5 years after surgery.

5.1.3.4 Ethical considerations

The ethical considerations for this study were the same as study I and study II (except no control group was enrolled.

5.1.4 Study IV: Precision of RSA of acetabular cup stability and polyethylene wear

5.1.4.1 Study design

Because beads were implanted into all polyethylene liners, the cohort enrolled into study III were utilized to conduct a comprehensive analysis of the various measurement techniques available in UmRSA and compare the difference in precision among these techniques.

5.1.4.2 Patients

This was a methodological analysis of RSA measurement techniques using the same patients who were enrolled in study III.

5.1.4.3 Material

As this study used the same cohort from study III, all surgical and component information is the same as study III. Depending on bead implantation, RSA films can often be measured multiple ways. This study thoroughly investigated each measurement method.

UmRSA allows up to nine beads to define any one segment. Five component and anatomic segments were defined: (1) the center of the femoral head was defined by assigning a sphere to its periphery using automated edge detection. (2) Up to nine beads were labeled in the polyethylene to define the liner segment. Five points were assigned to the backshell using automated edge detection to define the shell only segment. (4) Up to six beads labeled in the polyethylene and three points from the backshell defined the shell + liner segment. (5) The pelvis segment was defined by up to nine beads labeled in the pelvic bone (Figure 14).

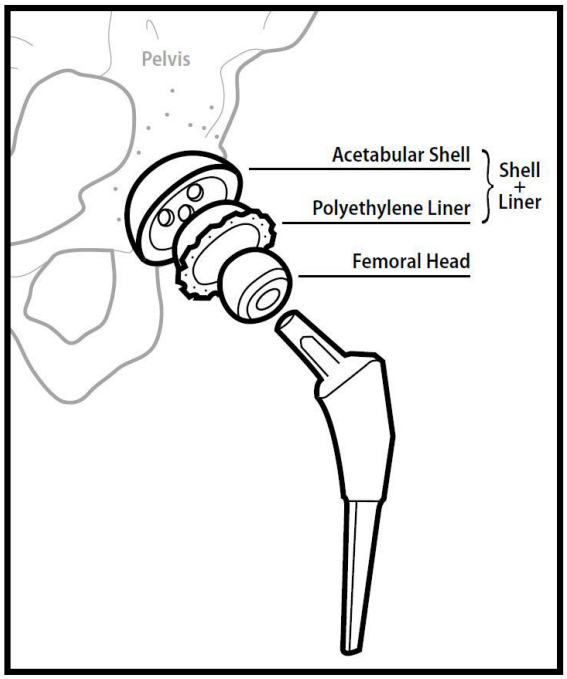


Figure 14: *Schematic of a total hip arthroplasty indicating the different segments defined by RSA*

Point motion of the center of the femoral head was used for measuring head penetration into the polyethylene (wear) with respect to three segments: (1) the liner-only segment, (2) the shell-only segment, (3) the shell + liner segment. Cup stability was measured by segment motion comparing the pelvis segment to (1) the liner segment, (2) the shell-only segment, (3) the shell + liner segment. Rotation of the acetabular cup was not reported for the shell-only method as we have historically experienced unacceptable precision when attempting to make these measurements using only the small number of points assigned to the backshell to define the cup. Liner stability within the shell was reported in two ways: (1) the liner-only segment compared to the shell-only segment, and (2) the liner-only segment compared to the pelvis segment.

Double examinations (taken at least once for each patient) were used to determine the precision of the various measurement methods. The precision was defined by multiplying the standard deviation

of the difference between the double exams by the appropriate critical value (t), from a standard t distribution table with the degrees of freedom equal to the number of observations (n) minus one. The best set of double exams, determined by the most optimal position of the acetabular shell and pelvic beads within the calibration cage, was used for each patient. If one set was not obviously superior to other, the highest point count was considered next, and finally the lowest condition number and mean error.

5.1.4.4 Ethical considerations

The ethical considerations for the enrollment of patients were the same as study III. Since this was solely a methodological analysis, no ethical considerations pertain specifically to this study.

5.2 Statistics

Table 1 presents a summary of all statistics performed in all studies. The Shapiro-Wilk test was used in all studies to determine normality of all data. Significance was set at $p \leq 0.05$ for all comparisons. The IBM SPSS Statistics Version 20.0 (studies I-III) and Version 17.0 (study IV) (IBM, Armonk, New York) software was used for all statistical analyses.

5.2.1 Study I: Long-term evaluation of HXLPE using RSA and CT

Ten patients were needed to detect a 50% difference in wear between conventional UHMWPE and HXLPE with 85% power. Paired t-tests determined differences in penetration, steady state wear, and steady state wear rate over time within the 28mm and 36mm groups and within the overall cohort combined. Independent sample t-test determined differences in the aforementioned variables between each head size group at all intervals.

5.2.2 Study II: Mid-term evaluation of vitamin E diffused HXLPE using markerless RSA

Twenty hips in each of the polyethylene groups were needed to detect a difference in femoral head penetration of 0.07mm, assuming a standard deviation of 0.15mm, with 80% power. The Wilcoxon signed rank test determined differences in penetration, steady state wear, and PROs over time within each polyethylene group. More patients than what was necessary were enrolled in each group in order to have a sufficient number of patients, after loss to follow-up, by the ten year interval. A one-sample Wilcoxon signed rank test was used to determine if penetration of both groups differed significantly from zero. Differences in the aforementioned variables between the two polyethylene groups at each interval were calculated using the Mann-Whitney test.

5.2.3 Study III: Mid-term evaluation of vitamin E diffused HXLPE using gold-standard RSA

Thirty-two hips were needed to detect a difference of 0.05mm in penetration from six months to five years, with 80% power, assuming a 0.10mm standard deviation. Several more patients than what was required were enrolled in order to account for lost to follow-up over time, as the study was designed to last ten years. A paired t-test determined differences in penetration, steady state wear, and PROs over time.

5.2.4 Study IV: Precision of RSA of acetabular cup stability and polyethylene wear

The Wilcoxon signed rank test determined differences in the condition numbers and bead counts among the three measurement methods for polyethylene wear and between the three methods for acetabular cup stability.

