Investigation of mechanisms leading to early aseptic loosening of hip prostheses

A retrieval study of 27 failed cases of cemented Spectron EF stem in combination with Reflection acetabular cup

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This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in Oral Sciences at the University of Bergen.

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1. Abstract

Background: More than 1 million people with arthroplasties undergo total hip arthroplasty (THA) surgery every year worldwide. In Norway more than 10 % of the THA cases needed revision operations due to aseptic loosening. The Spectron EF femoral stem was reported by the Norwegian Arthroplasty Register to have 3.8 times higher relative risk of revision than the Charnley total hip replacement. The aim of this research project was to determine the failure mechanisms responsible for the unexpectedly high rate of aseptic loosening of the Spectron EF hip stem in combination with the Reflection acetabular cup.

Methods: In this study 27 cases of failed hip prostheses were collected as part of an on-going retrieval program. The appearance of osteolytic lesions, the alignment of the components and linear penetration in the cups were measured from patient radiographs. The wear of components collected from revision surgery was graded. Tissue biopsies for adverse local chronic inflammation reactions were analyzed histologically. Additionally, wear particle exposure was quantified using different microscopy techniques and energy-dispersive X-ray analysis.

Results: The mean wear rate of the Reflection acetabular cup was 0.21 mm/year. The total linear wear was positively correlated with: 1. in vivo time of prosthesis; 2. the number of PE particles in tissue samples; 3. osteolysis area and percentage behind the cup. PE particle count was also positively correlated with osteolysis area.

Most of the cups were severely worn (grade 20 to 30) with 6 different wear modes:

pitting, scratching, burnishing, abrasion, permanent deformation, embedded particles. Scratching, abrasion and burnishing were observed on the stems (20% to 55%) due to stem-cement micro and macro-motion. Posterior medial and anterior lateral were the most worn parts.

Cases with stem loosening accompanied by relative movement within the cement shell had higher total particle count. Tissue samples near the stem also had higher total particle count.

Discussion: Mechanical load on the prosthesis during physical activity caused PE particles from wear of cups, cement and metal particles from wear in stem-cement interfaces. Particles migrating along joint space caused third body wear of the implants, which accelerated particle release. Mechanical loosening of the stem led to further release of cement and metal particles.

Conventional UHMWPE with low wear resistance was used as the cup material; proximal roughened “Spectron EF” was used as the stem. This combination was shown to be prone to causing increased number of different wear particles.

Conclusion: In this study of 27 failed cases of cemented Spectron EF stem in combination with Reflection acetabular cup, the loosening of cup was due to particle induced osteolysis in the acetabulum. The predominant cause of this osteolysis was PE particles. Loosening of stem was mainly mechanical, commonly occurring between the cement and stem. Under subsequent loading this led to release of wear particles and osteolysis.

Contents

2. List of abbreviations

THA	Total hip arthroplasty
SEM	Scanning electron microscope
EDXA	Energy dispersive X-ray analysis
FE-SEM	Field emission scanning electron microscopy
PMMA	Polymethylmethacrylate
PE	Polyethylene
UHMWPE	Ultra high molecular weight polyethylene
HPF	High power field microscopy (x400)

3. Acknowledgements

Paul Johan Høl as my main supervisor helped me a lot with understanding this project, which is relatively new to me. With his experience in this field, he guided me in histological analysis and wear particle characterization. He is friendly and patient, always there to offer me help and give suggestions.

Peter Ellison is my co-supervisor. He explained me how retrieval study worked and gave me support on X-ray analysis. With his background I got guidance in cup grading. He showed care about both my study and my life here.

Alex van Tol deserves lots of credit for developing the software for the X-ray analysis.

Geir Hallan, an experienced surgeon, showed me what osteolysis looked like around prosthesis in X-rays. Thanks to him we got good samples for our study.

Pathologists Hans Kristian Haugland and Peer Kåre Lilleng gave me advice related to histological analysis of chronic inflammation cells.

Scanning electron microscopy images were taken by Rainer Bahlo at IOW, Germany.

Professor Nils Roar Gjerdet helped me with the writing and editing process.

Special thanks to my family in China for their love and support always.

4. Scientific environment

This study was carried out at Biomatlab-Bergen. Scientific support has also been given by the staff at the Norwegian Arthroplasty Register, Haukeland University Hospital, Hagavik Hospital, Elverum Hospital and Lovisenberg Hospital.

This thesis is a part of the Master program at the Faculty of Medicine and Dentistry, University of Bergen.

5. Introduction

5.1 Total hip arthroplasty (THA)

Total hip arthroplasty (THA) is most commonly used to treat joint failure caused by osteoarthritis. It is a cost-effective surgical procedure to relieve pain and restore life quality of the patients. More than 1 million arthroplasties are done every year worldwide, and this number is projected to double within the next two decades (1). Sir John Charnley founded a classic and successful Low Friction Arthroplasty concept in the 1960s, which became the gold standard in THA (2).

In the year 2009 alone 765,000 patients underwent total hip replacement in the EU (3).The Norwegian Arthroplasty Register (NAR) has recorded data on primary and revision hip arthroplasty procedures since 1987. They reported that in 2012 approximately 9000 hip replacement procedures were carried out in Norway, with 14.3% of these being revision operations (4).

There are two types of THA according to fixation principles: cemented and uncemented THA. Components of each are showed in figure 1. In this thesis only cemented total hip design was studied.

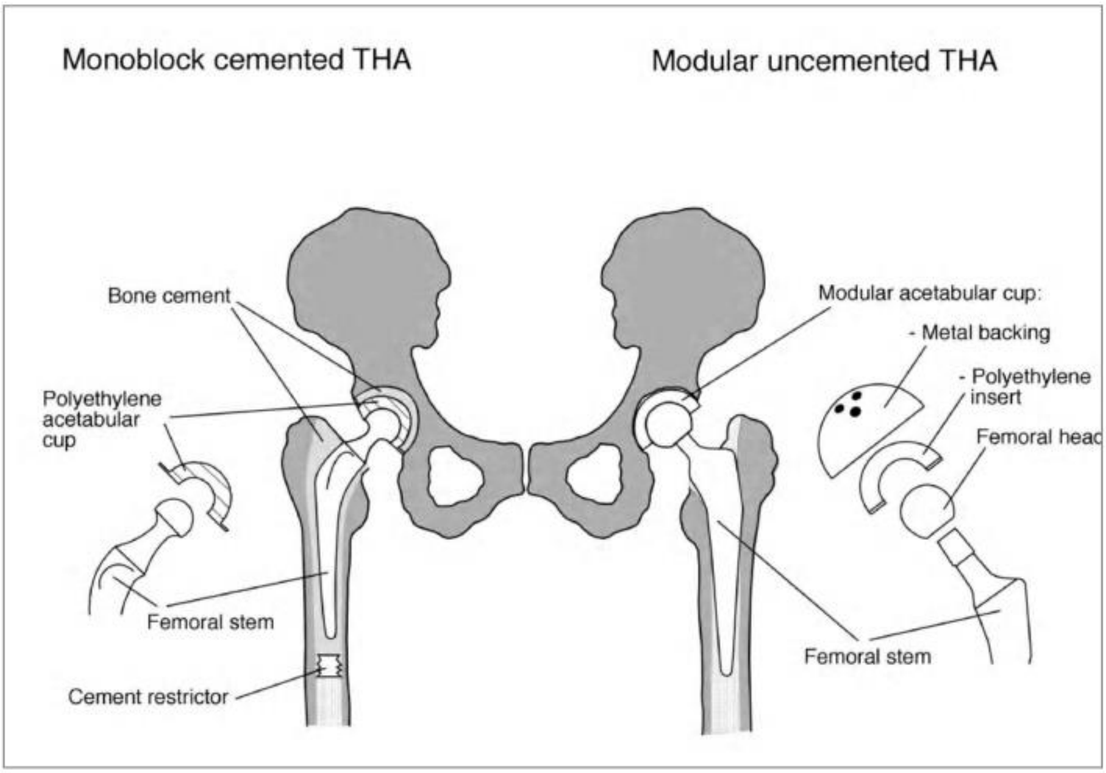


Figure 1. Components in THA (5)

Surgeons in Norway reported a high number of cases of mid-term aseptic loosening of the Spectron EF femoral stem when used in conjunction with the Reflection acetabular cup (Figure 2). The NAR have investigated the survivorship of these products, identifying that they have a relative risk of revision 3.8 times higher than the Charnley total hip replacement (6).

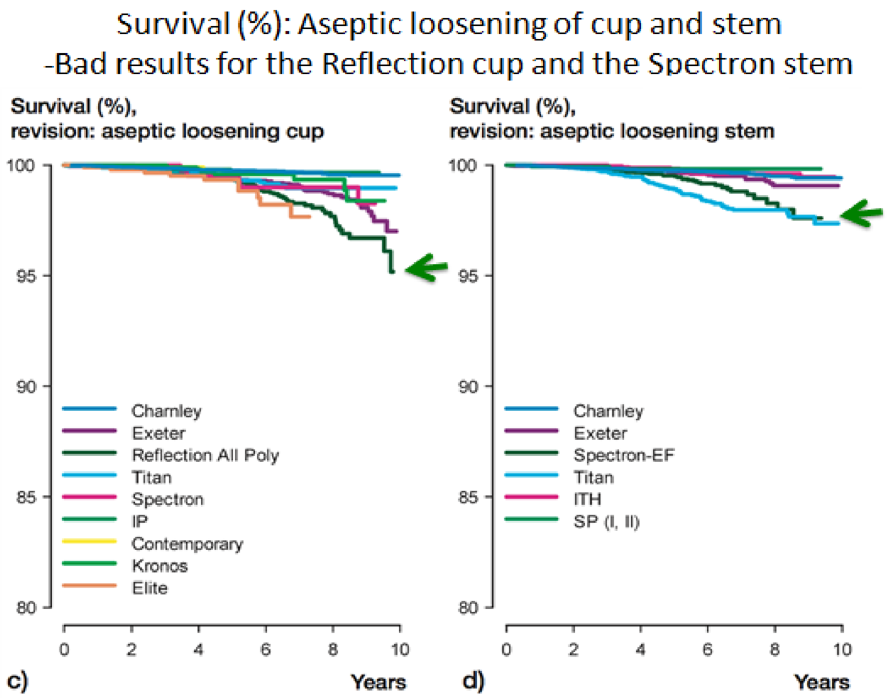


Figure 2. Survival of different kinds of cups and stems. Arrows pointing at the survival curve of Reflection acetabular cup (left); Spectron EF stem (right). (6)

More detailed analysis has indicated that the rate of femoral loosening may be related to the modern Spectron EF stems rough proximal surface finish, since the old version with smooth surface had much better long term results (7-9) (Figure 3).

Survival (aseptic loosening)	Spectron (Issack 2003)	Spectron-EF (NAR)
5 years	100%	99,3% (99,1-99,5)
7 years	100%	98,7% (98,4-98,8)
10 years	98%	96,0% (95,4-96,7)
15 years	96%	89,8% (87,1-92,5)

Figure 3. Survival of two different designs of the Spectron stem. After 15 years there was a big difference in survival between the old and new design.

However, a causal link between surface finish and failure could not be established as the stem has only been used with the Reflection acetabular cup in Norway which may be a contributing factor in the poor performance of the prosthesis. As a result Biomatlab-Bergen started to investigate the failures by collecting revised prostheses and tissue biopsies through their existing retrieval program (10) (Figure 4). Subsequently, a national program for the retrieval of failed Spectron EF hips has started in order to investigate the early aseptic loosening compared to other hip prostheses.

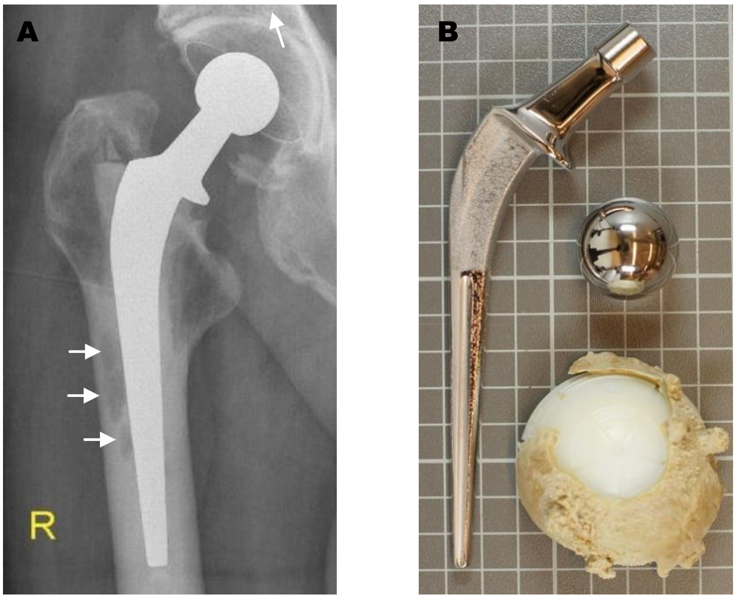


Figure 4. Spectron EF® femoral stem and Reflection All-Poly® acetabular cup that has failed 8 years after implantation due to pain and osteolysis. A) Radiolucency lateral of the femoral stem and surrounding the cup (indicated by arrows) indicates the implant is loose. B) Components retrieved ready for analysis.

5.2 Theories of aseptic loosening

Aseptic loosening is the main reason for failure of THA and accounts for 71% of the revisions (11). There are many theories developed to explain this: cell activation by particles, micromotion, stress shielding, high fluid pressure, endotoxin, individual or genetic variations and sealed interface (12). Aseptic loosening can't be explained by any theory alone, and it is difficult to separate factors above.

Nowadays, particles from wear of prosthesis are considered the main cause of aseptic loosening. The bioreactivity of wear particles is determined by its size, shape, composition and concentration (13-16). After phagocytosis of wear particles, macrophages, giant cells etc. increase the transcription of pro-inflammatory substances. These pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, appear to act synergistically on osteoclastogenesis and promote osteoclast function (17, 18). It causes periprosthetic bone degradation - osteolysis (Figure 5) (19) and subsequent aseptic loosening.

