IMPLANT FIXATION: THE INFLUENCE OF PATIENT AND IMPLANT CHARACTERISTICS IN TOTAL KNEE ARTHROPLASTY

by

Elise Laende

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ABSTRACT

Radiostereometric analysis (RSA) is a stereo imaging technique that permits evaluation of tibial component fixation in total knee arthroplasty (TKA) post-operatively. The overall aim of this thesis was to examine the influence of patient and implant factors on migration and inducible displacement measured with RSA in a combined dataset of 418 primary TKAs, with an overall goal of improving knowledge of how RSA-based measures can be used for clinical evaluation of patients post-operatively. Three connected studies are presented, which were used to address this global aim.

In the first study, migration patterns of cemented TKA fixation and uncemented fixation were compared, determining that while uncemented components had significantly higher one year migration, they achieved equivalent stability between one and two years post-operatively. This suggests that an initial period of settling does not compromise long-term fixation for uncemented components.

In the second study, longitudinal data analysis methods were used to further investigate differences in migration over two years for tibial components, examining the influence of implant factors (fixation, tibial component area), as well as patient characteristics (age, sex, body mass index, smoking status). Uncemented tibial components had higher magnitudes of migration in the first two post-operative years, and this difference was even more pronounced in female patients. Overall migration with cemented fixation was not different by sex. Analyzing uncemented tibial components separately by sex revealed that the effect of smoking was opposite in men and women. In women, smoking was associated with higher migration magnitudes. In men, smokers had lower migration compared to non-smokers, although there were relatively small proportions of smokers. Additionally, for uncemented tibial components in women, increasing age, especially above age 60 was associated with higher magnitude migration. For cemented components, the only significant factor was tibial component area, with larger sizes associated with greater migration in female patients.

The third study investigated the utility of inducible displacement data over ten years of follow-up from loaded single leg stance RSA exams as an alternative assessment method to migration data. Inducible displacement was significantly different for cemented and uncemented components, but not sensitive to patient factors. Uncemented components demonstrated higher early inducible displacement within the first three post-operative years, but lower late inducible displacement at ten years compared to cemented implants. The correlation between migration and inducible displacement was greatest for uncemented components in the first year post-operatively. Inducible displacements were significantly higher for continuous migrators as well, especially for uncemented components.

The overall findings of this thesis support the use of uncemented fixation of tibial components in TKA. While demographic factors influenced implant migration of female and male patients differently, there is no evidence that uncemented fixation is compromised in female patients. In addition to migration, inducible displacements are a viable metric to quantify the stability of implant fixation and have significant potential as an early screening tool. Future collaborative research has the potential to substantially enhance understanding around implant fixation as it will permit the study of increasingly specific groups.

LIST OF ABBREVIATIONS USED

CR	cruciate retaining
CS	cruciate stabilized
MP	medial pivot
MTPM	maximum total point motion
OA	osteoarthritis
PA	Peri-apatite®
PS	posterior stabilized
RBE	rigid body error
RSA	radiostereometric analysis
SD	standard deviation
TKA	total knee arthroplasty
TM	Trabecular Metal™

GLOSSARY

aseptic loosening	Loosening without the presence of infection. Also referred to as mechanical loosening.
condition number	$\text{condition number} = \frac{1}{\sqrt{d_1^2 + d_2^2 + \ldots + d_n^2}}$ where d = distance between each marker and a straight line passing through the marker cluster. The condition number is minimized mathematically to represent the best position and direction through the marker cluster. The larger the condition number, the more markers lie along the straight line and the lower the accuracy. Condition number upper limits are recommended to be 150 for knee RSA studies (Valstar et al., 2005).
continuous migration	Migration that does not demonstrate a decrease in rate after 1 year post-operation. Defined as migration of greater than 0.2 mm between years 1 and 2 as measured by MTPM (Ryd et al., 1995).
inducible displacement	Type of micromotion. Reversible movement in response to an external load.
marker	Tantalum marker (or bead) of approximately 1 mm in diameter embedded in the bone or the tibial component polyethylene insert for the purpose of defining a rigid body. Highly visible in radiographs.
maximum total point motion (MTPM)	Length of the translation vector of the marker which moved the most.
rigid body error (mean error of rigid body fitting)	Mean difference between the relative distances of markers in a rigid body between exams (Selvik, 1989). High rigid body errors indicate movement of individual markers and allow the exclusion of unstable markers from analyses. The recommended upper limit for this error is 0.35 mm (Valstar et al., 2005).
micromotion	Small relative movements between a total knee replacement and the bone it is implanted in. Two types of micromotion: migration and inducible displacement.

migration	A permanent displacement of the implant in the bone, generally taking place of a period of months or years. Type of micromotion.
revision	A revision surgery; a second surgery for a total knee replacement.
rigid body	Idealization of a solid which does not deform. Therefore all points on the rigid body remain in the same positions relative to each other. In radiostereometric analysis of total knee replacements, the tibia and the implant are each considered a rigid body. These two rigid bodies are defined by the markers embedded in them.

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Chapter 1

INTRODUCTION

1.1 Overview

In terms of cost benefit and return of quality of life, total joint arthroplasty is a highly effective procedure (Daigle et al. 2012). Total knee arthroplasty (TKA) specifically has seen steady increase in recent decades in Canada and around the world as a result of both growing incidence of severe osteoarthritis and recognition of the success of the procedure (Ethgen et al. 2004, Kurtz et al. 2005, Kurtz et al. 2007). However, the immense success of the procedure in reducing pain and restoring function has been tempered by concern over longevity of the implants. While failure of an implant requiring revision surgery is required in a relatively small proportion of TKA patients, this complication is devastating to individual patients and burdensome to the healthcare system (Bhandari et al. 2012, Kurtz et al. 2005). Failure due to aseptic loosening accounts for the greatest proportion of revisions and monitoring the quality of implant fixation to screen for aseptic loosening is an on-going challenge with follow-up care of TKA (Schroer et al. 2013). Radiostereometric analysis (RSA) is a stereo imaging technique that can quantify implant fixation by permitting the three dimensional reconstruction of the position of an individual's implant relative to the underlying bone. The insertion of small, bioinert markers during surgery provides the opportunity to measure the relative motion of an implant in bone with precision of tenths of a millimeter. RSA has been applied to clinical research studies examining the performance of implant designs and has been able to identify implants with sub-optimal fixation in smaller numbers of patients and shorter time frames than traditional survivorship studies require by determining the patterns of migration of the implants. While its use in the screening of orthopaedic implant designs is well recognized, there is potential for further development of RSA as a tool that can examine the specific implant and patient characteristics that contribute to implant migration, to gain a better understanding of the roles of these factors in implant fixation. Additionally, using RSA to measure inducible displacements of implants from loaded exams can potentially provide additional information about the bone-implant interface. Inducible displacement evaluations offer an advantage over longitudinal assessments of migration in terms of practical considerations of required follow-ups. Linking the migration and inducible displacement metrics remains an unmet challenge in RSA research. Using a large dataset of RSA results, this thesis examines the influence of implant and patient factors on implant migration and investigates the link between migration and inducible displacements. Two areas of focus are investigating differences in cemented and uncemented fixation as well as comparing female versus male patients.

1.2 Background and Literature Review

1.2.1 Total Knee Arthroplasty

The replacement of a complex biological construct such as the synovial knee joint with, on average, 420 - 510 grams of metal and plastic (Lee et al. 2005), may seem ill-advised in theory, but in practice total knee arthroplasty is a remarkably successful intervention (Jenkins et al. 2013). More than 60,000 total knee replacements are performed annually in Canada (2013), and almost 700,000 in the United States (Bhandari et al. 2012). As the treatment for end-stage arthritis, knee replacements have considerable success in relieving pain and restoring function. However, success is not universal, with approximately 20% of knee replacement patients reporting that they are not satisfied with the procedure (Bourne et al. 2010, Robertsson et al. 2000). Knee replacements also have a finite life span, and a patient younger than 60 is expected to outlive a knee replacement (Bhandari et al. 2012). Survivorship of TKA is generally excellent at 10 years after surgery (up to 95%) but drops to 71-76% at 20 years, depending on the type of implant (Mont et al. 2014). Even with these caveats, the numbers and profiles of patients undergoing total knee replacement surgeries have expanded as the success of the procedure has increased and the ability to relieve significant pain and disability outweighs the risk of potential complications.

1.2.2 Patient Demographics for TKA

The average patient undergoing TKA today in Canada is a 67 year old obese female (CIHI 2009, CIHI 2015). However, the range of patient demographics is vast, with patients as young as in their late teens and extending to nonagenarians (Jauregui, 2015). The higher proportion of female patients receiving TKA is consistent internationally (Ackerman et al. 2016, Kurtz et al. 2011).

Sex-related differences in TKA patients are significant, starting with prevalence of knee osteoarthritis (OA), which disproportionately affects women. While women are twice as likely as men to receive a TKA, they are also four times more likely to have an unmet need for arthroplasty surgery (Hawker et al. 2000). There is evidence that women receive a TKA at a further point in the disease progression and they do not recover functionally to the same level as men (Barrack et al. 2014, Dalury et al. 2009, Gustavson et al. 2016, Mehta et al. 2015, Sveikata et al. 2017). Pain may also be less relieved in women (Mehta et al. 2015). Questions around differences in access to care between women and men may be attributable partially to gender and societal issues (Novicoff and Saleh 2011), but biological differences are also apparent.

When considering sex-related differences that may affect TKA, changes in bone properties in post-menopausal women associated with a decrease in estrogen production are a clear consideration. As estrogen is an osteoclast inhibitor, estrogen deprivation contributes to a loss of bone mass by removing the inhibition of bone resorbing osteoclasts (Armas and Recker 2012). Additional effects of estrogen loss are decreased absorption and increased excretion of calcium (Armas and Recker 2012). The total effect on bone mass is a loss of approximately 10% of bone mass in the 5-7 years surrounding menopause (Recker et al. 2000). Pertinently, changes to the bone are seen as thinning and loss of trabeculae in trabecular bone and increasing porosity and thinning of cortical bone (Armas and Recker 2012). The structural changes are as relevant as the mass changes; teenagers have similar bone mineral density as the elderly, but without the associated increased fracture risk (Judex et al. 2003).

Independent of menopause, age alone is a factor in decreasing bone mineral density with peak bone mass occurring before age 30 and decreasing afterward. By about age 75 the effects of age once again outweigh the effects of estrogen deprivation and are a larger factor in declining bone density (Recker et al. 2000).

Smoking has been shown to increase the risk of fracture in post-menopausal women, possibly by interfering with calcium absorption (Law and Hackshaw 1997). Although not as widely studied, there is evidence that there is a similar effect in elderly men (Law and Hackshaw 1997).

Obesity, while traditionally thought to result in increased bone formation due to higher mechanical loads, has now been shown to have metabolic effects related to chronic inflammation that have a negative impact on bone as well as cartilage (Cao 2011, Wang et al. 2009). Obesity seems to be linked to a greater risk for women of developing knee OA, although interestingly this is not the case for hip OA (Lohmander et al. 2009, Whitlock et al. 2016).

Current patient demographics for total knee replacements have greater rates of younger patients with higher BMIs than 10 years ago (CIHI 2013). This trend of younger and heavier patients is expected to continue for TKA and in increasing volume due to an aging population (Kurtz et al. 2009). The cumulative result of demographic trends for TKA will place increasing demands on the implants, especially when considering the decreasing age of patients, as they are expected to be more active while at the same time requiring a longer service life from implants (Julin et al. 2010).

1.2.3 Implants for TKA

In addition to patient factors, the design of the implant is a factor in the success of the TKA. Historically, implants for TKA underwent rapid design evolution from the first ivory hinged replacement in the 1890s to the dual condylar implants that are the precursor to modern knee replacements, first introduced in 1968 (Ranawat et al. 2012). Today, implant designs for TKA are numerous with new designs continually entering the market; the Australian National Joint Replacement Registry has reported more than 500 combinations of tibial and femoral components (AOA 2016) and ninety-nine new knee implants were introduced in a five year period to the Australian market alone (Anand et al. 2011). Current TKA tibial and femoral components are typically made of biocompatible metals such as stainless steel, titanium alloys, or cobalt chrome alloys with ultra-high-molecular-weight polyethylene tibial inserts that provide an articulating surface (Katti et al. 2008). The geometry of the articulating surface is one of the most significant design variations for TKA, with two main approaches: posterior-stabilized implants and non-posterior-stabilized implants (also referred to minimally stabilized designs, or cruciate retaining designs). Posterior stabilized (or "cruciate substituting") designs for TKA take the form of a cam and post design to constrain translation of the femoral component relative to the tibia while allowing femoral rollback during flexion following the resection of the posterior-cruciate ligament (Bercik et al. 2013, Kolisek et al. 2009). Posterior-stabilized implants may be employed routinely by surgeons or may be selected for patients with compromised posterior cruciate ligaments or significant deformities (Graves et al. 2014). Cruciate retaining designs leave the posterior cruciate ligament intact and proponents suggest that this provides better mechanics (Comfort et al. 2014). The differences in function and survivorship between posterior stabilized and cruciate retaining implants remain unclear, with a meta-analysis finding better function and no difference in complication rates for posterior-stabilized implants (Bercik et al. 2013) while a compilation of international registry data found poorer survivorship with posterior stabilized designs, confounded by patella resurfacing status (Comfort et al. 2014). An additional classification of articulating surface geometry is a "medial pivot" design where the tibial insert is contoured to provide a ball-and-socket geometry on the medial side to act as a pivot point (Blaha 2002, Schmidt et al. 2003). This type of articulation can be used with the posterior cruciate ligament resected or intact (Bae et al. 2011) and medial pivot implants have demonstrated good survivorship to date (Brinkman et al. 2013, Macheras et al. 2017).

An additional variation of the type of articulation is the use of mobile bearings where the tibial insert is free to rotate and/or slide . Mobile bearings can be used with both posterior-stabilized and cruciate-retaining designs. The rationale for mobile bearing designs is to decrease polyethylene wear through greater conformity between the femoral component and tibial insert (Smith et al. 2011). Higher revision rates have been found for both posterior-stabilized and non-posterior-stabilized mobile bearing implants compared to fixed bearing designs in some studies (Graves et al. 2014, Namba et al. 2014) while others have found equivalent rates between fixed and mobile cruciate retaining implants (Hofstede et al. 2015).