Statistical Methods Summary	
Study I	• Continuous, normally distributed data • *Post hoc* power calculation • Paired t-test for intra-group comparisons • Independent sample t-test for inter-group comparisons
Study II	• Continuous, not normally distributed data • *a priori* power calculation • Wilcoxon signed rank test for intra-group comparisons • Mann-Whitney U test for inter-group comparisons
Study III	• Continuous, normally distributed data • *Post hoc* power calculation • Paired t-test test for intra-group comparisons
Study IV	• Continuous, not normally distributed data • *Post hoc* power calculation • Wilcoxon signed rank test for intra-group comparisons

Table 1: *Description of data, power and sample calculations, and comparison tests for all studies*

6 Results

6.1 Study I: Long-term evaluation of HXLPE using RSA and CT

6.1.1 Radiostereometric analysis

The 13 year mean ± SEM proximal femoral head penetration of the overall cohort was 0.06 ± 0.03mm with no significant differences among any time points after two years. The 28mm group had 0.10 ± 0.03mm of penetration at 13 years with no differences after two years and the 36mm group showed 0.03 ± 0.02mm of penetration at 13 years with no differences among any intervals. There were no significant differences in penetration between the two groups at any time points. The steady state wear (eliminating the bedding-in period of 1 year) of the overall cohort was 0.05 ± 0.02mm at 13 years with no differences over time. No intragroup or intergroup differences in steady state wear were observed. The steady state wear rate of the overall cohort from 1 to 13 years was 0.001mm/ year. Double exams taken at 13 years indicated a precision of 0.06mm in the proximal direction.

6.1.2 Plain radiograph and CT analysis

A continuous acetabular radiolucency (zones two and three) was found in one patient's 13 year plain films, which was deemed a result of a loose cup. No other patient showed any radiolucencies or evidence of osteolysis on the acetabular or femoral side. Two patients' (28 mm, n=1; 36mm, n=1) CT scans had regions of acetabular bone loss at 13 years. One patient had a cyst that was grafted during surgery and visible on immediate postoperative and all subsequent plain radiographs. The second patient had a protrusio, also treated with graft during surgery, which had resorbed over time.

6.2 Study II: Mid-term evaluation of vitamin E diffused HXLPE using markerless RSA

6.2.1 Radiostereometric analysis

By five years, five patients were revised: two E1 (dislocation) and three ArComXL (one dislocation, two periprosthetic fractures); and two E1and six ArComXL patients were lost to follow-up. Therefore, 28 E1 and 26 ArComXL patients were analyzed at five years. The five year median (IQR) proximal femoral head penetration in the E1 liners was -0.04mm (-0.13 to 0) with early differences between six weeks compared to three and five years ($p<0.001$ for both comparisons) and

between one year compared to three and five years (p=0.005 and p=0.001, respectively). The ArComXL group had five year penetration of 0.07mm (-0.03 to 0.16) with no differences over time. The two polyethylene groups had significantly different penetration at three and five years (p=0.029 and p=0.019, respectively). The five year proximal steady state wear was -0.08mm (-0.18 to -0.04) for the E1 liners and 0.01mm (-0.06 to 0.16) for the ArComXL liners, with no intragroup differences, but intergroup differences at three and five years (p=0.046 and p=0.003, respectively). Double exams taken at three years specified a precision of 0.16mm in the proximal direction.

6.2.2 Patient-reported outcome measures

All PROs improved significantly from the preoperative scores, with no improvements thereafter for both polyethylene groups (p<0.001). The median (IQR) HHS was 93 (88 to 98) for the E1 group and 97 (93 to 100) for the ArComXL group at five years. Patients in both polyethylene groups reported the same EQ-5D-3L score (1 [0.7 to 1] for E1 and 1 [0.8 to 1] for ArComXL) and were equally satisfied (0.5 [0 to 1.5] for E1 and 0.5 [0 to 1] for ArComXL) at the mid-term. There were no differences in PROs between the two groups at any time point.

6.3 Study III: Mid-term evaluation of vitamin E diffused HXLPE using gold-standard RSA

6.3.1 Radiostereometric analysis

One hip was revised for an infection before six months and was subsequently removed from the study. The mean ± SEM proximal femoral head penetration into the E1 liners was 0.06 ± 0.01mm at the latest follow-up of five years. Differences in penetration were observed between six months and two-five years (p≤0.021 for all comparisons) and between one year compared to two and three years (p=0.022 and p=0.014, respectively). There was no difference between one and five years or between two years and any later intervals. The five year steady state wear was 0.02 ± 0.01mm with no differences over time. Precision in the proximal direction was 0.12mm.

6.3.2 Patient-reported outcome measures

All postoperative PROs improved significantly from the preoperative scores (all p<0.001). No differences were observed from six months to five years, demonstrating that patients maintained favorable outcomes to five years. At five years, the HHS was 92 ± 2, suggesting an excellent mid-term outcome. The pain VAS was also favorable at five years with a mean score of 1.1 ± 0.3.

6.4 Study IV: Precision of RSA of acetabular cup stability and polyethylene wear

6.4.1 Femoral head penetration

Double exams from 50 hips were included in the analysis. The precision of the proximal femoral head penetration measurements was 0.086mm when using the liner-only method, 0.257mm when using the shell-only method, and 0.115mm when using the shell + liner methods. The shell + liner method was the most precise of all methods in the medial/ lateral and anterior/ posterior planes, while the shell-only method was the least precise for measuring penetration in any plane. The shell + liner method utilized a significantly greater bead count and significantly lower condition number than both the liner-only and shell-only methods (both $p<0.001$).

6.4.2 Acetabular cup migration

The precision of superior cup translation was 0.105mm for the liner-only method, 0.278 for the shell-only method, and 0.108mm for the shell + liner method. The shell + liner bead count was higher and condition number was lower compared to the liner-only and shell-only methods ($p<0.001$ for both comparisons). The shell-only method was the least precise method for measuring cup translation in any plane. The shell + liner method was more precise than the liner-only method for measuring cup rotation in all three planes.