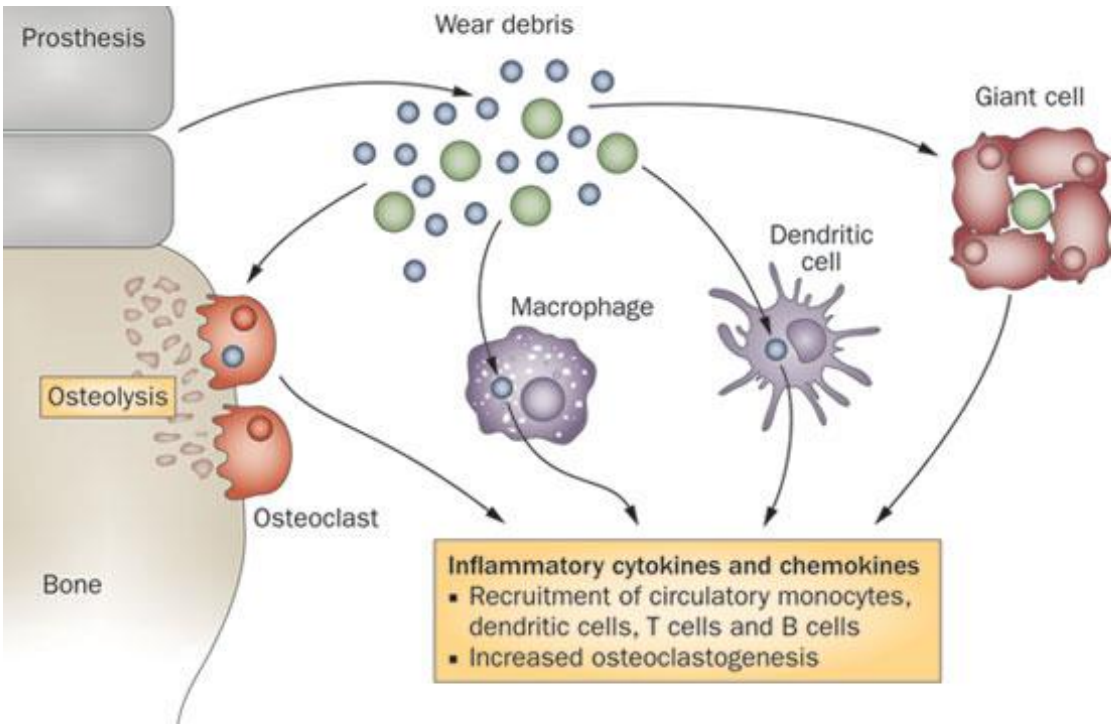


Figure 5. Schematic of periprosthetic inflammation and aseptic osteolysis (19)

6. Aims of study

General objective:

The present study was an approach to determine the failure mechanisms responsible for the unexpectedly high rate of aseptic loosening of the Spectron EF hip stem in combination with the Reflection acetabular cup.

Specific objectives:

1. To measure the appearance of osteolytic lesions, positioning and the alignment of the components from patient radiographs. Relevant information including: onset, size and location of osteolytic lesions; size and onset of radiolucent lines; positioning and alignment of the acetabular and femoral components.

2. To grade the wear of components collected from revision surgery and observe the wear patterns.

3. To analyze tissue biopsies histologically for adverse local biological reactions and quantify wear particle exposure.

7. Methods

7.1 Ethics

All participants in the proposed study had provided written, informed consent prior to participation. All data would be held in de-identified format.

The study has got ethical approval from the Regional Committees for Medical and Health Research Ethics, REK number 2010/2817 (17.11.2010).

7.2 Materials

Cases of failed Spectron EF hip stem in combination with the Reflection acetabular cup were collected as part of the on-going retrieval program (currently n = 27, mostly from Haukeland university hospital) (Table 1). Retrieval included implant components, cement, soft tissue surrounding joint, blood samples, X-rays, patient's clinical record etc.

Table 1. Patient data

Rec number	Gender	Age at retrieval(yr)	Years implanted	Loose component	Paprosky acetabulum	Paprosky femur
1	M	81	8.08	cup and stem	III B	II
7	M	59	6.39	cup	II C	I
15	F	38	11.52	cup and stem	III A	III A
20	M	82	7.73	cup	III A	0
42	F	38	3.32	cup	II A	0
140	M	87	7.73	cup and stem	II A	III A
142	M	71	10.94	cup and stem	II A	I
147	M	65	9.47	cup	I	I
151	M	68	7.82	cup and stem	II A	II
152	M	68	6.02	cup	II B	0
154	F	73	11.29	cup	II C	0
155	F	78	6.41	cup	II B	0
156	F	73	7.20	stem	II A	I
159	M	73	4.31	stem	0	II
161	M	60	3.25	cup and stem	II A	II
166	M	66	7.28	cup and stem	I	II
167	F	84	12.02	cup and stem	I	I
170	F	51	11.04	cup	II B	0
171	M	69	11.90	cup and stem	II B	II
172	F	68	7.89	cup and stem	II C	II
173	M	66	9.03	cup and stem	II B	III A
177	M	77	12.07	cup and stem	II C	II
178	M	74	9.51	cup and stem	II A	II
179	F	74	8.11	cup	I	I
181	M	60	6.84	cup	II B	0
182	M	86	15.14	stem	0	III A
183	F	68	11.38	cup and stem	II B	II

7.3 X-ray analysis

The appearance of osteolysis, the positioning and alignment of the components were measured from patient radiographs. Relevant information including: onset, size and location of osteolytic lesions; size and onset of radiolucent lines; positioning and alignment of the femoral and acetabular component.

7.3.1 Degree and position of osteolysis

Area behind the cup was divided into three sectors (20) (Figure 6). ***Osteolysis score*** was measured as the number of sectors that osteolysis appeared.

Osteolysis percentage was the coverage of osteolytic lesions behind the cup. Area behind the cup was divided into 180 degrees. The number of degrees that osteolysis involved was added up and then divided by 180 to calculate the percentage.

Osteolysis area was the actual 2D area seen on the X-rays.

Proposky classification[1] of bone loss was registered by surgeons, criteria see table 2, table 3.

Table 2. Paprosky classification of femur bone loss

Score	Criteria
I	Minimal metaphyseal cancellous bone loss / intact diaphysis
II	Extensive metaphyseal cancellous bone loss / intact diaphysis
IIIA	Metaphysis severely damaged / > 4cm diaphyseal bone for distal fixation
IIIB	Metaphysis severely damaged / < 4cm diaphyseal bone for distal fixation
IV	Extensive metaphyseal and diaphyseal bone loss / isthmus non supportive

Table 3. Paprosky classification of acetabular bone loss. (21)

Classification	Teardrop (medial wall)	Hip center (superior dome)	Kohler line (anterior column)	Ischium (posterior column)	Bone loss (remaining bone bed)
Type 1	Intact	No migration	Intact	Intact	Mild (> 50% cancellous)
Type 2					
2A	Intact	Mild migration < 2 cm superomedial	Intact	Intact	Moderate (< 50% cancellous)
2B	Intact	Moderate migration < 2 cm superolateral	Intact	Intact	Moderate (< 50% cancellous)
2C	Moderate lysis	Mild migration < 2 cm medial	Disrupted	Intact	Moderate (< 50% cancellous)
Type 3					
3A	Moderate lysis	Severe migration > 2 cm superolateral	Intact	Moderate lysis	Severe 10–2 o'clock loss (40%–70% sclerotic)
3B	Severe lysis	Severe migration > 2 cm superomedial	Disrupted	Severe lysis	Severe 9–5 o'clock loss (30% sclerotic)

[1] In order to use the classification in statistical analysis, the scores were graded as: Paprosky acetabulum: type I=1, type II A=2, type II B=2, type II C=2, type III A=3, type III B=3; Paprosky femur: type I=1, type II=2, type III A=3, type III B=3, type IV=4.

7.3.2 Positioning and alignment of cup

The positioning and alignment of the acetabular component were measured using predefined methods:

- Linear wear / penetration and implant migration (22, 23)
- Inclination and anteversion (24)

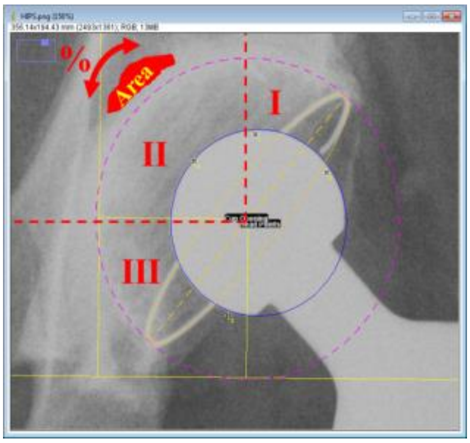


Figure 6. Degree and position of osteolysis

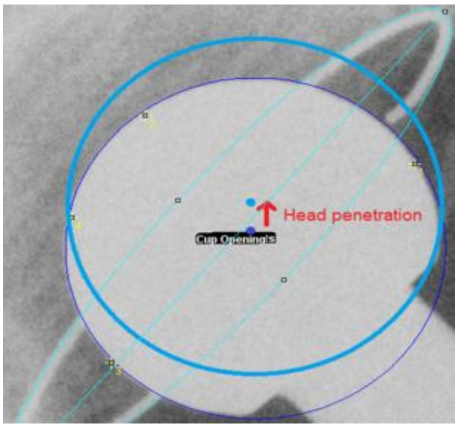


Figure 7. Positioning and alignment of cup

7.4 Wear of stems and cups

The wear of components collected from revision surgery was graded. Macroscopic inspection and light microscopy were performed. Pictures were taken by camera (SONY SLT-A55VL, Tokyo, Japan) and microscope (LEICA M205 C, Switzerland).

7.4.1 Stem grading

Three common damage modes: burnishing, abrasion and scratching were observed on the stems retrieved (25). Burnishing and abrasion always accompanied each other and presented most of the wear with a few scratching. So percentage of the burnishing and abrasion area out of the total surface area was used to present the stem wear.

7.4.2 Cup grading

Six common damage modes: pitting, scratching, burnishing, abrasion, permanent deformation, embedded particles were graded in quadrants I to IV respectively according to Bradford et al. (2004) (criteria see table 4) (26). Bradford gave the following definitions: "Pitting was a small depressed circular area, <1 mm in diameter, where material had been removed. Scratching was characterized by unidirectional lines that had been cut into the polyethylene. Burnishing was shallow multidirectional swirled lines on the articular surface, resulting in a highly polished appearance. Abrasion was area of roughened texture on the articular surface due to repeated rubbing against a counterface. Permanent plastic deformation was area particularly at the edges, where the polyethylene showed signs of flow and was deformed from its original shape. Particles of cement or metal that had become embedded in the polyethylene also were identified." The maximum possible surface-damage score for one quadrant was 18, representing a grade of 3 for each of the six different types of wear. The damage scores for each quadrant were then combined to give an overall score; the maximum possible score was 72.

Table 4. Criteria used to score cup (27)

Score	**Criteria**
0	the type of wear is absent
1	< 10% of the surface area is affected
2	10% - 50% of the surface area is affected
3	> 50% of the surface area is affected

7.5 Histological analysis and wear particle characterization

Tissue biopsies were analyzed histologically for adverse local biological reactions. Additionally, wear particle exposure were quantified using existing protocols (28, 29). Tissue surrounding the joint along with blood samples were collected and stored in the established Retrieval Biobank. Data such as wear particle exposure and histology acquired by optical microscopy, scanning- and transmission EM were collected and this information along with patient phenotypic information were entered into the Bergen Retrieval Database and analyzed in order to establish potential causality that may explain the failures observed in the retrieved specimens.

7.5.1 Histology and optical microscopy

All tissue sections had been digitalized and were stored in a research database at Haukeland University Hospital (Helse Bergen). The pathologists selected 3 cell-rich microscopic fields from each slide (two slides per patient) and stored them in the software Aperio ImageScope v12.1.0.5050. Macrophages, giant cells, and lymphocytes were counted from the selected area (criteria see table 5). Only in slide 1-2 were there some neutrophils, so neutrophil was excluded from result table. Median of cell grading for each slide was used in statistical analysis.

Table 5. Modified Mirra classification (30)

Histology	**1+**	**2+**	**3+**
Acute inflammatory cells (neutrophils)	1-5 cells/HPF	6-49 cells/HPF	50 or more/HPF
Mononuclear histiocytes (macrophages)	1-5 cells/HPF	6-49 cells/HPF	50 or more/HPF
Chronic inflammatory cells (lymphocytes, plasma cells)	1-9 cells/HPF	10-49 cells/HPF	50 or more/HPF
Giant cells (multinucleated histiocytes)	1 cell/HPF	2-4 cells/HPF	5 or more cells/HPF

HPF = high power field (x400)

7.5.2 Wear particle characterization

Light microscopy with polarization was used to detect polyethylene particles from the acetabular cup. Birefringent PE particles were identified by polarization microscopy (40x) and counted in a specified cell-rich area.

Dark field microscopy was used to image all kinds of particles: polyethylene, bone cement and metal particles. Particle characteristics were measured in the same sections with High-Resolution Optical Darkfield Microscopy (HR-ODM; Auburn, Al) as described (31). Using photographs (100x), the total amount of foreign body particles and equivalent diameter were measured with image analysis software (NIS-Elements 2.30, Nikon, Japan).

Three cell-rich microscopic fields were selected from each slide. Average of particle counting for each slide was used in statistical analysis.

7.5.3 Field emission scanning electron microscopy (FE-SEM) of tissue samples

Paraffin-embedded specimens were sectioned to a thickness of 5 µm and placed on 12 mm carbon tabs, which were fixed to 0.5" SEM-stubs (Agar scientific, Essex, England). It was necessary to remove paraffin from the sample to avoid contamination of the lenses in the electron microscopy instrument. Paraffin was removed by soaking the sample in xylene (Merck, Darmstadt, Germany), then in 100 %, 96%, 80% and 70% ethanol, (Arcus kjemi, Vestby, Norway), and finally rinsed in distilled water, 2 min in each bath. Before analysis the samples were coated by carbon, which is required to enable or improve the imaging of samples. Creating a conductive layer of metal on the sample inhibits charging, reduces thermal damage and improves the secondary electron signal required for topographic examination in the SEM. A carbon source, either in the form of a thread or rod is mounted in a vacuum system between two high-current electrical terminals. When the carbon source is heated to its evaporation temperature, a fine stream of carbon is deposited onto specimens (32).