Rates of use of posterior stabilized and cruciate retaining designs as well as fixed versus mobile bearing inserts vary substantially. Data from registries puts the use of fixed bearings at 78% of TKA cases in Australia (AOA 2016), 64% in Norway (Paxton et al. 2011), and 87% in the USA (Paxton et al. 2011). Of the fixed bearing insert designs, posterior stabilized articulation account for 27% of cases in Australia (AOA 2016), 5% in Norway (Paxton et al. 2011), and 65% in the USA (Paxton et al. 2011).

Along with material and geometric variations, the methods of implant fixation can vary significantly, with the use of bone cement or reliance on uncemented techniques representing two major approaches to fixation (Ranawat et al. 2012).

1.2.4 Implant Fixation

Cemented and uncemented (or cementless) fixation represent two separate approaches to implant fixation. While cemented fixation has a proven record in joint replacement registries (Mont et al. 2014), the theoretical advantages of uncemented fixation means that it has continued to be investigated and developed.

Cemented fixation involves the mixing and application of polymethylmethacrylate (PMMA) as the cementing agent (Freeman and Tennant 1992). The use of cement can overcome imperfections in the bone cuts and provides an immediate interface between the implant and bone (Drexler et al. 2012). First developed for orthopaedic applications in the 1950s, PMMA remains unrivaled for use in total joint arthroplasty (DiMaio 2002, Webb and Spencer 2007). The constituents of bone cement allow polymerization to a solid at room temperature after a liquid working phase (Webb and Spencer 2007). Commercial bone cements have similar ingredients in varying proportions to control the properties of viscosity and working time (Lewis 1997). Concerns around the use of bone cement are related to the potential for chemical and thermal damage from the exothermic polymerization process to bone tissue as well as the mechanical properties of hardened PMMA. The mechanical properties of bone cement are sensitive to mixing and handling techniques, especially how this affects porosity which in turn influences crack initiation (DiMaio 2002). Vacuum mixing reduces pore size in bone cement, improving mechanical properties (DiMaio 2002, Lewis 1997). The inclusion of antibiotics in bone cement, most commonly tobramycin, is a further variable that can impact mechanical properties, but has gained wide-spread use despite some controversy (Bourne 2004, Hanssen 2004).

In contrast to cemented fixation, uncemented fixation depends on an initial mechanical press fit, with current designs aiming for longer term osseointegration as the host bone grows into a porous surface of the implant (Freeman and Tennant 1992). Osseointegration, or bone ingrowth, similar to fracture healing, depends on the recruitment and function of cells in the peri-prosthetic bone (Moritz et al. 2011).

Purported advantages of uncemented fixation are a “biologically adaptive fixation” and shorter operating times due to the elimination of cement cure time (Meneghini and Hanssen 2008). Disadvantages of cemented fixation include its poor performance under tension and shear forces (Drexler et al. 2012) and macrophage responses to PMMA particulate debris which contribute to osteolysis (Freeman and Tennant 1992). Osteolysis, or resorption of bone, around cemented tibial components has been shown to be an issue especially in younger patients (Naudie et al. 2007).

While initial versions of uncemented tibial baseplates introduced in the 1980s had inferior performance compared to cemented designs, there is renewed interest with modern biomaterials (Meneghini and Hanssen 2008). Two materials garnering significant attention are hydroxyapatite coatings and porous metals (Lombardi et al. 2007, Meneghini and Hanssen 2008). Hydroxyapatite (HA) is an osteoconductive calcium phosphate material that encourages bone formation (van der Linde et al. 2006, Voigt and Mosier 2011). An additional intriguing property of HA is the ability to convert fibrous tissue to bone (Soballe et al. 1993). RSA studies and a meta-analysis have demonstrated equivalent durability to cemented components to 10 or more years (Pijls et al. 2012, Voigt and Mosier 2011). Porous metals, particularly tantalum trabecular metal, have also shown promising outcomes (Niemeläinen et al. 2014, Wilson et al. 2012).

Use of uncemented fixation is generally less common than cemented fixation. Joint replacement registries report the use of cemented fixation at about 60% in Australia (AOA 2016); above 80% in Canada, Norway, and the USA (CIHI 2015, Paxton et al. 2011); and over 90% in Sweden (Sundberg et al. 2016).

1.2.5 TKA Failure

The time-limited success of joint replacements is unfortunately a reality for many patients. While innovation continues in the areas of implant design and surgical technique, the mechanisms of fixation and failure remain poorly defined. As increasing numbers of patients undergo total joint replacement surgery, the incidence of failures of joint replacements is a growing concern in terms of individual patient debilitation and cost to the healthcare system (Bhandari et al. 2012, Kurtz et al. 2005). In TKA, failure is most often related to the tibial component rather than femoral components, which account for only 1% of revisions (Sundberg et al. 2013).

Failure in TKA is still most often due to aseptic loosening, or loosening without infection, which accounts for approximately a third of revisions (Schroer et al. 2013). This slow process is difficult to detect with conventional clinical methods. Current clinical tools to detect aseptic loosening are limited, but research tools for joint replacement outcomes include registry data, implant retrievals (including wear analysis and histology), animal models, and imaging studies. As an imaging technique, radiostereometric analysis (RSA) is a significant tool that permits high resolution tracking of implant movement in the host bone over selected time intervals and in response to joint loading.

1.2.6 Radiostereometric Analysis (RSA)

The value of RSA as a research tool to study the introduction of implant designs and surgical techniques has been shown in the literature, especially for total knee arthroplasty (Pijls et al. 2012, Ryd et al. 1995) and with less specific implications for total hip arthroplasty (Karrholm et al. 1994, Pijls et al. 2012). It is also one of the few tools that permits a high-resolution analysis of an implant in situ under both static and dynamic conditions.

The RSA technique uses a calibration or reference object in the field of view during stereo radiographic imaging to permit the three dimensional reconstruction of points of interest. The calibration box described in Selvik's work (Selvik 1989) and the rigid body calculations outlined are not significantly different from the methods used today (Figure 1.1). The advent of digital x-ray imaging has significantly improved both accuracy and efficiency (Valstar et al. 2000). Additional advancement has been the introduction of model-based methods for determining the position of a whole implant, rather than individual points on the implant (Valstar et al. 2001). Both methods for determining the position of the implant (marker-based or model-based) currently depend on the insertion of tantalum markers into the bone supporting the implant to act as a reference rigid body for the calculation of relative motions of the implant (Figure 1.1). For marker-based methods, the 1 mm diameter tantalum markers are also inserted into the periphery of the polyethylene tibial insert of the implant.

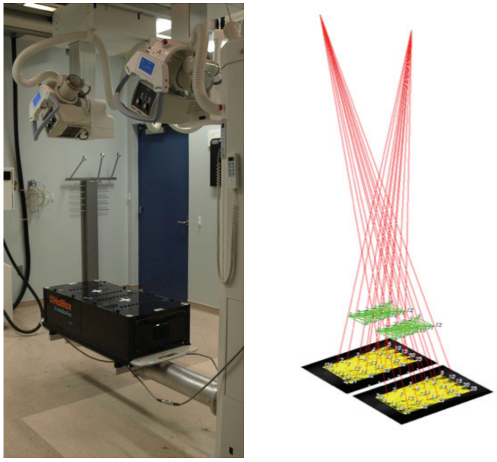
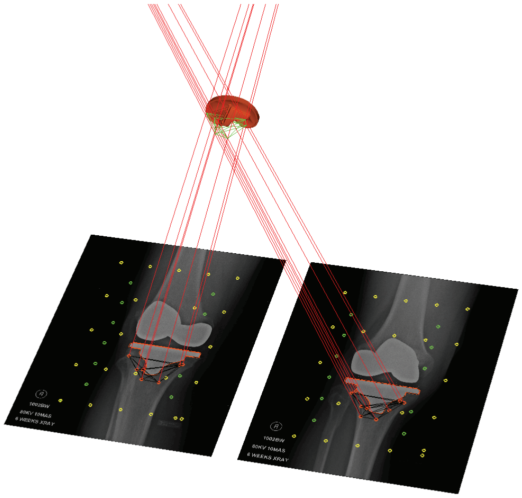
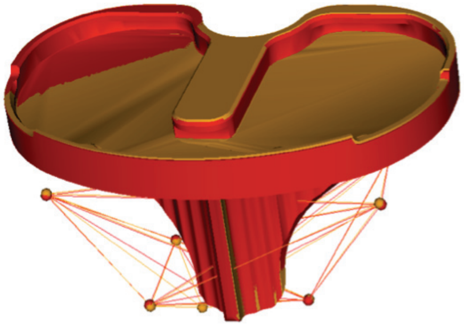
 1. Tantalum (a bio-inert, highly radiopaque element) markers, typically 1 mm in diameter, are used to mark the bone and implant	 2. Tantalum markers are inserted during surgery
 3. RSA exams are taken post-operatively and at follow-up visits. The patient is positioned above the calibration box. Two x-ray heads are positioned so that the beams intersect at the knee and expose the digital detectors underneath the calibration box.	 4. During analysis, the know locations of the markers in the calibration box and their projections on the detectors are used to locate the foci of the 2 x-ray heads.
 5. In image analysis, bone and implant markers are located at intersection of the projection lines. The implant position is determined from contour projections (model-base method) or from the markers embedded in the polyethylene liner.	 6. To calculate micromotion bone markers from exam 1 and exam 2 are aligned. The difference in the position of the implant model or implant markers is the relative motion of the implant to the bone.

Figure 1.1. Radiostereometric analysis (RSA) in steps.

Applications of radiostereometric analysis in orthopaedics have been well reviewed (Karrholm et al. 2007, Valstar et al. 2002) and have primarily focused on the evaluation of total knee and total hip replacement components. In addition to these uses, RSA has been employed in the study of spinal fusion, spinal mobility, ligament reconstruction, polyethylene wear, fixation techniques, and fracture fixation (Karrholm 1989, Karrholm et al. 2007, Madanat et al. 2006) as well as dynamic analyses to permit the measurement of in vivo kinematics (Garling et al. 2005, Uvehammer and Karrholm 2001).

The evaluation of total joint arthroplasty with RSA has primarily focused on the stability of implant fixation, primarily how a implant migrates over time within the host bone, and, to a lesser degree, how much relative motion occurs between the bone and implant in response to an instantaneous external loading (inducible displacement) (Figure 1.2). For total knee arthroplasty, these measurements of implant micromotions have formed the basis of the evaluation of implant designs, materials, and surgical techniques.

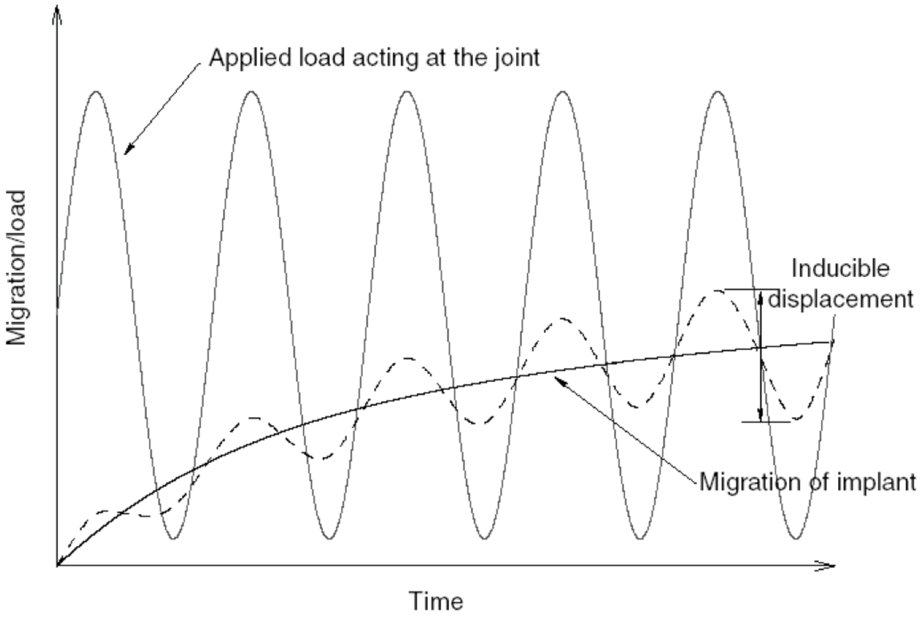


Figure 1.2. Schematic of two types of micromotion (Britton et al. 2004).
Migration - a permanent displacement of the implant in the bone. Inducible displacement - a reversible motion in response to an applied external load.

1.2.7 Measurement methods with RSA

RSA typically uses a reference post-operative exam (taken immediately post-operatively) and a series of follow-up exams over two years to determine the migration of the implant relative to the host bone. Migration data is most commonly calculated as cardan translations and rotations, as well as maximum total point motion (MTPM) (Figure 1.3). MTPM is the vector length of the point on the implant that moved the most and is considered a summary metric for the overall motion of an implant (Ryd et al. 1986). As the markers inserted in the implant polyethylene are not necessarily inserted in identical locations for all subjects, may not all be visible in all exams, or may not be used in the case of model-based methods, the use of "fictive markers" (or virtual points) for MTPM calculation ensures consistency of marker locations (Nilsson et al. 1991). MTPM can be a challenging metric to interpret as it has no directional information and has shortcomings in terms of clinical relevance, and a tendency to non-normal distribution due to its absolute value (Valstar et al. 2005). However, as the translations and rotations about the individual axes tend to be small, evaluating the overall motion captured in the MTPM value is more likely to exceed the limit of detection of the RSA system as well as providing an overall three-dimensional measure of implant motion. Perhaps most pertinently, MTPM has historically been commonly reported and used to define continuous migration (Ryd et al. 1995), so it continues to be propagated through the literature.