6.4.3 Liner migration

The mean (SD) superior translation of the liner with respect to the shell was -0.039 (0.16)mm, which was within the error of detection (-0.187, 0.199) for this method. Both translation and rotation of the liner with respect to the pelvis were within the precision interval, thus no true motion was detected, which justified combining the shell and liner into one segment since they do not move with respect to one another.

6.5 Comparative results

6.5.1 E1 versus HXLPE using gold-standard RSA

The E1 liners showed less settling-in and overall penetration than the HXLPE at five years, when comparing the results of studies I and III (Figure 16). While the magnitude of the difference was small, a statistical comparison of the penetration of these two materials was not performed. The penetration of both materials was analyzed using the shell + liner technique in UmRSA.

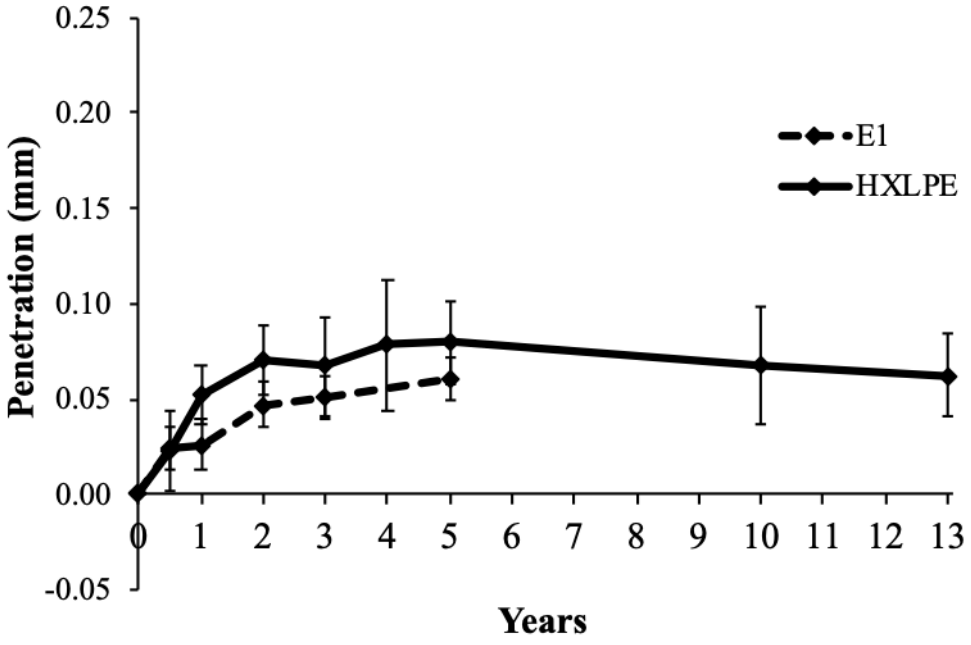


Figure 16: *Mean ± SEM proximal femoral head penetration (mm) into HXLPE and vitamin E diffused HXLPE over time. Both penetration analyses were performed using the shell + liner technique.*

6.5.1 E1 penetration using gold-standard RSA versus E1 penetration using markerless RSA

While only a small difference in penetration was observed between the HXLPE and E1 polyethylene, when comparing the penetration into the E1 liners using the shell + liner (gold-standard) method versus the markerless (shell only) method, a difference of a larger magnitude was observed. In fact, negative penetration into the E1 liners was observed in study II when utilizing the markerless UmRSA technique, and positive penetration was observed in study III, which used the shell + liner UmRSA. To attempt to reconcile this difference, the penetration of the patients in study III (shell + liner) was also analyzed in the markerless method, in addition to the reported shell + liner penetration. When using the shell + liner method to analyze the penetration of patients in study III, a mean ± SEM of 0.06 ± 0.01mm was observed at five years. However, if these same patients are analyzed in the markerless UmRSA technique, penetration of -0.02 ± 0.02mm was observed at five year (Figure 17).

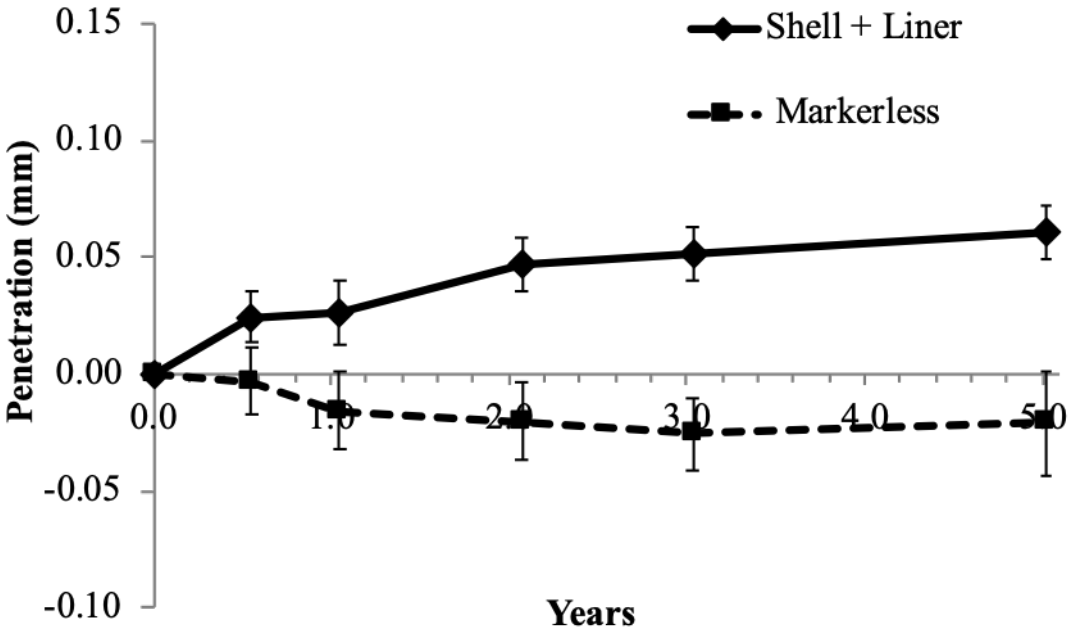


Figure 16: *Mean ± SEM proximal femoral head penetration (mm) into the E1 liners over time, calculated using both the shell + liner (gold-standard) and markerless UmRSA methods.*