Dense wear particles were observed using a field emission scanning electron microscope (FE-SEM; Merlin VP Compact, Carl Zeiss AG, Germany) both in secondary emission and back scattered modus operated at 15kV. Their chemical composition was determined by energy dispersive X-ray spectrometer with Oxford EDS Detector.

7.6 Statistics

The software package IBM SPSS Statistics 22 was used for statistical tests. For scale parameters, both Pearson (parametric) and Spearman (non-parametric) correlation were detected; for ordinal or nominal parameters, Spearman correlation was used. For cell grading, median was used to present the 3 cell-rich microscopic fields; for particle counting, mean was used to present the 3 cell-rich microscopic fields. One-way ANOVA was done for all parameters using different loose components as factor. Independent-Samples t-test was performed for cell numbers and particle numbers using different sample locations as factor.

8. Results

8.1 Patients information

There were 27 patients (17 male and 10 female) in this study. The average time of the prosthesis in situ before revision was 8.66 years. (Table 1)

In the group of patients with only cup loosening, the mean Paprosky score in acetabulum was 1.90, in femur was 0.30; in the group of patients with only stem loosening, the mean Paprosky score in acetabulum was 0.67, in femur was 2.00; in the group of patients with both cup and stem loosening, the mean Paprosky score in acetabulum was 2.00, in femur was 2.07.

The Paprosky score in acetabulum was positively correlated with other osteolysis parameters in the acetabulum in this study (osteolysis percentage: $r_{Spearman}$=0.635, p=0.020; osteolysis area: $r_{Spearman}$=0.568, p=0.034; osteolysis score: $r_{Spearman}$=0.731, p=0.005).

8.2 X-ray analysis

The linear penetration of the head into the cup was measured from the antero-posterior X-rays. Result showed wear rate ranged from 0.11 mm/year to 0.36 mm/year (more details see table 6). The median was 0.20 mm/year; mean

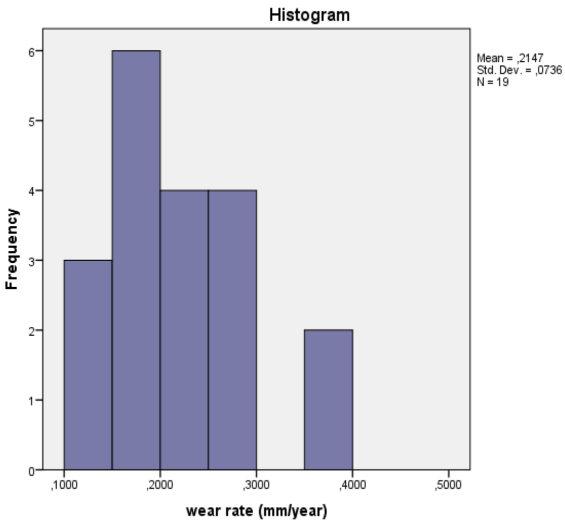


Figure 8. Histogram of wear rate (mm/year)

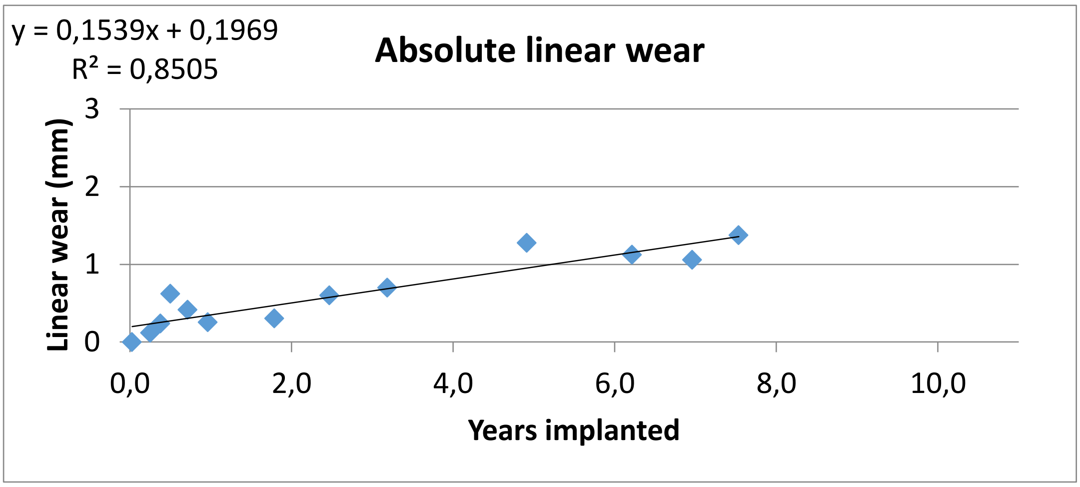
was 0.21 mm/year; 95% confidence interval of mean was (0.18; 0.25) mm/year (Figure 8). The total linear wear ranged from 0.50 mm to 4.05 mm. The median was 1.38 mm; mean was 1.59 mm.

Table 6. Linear penetration and osteolysis

Rec number	Linear wear rate (mm/year)	Total linear wear (mm)	Osteolysis percentage* (%)
1	0.24	1.73	34
7	0.15	0.98	28
15	0.20	2.31	64
20	0.27	2.10	77
140	0.11	0.50	
142	0.13	1.44	51
147	0.25	1.60	22
151	0.17	1.36	37
152	0.28	1.68	
154	0.23	2.65	57
155	0.19	1.20	
156	0.13	0.94	38
161	0.36	1.16	
166	0.16	1.16	21
170	0.21	2.07	
177	0.36	4.10	44
178	0.30	2.83	52
179	0.15	1.25	36
181	0.18	1.20	

* Some values were missing due to lack of osteolysis or bad image quality.

The cup wear showed linear correlation with implanted years. In other words, wear rate was relatively constant for each patient. Osteolysis in the acetabulum appeared soon after primary surgery and developed fast the first 2 years in most cases in this study. But after 2 years, osteolysis slowed down until it reached a plateau/maximum (Figure 9).



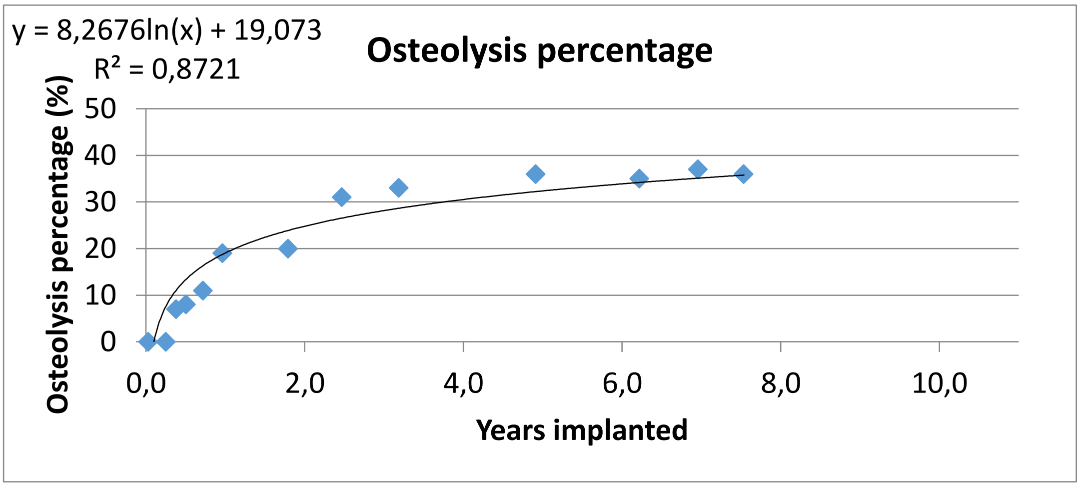


Figure 9. An example of linear cup wear (mm) as function of time (years) and osteolysis percentage (%) as function of time (years)

But there were some exceptions that total linear wear was not linear correlated with implanted years. The inclination angle (Figure 10) showed the cup started to rotate severely after 6 years in vivo. Meanwhile the wear was not linear anymore as function of time.

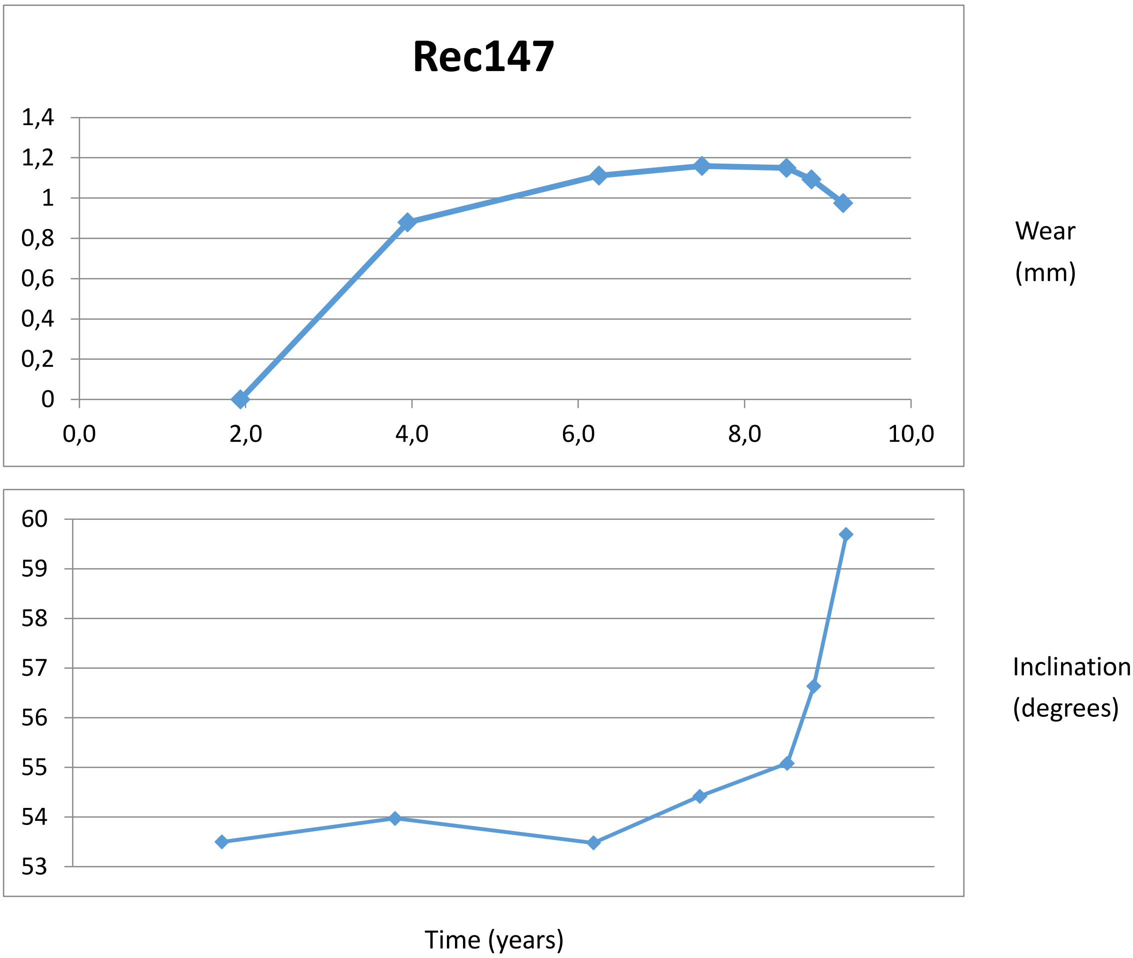


Figure 10. An example of non-linear wear due to change of cup inclination angle, indicating cup loosening

Most cases (13 out of 19) developed osteolysis in the acetabulum which could be seen from antero-posterior X-rays. The wear rate and osteolysis percentage in the acetabulum were positively correlated, but not statistically significant ($r_{Pearson}=0.308$, $p=0.307$) (Figure 11).

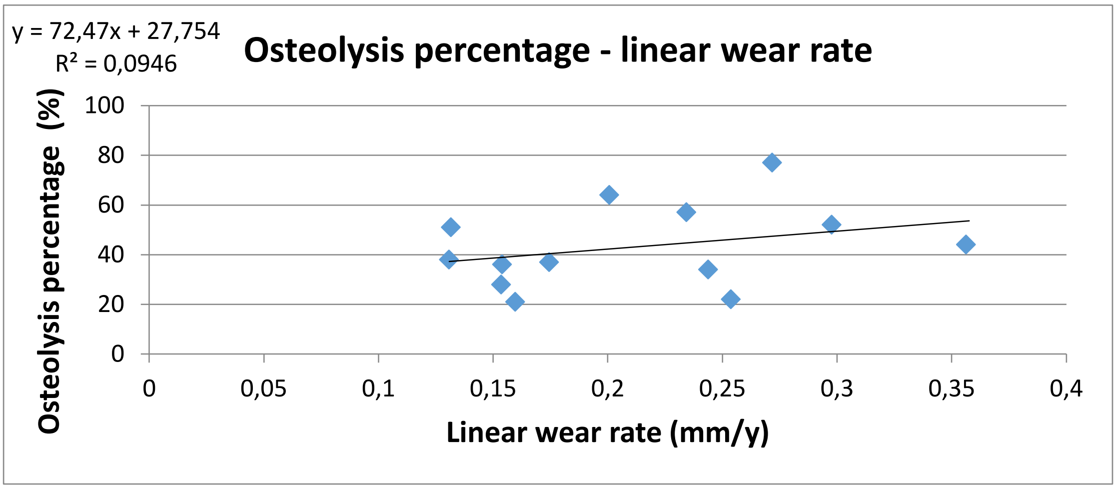
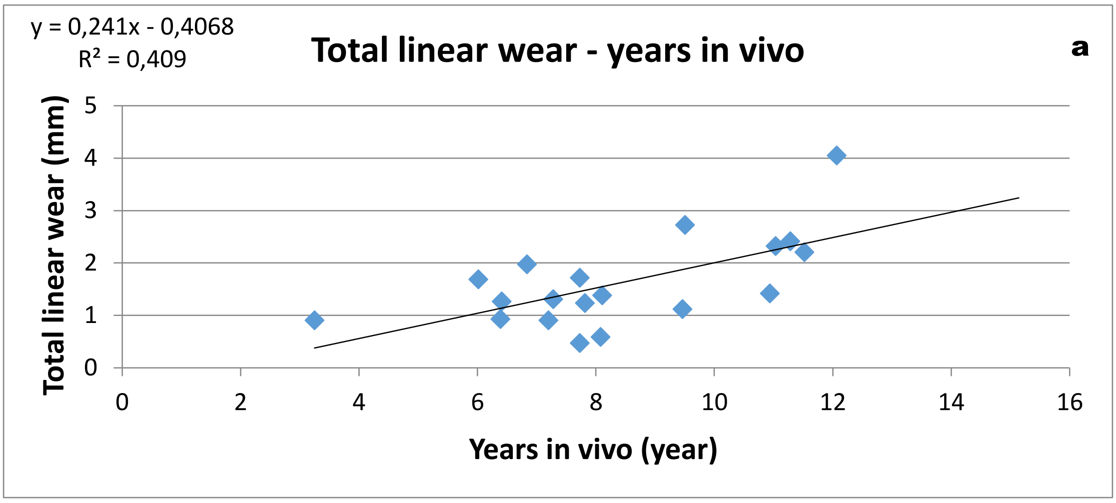


Figure 11. Osteolysis percentage – linear wear rate

The total linear wear was positively correlated with: 1. in vivo time of prosthesis ($r_{Pearson}$=0.629, p=0.004) (Figure 12a); 2. the number of PE particles in tissue samples collected from patients ($r_{Pearson}$=0.548, p=0.034) (Figure 12b); 3. osteolysis area behind the cup ($r_{Pearson}$=0.609, p=0.021) (Figure 12c).