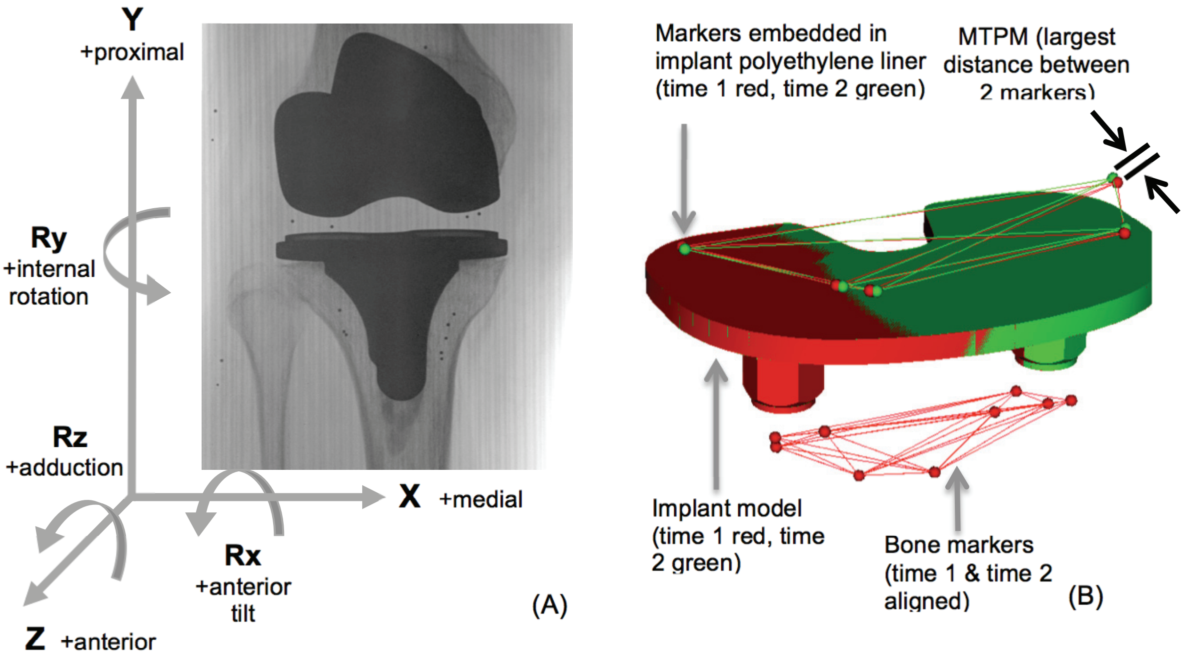


Figure 1.3. (A) Conventions for positive translations and rotations in reporting implant motion. (B) Model-based and marker-based assessment of implant motion, illustration of MTPM.

Reported accuracies for the kinematic results from RSA systems are 0.05 to 0.5 mm for translations and 0.15º to 1.15º for rotations (Valstar et al. 2002). Accuracy depends on a number of factors including the distribution and stability of the markers, the number of markers, and the radiograph quality (Karrholm et al. 1997, Yuan and Ryd 2000). The accuracy of RSA can be improved by ensuring that no markers have shifted in the bone and that the markers are well dispersed. To evaluate marker stability, the mean error of rigid body fitting calculates the mean difference between the relative distances of markers in a rigid body between exams (Selvik 1989). High rigid body errors indicate movement of individual markers and allow the exclusion of unstable markers from analyses. The recommended upper limit for this error is 0.35 mm (Valstar et al. 2005). To evaluate marker distribution, the condition number is calculated for each subject. The condition number is infinitely high for markers that are positioned in a straight line, therefore low condition numbers indicated well dispersed markers (Soderkvist and Wedin 1993). The recommended limit for condition numbers in RSA studies is 150 (Valstar et al. 2005). Cases with poor marker distribution can be identified and excluded from study results (Ryd et al. 1986, Ryd et al. 2000).

Limitations of RSA include the relatively resource intensive cost of obtaining and analyzing RSA exams. It is also unable to detect compromised implants unrelated to mechanical loosening. However, in contrast to the end-point data documented in registry or histological studies, one of the advantages of RSA data is that it can capture in vivo assessments of implant fixation at multiple time points.

1.2.8 Longitudinal Tibial Component Migration

The value of RSA for evaluating orthopaedic implants stems from the ability of this high resolution tool to predict longer-term successful implant fixation with small sample sizes and in relatively short follow-up periods (Grewal et al. 1992, Karrholm et al. 1994, Ryd et al. 1995, Valstar et al. 2012). A number of studies have linked early RSA migration data to other long-term outcomes, with revision rates, registry data, clinical outcomes, and meta-analyses being the most common outcome measures (Karrholm et al. 1994, Pijls B.G. 2010, Pijls et al. 2012, Pijls et al. 2012, Ryd et al. 1995).

It has been suggested that the majority of total knee replacements migrate in the first year following surgery; it is whether or not this initial migration levels off that suggests effective or defective implant fixation. In the first year, typical levels of migration have been suggested to be 0.7 mm (MTPM) for cemented implants and higher, at 1.7 mm, for uncemented implants (Ryd et al. 1995) although more recent publications suggest slightly lower values are typical: 0.3 – 0.7 mm for cemented tibial components (Ejaz et al. 2015, Meunier et al. 2009, Molt et al. 2013, Molt et al. 2012, Molt and Toksvig-Larsen 2014, Petursson et al. 2017, van Hamersveld et al. 2017) and 0.8 to 1.7 mm for uncemented components (Andersen et al. 2016, Andersen et al. 2017, Henricson et al. 2008, Molt and Toksvig-Larsen 2014, van Hamersveld et al. 2017, Winther et al. 2016), based on mean MTPM at one year post-operatively. The largest migrations generally occur immediately after surgery; migration at 6 months has been found to be 93% of migration at two years (Fukuoka et al. 2000). The very early migrations immediately following surgery may be attributable to remodeling of interface bone that was damaged during the operation by factors such as high temperatures or unevenly cut surfaces (Fukuoka et al. 2000, Hilding et al. 1995, Ryd et al. 1995). Necrotic bone that has been damaged during surgery may be compacted by mechanical loading or resorbed by osteoclasts (Hilding et al. 2000, Linder 1994, Regner et al. 2000, Taylor and Tanner 1997). The hypothesis that initial migration is due to the resorption of necrotic bone adjacent to the implant has been supported by studies in which migration was lower in subjects who had treatment with osteoclast inhibiting bisphosphonates (Hilding and Aspenberg 2007, Hilding and Aspenberg 2006, Hilding et al. 2000).

Preliminary studies of implant migration suggested that long-term migration could be predicted by early migration levels measured with RSA (Grewal et al. 1992, Karrholm et al. 1994, Ryd et al. 1995). A key study identified a specific measure of RSA that indicated a knee replacement was at risk for future loosening: if the implant "continuously migrated" between years one and two, implant loosening could be forecasted with a predictive power of 85% (Ryd et al. 1995). It was found that continuous migration of more than 0.2 mm between one and two years after surgery was predictive of later loosening (Ryd et al. 1995). This 0.2 mm cutoff value has been adopted as the standard measure in migration studies evaluating knee replacement fixation (Carlsson et al. 2005, Catani et al. 2004, Hilding and Aspenberg 2007, Hilding et al. 1996, Hilding et al. 1995, Hyldahl et al. 2005).

A more recent study linked migration data at one year with survivorship data on the same implant designs to define acceptable thresholds of one year migration, concluding that MTPM at 1 year of greater than 0.5 mm put an implant design "at risk" and greater than 1.6 mm was "unacceptable" based on the revision rates at 5 years (Pijls et al. 2012). In this meta-analysis, at total of 847 subjects were included from 50 RSA studies that were matched to survival studies of the same implant designs (20,599 subjects in 56 studies) (Pijls et al. 2012). Of the 28 implant designs included, 18 had cement fixation and 10 were uncemented. The one year thresholds apply to all implant designs, regardless of fixation method.

While continuous migration may be an indication of unstable implant fixation, the cause or causes of this type of migration have not been confirmed. As opposed to initial migration which stabilized, one theory is that continuous migration represents defective fixation and is established as early as during the operation (Fukuoka et al. 2000, Ryd et al. 1995). The high accuracy, smaller sample sizes, and shorter study periods are the reasons that researchers are now recommending that an RSA evaluation be part of the introduction of any new implant design or surgical technique (Pijls 2014, Valstar et al. 2005).

While RSA studies on implant migration have typically collected data during the first two post-operative years as this has been shown relatively early on to be predictive of later loosening in knee arthroplasty as well as total hips, these initial conclusions have now been supported with results from long-term migration studies. In the study of total knee implant migration, five studies have collected migration results beyond 5 years (Henricson and Nilsson 2016, Pijls et al. 2012, Pijls et al. 2012, Ryd et al. 1999, Teeter et al. 2016). The conclusions made based on two year migration data have largely withstood the test of time with longer follow-up. A study of partial cementation over 8 years found continued migration to 8 years of the implants identified as continuous migrators at 2 years, although none had been revised by the 8 year follow-up Ryd et al. (1999). A study comparing the migration of mobile-bearing and fixed-bearing total knee replacements found consistently comparable mean migration between the two groups at 2 years (Garling et al. 2005) and 10-12 years (Pijls et al. 2012). Similarly, a ten year follow-up of a series of cemented components found no significant change in migration from two to ten years (Teeter et al. 2016). In studies comparing cemented and uncemented fixation, there have been similar findings. A trabecular metal monoblock component and a cemented baseplate showed stabilization at 2 years post-operatively (Henricson et al. 2008) which was maintained at ten years (Henricson and Nilsson 2016). The conclusions of the original two year study of HA-coated, uncoated, and cemented tibial components (Nelissen et al. 1998) were confirmed at 16 years after surgery (Pijls et al. 2012). One new finding in this study was the identification of secondary loosening, in one case due to a late infection and in one case due to osteolysis which only became evident after approximately 7 years following an initial period of stabilization (Pijls et al. 2012).

1.2.9 Inducible Displacement Measured with RSA

Compared to migration, inducible displacement assessments of TKA are much less common in the RSA literature. Inducible displacements of the tibial component relative to the bone can be seen when comparing the position of the implant in the bone between unloaded and loaded radiographs.

The first papers describing an evaluation of TKA with inducible displacement were published in 1986 (Ryd 1986, Ryd et al. 1986). Interestingly, most research on the application of inducible displacements, and specifically on total knee joint replacements, was performed in the 1990s and earlier (Albrektsson et al. 1990, Hilding et al. 1996, Hilding et al. 1995, Karrholm 1989, Linder 1994, Nilsson and Karrholm 1996, Nilsson et al. 1990, Petersen et al. 1999, Ryd 1986, Ryd 1992, Ryd 1992, Ryd et al. 1988, Ryd et al. 1993, Ryd et al. 1999, Ryd and Linder 1989, Ryd et al. 1987, Ryd et al. 1986, Ryd et al. 1990, Ryd et al. 1992, Ryd et al. 1990, Ryd and Toksvig-Larsen 1993, Toksvig-Larsen et al. 1998, Toksvig-Larsen et al. 1994, Toksvig-Larsen et al. 1995), with a smaller number of studies taking place in the past 15 years (Allen et al. 2012, Bragonzoni et al. 2005, Fukuoka et al. 2000, Hansson et al. 2005, Regner et al. 2000, Toksvig-Larsen et al. 2000, Uvehammer 2001, Uvehammer and Karrholm 2001, Wilson et al. 2010) (Figure 1.4).

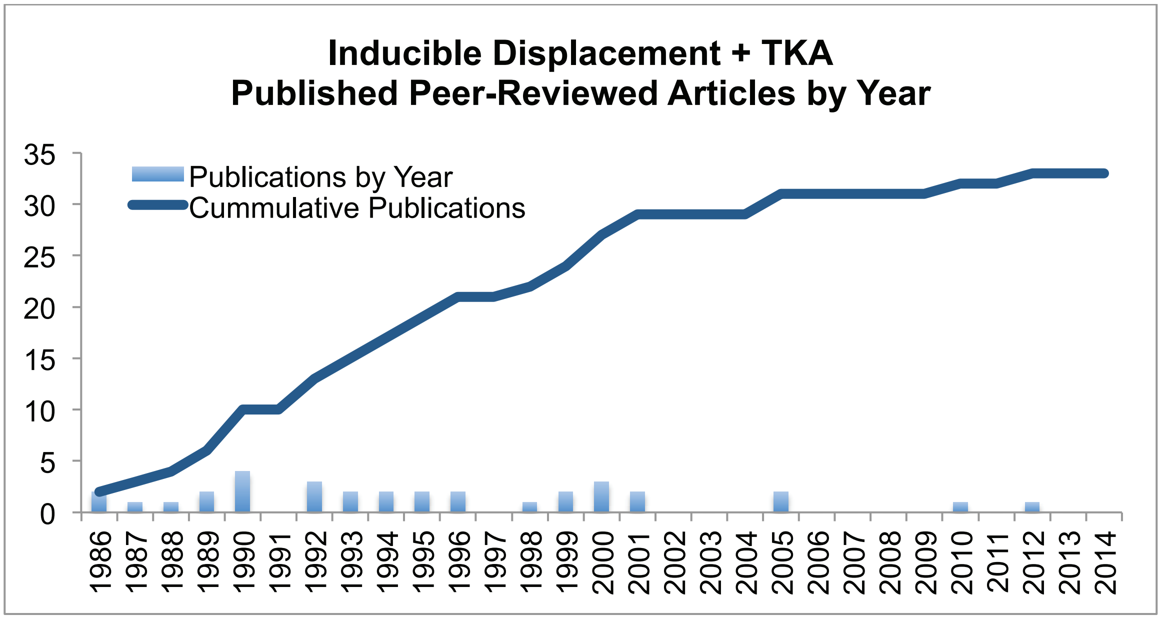


Figure 1.4. Publications by year on inducible displacement and total knee arthroplasty.

The protocols employed to generate inducible displacements during RSA exams have been varied. These so-called stress tests have commonly included weight-bearing on the affected limb and weight-bearing with a torque applied at the foot to induce a rotary stress (Albrektsson et al. 1990, Petersen et al. 1999, Regner et al. 2000, Ryd et al. 1988, Ryd et al. 1993, Ryd et al. 1999, Ryd et al. 1987, Ryd et al. 1986, Ryd et al. 1990). Squatting stress tests have also been used (Hilding et al. 1995, Ryd et al. 1993, Ryd and Toksvig-Larsen 1993, Toksvig-Larsen et al. 2000, Toksvig-Larsen et al. 1998, Toksvig-Larsen et al. 1994), and inducible displacements have been assessed at flexion increments during a step-up task captured with dynamic radiostereometry (Uvehammer and Karrholm 2001).

Possible mechanisms for inducible displacements are movements at the bone-implant interface, elasticity within the implant, or elasticity within the bone (Uvehammer and Karrholm 2001). When considering the bone-implant interface, the type of tissue that develops after surgery may influence inducible displacements. Possible tissues are bone ingrowth, fibrocartilage, or a fibrous membrane (Huiskes 1993, Regner et al. 2000, Ryd and Linder 1989). Tissue differentiation is believed to be influenced by mechanical factors including micromotions at the interface (Huiskes 1993), and the formation of a fibrous membrane is common in total knee replacements (Linder 1994). Inducible displacements in every day living could be caused by repetitive loading as occurs with walking. With this cyclic nature, inducible displacements have also been theoretically connected with fatigue failure of cancellous bone (Ryd 1992).