7 Discussion

7.1 Measuring polyethylene wear using RSA

The aim of the thesis was to use RSA as the primary outcome assessment tool to evaluate current generations of polyethylene to determine their performance and safety at various stages *in vivo*. Since osteolysis is a direct result of wear particles, it is necessary to closely monitor wear, particularly in the mid-term and beginning stages of the long-term, to ensure that wear-related failure will not be a concern into the long-term. HXLPE has revolutionized THA by drastically reducing wear and consequently the incidence of osteolysis, a disease that once plagued the survivorship of THA and made revision surgery more difficult and less successful. Vitamin E diffused HXLPE entered the marketplace less than a decade after HXLPE, and *in vitro* studies have shown evidence of its superiority over HXLPE. *In vivo* studies have also demonstrated that vitamin E diffused HXLPE does not wear more than HXLPE, however it is unclear at this stage if its improved strength over HXLPE demonstrated *in vitro* is maintained *in vivo*. While vitamin E diffused HXLPE appears to deform and wear less than first generation HXLPE, the clinical relevance of this difference is unknown at this time.

RSA is the most accurate and precise method of measuring femoral head penetration and steady state wear over time[107,117,118,121,122]. Penetration measured by RSA detects an early femoral head migration pattern that is otherwise undetectable on plain radiographs and therefore may foretell a future problem that other metrics are not sensitive enough to identify. A high incidence of osteolysis (40%) from conventional UHMWPE has been reported as early as approximately seven years after surgery, making early detection of wear absolutely crucial[46]. While reports on HXLPE and vitamin E diffused HXLPE do not show wear rates as high as conventional UHMWPE, wear particles may still accumulate over time, albeit at a slower rate, which could lead to osteolysis at later stages than what was observed with UHMWPE. Long-term follow-up using accurate and sensitive measures, such as RSA, is critical to understand the wear pattern of these newer materials over time. With more sensitive methods, it is also important to understand the clinical significance of the early wear detection and the optimal timing for revision.

RSA was the common tool used in all of the studies in this thesis and provided the most accurate assessment of the central outcome: femoral head penetration into the polyethylene. While femoral

head penetration was the most pivotal outcome for determining the future success of a patient's THA and the polyethylene material under study, other outcome assessment tools were used to supplement and contextualize the RSA data. Plain radiographs and CT scans were used to determine if early manifestations of bone remodeling and osteolysis existed without significant wear measured by RSA. Finally, PROMs were used to assess the patient's perception of the outcome of their surgery. While wear, radiolucencies, and osteolysis are certainly essential metrics to monitor implant performance, PROMs are becoming increasingly important to provide valuable patient-specific information, which cannot be obtained through all aforementioned radiographic outcomes. There is a need to assess performance in multiple dimensions in order to glean the most comprehensive evaluation of a patient with a particular implant. The combined use of RSA, plain radiographs, CT scans, and PROMs allows for a multifaceted depiction of implant performance that is inclusive of patient factors and perception.

7.2 Long-term HXLPE performance

The femoral head penetration and steady state wear of HXLPE was low relative to reported wear of UHMWPE at the long-term interval of 13 years. No differences in penetration were observed after one year, and no differences in steady state wear were observed at any time point. Furthermore, there were no differences in penetration or steady state wear between the 28mm and 36mm heads groups. Johansen et. al reported a ten year proximal penetration into conventional UHMWPE and HXLPE of approximately 0.6mm and 0.2mm, respectively, using marker-based RSA[166]. The 13 year proximal penetration into the HXLPE observed in our series was an order of magnitude smaller than the 0.6mm penetration into conventional UHMWPE reported in the aforementioned cohort, using the same gold-standard method of UmRSA. Furthermore, the 13 year steady state wear rate was well below the osteolysis risk threshold of 0.1mm/year[47]. Our long-term series also supported the notion that HXLPE tolerates larger head sizes as well as their smaller diameter counterparts. This is a large advantage of HXLPE as the previous generation of UHMWPE proved to be unsuitable for large head articulations[34]. The use of larger head sizes allows for greater impingement-free range of motion, thereby reducing the risk of dislocation.

Analysis of the plain radiographs showed one patient had a continuous acetabular radiolucency as a result of a loose cup; no other radiolucencies or evidence of osteolysis werefound on the plain radiographs. CT scans taken for all long-term HXLPE patients confirmed the results of the RSA and plain radiographic analyses: that this material is wearing a nearly imperceptible amount and that osteolysis is not present. While two patients' 13 year CT scans did show evidence of bone resorption

in the acetabulum, it was obvious that both of these areas were degenerative cysts that were present before surgery. Each cyst was treated with bone graft during surgery, which had resorbed slightly by the 13 year mark. However, the overall size of each area of lesser density was not larger than what was observed on the preoperative plain films. These were nonprogressive cysts present at the time of surgery and thus completely independent of the implant. The use of CT scans in this study only confirmed what was concluded from the RSA and plain radiograph analyses. At this time, the CT scans added no clinically actionable data regarding the wear performance of HXLPE. Therefore, we cannot recommend the routine use of CT scans on all long-term HXLPE patients, particularly due to the high cost and radiation levels. Perhaps there would be a role for CT if the RSA analyses showed wear values greater than the expected norm, or at a later follow-up interval, such as the beginning of the third decade.

7.3 Mid-term performance of E1 and ArComXL using markerless RSA

The mid-term results of the randomized controlled trial comparing E1 and ArComXL are encouraging and substantiated our hypothesis that the E1 polyethylene wear would be non-inferior to that of the ArComXL. While the early penetration of E1 and ArComXL was equal, differences in both penetration and steady state wear were observed at three and five years between the groups, and within the E1 group up to three years after surgery. The observed penetration and steady state wear values were small, and further, their clinical significance was not clear. The observed negative penetration in the E1 group at three and five years suggest that the obtained results could be due to measurement error of the RSA software using the markerless technique. This unexpected result has been seen in other studies as well. A recent report from Sillesen et al., who also utilized the markerless UmRSA method, measured negative femoral head penetration into E1 liners at three years. There was also a slight increase in penetration between three and five years in the ArComXL group. This was not a statistically significant increase, however it was notable that the penetration curve had a positive slope over time compared with the E1 group, which had a slope that remained stable at zero. Additional long-term studies with close monitoring are needed to investigate whether this positive slope is maintained into the future.