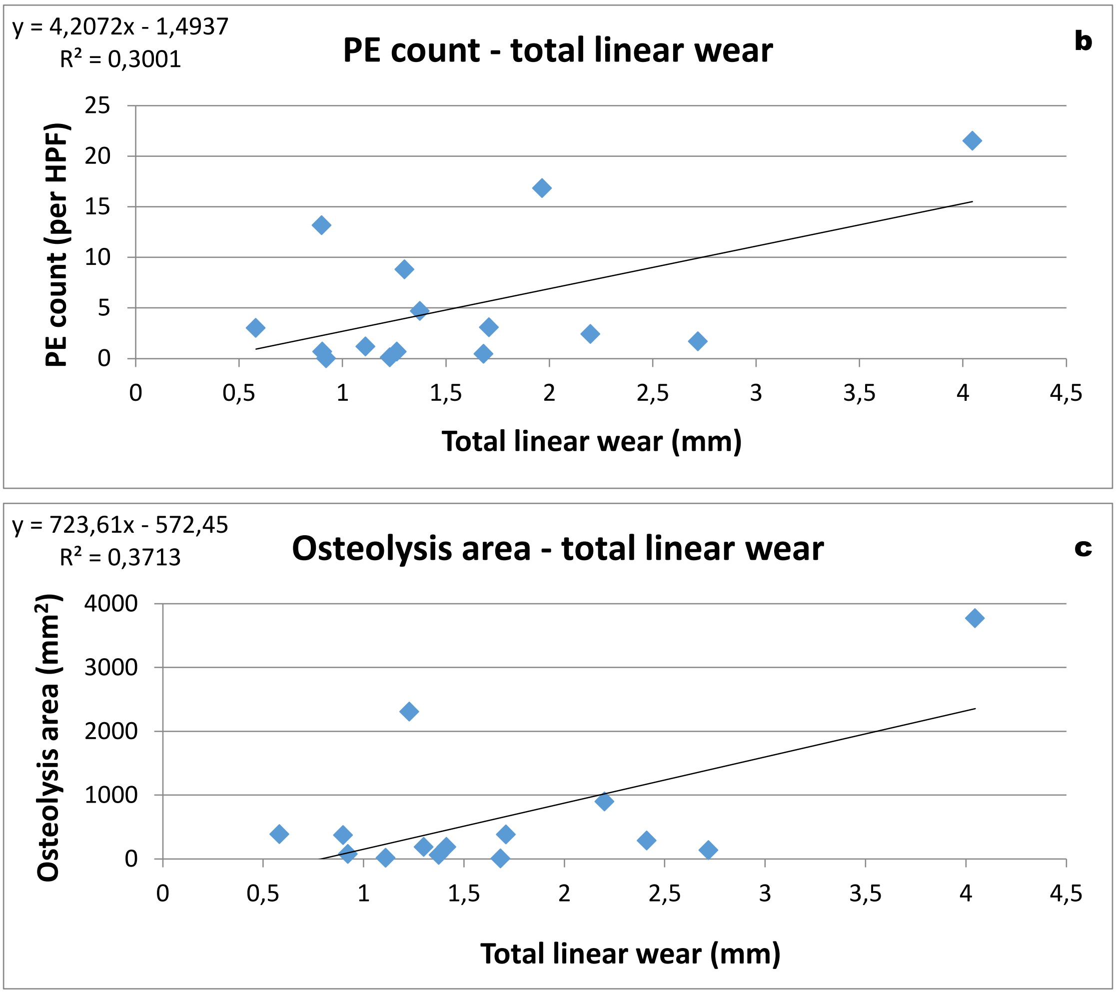


Figure 12. Total linear wear correlations (a,b and c)

Osteolysis parameters were correlated with concentration of particles (PE and total particle) in the biopsies and only one significant correlation was found: PE count and osteolysis area ($r_{Pearson}$=0.605, p=0.037) (Figure 13). Two cases were found with extremely large osteolysis area behind the cup (Figure 14).

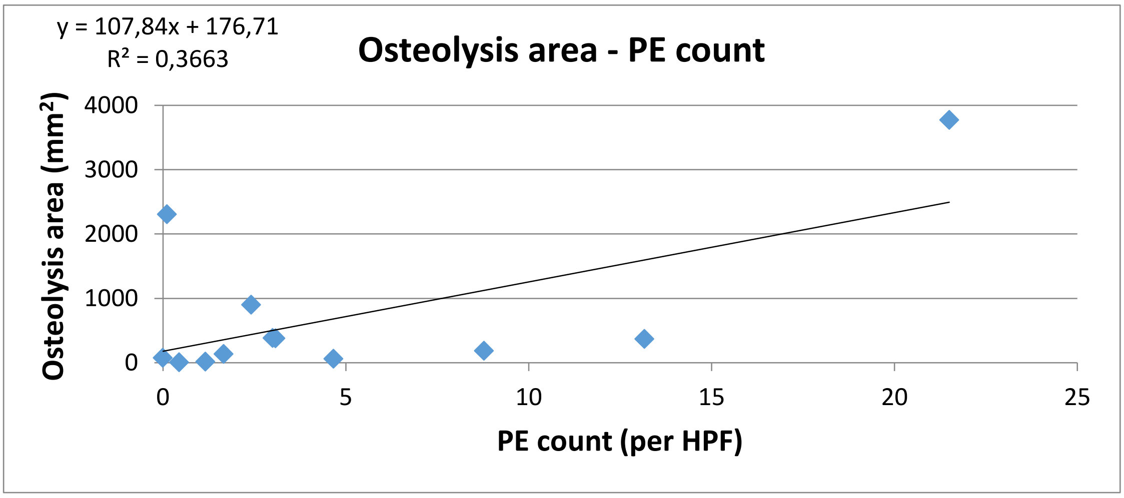


Figure 13. Osteolysis area - PE count

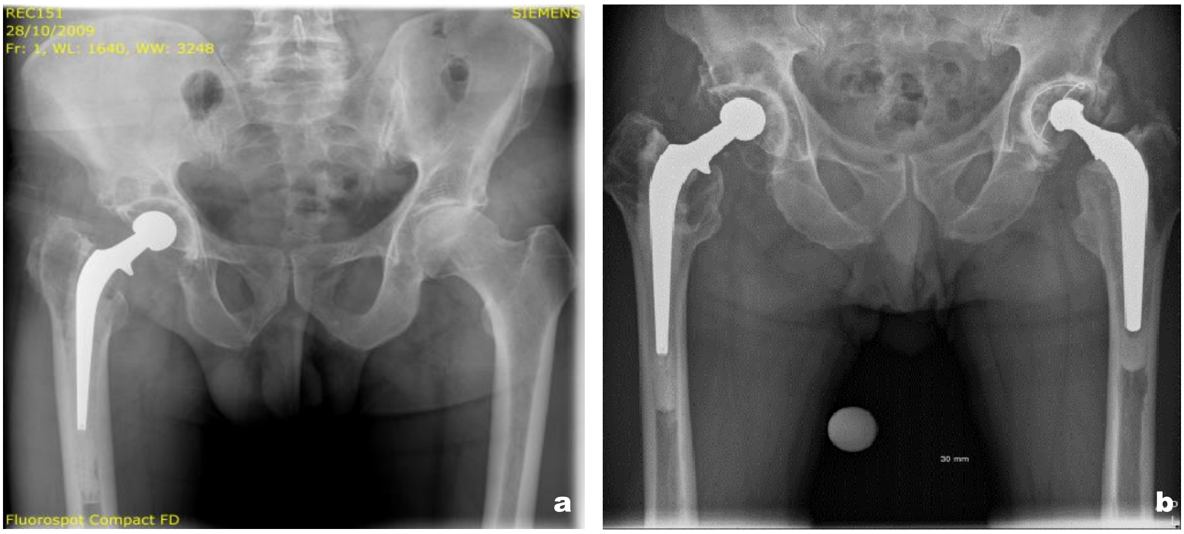


Figure 14. a. Rec151; b. Rec177(right hip) presented massive osteolysis behind the cup

There were also some cases with massive osteolysis around the stem (Figure 15). Tissue sample around the femur of Rek15 showed grade 2+ of mononuclear histiocytes and 3+ of multinucleated giant cells; PE count was 4 per HPF, total particle count was 1840 per HPF. Tissue sample (location unknown) of Rek173 showed grade 2.5+ of mononuclear histiocytes and 2.5+ of multinucleated giant cells; PE count was 2 per HPF, total particle count was 400.83 per HPF.

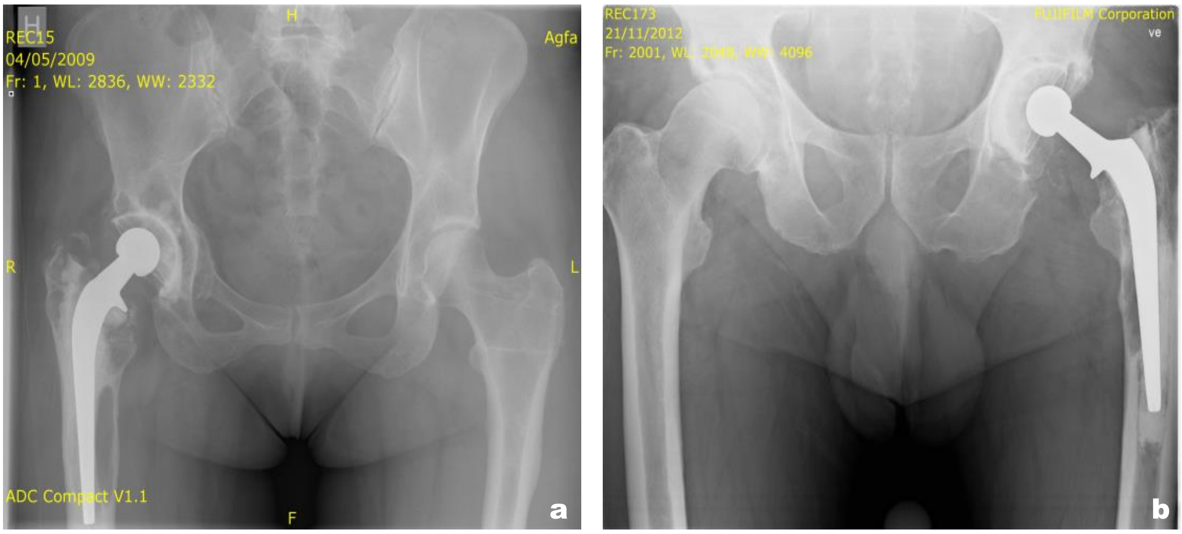


Figure 15. Examples of X-rays presented massive osteolysis around the stem (a. Rec15; b. Rec173)

Inclination and anteversion angles sometimes started differently other than 45 degree and 0 degree respectively because of surgery. They also went up and down at different time points after implanted. Most cases in this study changed about 5 degree in both inclination and anteversion angles. Figure 16 showed patient X-rays with abnormally high inclination angles which presented rotated cup.

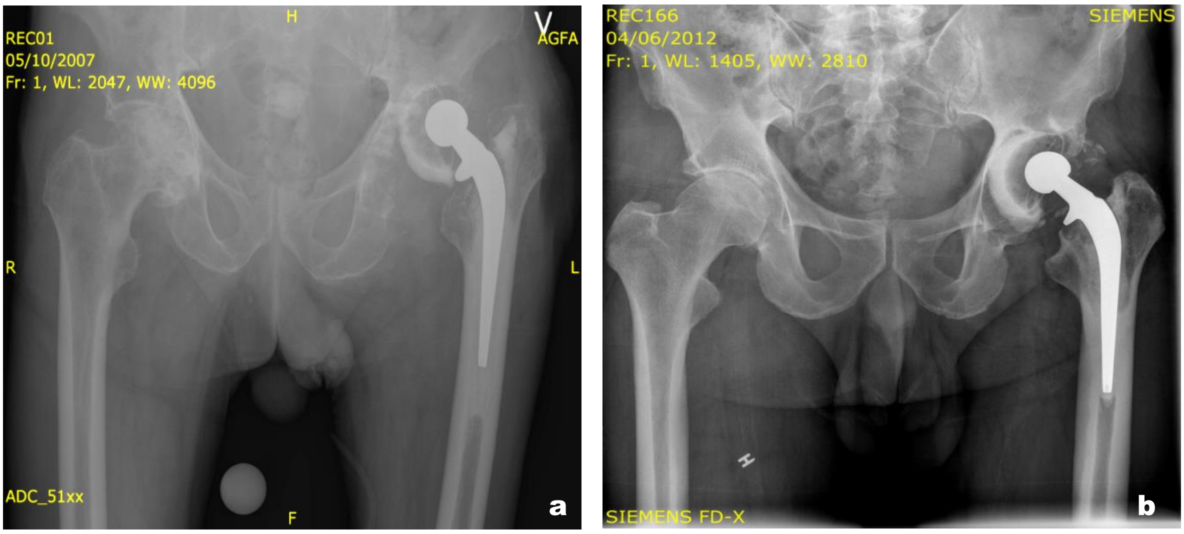


Figure 16. Examples of X-rays presented rotated cup (a. Rec1; b. Rec166)

Osteolysis percentage in the acetabulum was positively correlated with total linear wear (only significant in nonparametric correlation: $r_{Spearman}=0.676$, $p=0.011$;

$r_{Pearson}$=0.438, p=0.135).