Studies have typically evaluated inducible displacements at one or two years post-operatively, but a small number of studies have measured inducible displacements in the early post-operative period, offering information about the interface as fixation is being established (Ryd and Toksvig-Larsen 1993, Toksvig-Larsen et al. 1998, Toksvig-Larsen et al. 1994). Inducible displacements were measured 4-8 weeks after surgery in 19 patients with cemented or uncemented total knee replacements, and all but one demonstrated measurable inducible displacement in the range of 0.3 – 1.3 mm MTPM (Ryd and Toksvig-Larsen 1993). For cemented implants, with inducible displacements of 0.2 – 0.4 mm, the authors concluded that this was due to bone elasticity or possibly tibial component lift-off due to eccentric loading, rather than fibrous membrane formation. This early motion was seen to mean that inducible displacement is not only the result of poor fixation via soft tissue membranes, but might also have a causative effect in the development of the membranes (Ryd and Toksvig-Larsen 1993). In a similar study of cemented and uncemented knees at 6 weeks post-operation, inducible displacements ranged up to 1.4 mm MTPM for the cemented cases and up to 1.2 mm for the uncemented implants. Over the same period, permanent migration also occurred, up to 3 mm for cemented and 1.8 mm for uncemented at 6 weeks. The authors attributed both the inducible displacement and migration to bone elasticity as "modern cementing techniques make fibrous membrane formation unlikely" (Toksvig-Larsen et al. 1995). Inducible displacements at 6 weeks and 1 year had significant correlations in a third study of cemented and uncemented tibial components, with both groups having on average a consistent 0.5 mm (MTPM) of motion (Toksvig-Larsen et al. 1998).

A unique study assessed intra-operative inducible displacement by applying a load directly to the tibial component after uncemented implantation. Three non-contact displacement transducers measured displacements which were later compared to two-year migration data (Fukuoka et al. 2000). Intra-operative displacements were small, not exceeding 0.2 mm, but the authors reported correlations of these measures with implant migration at 2 years.

The three studies that looked at post-operative inducible displacement earlier than 8 weeks after surgery concluded that any motion measured could not be due to the elasticity of a fibrous membrane because it would be too early for these tissues to have developed. One hypothesis is that inducible displacements are dependent on the quality of bone in the proximal tibia (Bragonzoni et al. 2005, Toksvig-Larsen et al. 1998). However, histological studies have found bone ingrowth as early as 4-6 weeks after surgery (Engh et al. 1987, Matsuda et al. 1999) and in one case as early as one week (Revell 2008). Other studies have suggested that as part of the healing process, the remodeling of the initial tissue begins by 3-4 weeks post-operatively (Moucha et al. 2006) and may be complete by 4 weeks (Goriainov et al. 2014). It seems unclear that at 4-8 weeks it can be concluded that there would be no fibrous membrane.

A number of studies have found significant, but not strong correlations between inducible displacement and migration (Fukuoka et al. 2000, Hilding et al. 1995, Regner et al. 2000, Toksvig-Larsen et al. 1998, Uvehammer and Karrholm 2001). Taking into consideration the separation of stable and continuously migrating implants, differences in inducible displacements for these two groups have been measured. Inducible displacements measured with standing stress tests and inward-outward torque stress tests in one study were on average 0.2 mm greater for continuously migrating implants compared to the stable group, a statistically significant difference (Ryd et al. 1999). Similar results were found by (Hilding et al. 1995). However, another study found no differences in inducible displacements between continuously migrating and stable groups (Toksvig-Larsen et al. 1998).

The rotary stress tests (inward/outward torque) have commonly been found to induce the greatest motion (Albrektsson et al. 1990, Bragonzoni et al. 2005, Ryd et al. 1988, Ryd et al. 1987, Ryd et al. 1986, Ryd et al. 1990), with rotations up to 1.2 degrees in cemented knees (Ryd et al. 1986) and up to 5.6 degrees for an uncemented implant design (Ryd et al. 1988) evaluated 1-2 years after surgery. This was consistent in early inducible displacement assessments as well (Ryd and Toksvig-Larsen 1993). It is possible that this is related to the typical central stem design of knee replacements which may not counter torque effectively or it may be indicative of the lower resistance of bone cement to shear forces in the cemented cases.

It is striking that inducible displacements of a similar magnitude exist over a wide time frame (from 6 weeks to 2 years post-operatively), but it does not mean that the same mechanisms are behind these equal displacements. The low modulus of elasticity found in fibrous tissue membranes (1.65 MPa on average for uncemented implants, 1.85 MPa for cemented) (Kraaij et al. 2014) compared to approximately 5 GPa for bone (Choi et al. 1990) suggests that if fibrous membranes are present, and depending on the extent of tissue, they would be a factor in measured inducible displacements. Depending on the timeframe of fibrous membrane formation, an early inducible displacement may be due to relative motion between the bone and implant, while at a later time it could be capturing the elasticity of the fibrous membrane that developed, possibly due to the relative motion between the implant and bone which may inhibit bone formation (Pilliar et al. 1986). It seems reasonable that high inducible displacements would be suggestive of a poor interface and possibly predictive of loosening, but this has not been proven to date. A non-bone interface itself is not necessarily negative. Fibrocartilage in cemented implants has been postulated to be a stable biological interface and may allow inducible displacements of up to 0.5 mm with good long-term outcomes (Ryd et al. 1992).

Inducible displacements have been studied only rarely in symptomatic patients. Bragazoni et al. (2005) examined inducible displacement results for two subjects with unexplained pain after unicompartmental knee replacements and found greater rotations about the transverse axis during stress tests compared to the asymptomatic group. A study of a small group of symptomatic patients with revision knee components found a variety of inducible motions, but was able to identify definitively loose and well-fixed components, which can be a tool in planning surgical interventions (Laende 2013).

Migration is a common occurrence, even in successful implants, and not necessarily synonymous with loosening (Ryd et al. 1987). Migration and inducible displacement assessments with RSA offer an in vivo approach to mechanically characterize the achieved fixation (Ryd 1992), but it is still unclear what mechanisms contribute to the magnitudes of implant motion being detected, and how, patient demographics and implant characteristics, especially cemented and uncemented fixation, affect these values.

1.3 Thesis Objectives and Hypotheses

The overarching goals of the research undertaken in this thesis are two-fold: 1. To understand current performance of implant fixation and how patient and implant factors influence fixation. 2. To investigate opportunities for incremental improvement of RSA-based indicators of implant fixation by incorporating implant and patient factors and considering inducible displacements in addition to migration.

Objective 1.

Compare migration of cemented and uncemented fixation in TKA with specific reference to published thresholds of acceptable migration, namely MTPM migration at one year (Pijls et al. 2012) and the change in MTPM migration from one to two years (Ryd et al. 1995).

Hypothesis

Uncemented implants will have higher migration at one year compared to cemented implants, but equivalent stabilization between one and two years post-operatively.

Rationale

In cases of uncemented fixation of tibial components in TKA, a period of settling, and consequently higher mean one year migration, is commonly reported in the RSA literature. However, this does not appear to compromise stabilization after one year as assessed by the change in migration from one to two years in most cases.

A refinement of the thresholds of acceptable migration, especially at one year, may be appropriate for cemented and uncemented fixation considered separately. It may be possible to then reduce the wide range of uncertainty in the first year threshold which currently requires additional two year migration data to predict outcomes.

Approach

Tibial component migration measured as MTPM for cemented and uncemented groups was compared at one year and between one and two years. Patient demographics were controlled for in multiple regression analysis.

Objective 2.

Investigate the influence of implant and patient factors on overall implant migration in the first two post-operative years.

Hypothesis

Patient demographics and implant characteristics will significantly influence overall migration, and will not be consistent by sex.

Rationale

Preliminary data showed significant spread in the migration of individual TKA tibial components, especially for uncemented implants.

The patient characteristics today are significantly different from historical RSA studies. Long-term evaluations of cemented fixation have generally been favourable, but the patient population undergoing knee replacement today is vastly different from the population representing historical long-term follow-ups. It is unclear if these results will hold for current patient demographics. The rationale for cemented and uncemented fixation represents two differing theories of implant fixation. There is no current rationalization for which patients should receive which implants, so the data we have includes varied combinations of implant and patient characteristics. It is hoped that examining patient and implant factors will account for variation in migration curves, which although different, will all represent stable implant fixation.

Approach

The following variables were examined to determine the influence on implant migration: age, sex, BMI, smoking status, implant fixation method, implant design, implant size. Longitudinal data analysis was performed using general estimating equations to analyze repeated migration assessments.

Objective 3.

Investigate the utility of inducible displacement from single leg stance as an alternative assessment method to migration data. Specifically:

i) Evaluate the influence of patient and implant factors on inducible displacement.

ii) Investigate the relationship between inducible displacement and migration measured at the same follow-up visit over a range of time points from 0.5 to 10 years post-operatively.

iii) Determine the relationship between inducible displacement and the change in migration from one to two years post-operatively years, as well as classification as continuously migrating or stable.

Hypothesis

Inducible displacement will be influenced by patient and implant factors. Migration and inducible displacements will be correlated, and higher inducible displacements will be associated with continuous migration after one year post-operatively.

Rationale

Assessment of longitudinal implant migration requires a series of RSA follow-ups over two years. As the patient is typically supine during these examinations, implants are assessed in an unloaded position and potential plastic deformation in the implant support is not evaluated. Mechanisms for loosening such as failure to achieve osseointegration, fibrous tissue development, or stress shielding may be better assessed by comparing implant motion due to an applied load. The potentially time-independent nature of inducible displacements makes them much easier to implement in a clinical setting. To date, the utility of inducible displacement exams have not been proven in small clinical trials, but it is theorized that inducible displacements will be sufficiently correlated to implant stability measured by migration to permit substitution of inducible displacement exams for migration in characterizing implant fixation.

Approach

Evaluation of inducible displacements will be performed to determine if inducible displacements are dependent on patient and implant characteristics, if these inducible displacements and migration patterns are correlated and if the relationship is dependent on patient and implant variables, and if inducible displacements differ for migration patterns classified as stable or continuously migrating.

1.4 Structure of Thesis and Source of Data

The following three chapters serve as stand alone papers to address the three objectives outlined above. A common dataset of RSA-measured migration and inducible displacement results on primary TKA was used to address all three objectives. This data was collected on subjects undergoing TKA between 2002 and 2015, with data collection up to 2017. The primary TKA RSA dataset analyzed here is part of a larger initiative to study RSA-based assessments of a range of arthroplasties including total hip arthroplasty, total and unicondylar knee arthroplasty, and revision as well as primary procedures. This work was undertaken following funding by the Atlantic Canadian Opportunities Agency (ACOA) Atlantic Innovation Fund (AIF), a Canadian federal government granting agency for the project entitled "*Development of Clinical Diagnostic System for Assessing Orthopaedic Implant Stability*" with Dr. Michael Dunbar as the principal investigator. The conclusions of this thesis contribute to the overall goals of the project to investigate RSA as a clinical, in addition to research, tool.

Chapter 2

NO ADVANTAGE OF CEMENTED TKA OVER UNCEMENTED AT TWO YEARS DESPITE HIGHER EARLY VARIATION IN UNCEMENTED FIXATION

2.1 Introduction

Cemented fixation in total knee arthroplasty (TKA) remains the gold standard, but there is increasing interest in uncemented TKA in an effort to provide longer lasting constructs to the young, active patient through osseointegration of the tibial component (Brown et al. 2013, Cherian et al. 2014, Drexler et al. 2012, Mont et al. 2014). A concern with uncemented TKA is that failure to achieve initial fixation may lead to revisions due to aseptic loosening. Early patterns of implant migration measured with radiostereometric analysis (RSA) have been shown to be predictive of long-term implant fixation. In particular, two studies have demonstrated the predictive value of migration one year post-operation (Pijls et al. 2012) and the change in migration between one and two years postoperatively (Ryd et al. 1995) in determining long-term survivorship. Notably, both of these studies pooled cemented and uncemented tibial components in their analyses. In contrast, a Cochrane Review (Nakama et al. 2012) concluded that although cemented tibial components had lower initial migration, uncemented fixation provided a lower risk of future aseptic loosening, as measured indirectly as a change in migration between one and two years, despite higher early migration. While cemented fixation depends on an immediate mechanical interlock provided by cured bone cement, uncemented fixation requires bone in-growth into the implant surface, which occurs in the early post-operative period (Dalury 2016, Freeman and Tennant 1992). Because of these fundamental differences in the mechanisms of early fixation for cemented and uncemented components, it is debatable if it is appropriate to evaluate cemented and uncemented tibial components under the same thresholds of early migration for prediction of successful fixation.

The purpose of this study was to compare the magnitudes of implant migration in cemented and uncemented implant fixation in TKA at one year post-operatively and between one and two years post-operatively.

2.2 Methods

This study included RSA data on subjects who received a primary TKA between 2002 and 2015 at two institutions (Halifax Infirmary, Halifax, Nova Scotia and St. John of God Hospital Subiaco, Perth, Australia). Ethics approval was obtained and subjects provided written consent (Appendix A).

All subjects had tantalum RSA markers inserted into the proximal tibia and into the non-articulating periphery of the polyethylene component at the time of surgery.
Subjects received post-operative care that included antibiotics, anticoagulation medication, and physiotherapy in hospital and after discharge. The choice of anticoagulation was at the discretion of the treating surgeon. All subjects were mobilized to full weight bearing post-operatively.

Subjects were followed for two years and had RSA exams immediately post-operatively (reference exam) and at a minimum of one and two years post-operatively (refer to Appendix B for details of the RSA equipment). Inclusion criteria for this analysis were a primary diagnosis of osteoarthritis, no previous knee replacement, and RSA migration data at both one and two years post-operatively. Exclusion criteria included severe joint deformity requiring revision components in primary cases and revision of the tibial component. Cases were also excluded if there were technical problems with RSA analysis (insufficient markers visible, condition number > 150, or rigid body error > 0.35) (Valstar et al. 2005).

The primary outcome measure studied was RSA-defined implant migration calculated as maximum total point motion (MTPM). MTPM is the vector length of the point on the implant that moved the most and is considered a summary metric for the overall motion of an implant (Ryd et al. 1995). All analyses used fictive markers at standardized locations for MTPM calculations (Nilsson et al. 1991). Rigid body motions were calculated using marker-based methods (Selvik 1989) to eliminate any differences due to model fitting that may occur with model-based RSA. Migrations at one and two years were calculated relative to the immediate post-operative reference exam.