All PROs for both groups improved significantly compared to the preoperative scores, and there were no differences between the groups at any interval. We did observe a slight decrease in Harris hip score, UCLA activity scale, and the SF-36 physical function score within the E1 group from three to five years, however these differences were not significant. The observed non-significant differences are unlikely to be attributable to the E1 implant, and are more likely a reflection of the

patient demographics in the two groups. While there were no statistical demographic differences between the polyethylene type groups, the E1 groups did have a median age that was two years greater than that of the ArComXL group. Therefore, it may be that the declines in their scores were due to expected age-related change in physical function over time. Despite this negligible decline in the E1 group, all PROs for both groups remained favorable at the most recent assessment of five years.

7.4 Mid-term performance of E1 using gold-standard RSA

Proximal penetration into the E1 liners in study III was positive and minimal at the mid-term follow-up of five years. Although early differences in penetration were observed, there were no differences between one and five years nor were there differences between two years and any later time points, suggesting a bedding-in period of one year with minimal wear thereafter. Additionally, there were no differences in steady state wear among any intervals. Shareghi et. Al. also employed the gold-standard method of UmRSA (shell + liner) to measure penetration into E1 liners and reported 0.06mm of proximal femoral head migration at two years. We report similar penetration of 0.05mm at two and three years, and 0.06mm at five years using the same measurement technique.

Patients in this cohort had encouraging outcomes on all PROs throughout all postoperative intervals. All PROs improved significantly from the preoperative scores and remained satisfactory at five years with no further differences observed after six months. A somewhat unexpected outcome was the average score of three on the VAS satisfaction scale at five years. A closer look at the PROs data raised a possibility that the patients misunderstood the satisfaction VAS scale and in their haste to complete the many surveys quickly, did not realize that a score of 0, rather than 10, translated to complete satisfaction. Furthermore, all patients who were “dissatisfied” at five years on the VAS reported nearly the highest possible outcome on all other surveys at five years. This discordance adds validation to our hypothesis that patients may have inadvertently reported satisfaction values that are not representative of their true perception on that particular scale.

7.5 Differences in UmRSA techniques

The seemingly contradictory results from the measurement of penetration into E1 liners using two different methods of UmRSA highlights the importance of measurement technique. Study II, which used the markerless method (backshell only) showed negative penetration into the E1 liners at five years while study III, which used the marker-based method (shell + liner) showed positive penetration at five years. While the absolute values of penetration obtained in both studies are small

relative to that of non-vitamin E diffused HXLPE, the discrepancy nevertheless justifies closer scrutiny. This unexpected result prompted the investigation of the precision of the three techniques available to measure femoral head penetration in UmRSA.

Since study III implanted beads within the liner, the unique opportunity arose to analyze and compare the methods of using the shell only, liner only, and the shell + liner combined to measure femoral head penetration and acetabular cup migration within the same group of patients. Precision calculations from the double exam measurements showed that the liner only method had the highest precision value for measuring both penetration and migration. However, the value was only marginally better than the shell + liner method. Overall, we concluded that the shell + liner method, which added a significantly greater point count and lower condition number was the most desirable method because of the added information and greater dispersion[120,128].

After decisively concluding that adding beads to the liner increases RSA reliability and that the shell + liner method is superior to using the shell alone to measure femoral head penetration, one can reasonably argue that the negative penetration values seen in study II were likely due to measurement error and inherent lack of precision within the measurement technique used. In support of this point, the same formulation of vitamin E diffused HXLPE (E1) was evaluated for the same amount of time in both studies II and III, however the RSA penetration results were quite different. Patients from studies II and III were combined and analyzed using markerless UmRSA in the Sillesen et al. three year E1 report, which also demonstrated negative penetration[97]. In this report, two centers were included however only one center implanted liner beads, therefore all penetration was measured using the markerless technique to allow comparison between the two centers. Sillesen et al. reported an overall negative penetration into the E1 liners at three years, and study III which included some of the patients from the Sillesen et al. report but utilizes the shell + liner method, reported low positive penetration into the E1 liners at five years. Therefore, we conclude that the negative penetration seen in study II was a function of measurement technique, and not an issue with the E1 material.

Furthermore, an *ad hoc* analysis of the penetration observed in study III was performed to determine if negative wear would also be observed in this cohort if the films were measured using the markerless technique. Since both the shell + liner and markerless (shell only) methods could be applied to these patients, we could easily test this hypothesis in the same group of patients. The results of this analysis also showed negative E1 penetration when using the markerless UmRSA

method, which leads us to believe that the error inherent in this technique is responsible for the negative wear values. Because of the suspected error of the markerless technique, it may be possible that the penetration observed in the ArComXL group was dampened by the error, and thus the reported results may not be reflective of all the penetration that has occurred in these patients. Since the error seems to yield more negative penetration values, it is likely that the true ArComXL penetration is greater than what was actually measured.

One of the explanations for the poorer performance of the markerless technique observed in the studies of this thesis could be due to interference from the acetabular component. Study II utilized a maximum of five points automatically assigned to the acetabular backshell by the software. In contrast, study III utilized up to six beads labeled in the polyethylene liner and only three points from edge-detection of the backshell, for a maximum of nine points. Since a highly porous acetabular construct (Regenerex) was used in both studies, the software algorithm for finding the tightest fit of the backshell may have been compromised by the increased pixilation along the edge caused by the porous material. Therefore, fewer points and an inferior dispersion of those points inherently limited the precision of the markerless technique used in study II. This lower precision may have contributed to the negative penetration values observed in study II. It is possible that the penetration of both E1 and ArComXL in study II may have been dampened by the measurement technique and could in fact be greater in magnitude (more positive) than what was actually measured. Since the ArComXL has less cross-link density than the E1, it is expected that it would exhibit greater penetration at the mid-term than E1. The conclusion of these findings is that E1 is wearing (or deforming) an amount too little to be detected by the markerless UmRSA method. As bearing surface technologies improve, it is crucial to use the most sensitive measurement methods in order to accurately detect any micromotion that may be occurring in these materials.