Osteolysis was found more severe on the right side (osteolysis percentage: $r_{Spearman}$=0.742, p=0.004; osteolysis area: $r_{Spearman}$=0.656, p=0.011).

8.3 Stem and cup analysis

8.3.1 Stem

Burnishing and abrasion always accompanied each other and presented most of the wear with a few scratching marks (Figure 17).

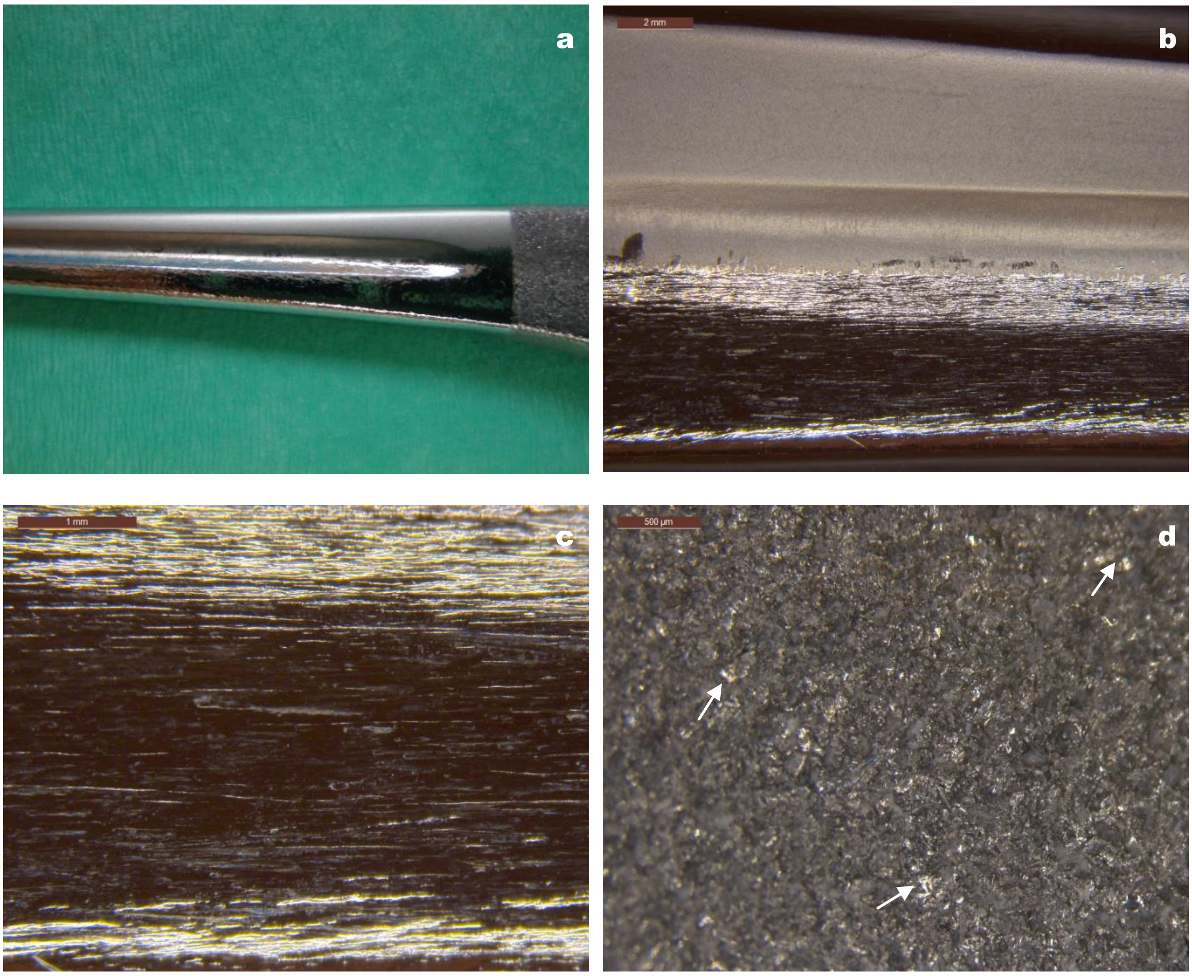


Figure 17. Stem sample with scratching, abrasive wear and burnishing. b and c. distal/smooth part; d. proximal/rough part, white arrows indicated a few of the scattered burnishing spots.

Most of the stems had 20% to 55% of surface wear (mean=35.9%, median=37.6%) (Figure 18) (more details see table 7).

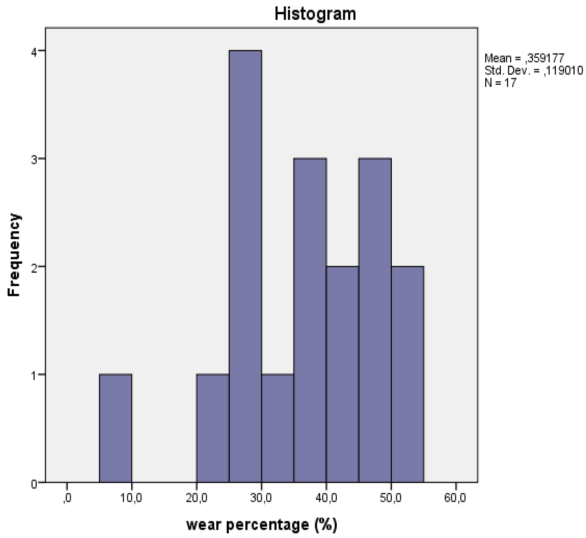


Figure 18. Histogram of wear percentage (%) of total surface area of stem

Within each stem, the posterior medial and anterior lateral were the most worn parts. In general, posterior side wear was more severe, especially in proximal rough part. For distal part, posterior side (40.3%) was more worn than anterior side (28.2%) ($p=0.001$); for proximal part, posterior side (54.0%) was also more worn than anterior side (11.9%) ($p<0.001$).

There was a correlation between gender and stem size ($r_{Spearman}=0.505$, $p=0.012$), offset ($r_{Spearman}=0.588$, $p=0.001$) and absolute offset value ($r_{Spearman}=0.639$, $p=0.001$). It showed males tended to use larger stem, high offset and the absolute offset value was also higher compared to females.

The Paprosky score in femur was positively correlated with absolute offset value of stem ($r_{Spearman}=0.403$, $p=0.046$).

8.3.2 Head

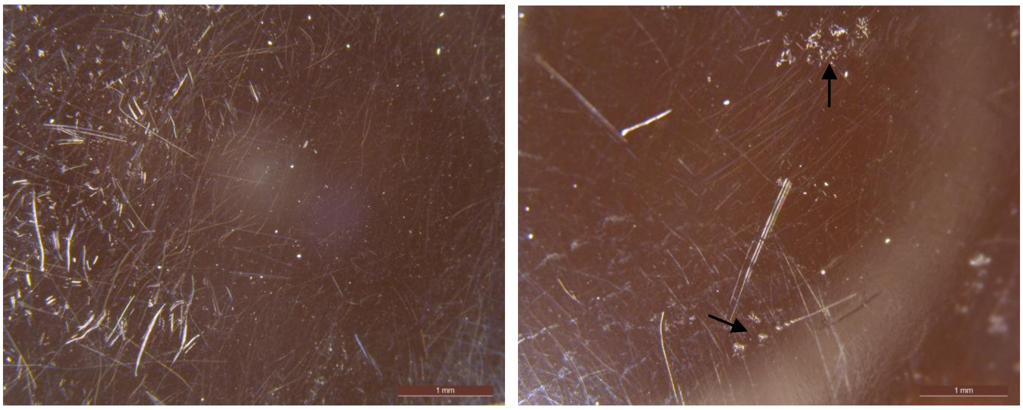


Figure 19. Head with scratching and pitting (black arrows)

8.3.3 Cup

Six common damage modes: pitting, scratching, burnishing, abrasion, permanent deformation, embedded particles were observed on retrieved cups (Figure 20).

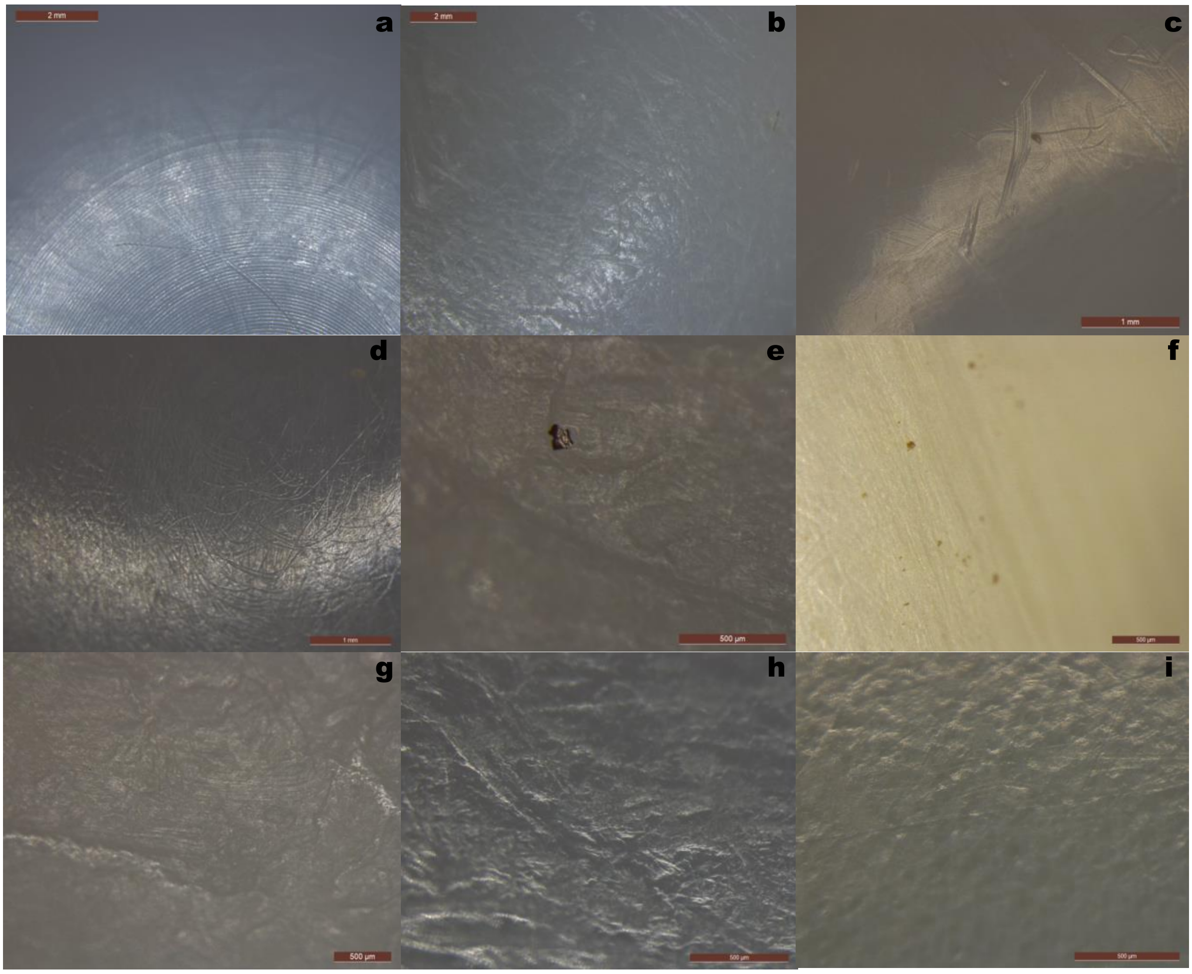


Figure 20. a. Unused cup with machined surface; b. cup sample with scratching, pitting and abrasive wear; c. burnishing; d. scratching; e. CoCr particle (third body) from the stem; f. ZrO_2 particles (third body) from the cement; g. scratching and pitting; h. abrasion; i. pitting.

Most of the cups were graded 20 to 30 (mean=20.25, median=24) (Figure 21) (more details see table 7).

Scratching (96%, mean score=1.43) and pitting (96%, mean score=1.38) were the most common damage modes in the acetabular cups, followed by burnishing (82%, mean score=2.12), abrasion (46%, mean score=0.76), permanent deformation (29%, mean score=0.45), embedded particles (25%, mean score=0.25). There was no statistical difference between quadrants I to IV in all kinds of damage modes except for permanent deformation: quadrant IV had higher score than quadrant II ($p<0.05$).

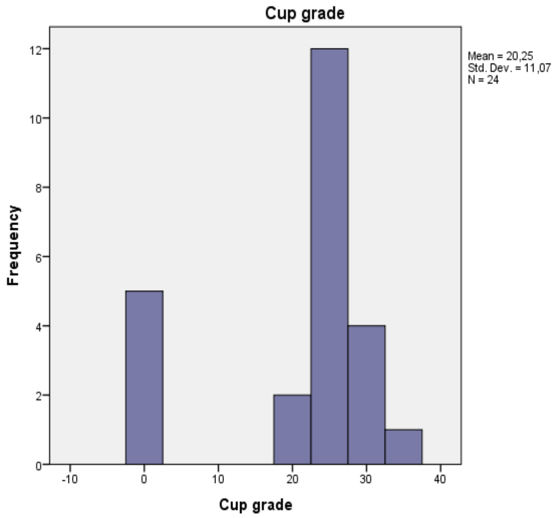


Figure 21. Histogram of cup grade

Cup grade was positively correlated with PE count from tissue samples ($r_{Spearman}=0.642$, $p=0.018$) (Figure 22).