2.2.1 Statistics

Multiple regression models were fitted to determine if fixation (cemented or uncemented) had a significant effect on (i) migration at one year relative to the immediate post-operative reference exam and (ii) the change in migration between one and two years post-operatively. The models included sex, age, and BMI, to control for these variables. For one year migration, log(MTPM) used for the outcome variable due to the non-normal distribution of this metric (Astephen et al. 2010, Pijls et al. 2012). For the change in migration from one to two years, the proportion of subjects exceeding the 0.2 mm threshold indicating continuous migration was also calculated (Ryd et al. 1995). Additional regression models were fit for cemented and uncemented groups separately to investigate the influence of implant design (in addition to age, sex, and BMI) on one year migration and the change in migration from one to two years. To compare demographics between the cemented and uncemented groups, *t*-tests and Fisher's exact tests were used for normally distributed continuous data and count data respectively. Significance was set at $p < 0.05$.

2.3 Results

2.3.1 Subjects

Four hundred and seventy-two primary TKA were performed between January 2002 and January 2015 with RSA markers inserted. Sixteen subjects with revision components used in a primary TKA were excluded. Within the first two post-operative years, 9 tibial components were revised: 3 for reasons related to mechanical loosening (two due to aseptic loosening (one cemented, one uncemented) and one due to a peri-prosthetic fracture (uncemented)), 4 due to infection, one due to instability, and one for avascular necrosis. Of the early revisions not related to mechanical loosening, 5 were cemented and 1 uncemented. A further 5 implants were revised after 2 years (two due to pain, two due to instability, and one due to infection; 3 cemented, 2 uncemented; mean time to revision of 3 years) and were also excluded. Details of revised cases are included in the supplementary data, Appendix C. Technical problems with the RSA analysis excluded 9 subjects. Missed follow-up visits at one year (n=24), two years (n=32), or both (n=18) accounted for the remaining exclusions. In total, 359 primary TKA in 332 patients were analyzed; two hundred and twenty-one knees had cemented tibial baseplates and 138 were uncemented. Seven surgeons participated and eight implant designs were used (five uncemented) (Table 2.1). Simplex P cement (Stryker, Mahwah, NJ, USA) was used for all cemented components.

Demographics for the subjects receiving the different implant designs and the combined cemented and uncemented groups are given in Table 2.1. Comparing demographics between the cemented and uncemented groups, age was not significantly different ($p = 0.07$, *t*-test), but BMI was lower for the uncemented implants ($p < 0.001$, *t*-test) and the cemented group had a higher proportion of female subjects ($p < 0.001$, Fisher’s exact test).

Table 2.1. Subject demographics by fixation (cemented and uncemented) and by implant design. Short implant name in bold. Insert types: medial pivot (MP), posterior stabilized (PS), cruciate retaining (CR), and cruciate stabilized (CS). *Indicates posterior cruciate ligament (PCL) resected.

Prosthesis	Fixation	Insert	n	**Age** (years) **mean (SD)**	**BMI** (kg/m2) **mean (SD)**	**Female:Male (%Female)**
All Implants			359	64 (7.8)	32.4 (6.1)	219:140 (61%)
All Cemented Implants			221	64 (8.3)	33.2 (6.4)	151:70 (68%)
Advance® (Wright Medical Technology, Inc., Arlington, TN)	Cemented	MP*, PS*	59	64 (7.8)	32.2 (5.6)	41:18 (69%)
NexGen® (Zimmer,Warsaw, IN)	Cemented	PS*	30	66 (8.7)	32.4 (5.7)	18:12 (60%)
Triathlon® (Stryker, Mahwah, NJ)	Cemented	PS*, CR, CS	132	64 (8.4)	33.9 (6.9)	92:40 (70%)
All Uncemented Implants			138	65 (7)	31.1 (5.2)	68:70 (49%)
Advance® **Biofoam™**, (Wright Medical Technology, Inc., Arlington, TN)	Uncemented (porous coated, without screws)	MP*	22	69 (5.2)	30.1 (3.8)	12:10 (55%)
Advance® **Biofoam™**, (Wright Medical Technology, Inc., Arlington, TN)	Uncemented (porous coated + **screws**)	MP*	20	69 (5.2)	30.5 (4.6)	7:13 (35%)
Trabecular Metal™ (**TM**) **Monoblock** (Zimmer,Warsaw, IN)	Uncemented (trabecular metal)	PS*, CR	48	64 (7.7)	32 (5.4)	29:19 (60%)
Trabecular Metal™ (**TM**) **Modular** (Zimmer,Warsaw, IN)	Uncemented (trabecular metal)	PS*	16	62 (8.7)	34.9 (4.8)	10:6 (63%)
Triathlon® PA®-Coated (Stryker, Mahwah, NJ)	Uncemented (porous coated + Periapatite)	PS*, CR, CS	32	65 (8.4)	28.8 (5)	10:22 (31%)

2.3.2 One Year Migration

Tibial component migration measured as MTPM at one year was significantly lower for the cemented group (median = 0.31 mm, range 0.03 – 2.98 mm) compared to the uncemented group (median = 0.63 mm, range 0.11 – 5.12 mm; p < 0.0001) (Figure 2.1, Table 2.2).

Within the cemented group, the NexGen implant group had significantly more one year migration than the other implants (p = 0.03, Figure 2.2). For the uncemented implants, no other variables were significant (Refer to the supplementary data in Appendix C for details of the regression analysis).

Table 2.2. Tibial component one year MTPM migration and change in MTPM migration from one to two years by fixation and implant groups.

		One Year Migration (MTPM, mm)					**Change in Migration from One to Two Years** (MTPM, mm)				
Prosthesis	n	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
All Cemented Implants	221	0.41	0.36	0.31	0.03	2.98	0.06	0.19	0.04	-0.38	1.76
Advance	59	0.40	0.24	0.30	0.16	1.13	0.04	0.14	0.06	-0.31	0.36
NexGen	30	0.49	0.34	0.38	0.14	1.66	0.13	0.38	-0.01	-0.16	1.76
Triathlon	132	0.40	0.41	0.27	0.03	2.98	0.05	0.14	0.03	-0.38	0.53
All Uncemented Implants	138	0.98	0.94	0.63	0.11	5.19	0.07	0.27	0.04	-0.76	1.30
Biofoam	22	1.08	1.05	0.68	0.18	4.09	0.05	0.32	0.01	-0.62	1.25
Biofoam + Screws	20	0.82	0.75	0.66	0.29	3.80	0.04	0.31	0.04	-0.55	0.94
TM Monoblock	48	0.89	0.77	0.55	0.14	3.06	0.05	0.21	0.04	-0.76	0.78
TM Modular	16	1.52	1.24	1.20	0.31	5.19	0.32	0.35	0.19	-0.10	1.30
Triathlon PA	32	0.85	1.00	0.50	0.11	4.17	-0.01	0.19	0.00	-0.72	0.43

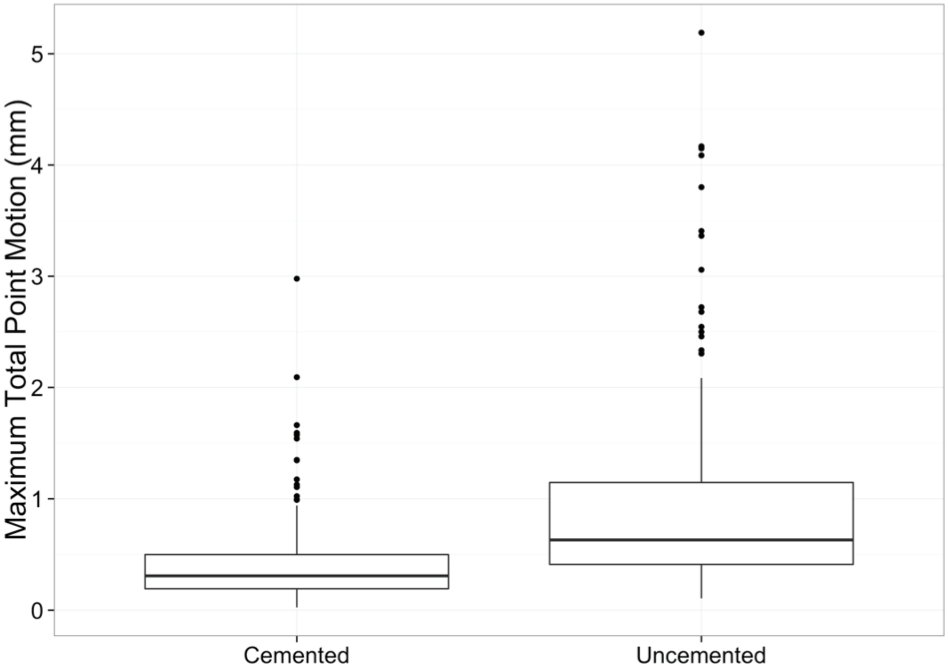


Figure 2.1. One year MTPM migration by fixation (cemented, n= 221; uncemented, n = 138)

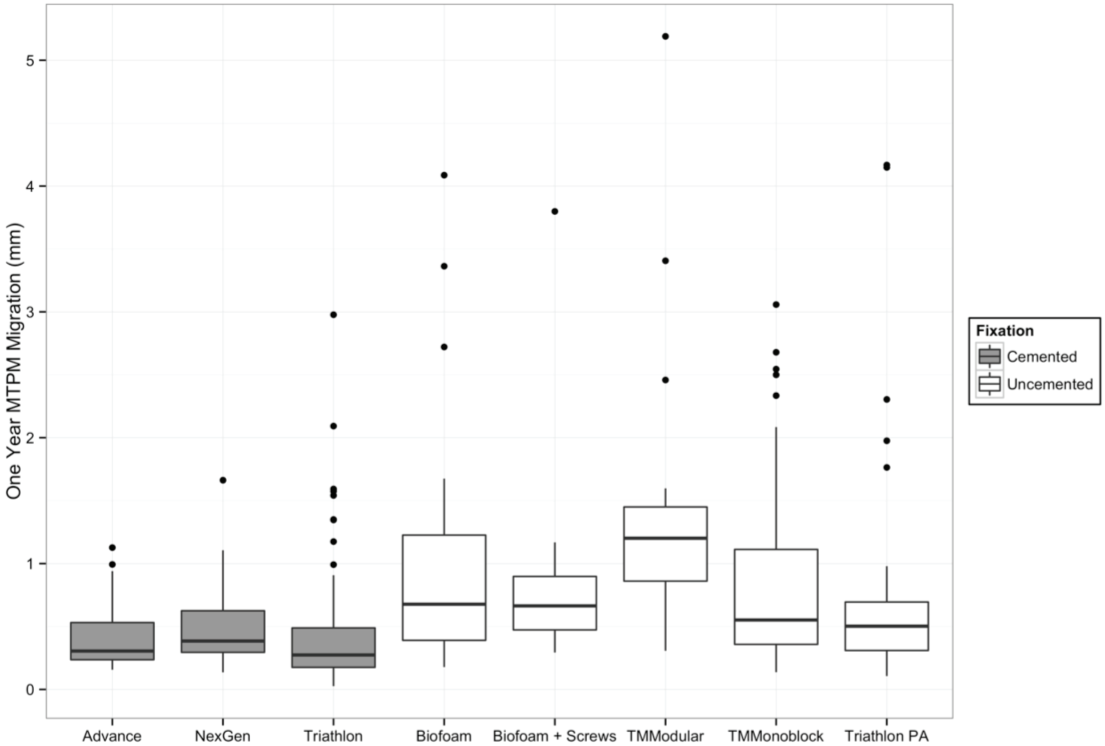


Figure 2.2. One year MTPM migration for cemented and uncemented tibial components by implant design

2.3.3 One to Two Year Migration

Tibial component migration measured as MTPM between one and two years was not significantly different between the cemented (mean±SD = 0.06±0.19 mm) and uncemented (mean±SD = 0.07±0.27 mm) groups (p-value = 0.59) (Figure 2.3, Table 2.2). Additionally, the proportion of implants with migration between one and two years of more than 0.2 mm was not different between groups with 29/221 (13%) in the cemented group and 21/138 (15%) in the uncemented group (p = 0.64 Fisher Exact Test, 2 tailed).

When comparing the migration of individual implant designs in the cemented group from one to two years, the NexGen group was found to be significantly different (p = 0.03) (Figure 2.4, Table 2.2). The NexGen group contained one significant outlier, defined as having a change in MTPM of more than two standard deviations from the mean. Removing this subject did not alter the overall conclusion of the analysis (cemented and uncemented implants did not have a different change in migration between one and two years), but removed the difference between cemented implant groups for both the one year migration value and the change in migration from one to two years.

When examining the five prosthesis designs in the uncemented group, the Trabecular Metal Modular group had a significantly greater change in migration from one to two years compared to the other implant designs (p = 0.04) (Figure 2.4, Table 2.2).

Excluding the uncemented TM Modular group (n = 16) and reanalyzing the data with a modified uncemented group did not alter the conclusions: Migration at one year was significantly higher for the modified uncemented group (median = 0.57 mm, range 0.11 – 4.17 mm, n=122) compared to the unchanged cemented group (p < 0.001) and the change in migration between one and two years for the modified uncemented group (mean±SD = 0.03±0.24 mm) was not significantly different from the cemented group (p = 0.55). Of the continuous migrators, eight were TM Modular implants, representing 50% of this implant group.