7.5 Generational progression of polyethylene in THA

Despite the differences in penetration of the E1 liners across studies II and III, both reports suggest that E1 does not wear more than previous generations of non vitamin E diffused HXLPE. Longer-term *in vivo* evaluation, particularly under adverse loading conditions, may confirm whether improved strength of the vitamin E diffused HXLPE material over HXLPE seen *in vitro* is maintained *in vivo.* Reduced strength of the HXLPE due to irradiation and subsequent melting has been shown *in vitro*, however, the 13 year cohort in study I has not shown any evidence that this reduced strength is a problem *in vivo*[65]. However, the majority of patients across all studies had optimal cup positioning within the generally accepted safe zone, thus, the limits of both the HXLPE

and vitamin E diffused HXLPE liners were not tested under adverse loading conditions *in vivo*. Most notably, all penetration observed across all studies into the HXLPE, the medium cross-linked polyethylene (ArComXL), and the vitamin E diffused HXLPE (E1), was dramatically lower compared to the reported values for conventional UHMWPE[47,55]. A thorough analysis of the bone remodeling in the long-term patients of study I confirms that osteolysis is not a concern at 13 years in these patients with HXLPE. This thesis, utilizing the most accurate and sensitive wear measurement method of RSA, decisively confirms the wear superiority of HXLPE and vitamin E diffused HXLPE over conventional UHMWPE.

8 Limitations

8.1 General limitations

All surgeons participating in each study are generally regarded as expert hip arthroplasty clinicians and surgeons worldwide and are associated with large academic teaching hospitals, restricting the applicability and generalizability of all reported results and conclusions. While cup positioning was not reported in any study, all acetabular components were placed within the generally accepted safe zone. Surgeon expertise may have diminished the otherwise probable number of patients with complications associated with a malpositioned shell, such as dislocation, and adverse polyethylene loading conditions leading to polyethylene rim fractures.

Obtaining the first set of RSA films immediately after surgery and before hospital discharge would have provided a more accurate baseline for studies conducted at MGH (study II, conducted in Denmark, captured postoperative films before hospital discharge). Since the first set of films serves as the baseline point for all future comparisons, it is imperative that these films are captured before any possible micromotion has taken place. Studies I and III captured baseline RSA films at the two-six week postoperative visit, by which time the implant has been loaded from the patient walking. Our methods would not have caught any initial deformation of the material occurring before the first postoperative visit. In the future, streamlined processes for patient transport to the RSA lab prior to leaving the hospital will ensure that the most accurate baseline is obtained, thus enabling the most conclusive depiction of material performance.

RSA was used as the central assessment tool in all studies because of its high accuracy, sensitivity, and ability to predict potentially poor outcomes by early detection of component migration. However, the widespread application of RSA is unrealistic due to the high cost of the RSA lab and specially trained staff to obtain and analyses the radiographs. Despite this, these studies are important contributions to the literature due to their use of RSA, and should serve as accurate and reliable comparisons to other studies analyzing similar polyethylene materials.

8.2 Study-specific limitations

8.2.1 Study I: Long-term evaluation of HXLPE using RSA and CT

A control group was not enrolled which limited the direct comparison of the newer generation HXLPE to the previous conventional UHMWPE. However, when this study was designed in 2001, the catastrophic outcomes with conventional UHMWPE were well documented. Therefore, all collaborating surgeons made the decision to make this an efficacy study on HXLPE and not enroll a group of patients with conventional UHMWPE, potentially putting this group at greater risk for a poor outcome. Second, achieving adequate long-term follow-up was difficult. Several patients were unreachable or were not interested in returning as they were feeling well and did not want to subject themselves to extra radiation from the CT scan. While we obtained the necessary number of patients to sufficiently power an RSA analysis of the overall group, the power would have been augmented if there were more patients in each of the head size groups. Long-term monitoring utilizing sensitive techniques that assess many dimensions, such as RSA and CT scans, is especially critical in this study as the previous generation of UHMWPE had poor outcomes and increased wear with larger head sizes. Furthermore, insufficient and highly varied PROM capture over the 13 years due to patient refusal and malfunction of the survey administration tool, prohibited the inclusion of PROMs in the analysis. A patient-specific dimension would have enhanced the analysis by allowing for assessment of how patients perceive their intervention and its effects on their general health and disease-specific health in the long-term. A truncated battery of PROMs that still captures all necessary patient-reported outcome parameters, coupled with convenient and user-friendly access to these surveys, such as an at-home administration tool, may improve the patient response rate in the future.

8.2.2 Study II: Mid-term evaluation of vitamin E diffused HXLPE using markerless RSA

The primary limitation of the study was the use of markerless UmRSA to measure femoral head penetration into the polyethylene. Polyethylene liner beads were not inserted because of the extra operating room staff required to drill and insert the beads into the liner prior to implantation in the patient. Study IV in this thesis compared the precision of the shell only (markerless UmRSA) technique to the shell + liner (gold-standard UmRSA) technique and determined that the shell + liner was more precise and included significantly greater point count and lower condition number, making it the most desirable method for measuring femoral head penetration. The use of markerless UmRSA may explain the unexpected result of negative penetration in the E1 cohort. The use of only five points and a limited topographic area of the radiograph defining the cup inherently limits the markerless technique. Furthermore, the technique could have been further disadvantaged by the use of a highly porous acetabular shell, producing greater pixilation on the radiograph at the shell-bone interface, which may have hindered the software's ability to detect a clear edge. Since the five

points of the edge of the backshell solely compromises the shell segment, it is crucial to obtain a well-fitted edge. The shell + liner technique utilizes a broader distribution of points on the radiograph, including six from the polyethylene liner and three from the backshell, thus more information contributes to the definition of the cup, yielding a more precise analysis.

Even though the study was well-conceived and utilized a randomized controlled trial design, there were many exclusions that limited the number of patients allocated to each intervention. After randomization, several patients were excluded due to last-minute changes to a surgeon who was not participating in the study, and use of components other than those specified for the study. Despite this unexpected drop in patients after randomization, an adequate number of patients were allocated to each polyethylene type for sufficient statistical power and comparison between both groups.