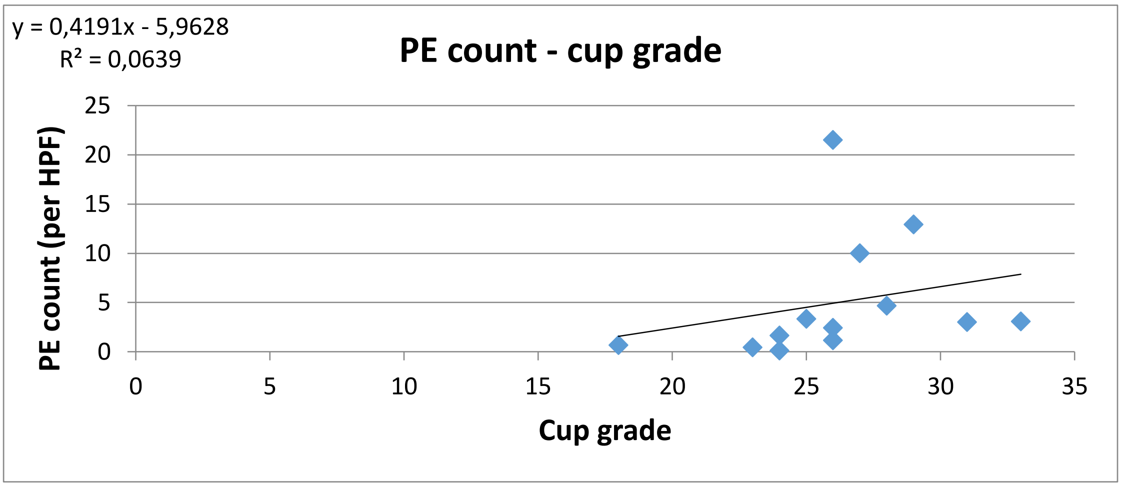


Figure 22. PE count – cup grade

Table 7. Stem and cup information

Rec number	Stem wear percentage* (%)	Cup grade*	Loose component	Stem size (mm)	Offset	Absolute offset value**
1	42	31	cup and stem	115	normal	38
7			cup	125	high	47
15	40	26	cup and stem	125	normal	36
20		33	cup	125	high	42
42			cup	125	normal	39
140	26	21	cup and stem	125	high	42
142	51	23	cup and stem	135	normal	41
147		26	cup	135	high	51
151	47	24	cup and stem	115	high	41
152		23	cup	RSA, str. 2	normal	42
154		27	cup	115	normal	35
155		18	cup	115	normal	35
156	46		stem	115	normal	
159	38		stem	125	high	44
161	27		cup and stem	135	normal	38
166	49		cup and stem	115	normal	
167	22	23	cup and stem	115	normal	38
170		29	cup	115	normal	35
171	50	23	cup and stem	135	high	54
172	37	27	cup and stem	RSA, str. 2	normal	39
173	38		cup and stem	135	high	51
177	27	26	cup and stem	125	high	47
178	34	24	cup and stem	125	normal	36
179		28	cup	RSA, str. 2	normal	36
181			cup	125	normal	36
182	29	25	stem	135	high	54
183	7	29	cup and stem	125	normal	39

RSA, str. 2: 125 mm in stem length

* Some values were missing because the component was not revised (still well-fixed) or not collected.

** Some values were missing due to lack of information (of the head) in the database.

For the causes of revision, there was loosening of cup, loosening of stem and loosening of both. They were grouped as 1, 2 and 3 respectively.

The result of one-way ANOVA for all parameters using different loose components as factor showed only total particle count was significantly different between groups:

cases with cup loosening and cases with cup and stem loosening were different (p=0.003) (Figure 23). The mean values of particle number were 285.41, 1309.47 and 724.95 respectively; the median values were 134.00, 1317.83 and 786.50 respectively.

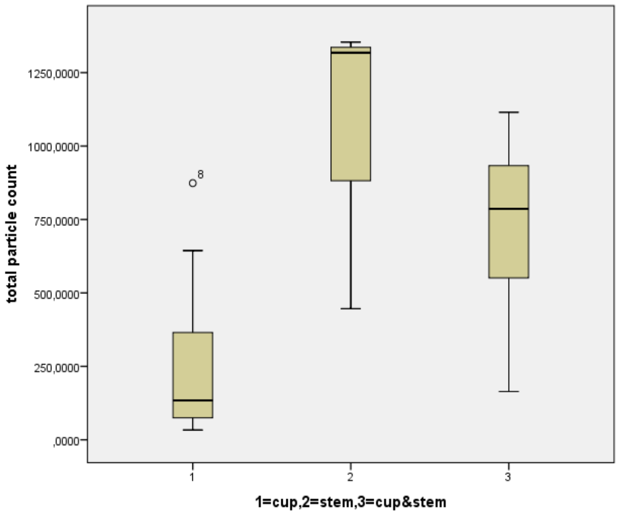


Figure 23. Box plot of total particle count of different loosening components

In this study, retrievals showed the loosening of cups mainly occurred between cement and bone; the loosening of stems mainly occurred between cement and stem.

8.4 Histological analysis and wear particle characterization

The histological study showed a large amount of mononuclear histiocytes and multinucleated giant cells, some lymphocytes, few neutrophils in peri-prosthetic tissue samples from patients (Figure 24). Light microscopy with polarization was used for detection of polyethylene particles (Figure 25). Dark field microscopy was used for detection of the total number of wear particles (Figure 26).

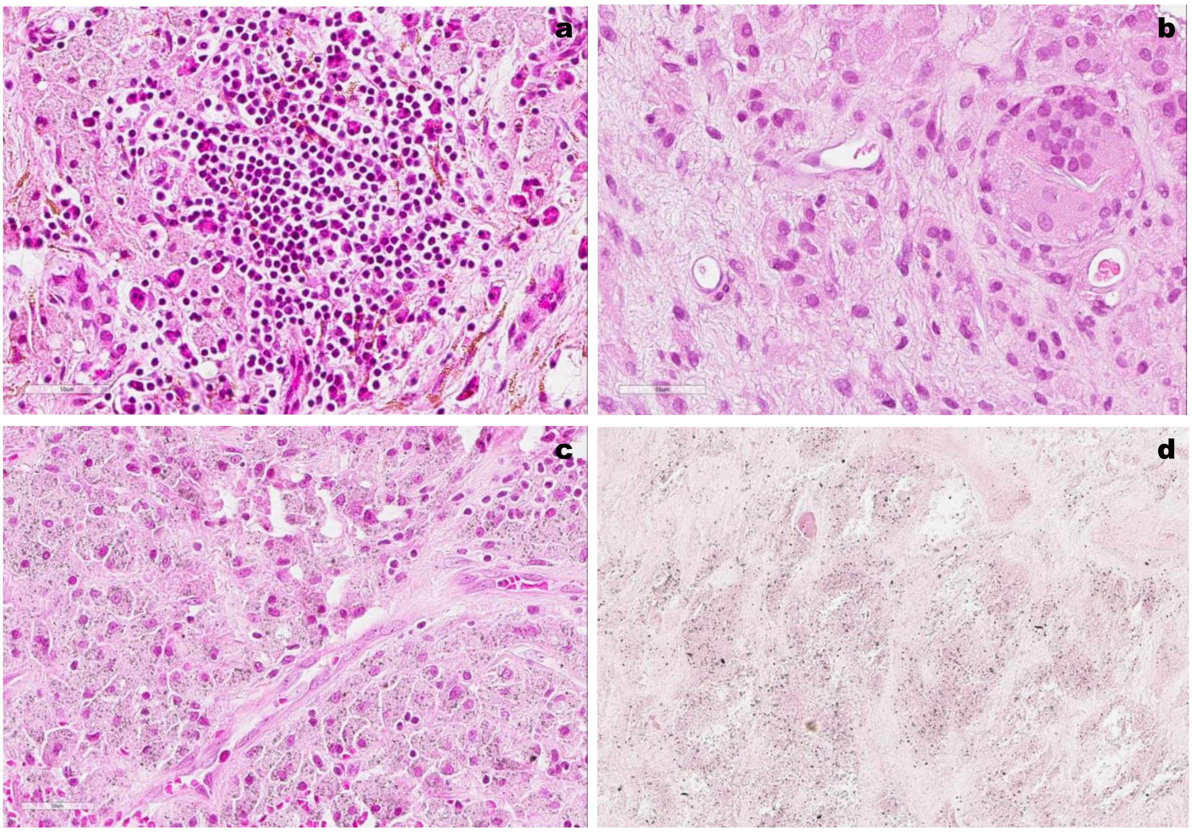


Figure 24. Examples of different cell type (Hematoxilin-eosin stained tissue section). a. Lymphocytes accumulation (graded 2+) from slide Rec147-1A; b. giant cell formation (graded 3+) from slide Rec42-3; c. macrophage (graded 2+) phagocytosing bone cement wear particles (ZrO_2) from slide Rec156-3A; d. massive necrosis with fibrosis, no cell but ZrO_2 particles left from slide Rec166-2A. Scale bar=50 um

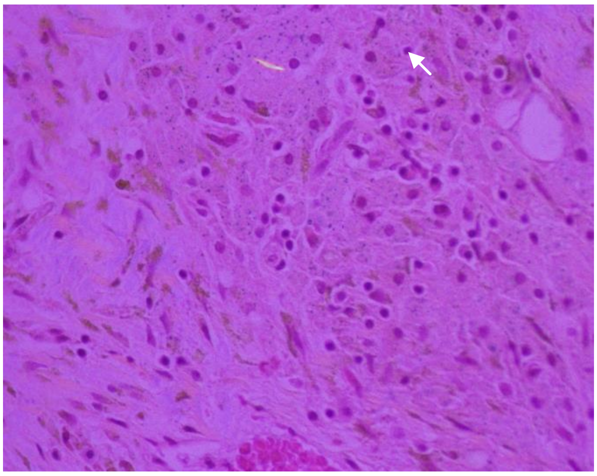


Figure 25. Light microscopy with polarization for detection of polyethylene particles (white arrow), numerous bone cement wear particles (ZrO_2) inside macrophages. (x400)

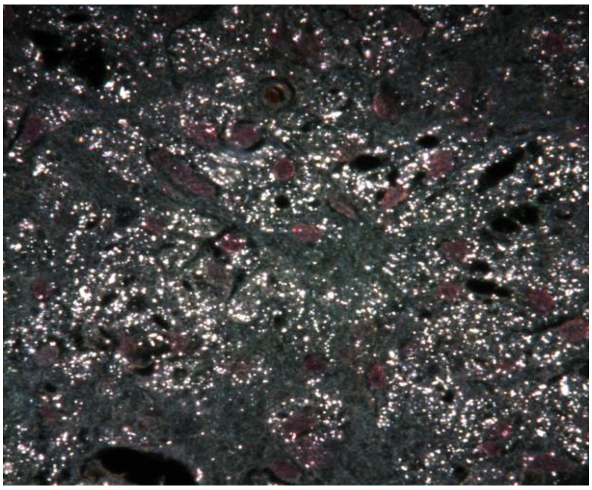


Figure 26. Dark field microscopy for detection of all kinds of particles: polyethylene, bone cement and metal. (x1000)

Fifty-one percent of the slides were graded 2+ in macrophages, 42% of the slides were graded 3+ in giant cells and 78% of the slides were graded 1+ in lymphocytes (Figure 27) (more details see table 9 in appendix).

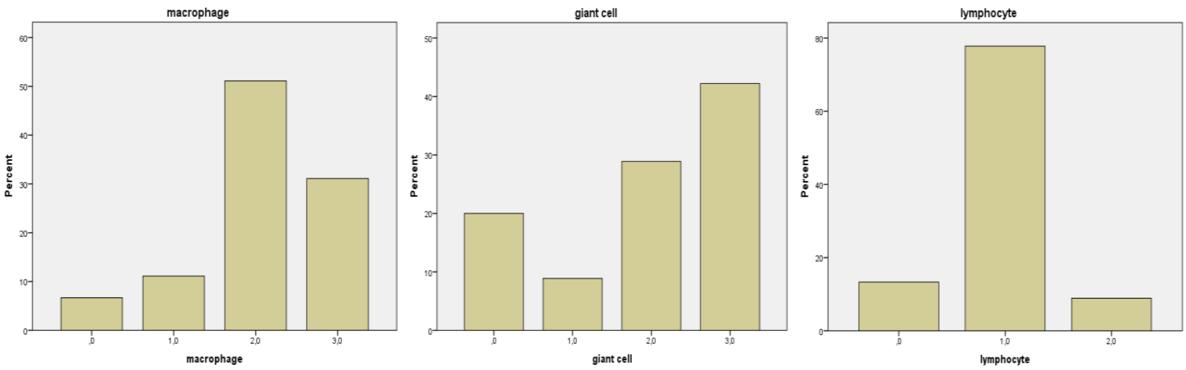


Figure 27. Histograms of cell grading according to modified Mirra classification (macrophage, giant cell and lymphocyte)

Particle density ranged from 1451 to 58952, mean=25864, median=28044 (per mm^2). Median equivalent diameter ranged from 0.37 to 0.85, mean=0.56, median=0.57 (um). PE count ranged from 0 to 21.5, mean=5.77, median=3.08 (per HPF) (Table 8).

The measured particles ranged from 0.08 um to 10.10 um in equivalent particle diameter (Figure 28). These particles included CoCr from the stem, PMMA from the cement and PE from the cup.

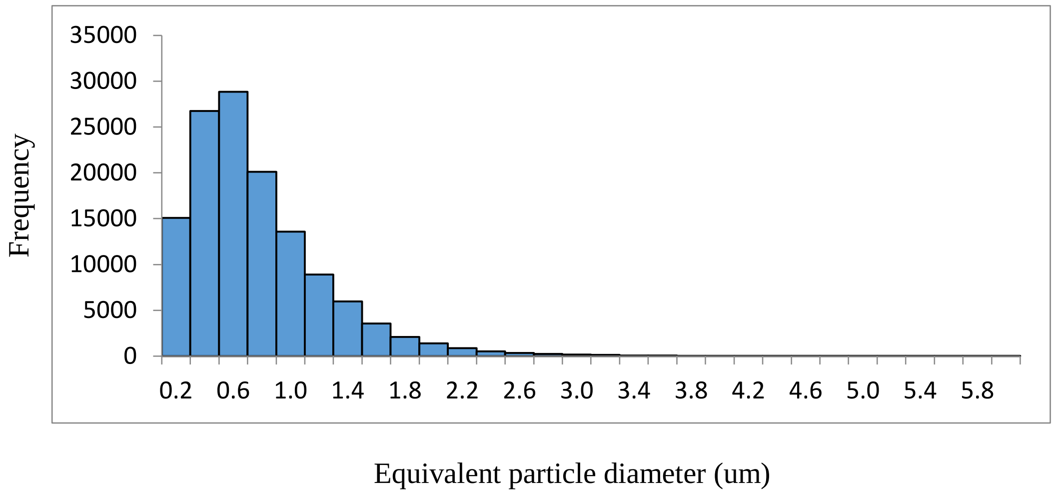


Figure 28. Frequency distribution of the equivalent particle diameter (um) of the particles counted under darkfield microscope.