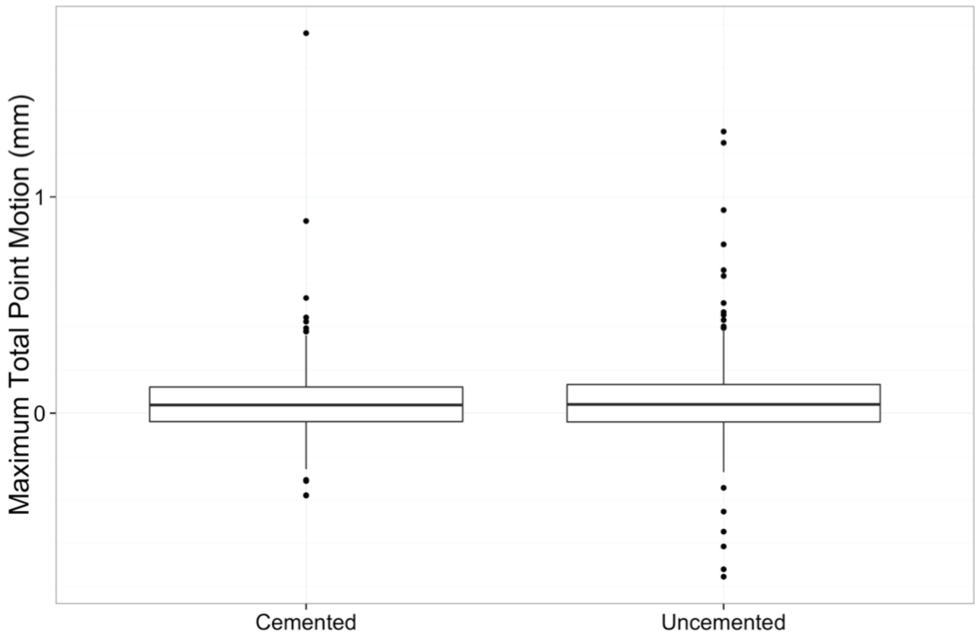


Figure 2.3. Change in MTPM migration from one to two years by fixation (cemented, n= 221; uncemented, n = 138)

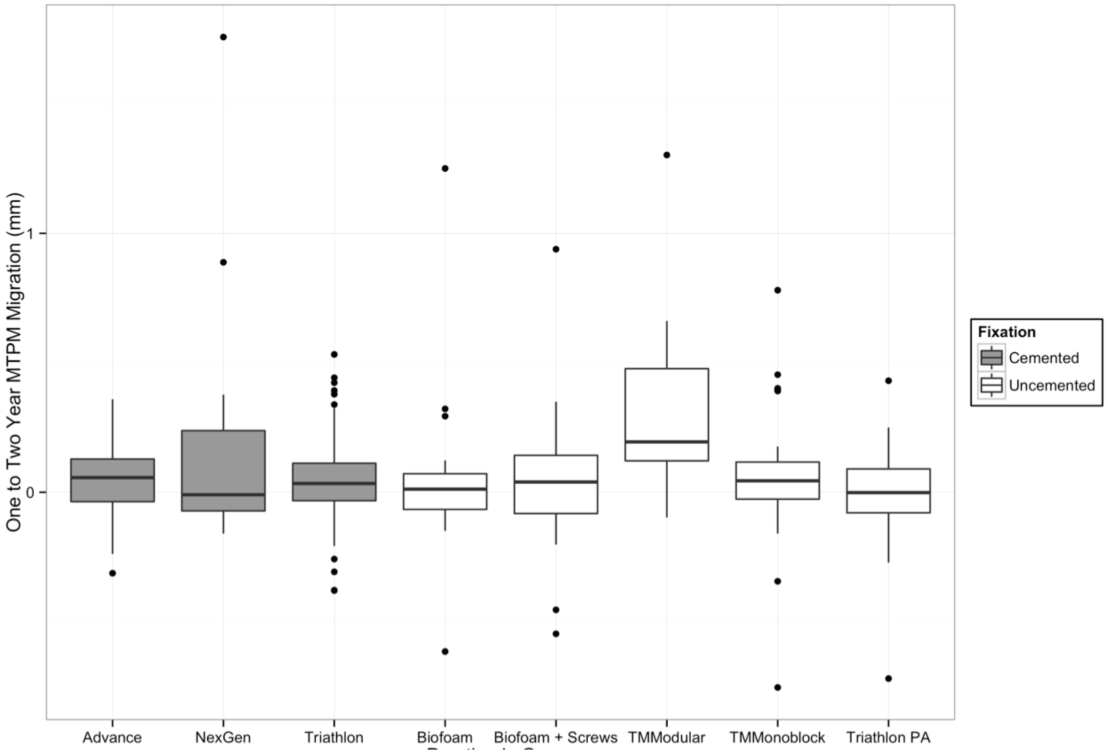


Figure 2.4. Change in MTPM migration from one to two years for cemented and uncemented tibial components by implant design

2.4 Discussion

The application of equivalent thresholds of safe RSA migration at one year for cemented and uncemented TKA appears to be suboptimal, as higher initial migration seen in the first post-operative year for uncemented components did not coincide with greater migration between one and two years.

The pooling of RSA data of both cemented and uncemented tibial components has been employed in two influential studies using early RSA data to predict long-term implant outcomes. In the first study, Ryd *et al.* found that MTPM migration between 1 and 2 years post-operatively of greater than 0.2 mm was predictive of later loosening with 85% predictive power (Ryd et al. 1995). One hundred and fifty-eight cases were included in the analysis, composed of 97 cemented components and 46 uncemented components. In the second study, Pijls *et al.* concluded that mean MTPM migration at 1 year of greater than 0.5 mm put an implant design "at risk" and greater than 1.6mm was "unacceptable" based on the predicted revision rate at 5 years (Pijls et al. 2012). In this meta-analysis, a total of 847 subjects were included from 50 RSA studies that were matched to survival studies of the same implant designs (20,599 subjects in 56 studies). Of the 28 implant designs included, 18 had cemented fixation and 10 were uncemented. The current analysis may help to further refine the inconclusive "at risk" region of the results between 0.5 and 1.6 mm of MTPM at 1 year.

In the current paper, the differences at one year are statistically significant and clinically relevant because the differences in means place the cemented group, as well as each cemented implant design, in the "stable" category and the uncemented group, and all individual uncemented implant designs, in the "at risk" category according to Pijls *et al.* (2012). Extrapolating these results in the context of the Pijls paper would suggest that uncemented implants have a higher likelihood of poor survivorship. The Cochrane review, however, concluded that uncemented implants had a lower risk of future aseptic loosening for (Nakama et al. 2012). The results of the current study are in accordance with the conclusions of the Cochrane review, showing equivalent migration between one and two years, indicating no greater risk for uncemented implants despite greater uncertainty at one year based on the current threshold. Higher one year migration for uncemented implants compared to cemented components is not unexpected as uncemented components may undergo a "settling" period prior to bone ingrowth (Molt and Toksvig-Larsen 2014, Onsten et al. 1998). Once osseointegration is achieved, the potential for long-term fixation is good for uncemented tibial components while cemented components are susceptible to cement-related complications such as cement delamination (Dalury 2016). Previous RSA studies comparing cemented and uncemented implants have reported higher early migration for the uncemented components while achieving good long-term performance with contemporary uncemented fixation, including hydroxyapatite coatings and trabecular metal monoblock components (Carlsson et al. 2005, Hilding et al. 1995, Nilsson et al. 2006, Nilsson et al. 1999, Pijls et al. 2012, Regner et al. 2000, Toksvig-Larsen et al. 2000, van Hamersveld et al. 2017, Wilson et al. 2012). Recent review papers of cemented versus uncemented fixation have been inconclusive, citing a lack of long term follow-up studies, but do conclude that there are promising results, especially with hydroxyapatite coatings and trabecular metal in short term and RSA studies (Brown et al. 2013, Mont et al. 2014), which is supported by our findings.

Differences in one year migration were found between different types of uncemented fixation suggesting that not all uncemented fixation is equivalent. Interestingly, the uncemented group with screw fixation did perform equivalently to the same implant without screw fixation although the intention of screw fixation is to provide immediate stability. This finding of lack of immediate stability with screw fixation has been seen in previous RSA studies (Nilsson et al. 2006, Stilling et al. 2011).

For the TM Modular group, the trend towards greater migration at both one year and significantly higher migration between one and two years suggests that this implant design is at greater risk of poor long-term survivorship. The differences in magnitudes between the uncemented subgroups may offer a preview of the refined thresholds for one year screening of uncemented implants: the median one year migration of the TM Modular group was 1.2 mm compared to 0.5 – 0.7 mm for the other four uncemented groups. Matching of RSA and survivorship studies will be required to perform the robust analysis of Pijls et al. (2012) to determine if a revised one year threshold for uncemented components is valid. Previous studies on the TM Modular component have reported 4 failures due to aseptic loosening in 167 cases (2.4%, all within the first post-operative year) (Zandee van Rilland et al. 2015), 7 revised or radiographically loose components in a series of 51 subjects (Behery et al. 2017), 1 revision for subsidence out of 50 cases (Fricka et al. 2015), and significantly higher overall migration compared to the TM Monoblock component, but no difference between groups in change in migration from one to two years in 53 subjects (Andersen et al. 2016). It has not been possible to date to identify the TM Modular component in isolation in any national knee registry reports, so the survivorship of this implant in general use remains to been seen. Of note, a similar uncemented implant design by the same manufacturer employing trabecular metal and a modular tibial tray was recalled in 2015 due to an increase in complaints of loosening and radiolucent lines (FDA 2015). While both the TM Modular and TM Monoblock tibial components rely on bone in-growth into the porous trabecular metal structure, the benefits of the lower modulus monoblock component may be compromised with the addition of a stiff baseplate in the modular component to allow polyethylene inserts to be locked in place.

A limitation of this study is that subjects were not randomly assigned to the cemented and uncemented groups. The demographic data show statistical differences between groups, although the clinical relevance of a BMI difference of 2 kg/m^2 (with both groups > 30 kg/m^2) is likely negligible. The proportion of females in the cemented group (68%) versus the uncemented group (49%) was unexpected and may reflect an unconscious bias by operating surgeons in not using uncemented implants in women due to bone quality concerns. These demographic variables were accounted for in the statistical models, so the differences between fixation cannot be attributed to mismatched demographic factors between the cemented and uncemented groups. It is likely that demographic factors do influence implant migration and may account for some of the variability in early migration, which is higher in the uncemented components.

Revised implants were excluded in this study to allow a comparison of the two methods for thresholds of allowable motion. Only three revisions were performed for reasons related to mechanical loosening (one peri-prosthetic fracture and two for aseptic loosening) and all three revisions were performed within the first two post-operative years so these cases would have been excluded from the analysis by default as the change in migration from one to two years could not be evaluated. Excluding the remaining cases ensured that no misclassified revision was included as our data captures only the most responsible reason for revision in what may be a multifactorial process.

The indirect measure of long-term performance used in the Cochrane review was the criteria Ryd et al. presented for defining continuous motion as MTPM migration between one and two years of more than 0.2 mm (Ryd et al. 1995). The data in the current analysis match the conclusions of the Cochrane review and demonstrate a lack of continuous migration for both the cemented and uncemented groups overall. The data lend support to the universality of Ryd's method for assessing cemented and uncemented tibial components. However, in a model of phased innovation (Malchau 2000, Nelissen et al. 2011, Pijls 2013), the one year time point for safety thresholds is appealing as it halves the follow-up time required, providing more timely assessment of implant designs to patients, surgeons, and manufacturers.

2.5 Conclusions

This study finds that the pattern of migration between one and two years does not differ between cemented and uncemented groups and therefore supports the previous findings that this metric is appropriate to evaluate all tibial component fixations (Ryd et al. 1995). However, the magnitudes of migration at one year are significantly higher for the uncemented group suggesting that thresholds at one year may not apply equally to cemented and uncemented implants for predicting revision rates as suggested by Pijls et al. (2012). A further refinement of the one year threshold may be appropriate for uncemented implants.

Chapter 3

THE INFLUENCE OF PATIENT AND IMPLANT CHARACTERISTICS ON MIGRATION IN TOTAL KNEE ARTHROPLASTY

3.1 Introduction

The screening of implant designs for total knee arthroplasty (TKA) using short-term implant migration data from radiostereometric analysis (RSA) has been shown to be predictive of longer term outcomes (Pijls et al. 2012, Ryd et al. 1995). However, there has been minimal examination of the influence of individual patient factors on tibial component migration patterns. Additionally, these previous studies showing the predictive value of RSA have not considered modes of implant fixation separately, analyzing both cemented and uncemented tibial baseplates together (Pijls et al. 2012, Ryd et al. 1995).

In subjects with tibial components defined as “well-fixed” by RSA, there is nonetheless significant variation in patterns of implant migration in the first two post-operative years. Some of this variation can likely be attributed to differences in implant design, especially fixation method; however, it is probable that individual subject characteristics also influence overall implant migration, the magnitude of which has not been well established. The fundamentally different philosophies of cemented and uncemented tibial component fixation are likely contributors as cemented fixation depends on an immediate mechanical interlock created by the intra-operative curing and hardening of polymethylmethacrylate (PMMA) one cement while uncemented fixation relies on the growth of the underlying subject bone into the implant over a period of time on the order of weeks or months (Freeman and Tennant 1992). Uncemented, or cementless, fixation in particular may be sensitive to individual patient factors such as initial bone quality, anthropometrics, and medication use that may influence bone ingrowth. In post-menopausal women, bone health questions may be of particular concern for uncemented fixation (Armas and Recker 2012). Additional sex-related differences in TKA include higher rates of obesity in female patients (Whitlock et al. 2016) and questions of appropriate sizing of implants for smaller bones (Bellemans et al. 2010). For these reasons, we were interested in not only the influence of implant and subject demographics on implant migration, but also in examining these influences in subgroups composed of separate cohorts of cemented and uncemented female and male subjects.

The objective of this study was to examine the influence of both patient and implant factors on the pattern of tibial component migration in the first two post-operative years to determine what factors influence the overall migration of tibial components.

3.2 Methods

RSA data was collected prospectively on patients undergoing primary TKA between 2002 and 2015 with varying implant designs and employing cemented or uncemented fixation. Ethics approval was obtained and subjects provided written consent (Appendix A). All subjects received comparable intra- and post-operative clinical care regimes including anti-coagulant medication and unrestricted post-operative weight-bearing as per the standard of care. The majority of cases were performed in Halifax, Nova Scotia by 6 surgeons, with 15 knees (4%) recruited by a single surgeon in Perth, Australia as part of a multicentre study on a single implant design.

Tantalum RSA markers were inserted into the proximal tibia and the polyethylene component intra-operatively. All subjects had a reference RSA exam within the first 4 post-operative days. Protocols for RSA follow-up varied slightly depending on the time of enrollment, with a minimum follow-up schedule of 6 months, 1 year, and 2 years post-operatively. Subjects enrolled from 2008 onward had additional exams scheduled at 6 weeks and 3 months post-operatively. Details of the RSA equipment used are provided in Appendix B.

Inclusion criteria were subjects undergoing total knee arthroplasty for a primary diagnosis of osteoarthritis and a reference RSA exam followed by a minimum of two follow-up RSA exams in the first two post-operative years. Exclusion criteria were: revision TKA, revision for any reason within 2 years or later, revision components used in a primary TKA case, and technical problems with RSA analysis (insufficient markers visible, condition number > 150, or rigid body error > 0.35 (Valstar et al. 2005)).

Marker-based analysis was used in all cases, with maximum total point motion (MTPM) calculated for standardized locations to reduce variation by implant design (Nilsson et al. 1991).