8.2.3 Study III: Mid-term evaluation of vitamin E diffused HXLPE using gold-standard RSA

MGH, the center at which study III was conducted, had a more difficult experience with obtaining complete mid-term RSA and PROM follow-up than Aalborg University Hospital, the center that conducted study II. A reason explaining this discrepancy remains elusive, however, it may be related to patient cost differentials between the Danish center of study II and the American center of study III. Patients at MGH were contacted multiple times to request their return for five year follow-up. All patients that did not return at five years (n=8; 16%) continually expressed their disinterest in returning, and emphasized that they were doing well and did not need to come back. In contrast, only three patients (4%), out of a much larger study cohort from Denmark, refused to return at five years. The funding source at MGH covers the cost of the RSA radiographs, but not the set of plain radiographs and office visit with the surgeon. Since several of the patients had poor insurance coverage and financial hardship, the extra costs were potentially prohibitive. The reduced patient healthcare costs in Denmark may explain why that cohort was more agreeable to mid-term follow-up.

Finally, a randomized controlled trial would have been stronger, however, more patients would need to be enrolled in order to have appropriate statistical power within both polyethylene groups. Given the projected enrollment and operating time, all participating surgeons decided that enrolling and operating on the number of patients necessary to have two polyethylene groups would take too long and the study would therefore not be a contemporary reflection of these materials in THA.

8.2.4 Study IV: Precision of RSA of acetabular cup stability and polyethylene wear

Similar to study II, the highly porous acetabular shell may have limited the ability of the software to detect the clearest edge of the backshell, thus reducing the precision of the shell only method. Although the shell + liner method also utilized points from the backshell of the highly porous construct, more points were devoted to the polyethylene liner, which dampened the effect of the backshell points on the precision of the shell + liner technique. Comparison with a less porous acetabular shell would have provided valuable information on just how much the porosity impedes detection of the edge. However, almost all acetabular shells contain some amount of porous coating, therefore significantly improving edge detection with the shell only method through the use of a different shell is unlikely. Although the porosity is a likely detriment to the shell only technique, the maximum point count remains unchanged, regardless of the type of shell used. Therefore, the precision of the shell only method will never reach that of the shell + liner, which can utilize more points with greater dispersion.

9 Conclusion

9.1 Current generations of polyethylene are safe for use in Total Hip Arthroplasty

The advent of the current generations of polyethylene has revolutionized THA. Medium cross-linked polyethylene, HXLPE, and vitamin E diffused HXLPE have shown their superiority over conventional UHMWPE, and are performing safely in patients at a critical time when problems with conventional UHMWPE first arose. No adverse outcomes or causes for concern related to the polyethylene were observed in any study, all of which vigorously analyzed these materials in multiple dimensions, including the most accurate and sensitive wear measurement method of RSA. Penetration and steady state wear values were all low relative to that of conventional UHMWPE, and well below the osteolysis wear rate threshold, above which osteolysis is significantly more prevalent[47]. Since wear was similar between multiple head sizes, larger head sizes can now safely be used on all materials studied to increase the range of motion and potentially help reduce the incidence of dislocation. Wear related osteolysis does not seem to be a concern, but continued longer-term follow-up is needed to definitively rule out the possibility of osteolysis. Patients in all studies were generally pleased at the mid- and long-term intervals as they reported low pain, high function, good health-related quality of life, and a high level of satisfaction.

9.2 RSA as a sensitive method to measure polyethylene wear

All studies in this thesis provide evidence and justification for the use of RSA in monitoring mid- and long-term polyethylene wear. Studies III and IV provide further justification for implanting tantalum beads into the polyethylene liner as combining these liner beads with points on the backshell yields the most precise and reliable analysis. If other available wear measurement methods were used, substantially more patients (often several hundred) would be needed to retain the same power achieved in these studies, and accuracy may be sacrificed. Revision with osteolysis as an indication is often very challenging due to reduced bone stock from the particle-induced inflammatory response. RSA was employed in all studies to closely monitor very small amounts of wear to ensure that the disastrous outcome seen in conventional UHMWPE patients does not ensue. If any patients in these studies were at risk for future revision due to osteolysis, RSA would have detected the potentially dangerous wear rates before more obvious plain radiographic evidence surfaced. Although the ideal timing of revision surgery based on early detection of wear using these

sensitive methods is not clear, one would expect that operative outcomes would be better than revisions done in response to late osteolysis detection.

In the United States, the demand for total hip arthroplasty is rapidly increasing and the importance of successful long-term patient outcomes to reduce revision, patient risk, and cost is crucial. Due to RSA's sensitivity in measuring micromotion, indications of implant failure are detectable much sooner than would otherwise be possible on plain radiographs. In addition, RSA is a more cost-effective and safer modality compared to CT. To ensure the best patient outcomes, new total hip technologies must be first vetted through clinical trials using RSA, which is the most powerful tool to predict, implant longevity. Because RSA is extremely accurate and precise, studies can be carried out using smaller patient groups without diminution of statistical power. This limits the potential risk that patients may incur in studying a new technology.

10 Future research

Since loosening from wear or other etiologies is the main reason for failure in THA, RSA should continue to be used to evaluate existing technology as well as all new THA technology before it is widely available to a large number of patients. Small cohort studies have proven the validity of using RSA to monitor wear; however, RSA could be used in a wider variety of surgeries and a larger number of patients to monitor wear and implant migration. This would give a more realistic assessment of using RSA in common practice. With greater use of RSA and a longitudinal *in vivo* study, it would be possible to determine whether early detection of wear could better inform the timing of revision. RSA is ideal for detecting small amounts of wear compared to other modalities, such as plain radiographs and could help inform which patients would benefit from early intervention.

In addition to measuring wear, RSA could be combined with other modalities such as plain radiographs, CT scans, and PROMs to create a multimodal revision risk calculator. Each one of the above metrics quantifies different aspects of prosthesis failure and thus likely no one factor alone would predict the need for revision. Using multiple metrics could help to balance the different factors such as wear and migration, bone remodeling, patient functional status, and patient satisfaction. This could help to reshape how surgeons think about the timing of revision.