FE-SEM showed tissues around the hip implants contained mainly ZrO_2 particles from the bone cement, a few CoCr particles from the stem and head (Figure 29).

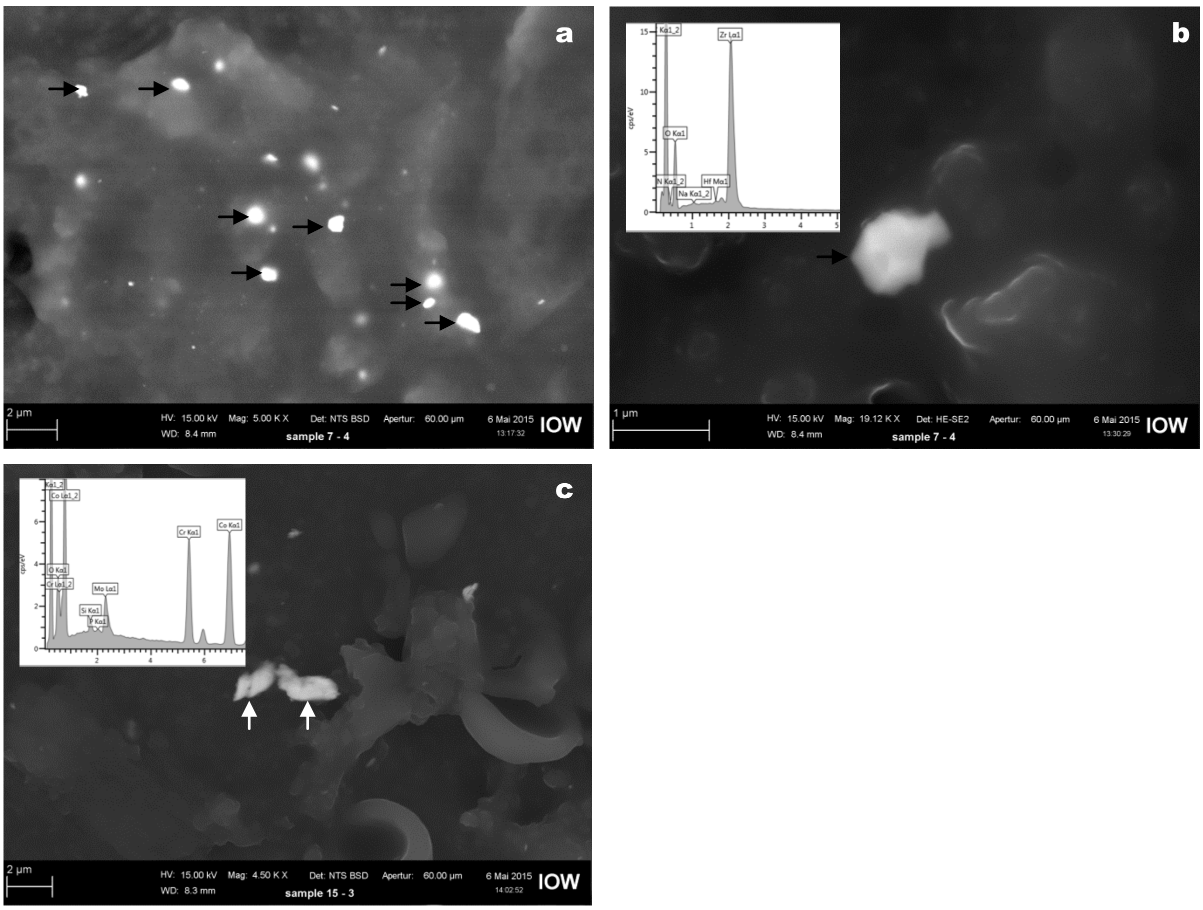


Figure 29. Scanning electron microscopy (SEM) images of particles. a. Black arrow highlighting dense ZrO_2 particles, which were found most frequent in tissue; b. ZrO_2 particle (black arrow) with EDXA spectra; c. CoCr particles (white arrow) with EDXA spectra.

Giant cell was in positive correlation with osteolysis score measured in acetabulum ($r_{Spearman}$=0.616, p=0.033).

The score of Paprosky femur was in positive correlation with total particle count, with almost significant p-value ($r_{Spearman}$=0.411, p=0.051).

Histological results for all slides were listed in table7 in Appendix. For PE particle count, the mean values were 14.17 (median=3.17)/HPF in acetabulum, 12.21 (median=2.33)/HPF in capsule and 17.52 (median=5.67)/HPF in femur. There was no statistical difference.

For total particle count, the mean values were 1055.91 (median=935.50)/HPF in femur, 488.03 (median=217.00)/HPF in capsule and 361.75 (median=163.84)/HPF in acetabulum. There were statistical differences between different locations (femur and capsule: p=0.003; femur and acetabulum: p<0.001).

Cell results were correlated with particle results within the same slide to detect the adverse local chronic inflammation reactions caused by wear particles. It showed giant cell was positively correlated with total particle count ($r_{Spearman}$=0.393, p=0.008).

Slides from acetabulum showed positive correlation between PE count and total linear wear ($r_{Pearson}$=0.649, p=0.012).

Slides from capsule showed positive correlation between PE count and macrophages, giant cells (macrophages: $r_{Spearman}$=0.605, p=0.037; giant cells: $r_{Spearman}$=0.867, p<0.001).

Table 8. Particle characterization of peri-prosthetic tissues from patients

Rec number	Particle density (per mm²)	Median equivalent diameter (um)	PE count (per HPF)
1	43103	0.37	3
7	2358	0.54	0
15	30550	0.39	2.42
20	3255	0.85	3.08
42	5834	0.43	11
147	38046	0.62	1.17
151	40331	0.53	0.11
152	28044	0.53	0.44
154	15899	0.38	>150
155	1451	0.68	0.67
156	58952	0.61	13.17
159	57377	0.61	3.83
161	34243	0.50	0.67
166	32524	0.51	8.78
167	40931	0.61	>150
172	48546	0.66	10
173	17452	0.66	2
177	38517	0.60	21.5
178	13853	0.57	1.67
179	3824	0.78	4.67
181	13127	0.57	16.83
182	19444	0.43	3.33
183	7208	0.49	12.92

Tissue samples in this study were taken from three different locations: around the femur, capsule and behind the acetabulum. They were grouped as 1: tissue around the femur which was closely located with the stem; 2: tissue from capsule or behind the acetabulum which was closely located with the cup. Independent-Samples T Test for cell numbers and particle numbers using different sample locations as factor was done and showed that only total particle count was significantly different between groups: samples near the stem and samples near the cup were different ($p<0.001$) (Figure 30).

The mean values of particle number were 1055.91 and 434.86 respectively. The median values were 935.50 and 192.50 respectively.

The mean values of PE count were 17.52 and 13.05 respectively. The median values were 5.67 and 2.33 respectively. There was no significant difference (Figure 31).

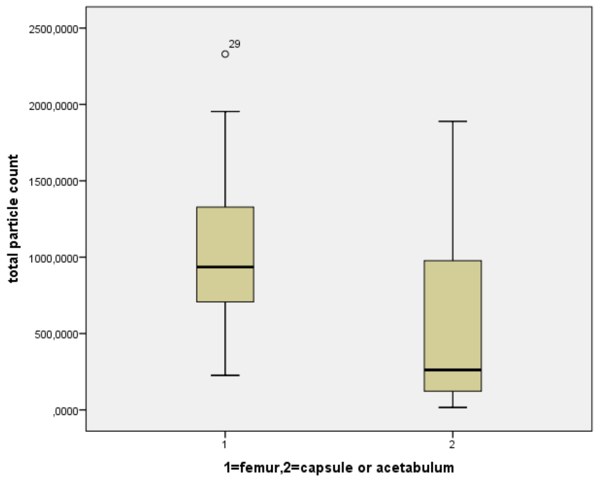


Figure 30. Box plot of total particle count of different sample locations

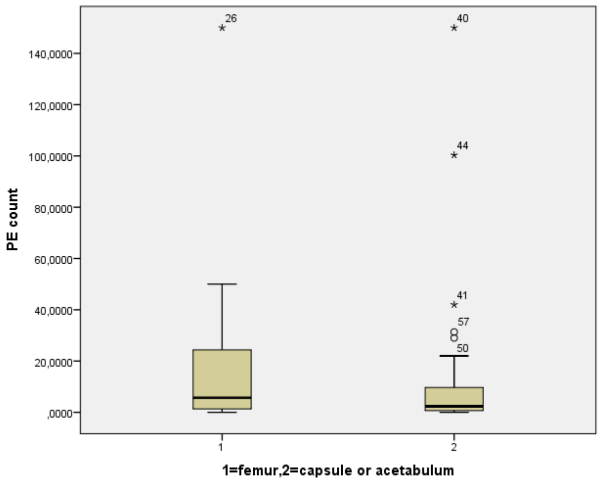


Figure 31. Box plot of PE count of different sample locations

9. Discussion

Total hip arthroplasty (THA) is most commonly used to treat joint failure caused by osteoarthritis. More than 1 million arthroplasties are done every year worldwide, and this number is projected to double within the next two decades (1). In Norway more than 10 % of these cases needed revision operations due to aseptic loosening. The Spectron EF femoral stem was reported by the Norwegian Arthroplasty Register to have 3.8 times higher relative risk of revision than the Charnley total hip replacement (6). In this study 27 cases of failed hip prostheses were collected and the appearance of osteolysis, the alignment of the components and linear penetration in the cups were measured from patient radiographs; the wear of components collected from revision surgery was graded; tissue biopsies for adverse local chronic inflammation reactions were analyzed histologically and wear particle exposure was quantified using different microscopy techniques and energy-dispersive X-ray analysis. This study aimed to determine the failure mechanisms responsible for the unexpectedly high rate of aseptic loosening of the Spectron EF hip stem in combination with the Reflection acetabular cup.

9.1 X-ray analysis

The cup wear rate found in this study (0.21 mm/year) is comparable with other studies using the same PE-quality (8, 33, 34). X-rays analysis also showed the linearity of the head penetration into the cup (34). The wear rate in all cases in this study exceeded the osteolysis threshold (0.1 mm/y) (35). Most cases (13 out of 19) developed osteolysis in the acetabulum which could be seen from antero-posterior

X-rays. However, plain radiographs may lead to underestimation of the extent of osteolytic lesions (13). In this study osteolysis appeared soon after primary surgery and developed fast in first 2 years in most cases. But after 2 years, osteolysis increased at a slower rate until the cup loosened and needed revision.

Previous study showed there was no relationship between the inclination angle and femoral head penetration and of the acetabular component (36), but the big change of inclination angle could still give a hint of massive osteolysis, cup loosening and rotation. (Figure 16)

The total linear wear was positively correlated with: 1. in vivo time of prosthesis, it indicated the constant wear of the cup inside the body; 2. the number of PE particles in tissue samples collected from patients; 3. osteolysis area behind the cup, it supports the theory that PE particles are historically thought the main cause of osteolysis and leads to the aseptic loosening of component (37) (Figure 12).

In the scatter chart of total linear wear – osteolysis area (Figure 12c), there were two extreme values (Rek151: 2306mm^2; Rek177: 3773mm^2) suggested intensive osteolysis behind the cup (Figure 14), which may also cause false positive correlation. Tissue sample around the cup of Rek151 showed severe necrosis, fibrosis and only a few macrophages were left; PE count was 0 per HPF, total particle count was 1520,67 per HPF. Tissue sample (location unknown) of Rek177 showed high grade of mononuclear histiocytes and multinucleated giant cells; PE count was high (21.5 per

HPF), total particle count was 884.67 per HPF. This showed massive osteolysis in the acetabulum could happen whether the PE number was high. It indicated PE was not the only cause of osteolysis in the acetabulum.

PE count and osteolysis area were found positively correlated (Figure 13). It agrees with PE particles can cause osteolysis and subsequently the aseptic loosening of components (37). There were also two extreme values that should be aware.

Osteolysis percentage in the acetabulum was positively related with total linear wear. It also supports the hypothesis that PE particles from cup wear could cause osteolysis (12, 37).

9.2 Stem and cup

9.2.1 Stem

Most of the stems had severe surface wear (20% - 55%). The wear pattern along the long side (Figure 17) and the certain part (posterior medial and anterior lateral) indicated the presence of relative movement within the cement shell while walking.

The correlation between gender and stem size, offset and absolute offset value showed males tended to use larger stem, high offset and the absolute offset value was also higher compared to females. This was possibly due to the different body size of different gender.

The score of Paprosky femur was positively correlated with absolute offset value of stem. Previous studies also found that high stem offset was a risk factor for stem revision (38, 39).

The wear of the stems was much more severe than that of the femoral heads (Figure 17, 19). It indicated that the CoCr particles found in the tissue were mostly from the stems.

9.2.2 Cup

Most of the cups were graded 20 to 30. The only statistical difference of different damage modes between quadrants I to IV was permanent deformation: quadrant IV had higher score than quadrant II. It agrees with the upper part of cup need to undertake the body weight above the hip. Some damage modes like scratching and embedded particles were the proof of third body wear (Figure 20).

Cup grade was positively correlated with PE count (Figure 22). This indicated cup wear released PE particles and these particles stored and spread in the peri-prosthetic tissue.

The result of one-way ANOVA for all parameters using different loose components as factor showed only total particle count was significantly different between groups: cases with cup loosening and cases with cup and stem loosening were different (Figure 23). The mean values of particle number were 285.41, 1309.47 and 724.95 respectively; the median values were 134.00, 1317.83 and 786.50 respectively.

Tissue samples from cases with stem loosening had higher number of total particles (mainly ZrO_2) indicated stem loosening accompanied by relative movement within the cement shell may lead to massive cement particles releasing while walking.