3.2.1 Statistics

Longitudinal data analysis using marginal models was undertaken to examine the influence of demographic and implant variables on overall migration while modeling the repeated measures of implant migration over time on the same subjects (Zeger et al. 1988, Zeger and Liang 1986). The primary outcome measure was implant migration measured as maximum total point motion (MTPM), the vector length of the standardized point at the periphery of the tibial baseplate that moved the most (Ryd et al. 1995). Specifically, log(MTPM) was taken as the outcome variable in the models (Astephen et al. 2010, Pijls et al. 2012). The following variables were included as covariates in the analysis: age at the time of surgery, sex, body mass index (BMI in kg/m^2), smoking status, implant fixation (cemented or uncemented), and implant size (estimated tibial baseplate area in cm^2). All analyses were performed in R (Version 3.2.0)(R Core Team 2015) using the “gee” package (Carey 2015). An autoregressive correlation structure was employed. Bilateral subjects were included as independent samples. Analyses were repeated with individual translations (medial translation, subsidence, anterior translation) and rotations (anterior tilt, internal rotation, medial tilt) as outcome variables. Significance was set at $p < 0.05$.

To investigate the potential of decreased bone mineral density in older women compared to men, which may be of consequence especially with uncemented fixation, all above analyses were also performed on the following subgroups: uncemented females, uncemented males, cemented females, cemented males.

3.3 Results

3.3.1 Subjects

Four hundred and seventy-two primary total knee replacements were recruited. Subjects with revision components used in a primary case were excluded (n=16, 3%). Nine revisions performed before 2 years post-operatively were excluded (2 for aseptic loosening - one cemented case and one uncemented case, 1 peri-prosthetic fracture, 4 infections, 1 due to avascular necrosis, and 1 for instability), and nine subjects were excluded due to unacceptable RSA errors (2%). Fifteen subjects were excluded because they only had a single follow-up RSA exam (3%). Patient records were reviewed to determine if any knees had been revised after the 2 year study period. A further five knees were excluded for later revision (1 due to infection, 2 due to instability, 2 due to pain; median time to revision 2.5 years, range 2.2 – 4.7 years; 3% revision rate overall, 64% of revisions in cemented components, refer to Appendix D for additional details).

A total of 418 total knee replacements in 381 patients were available for study, comprising seven separate implant designs (Table 3.1). No tibial components employed mobile bearing inserts. Of the entire cohort, 265 were cemented tibial components and 153 uncemented in 256 female subjects and 162 males (Table 3.2). Simplex P cement (Stryker, Mahwah, NJ, USA) was used for all cemented components.

There were 38 bilateral patients included, representing 10% of the patient group. Of these, 18 had the same prosthesis-fixation-insert combinations in both knees while the remaining 20 had differing implants. Three patients had simultaneous bilateral knee replacements while the remainder had knee replacements on average 1.7 years apart (range 4 months to 8 years).

The median period of implantation for the all subjects was 7 years (range 2.2 – 15 years). Seventy-three percent of patients were more than five years from the date of surgery.

Table 3.1. Details of implant designs and subject demographics by implant design. Implant short name in bold. Insert types: medial pivot (MP), posterior stabilized (PS), cruciate retaining (CR), and cruciate stabilized (CS). *Indicates posterior cruciate ligament (PCL) resected.

Implant Design	**Fixation**	**Insert**	**n**	**Age** (years) **mean (SD)**	**BMI** (kg/m2) **mean (SD)**	**Female:Male (%Female)**
Advance® (Wright Medical Technology, Inc., Arlington, TN)	Cemented	MP*, PS*	74	64 (7.7)	32 (5.2)	111:47 (68%)
NexGen® (Zimmer,Warsaw, IN)	Cemented	PS*	33	65 (8.6)	32.4 (5.5)	20:13 (61%)
Triathlon® (Stryker, Mahwah, NJ)	Cemented	CR, CS, PS*	158	63 (8.3)	34.1 (7.0)	111:47 (70%)
Advance® **Biofoam™**, (Wright Medical Technology, Inc., Arlington, TN)	Uncemented (porous coated, with or without screws)	MP*	46	69 (5.4)	30.1 (4.1)	20:26 (43%)
Trabecular Metal™ **(TM) Monoblock** (Zimmer,Warsaw, IN)	Uncemented (trabecular metal)	PS*, CR	55	64 (7.5)	32 (5.6)	33:22 (60%)
Trabecular Metal™ **(TM) Modular** (Zimmer,Warsaw, IN)	Uncemented (trabecular metal)	PS*	19	62 (6.7)	34.7 (4.8)	11:8 (58%)
Triathlon® PA®-Coated (Stryker, Mahwah, NJ)	Uncemented (porous coated + Periapatite®)	CR, CS, PS*	33	65 (6.6)	28.7 (5.0)	11:22 (33%)

Table 3.2. Sample sizes and demographic data for complete cohort and subgroups by fixation and sex. Note: smoking status is unknown for 20 subjects (5%)

Fixation and Sex	**n**	**Age** (years) **mean (SD) [range]**	**BMI** (kg/m^2) **mean (SD) [range]**	**Smokers:Non-smokers (% Smokers)**
All *(61% Female)*	418	65 (7.8) [32-84]	32.5 (6.1) [20.1-58.3]	40:358 (10%)
Uncemented *(49% Female)*	153	66 (7.0) [42-79]	31.0 (5.2) [20.1-50.5]	18:118 (13%)
Uncemented Female	75	65 (6.8) [47-79]	32.0 (5.9) [20.1-50.5]	8:65 (11%)
Uncemented Male	78	66 (7.3) [42-79]	30.1 (4.4) [21.9-42.7]	10:53 (16%)
Cemented *(68% Female)*	265	64 (8.2) [32-84]	33.3 (6.4) [20.2-58.3]	22:240 (8%)
Cemented Female	181	63 (8.2) [32-84]	34.4 (6.7) [20.2-58.3]	13:165 (7%)
Cemented Male	84	66 (8.0) [42-84]	31.2 (5.1) [23.1-45.2]	9:75 (11%)

3.3.2 The Influence of Implant and Patient Factors on Implant Migration for All Implants

Investigating the influence of implant and subject factors on the overall MTPM migration of all tibial components found that only fixation had a significant effect (p<0.001, Figure 3.1, Table 3.3).

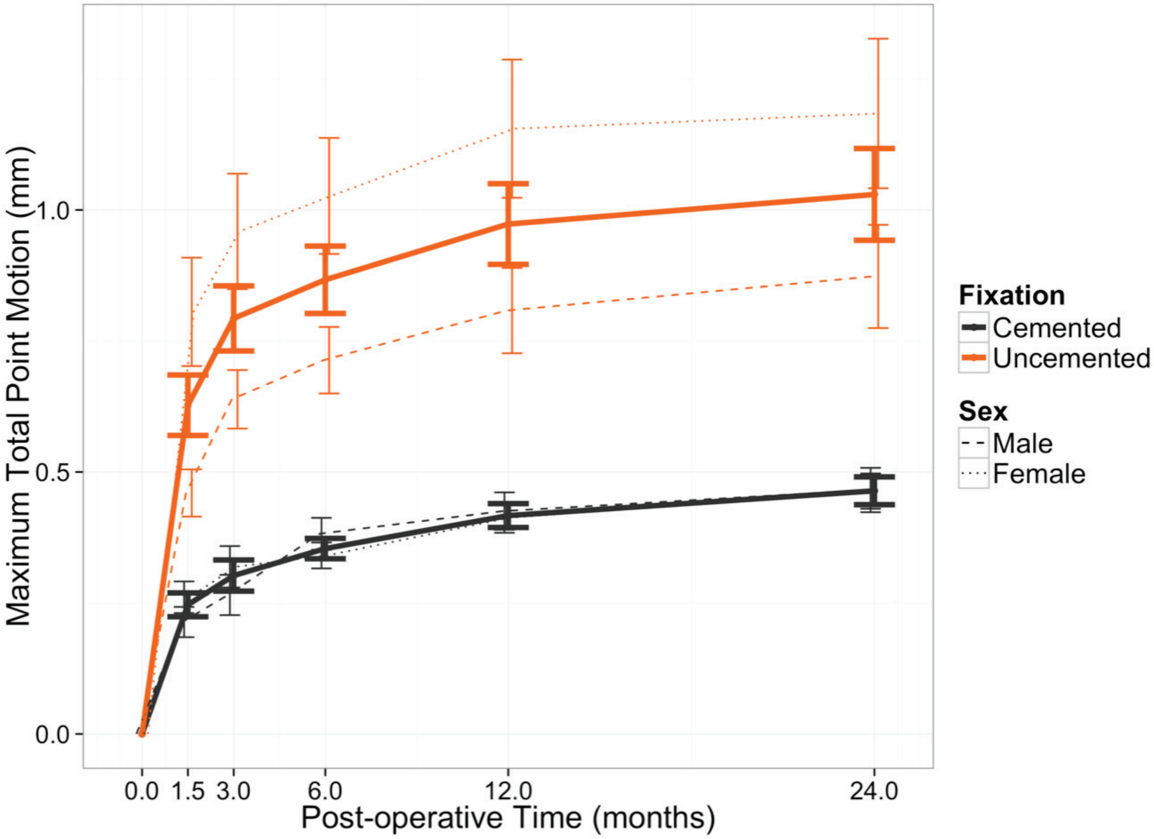


Figure 3.1. **Longitudinal implant migration (MTPM) by fixation (bold lines) and by fixation and sex.** Mean, standard error of the mean.

Table 3.3. Results of longitudinal data analysis for the influence of demographic variables on implant migration (MTPM) for tibial component groups

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented, male and female) n = 418					
Follow-up Exam Time	0.003	0.000	0.003	0.004	<0.001
Fixation	0.784	0.080	0.626	0.941	**<0.001**
Sex	0.135	0.115	-0.091	0.360	0.242
Age	0.006	0.005	-0.004	0.016	0.225
BMI	0.005	0.006	-0.007	0.017	0.388
Tibial Component Area	0.015	0.014	-0.011	0.042	0.256
Smoking Status	-0.016	0.136	-0.282	0.251	0.908
Subgroup 1: Uncemented Tibial Components in Female Subjects (n = 75)					
Follow-up Exam Time	0.001	0.001	0.000	0.003	0.004
Age	0.029	0.015	0.000	0.058	**0.048**
BMI	0.015	0.017	-0.018	0.048	0.365
Tibial Component Area	-0.040	0.041	-0.121	0.041	0.330
Smoking Status	0.602	0.300	0.014	1.190	**0.045**
Subgroup 2: Uncemented Tibial Components in Male Subjects (n = 78)					
Follow-up Exam Time	0.002	0.001	0.001	0.003	0.004
Age	-0.004	0.013	-0.030	0.022	0.754
BMI	0.039	0.022	-0.003	0.082	0.070
Tibial Component Area	0.012	0.032	-0.050	0.075	0.697
Smoking Status	-0.582	0.239	-1.051	-0.114	**0.015**
Subgroup 3: Cemented Tibial Components in Female Subjects (n = 181)					
Follow-up Exam Time	0.004	0.000	0.003	0.005	<0.001
Age	0.003	0.006	-0.009	0.015	0.606
BMI	-0.001	0.007	-0.014	0.011	0.827
Tibial Component Area	0.056	0.017	0.022	0.090	**0.001**
Smoking Status	-0.146	0.183	-0.504	0.212	0.423
Subgroup 4: Cemented Tibial Components in Male Subjects (n = 84)					
Follow-up Exam Time	0.004	0.001	0.003	0.005	<0.001
Age	-0.003	0.011	-0.024	0.018	0.795
BMI	-0.004	0.016	-0.035	0.026	0.774
Tibial Component Area	-0.001	0.022	-0.045	0.042	0.954
Smoking Status	0.178	0.234	-0.281	0.638	0.446

Independent variable: log(MTPM). Follow-up Exam Time is included in the model to account for the repeated measures and is significant as expected in all models since migration is not constant over time

*CI = 95% confidence interval

Subgroup Analyses

Subgroup 1: Uncemented Implants in Females

Uncemented tibial components in female subjects showed the highest overall migration (Figure 3.1). For this group, both age and smoking status had a significant effect on longitudinal migration (Table 3.3), with increasing age associated with higher overall MTPM migration and smokers having greater migration than non-smokers (Figure 3.2). BMI and tibial component baseplate area were not significant. Visual inspection of the relationship between age and migration suggests that migration differentiates at 60 years of age, with lower maximum migration before age 60 (Figure 3.3). No variables significantly affected implant migration for individual translation and rotation directions (supplementary data in Appendix D).

Subgroup 2: Uncemented Implants in Males

Smoking status was significant for uncemented tibial components in male subjects, but with the opposite effect as for female subjects (male smokers had lower overall migration compared to non-smokers, Figure 3.2). No other variables were significant (Table 3.3), although BMI approached significance. No variables were significant for individual translations and rotations (supplementary data in Appendix D).

Subgroup 3: Cemented Implants in Females

In females with cemented components, tibial component baseplate area was significant for MTPM migration (larger components associated with higher migration, Table 3.3). Additionally, when analyzing individual translations and rotations, both subsidence and external rotation were significantly influenced by smoking status, with greater subsidence and external rotation for smokers compared to non-smokers ($p = 0.001$ for subsidence, $p = 0.016$ for external rotation, supplementary data in Appendix D).

Subgroup 4: Cemented Implants in Males

In cemented males, no demographic or additional implant variables were statistically significant for MTPM migration (Table 3.3). However, smoking was statistically significant for anterior tilt, with smoking associated with positive anterior tilt and non-smoking associated with negative anterior tilt (posterior tilt) of similar magnitude (0.20 degrees versus -0.15 degrees at two years; supplementary data in Appendix D).