Another important area of future study is to determine whether the results that were seen in this collection of work are sustained in the long-term. Positive mid- and long-term results were observed for HXLPE as well as E1. Combining the results of Study I and III show that E1 has slightly better wear performance compared to HXLPE, however it would be important to do a randomized control trial using marker-based RSA comparing these two materials to determine whether one is truly superior to the other. Both of these materials have very little wear and although RSA is able to detect these differences in wear, it would be valuable to know whether these differences truly lead to differences in clinical outcome.

11 References

12 Appendix

Appendix A

This appendix includes all non-proprietary surveys.

Harris hip score

INSTRUCTIONS TO PATIENTS

The following questions concern your hips. Please give the *one* answer that you feel is best for each question.

Describe the pain in each of your hips:

	Left	Right
None.	❑	❑
Slight pain or occasional pain.	❑	❑
Mild, no effect on ordinary activity, pain after unusual activity, use aspirin or similar medication.	❑	❑
Moderate, pain that required medicine stronger than aspirin/similar medication. I am active but have had to make modifications and/or give up some activities because of pain.	❑	❑
Marked or severe pain that limits activity and requires pain medicine frequently.	❑	❑
Severe pain even in bed. I am totally disabled.	❑	❑

How do you climb stairs?

Normally (foot over foot without use of banister).	❑
Need a banister, cane or crutch.	❑
Severe trouble climbing stairs.	❑
Unable to climb stairs.	❑

Are you physically able to use public transportation (bus, etc…)?

- Yes. ❑
- No. ❑

In terms of sitting in a chair, are you:

- Comfortable in any chair for one hour. ❑
- Comfortable in high chair for one-half hour. ❑
- Unable to sit comfortably in any chair. ❑

In terms of putting on your sock and shoe on each side?

	Left	Right
Can put on sock and tie shoe easily.	❑	❑
Can put on sock and tie shoe with difficulty.	❑	❑
Unable to put on sock or tie shoe.	❑	❑

Amount and type of support used:

- None. ❑
- Single cane for long walks. ❑
- Single cane most of the time. ❑
- One crutch. ❑
- Two canes. ❑
- Two crutches. ❑
- Not able to walk at all. ❑

Distance you can walk:
(This should be judged with the aid of support if you use any.)

- Unlimited. ❑
- Six blocks. ❑
- Two or three blocks. ❑
- Indoors only. ❑
- Bed to chair. ❑
- Not able to walk at all. ❑

How much do you limp on each leg?
(This should be judged at the end of your longest walk using the amount of support indicated in the questions above.)

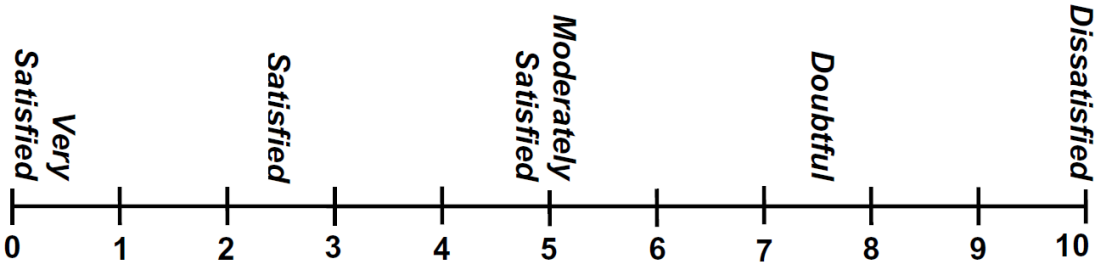
	Left	**Right**
None.	❑	❑
Slight.	❑	❑
Moderate.	❑	❑
Severe.	❑	❑

Satisfaction VAS

INSTRUCTIONS TO PATIENTS

Indicate how satisfied you are with the result of your most recent hip treatment. The line is a scale where a mark to the left means very satisfied and a mark to the right means not satisfied. If your hip has not been treated, please skip this question.

Satisfaction Scale

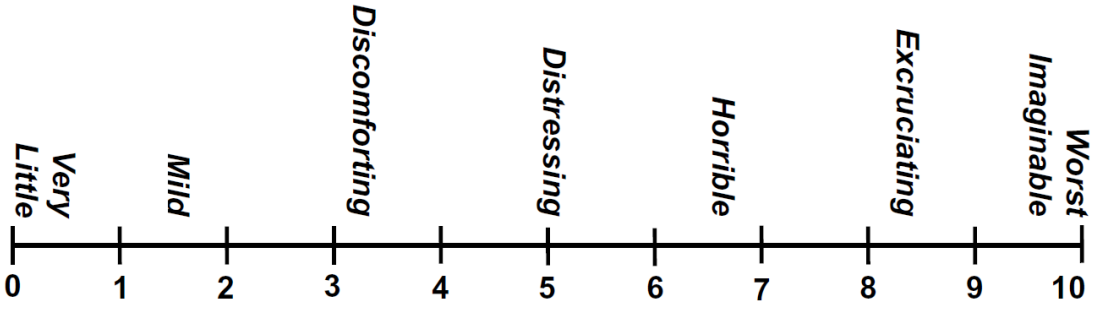


Pain VAS

INSTRUCTIONS TO PATIENTS

Indicate your average pain due to your most recently diagnosed / treated hip during the past month on the line below. The line is a scale where a mark to the far left means very little pain and a mark to the far right the worst imaginable pain. Place a mark on a suitable place on the scale to show how much pain you have.

Pain Scale



UCLA activity scale

INSTRUCTIONS TO PATIENTS

The following question concerns your activity level. Activity levels are listed from most active to least active. Please choose the one that MOST closely reflects your activity level.

Most Active

Regularly participate in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor or backpacking	☐
Sometimes participate in impact sports	☐
Regularly participate in very active events, such as bowling or golf	☐
Regularly participate in active events such as bicycling	☐
Regularly participate in moderate activities, such as swimming and unlimited housework or shopping	☐
Sometimes participate in moderate activities	☐
Regularly participate in mild activities, such as walking limited housework and limited shopping	☐
Sometimes participate in mild activities	☐
Mostly inactive: restricted to minimal activities of daily living	☐
Wholly inactive: dependent on others; cannot leave residence	☐

Least Active

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