For patients with stable stem, the average score of Paprosky femur was 0.30; for patients with stem loosening, the average score of Paprosky femur was 2.06. And the only parameter detected different was total particle count (among the patients with or without stem loosening). It indicated total wear particles may cause the extra bone loss in the femur. The score of Paprosky femur in this study was also in positive correlation with total particle count, with almost significant p-value ($r_{Spearman}=0.411$, $p=0.051$).

For patients with cup loosening (1 and 3), the average score of Paprosky acetabulum was 1.96; for patients with stem loosening (2 and 3), the average score of Paprosky femur was 2.06.

In this study, retrievals showed the loosening of cups mainly occurred between cement and bone; the loosening of stems mainly occurred between cement and stem.

In conclusion, stem loosening within the cement shell could lead to massive cement particles releasing, which aggravated the osteolysis in the femur (Paprosky femur score 2.06). But it was still not enough for the loosening between bone and cement and the loosening of stems mainly occurred between cement and stem.

9.3 Histological analysis

Histological study showed the most frequent grade for macrophages was 2+ (51%); for giant cells was 3+ (42%); for lymphocytes was 1+ (78%) (more details see table 9 in appendix). The large amount of mononuclear histiocytes and multinucleated giant cells were the media of spontaneous inflammation.

After phagocytosis of wear particles, monocyte/macrophage lineage cells (macrophages, foreign body giant cells, and osteoclasts) increase the transcription of pro-inflammatory substances, including cytokines, chemokines, reactive oxygen intermediates, prostaglandins, metalloproteinases, lysosomal enzymes, and other factors (15). These pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, appear to act synergistically on osteoclastogenesis and promote osteoclast function (17, 18). It breaks the local tissue homeostatis of bone formation and resorption, and leads to periprosthetic osteolysis (40).

The bioreactivity of wear particles is determined by its size, shape, composition and concentration (13-16). One study showed PE particles in the size range 0.1–1 um were 25-fold more active than the range 10–100 um using TNF-α as a marker. As a result, smaller submicron PE particles appear to activate cells most effectively (41). Another in vitro study found that particles in the size range from 0.3 to 10 um activate macrophages maximally whereas the biological activity of macrophages decreases with particle sizes out of this range (42). A bone-chamber model study showed particulate degradation products diminished bone ingrowth. It moderately decreased in the presence of high-density polyethylene particles and intensively decreased in the presence of cobalt-chromium particles (43).

Polyethylene debris less than 1-2 microns in size are phagocytosed by macrophages, while larger particles of more than 10 microns are surrounded by multinucleated giant cells (13, 44). In this study, giant cell was in positive correlation with osteolysis score. Cell results were correlated with particle results within the same slide to detect the adverse local chronic inflammation reactions caused by wear particles. It showed giant cell was positively correlated with total particle count.

Slides from capsule tissues showed positive correlation between PE count and macrophages, giant cells.

Only slides from acetabulum showed positive correlation between PE count and total linear wear of the cup. The quantitative relation confirmed that PE particles were released from the cup wear.

Independent-Samples T Test for cell numbers and particle numbers using different sample locations as factor was done and showed that only total particle count was significantly different between samples near the stem and samples near the cup (Figure 30). The mean value of particle number was 1055.91 near the stem and 434.86 near the cup. The median was 935.50 near the stem and 192.50 near the cup. Samples near the stem had higher number of total particles (mainly ZrO_2) indicated stem-cement interface wear caused most particles. They were released into tissues nearby and could also travel to the capsule and even behind the cup.

The mean value of PE count was 17.52 near the stem and 13.05 near the cup. The median was 5.67 near the stem and 2.33 near the cup (Figure 31). Samples from different locations had similar PE count indicated polyethylene particles caused by cup wear were released into tissues near the cup and spread evenly into the capsule and around the femur.

9.4 Wear particle characterization

Different microscopy techniques and energy-dispersive X-ray analysis proved wear particles originated from different sources. FE-SEM showed tissues around the hip implants contained mainly ZrO_2 particles from the bone cement, a few CoCr particles from the stem and head (Figure 29). It was likely that the wear particles came from the ongoing wear in cement-stem interface during and especially after loosening.

9.5 Failure mechanisms

In this study, conventional UHMWPE with low wear resistance was used as the cup material; proximal roughened “Spectron EF” was used as the stem. Polyethylene sterilized in ethylene oxide such as in the Reflection shell, has been reported to have approximately twice the head penetration compared to those sterilized with gamma irradiation (45). More detailed analysis has indicated that the rate of femoral loosening may be related to the modern Spectron EF stems rough proximal surface finish (7, 8), although it was intended to enhance the primary fixation. This combination was shown to be prone to causing increased number of different wear particles, possibly leading to aseptic loosening and osteolysis. (Figure 32)

After implantation, wear particles could be produced in the following two stages:

Primary stage:

Mechanical load on prosthesis during physical activity cause:

1. *PE particles releasing from wear of cups, which result from motion occurring*

between the prosthetic femoral head moving against the PE acetabular bearing surface;

2. Cement and metal particles releasing from wear in stem-cement interfaces, which result from micro-motion occurring between the prosthetic femoral stem against the cement shell due to different elastic modules.

These particles can cause osteolysis just after primary surgery and migrate with tissue fluid along joint space or tissue nearby.

Secondary stage:

Particle migration from the stem-cement interface can cause third body wear between the prosthetic femoral head and the cup which will aggravate the wear on this surface. It was supported by the wear modes observed on the head and inside the cup.

The micro-motion between the prosthetic femoral stem and the cement shell became after several years (typically 5-7 years) macro relative motion i.e. mechanical loosening. It was supported by the wear modes observed on the stem. The motion together with third body wear after loosening within cement shell caused high release of cement and metal particles and was the main source of particles around the femur. It was supported by the total particle count of patients with different loose component and the total particle count at different sampling locations.

Osteolysis was cause by particles produced in situ or migrated. It is difficult to differentiate between the osteolytic capabilities of the particles detected in this study. Non-highly cross-linked UHMWPE “Reflection” and proximal roughened “Spectron EF” were both negative factor for survival of prosthesis. It caused severe wear at primary stage and an early start of secondary stage following by massive osteolysis and component loosening.

In this study, loosening of cups mostly occurred between cement and bone due to osteolysis; loosening of stems mostly occurred between cement and stem due to mechanical reasons.

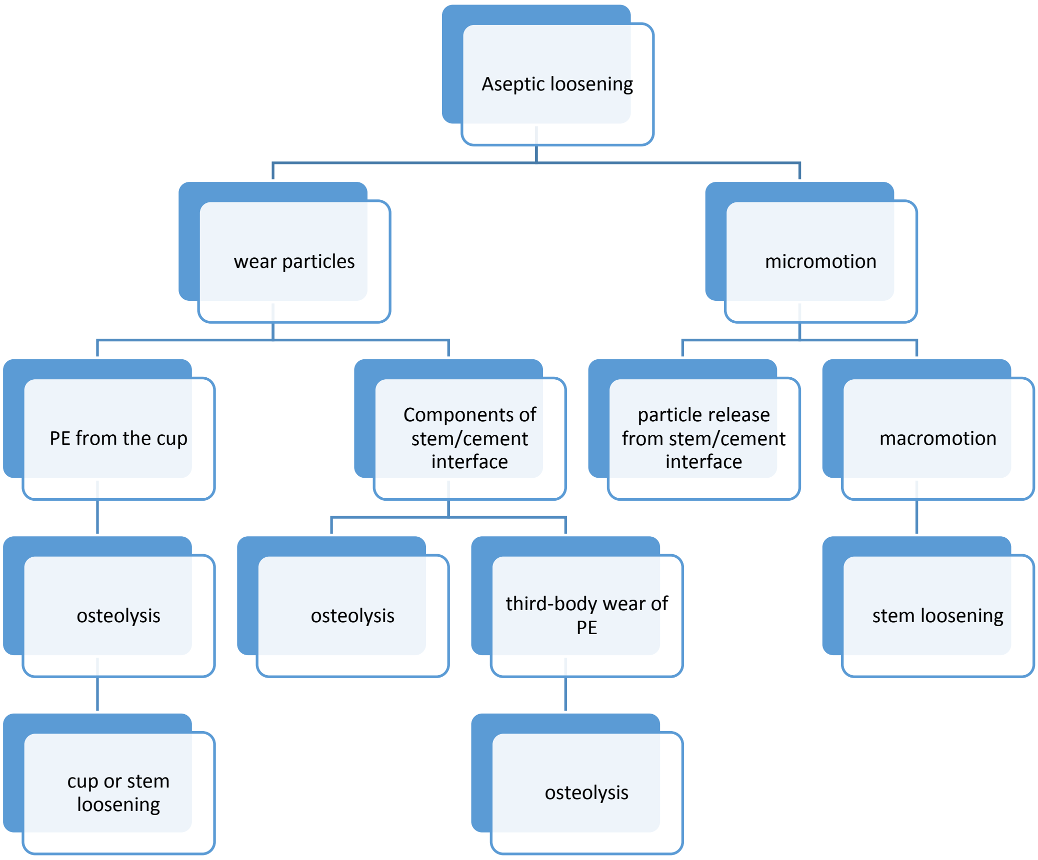


Figure 32. Mechanisms of aseptic loosening

9.6 Limitations

1. This study was a retrieval study. Only failed cases were collected and only endpoint (revision) data was available (except X-rays). X-rays were not taken regularly and time points were not scattered.

2. Small sample size: 27 cases in total and for each patient not all information was available such as X-rays, loose components and tissue samples. It made the N smaller for between group comparisons.

3. Big variance due to sampling location: several tissue samples were taken but it was difficult to judge if these samples were representative for the whole peri-prosthetic tissue.

4. Necrosis vs. cell grade: tissue with necrosis was naturally low in cell number as well as particle number, indicative of end-stage situation. It might be the reason why some expected associations were failed to correlate.

5. PE particle number under-estimation: polarized microscopy study showed mean size of polyethylene particles in cemented THA against CoCr alloy was 2.7*8.1um (46), but SEM studies of uncemented THA showed that 70 to 90 percent of the recovered particles are sub-micrometer polyethylene particles, with a mean size of about 0.5 um (44).

The resolution of polarized microscope in this study is about 1 um when the 40x object lens was used; the resolution of dark field microscope is 90 nm when using the 100x object lens. So the PE count from polarized microscopy was under-estimated due to detection limitations.

10. Conclusion

In this study of 27 failed cases of cemented Spectron EF stem in combination with Reflection acetabular cup, the loosening of cup was due to particle induced osteolysis in the acetabulum. The predominant cause of this osteolysis was PE particles. Loosening of stem was mainly mechanical, commonly occurring between the cement and stem. Under subsequent loading this led to release of wear particles and osteolysis.

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12. Appendix

Table 9. Histological cells, wear particles counting and sample location

Slide	Macro phage*	Giant cell*	Lymph ocyte*	PE count**	Total particle count**	Location
1-2	2	1	1	0.67	261	capsule
1-4	3	3	1	5.33	1719	capsule
7-1	2	1	1	0	20.33	capsule
7-4	3	2	1	N/A	88	capsule
15-1A				0	90.67	capsule
15-2A				1.33	215.67	capsule
15-3A	2	3	1	4	1840	femur
15-4A	2	3	1	4.33	660.33	acetabulum
20-1A	2	2	1	2	96.33	acetabulum
20-2A				0	22.33	acetabulum
20-3A	2	2	1	9.67	148.67	acetabulum
20-4A				0.67	31.67	acetabulum
42-3	2	3	1	11	134	capsule
147-1A	2	2	2	2	1337	capsule
147-2A	1	0	1	0.33	410.67	capsule
151-2A	0	0	0	0.33	910.33	capsule
151-2A				0.33	910.33	femur
151-3A	1	0	0	0	348	femur
152-1A				0	20.33	capsule
152-2A	2	3	1	0.67	821.67	acetabulum
152-3A	2	3	1	0.67	1090.33	acetabulum
154-1A	3	3	1	>150	556.67	capsule
154-2A	1	0	1	42	173.67	acetabulum
155-1A	2	1	1	0.67	31	acetabulum
155-2A	2	2	1	0.67	35.67	acetabulum
156-1A	3	3	1	0.67	1119	femur
156-3A	3	3	1	25.67	1589	femur
159-1B				3.33	1327.67	femur
159-2A	3	3	1	2.33	2329.67	femur
159-3A	2	0	1	2	779.33	femur
159-4A				7.67	834.67	femur
161-2A	3	3	2	0.67	612.33	femur
161-4A	3	3	1	0.67	960.67	femur
166-1A				5.33	226	femur
166-2A	0	0	0	13	1106.33	femur
166-3A	2	1	2	8	908.67	femur

167-1A				100.33	604.33	acetabulum
167-2A	3	3	0	33.67	975.67	femur
167-3A				24.33	1212	femur
167-4A				6	707	femur
167-5A				50	1953.67	femur
167-6A	1	0	1	40.33	396.33	femur
167-7A				>150	731.67	femur
172-7	2	2	2	22	1293.33	acetabulum
172-8				1.33	526.67	femur
172-9				6	1835.33	femur
172-10				4.33	30.33	capsule
172-14	2	3	1	16.33	1889.33	capsule
173-1A	3	3	1	1	594.33	unknown
173-2A	2	2	1	3	207.33	unknown
177-1	3	2	1	13.67	557.67	unknown
177-2	3	3	1	29.33	1211.67	unknown
178-1	2	3	1	2	558	unknown
178-2	1	0	0	1.33	78.33	unknown
179-1	2	2	1	0.33	21.67	acetabulum
179-2	2	2	1	9	154	acetabulum
181-1	2	2	1	29	211.33	acetabulum
181-2	0	0	0	4.67	391.67	acetabulum
182-1	2	2	1	8	287.67	capsule
182-2	2	2	1	3	1439.33	capsule
182-3				2.33	25.33	capsule
182-4				0	34	capsule
183-1				12.33	262.33	capsule
183-2	3	3	1	31.33	218.33	capsule
183-3				0	16	capsule
183-4	3	3	1	8	160	capsule

N/A: contaminated slide

* Median of cell grade of 3 cell-rich microscopic fields

Some values were missing because only two slides per patient were chosen for cell counting.

** Mean of particle count of 3 cell-rich microscopic fields