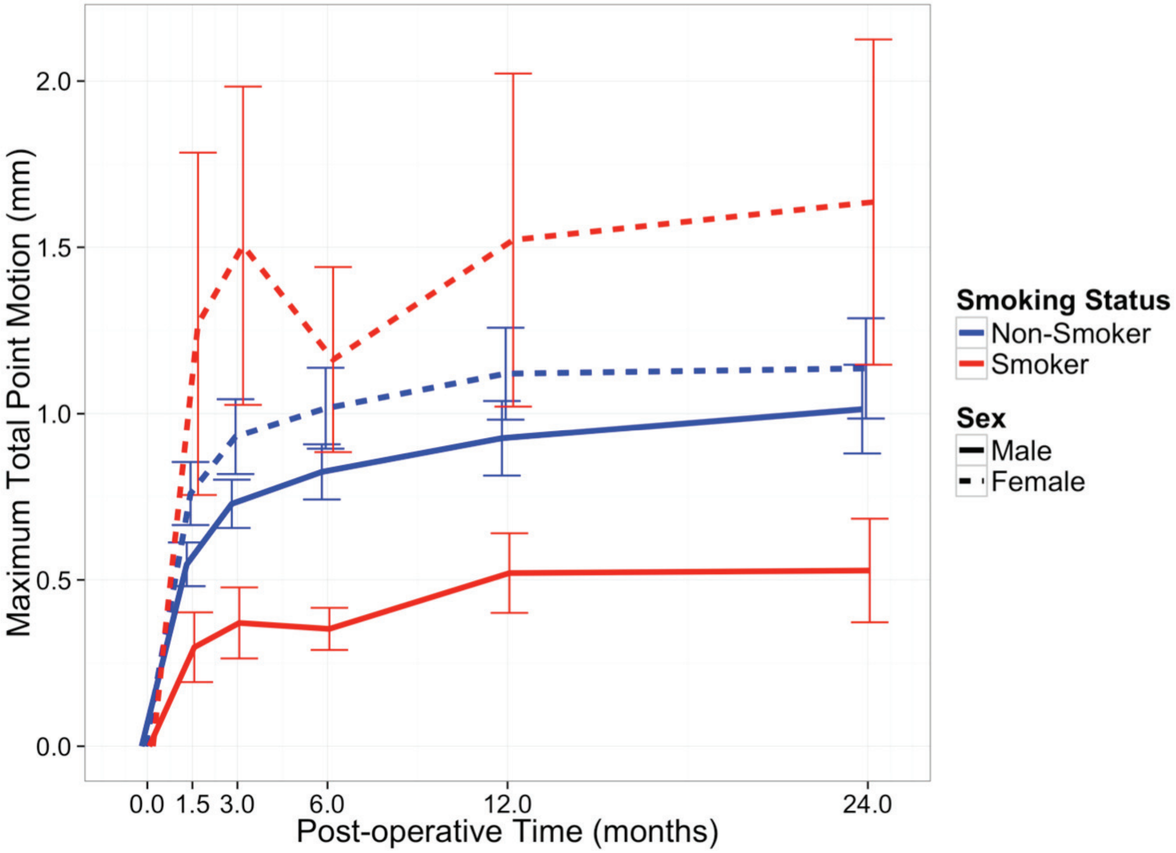


Figure 3.2. Longitudinal MTPM migration by sex and smoking status for uncemented tibial components.

Mean and standard error of the mean.

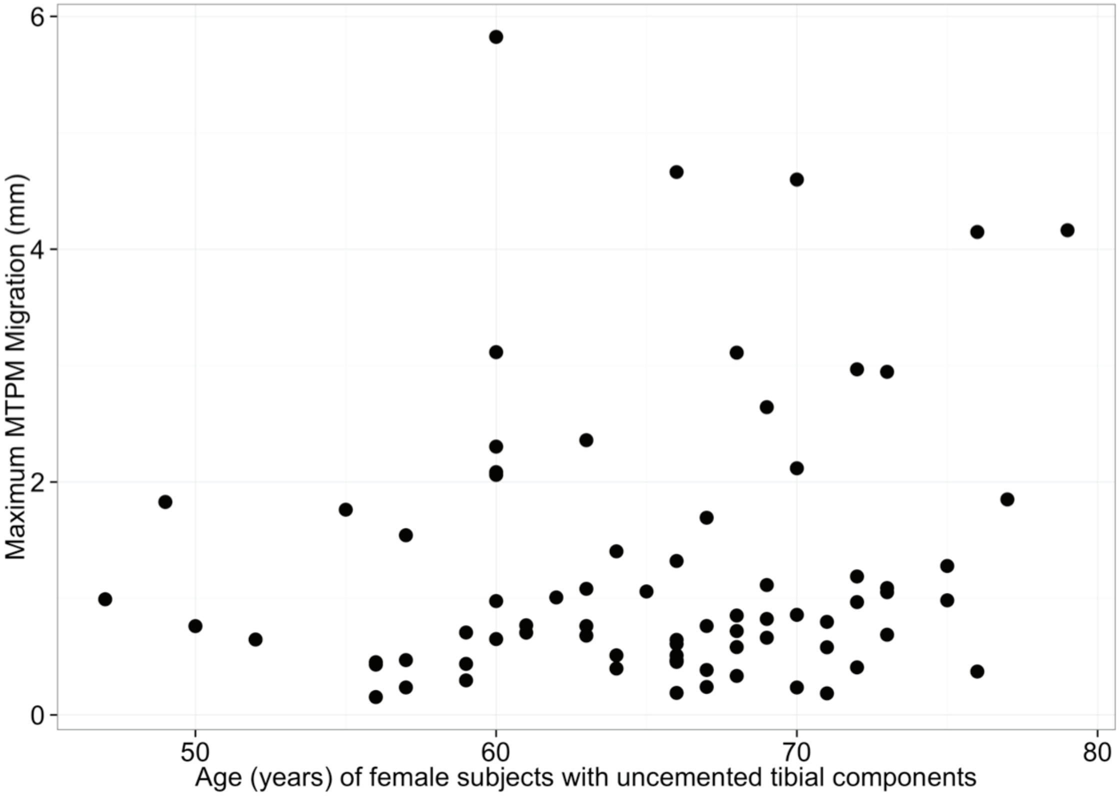


Figure 3.3. Maximum MTPM migration (of all visits in the first two post-operative years) for individuals female patients with uncemented tibial components relative to age at time of surgery.

3.4 Discussion

The compilation of a large dataset of RSA migrations in primary TKA has allowed the examination of the influence of patient and implant-specific factors on longitudinal tibial component migration in well-fixed components. The method of implant fixation had the greatest overall impact with significantly higher migration for uncemented components. This difference in magnitude, as well as greater variability, does not necessarily translate into less favourable outcomes as both of these groups are revision free to a median of 4 years after surgery. Neither do cemented and uncemented components have different rates of continuous migrators, defined as migration from one to two years of greater than 0.2 mm (Ryd et al. 1995) (15% for uncemented tibial components, 13% for cemented tibial components, Chapter 1). Stable fixation in uncemented tibial components despite higher initial migration has been reported in a number of previous RSA studies, with stabilization generally reported by three months to one year (Andersen et al. 2016, Hansson et al. 2008, Henricson et al. 2008, Hilding et al. 1995, Molt and Toksvig-Larsen 2014, Nelissen et al. 1998, Nilsson and Karrholm 1993, Petersen et al. 1999, Pijls et al. 2012, Ryd et al. 1995, Ryd et al. 1993, Ryd et al. 1990, Stilling et al. 2011, Toksvig-Larsen et al. 2000, Toksvig-Larsen et al. 1998, van Hamersveld et al. 2017).

While fixation with or without bone cement had the greatest impact on overall migration over the first two post-operative years, analyzing subgroups of fixation and sex revealed other significant covariates. As smoking has been shown to compromise healing and has been associated with higher revision rates (Duchman et al. 2015, Kapadia et al. 2012, Singh 2011), the decrease in overall migration of uncemented tibial components in male smokers was an unanticipated finding and one that the authors have been unable to find previous evidence of in the literature. The effect of smoking was reversed for females, with uncemented tibial components demonstrating greater migration for smokers. Critically, the significance of smoking on overall uncemented migration was masked when male and female subjects were analyzed together because of the opposite effect by sex. For cemented females, smoking was also a significant factor for subsidence and external rotation, with smokers having greater translations and rotations. In cemented men, the effect of smoking appears to be neutral, with a significant difference in the direction of anterior-posterior tilt from non-smokers, but not magnitude. We noted that BMI was not different between smokers and non-smokers.

While initially counter-intuitive, the finding of lower overall migration for male smokers with uncemented tibial components is in accordance with research into the effects of smoking on knee osteoarthritis. While findings are controversial (Dubé et al. 2016, Elloumi and Kallel 2007, Felson and Zhang 2015, Hui et al. 2011, Wilder et al. 2003), there is evidence that smoking is protective against severe OA and the resulting need for TKA (Anderson and Felson 1988, Felson et al. 1989, Johnsen et al. 2017, Leung et al. 2014, Mnatzaganian and Ryan 2013). Studies suggest that the effect of nicotine on bone cells, including osteoblasts, osteoclasts, and mesenchymal stem cells, in vitro is biphasic with low concentrations providing stimulatory effects while high concentrations are detrimental (Kallala et al. 2013, Kim et al. 2012). However, negative effects of smoking on total joint arthroplasty are documented, with smoking associated with higher early revision rates due to infection and wound healing complications (Duchman et al. 2015, Kapadia et al. 2012, Singh 2011). Particularly relevant for post-menopausal women, smoking is also associated with decreased bone density (Law and Hackshaw 1997, Ward and Klesges 2001), which may explain the findings of higher initial migration for the female smokers in this study.

There are limitations with the smoking data in this study as it is self-reported and does not permit an analysis of a dose effect. The low percentage of smokers in this study (10%) may indicate that patients are under-reporting smoking. Smoking rates in Nova Scotia vary substantially by age with an overall rate of 22% in the region (21% for males, 23% for females). In the 45-65 year old age group, smoking prevalence is 26%, which drops to 16% for the 65+ age group. The mean age of the study population, 65 years, is at the boundary of these reported smoking cohorts, but in either case, the proportion of smokers self-reporting in the current study is lower than in the general population. The small proportion of smokers also may lead to issues of sample size differences in the statistical analysis. In an effort to investigate the impact of this, the non-smoking group was randomly sampled to achieve equal sample sizes and the statistical analyses repeated. With matched sample sizes, the conclusions of significant covariates was unchanged from those using the complete non-smoking group, which supports the current findings, but does not eliminate the need to interpret these findings with caution.

The finding of higher magnitude migration with greater age in females with uncemented components may be related to effects of decreased estrogen production on bone in post-menopausal women. Post-menopausal changes contribute to the loss of bone mass as well as detrimental structural changes (Armas and Recker 2012, Recker et al. 2000). Additionally, age alone is a factor in decreasing bone mineral density, above the effects of estrogen deprivation, especially over the age of 75 (Recker et al. 2000). Our data suggest that age 60 represents a discontinuity in maximum migration of uncemented tibial components in women, which aligns with the timeframe of the end of maximum menopause-related bone loss. This finding is not confounded by smoking status as the over 60 group did not have a higher proportion of smokers.

For cemented components, the only significant covariate for overall MTPM migration was tibial component area in the cemented female subgroup, with higher magnitude migration associated with larger components. The interpretation of this finding is challenging, as this result is independent of BMI. Although not statistically significant, the trend was reversed for cemented components in males, with the greatest migrations occurring with the smallest sizes used in men. Examining these data together suggests that tibial components of mid-sizes have the greatest migration. One possible explanation is that this is related to the ratio of the size of the keel to the size of the baseplate; implants with wider keels relative to the width of the baseplate have greater migration. An oversized keel may be compromising the underlying bone stock. Other potential mechanisms are that the proportion of cortical bone contact relative to the surface area of the baseplate is lower in women with larger tibial components or that the geometry of the tibial component is associated with suboptimal coverage in mid-sized bones (Bellemans et al. 2010).

There was generally a lack of significant association of migration with BMI in any analysis (although BMI approached significance for males with uncemented components). The provision of TKA to obese patients is a contentious issue (Martin et al. 2017). Our findings support previous studies that have found higher BMI is not associated with negative outcomes post-TKA (Cherian et al. 2015, Daniilidis et al. , Dewan et al. 2009, Sveikata et al. 2017) including specifically for uncemented TKA (Bagsby et al. 2016, Lizaur-Utrilla et al. 2014). BMI was treated as a continuous variable in our analyses and a wide range of BMIs was included (20 to 58 kg/m^2), encompassing normal to super obese categories of BMI.

While this study aimed to examine a wide range of implant designs, the selection was affected by both the tendering arrangements of the institutions and industry-funded research studies on specific implant designs. However, there are eight separate implant designs included and differences in the patients selected are accounted for in the statistical models. Bilateral cases were included because in many cases different implant components were used in left and right knees and demographic variables, specifically age and weight, were not constant. To verify that the inclusion of bilateral cases did not influence the conclusions, one knee from each bilateral patient was randomly sampled and the analysis rerun with a single TKA per patient. There was no effect on the significance of the variables (supplementary data in Appendix D).

Overall, this study found that longitudinal migration of cemented and uncemented tibial components is not equivalent, even in well-fixed components, and that uncemented fixation is more sensitive to patient factors, specifically sex, age, and smoking status. These findings indicate that documenting smoking status may be warranted in future RSA studies when screening new uncemented implant designs specifically, especially in small groups of patients as this can be a confounding factor and may account for some variation in migration magnitudes.

It is important to reiterate that while overall magnitudes of migration differed by sex for uncemented tibial components, this does not imply worse fixation in women as the migration stabilizes in both sexes by one year. Equal to men, women demonstrate patterns of stable fixation from the first to second year period and the proportion of continuous migrators, those with more than 0.2 mm of migration from one to two years, was not different by sex. Initial high migration may be related to less robust bone stock in post-menopausal women that is more susceptible to surgical insult, but these apparent pre-operative static bone deficits appear to be independent of the ability to generate a biologic interface post-operatively.

Understanding sex-related differences can assist in creating relevant threshold for rapid evaluation of new implant designs and surgical techniques. As interest in patient-specific medicine increases, there is potential to use RSA data to build a model around targeted patient-specific approaches. What has been identified in this analysis as largely sex-related differences may be more accurately captured by considering individual patient differences. More granular analysis of RSA data may provide additional insights into mechanism of implant fixation and failure in future studies, motivating the compilation of larger, multi-centre RSA datasets.

3.5 Conclusions

Uncemented tibial components in women who are older and smoke have higher overall migration related to initial implant settling, but this does not appear to impair long-term fixation. Smoking had the opposite effect in male smokers with uncemented components. Analyzing migration of primary TKA patients by subsets of sex and fixation revealed significant factors that were not apparent when subjects were treated as a single cohort.

Chapter 4

TIMPLANTS, INTERFACES, AND INDUCIBLE DISPLACEMENTS: AN INVESTIGATION INTO THE INFLUENCE OF PATIENT AND IMPLANT CHARACTERISTICS ON IMPLANT FIXATION IN CEMENTED AND UNCEMENTED TOTAL KNEE ARTHROPLASTY

4.1 Introduction

Early migration of tibial components following total knee arthroplasty (TKA) has been shown as a predictor of longer term outcomes (Pijls et al. 2012, Ryd et al. 1995) and the use of radiostereometric analysis (RSA) to quantify migration has become an important step in evaluating implants. Migration at one year (Pijls et al. 2012) and the change in migration from one to two years, classified as continuous migration or stable (Ryd et al. 1995), have both been widely adopted as surrogate indicators of long-term success. However, limitations of migration as a screening tool include the degree of uncertainty in predicting successful outcomes, which is especially large with the one year migration threshold (Pijls et al. 2012). Additionally, obtaining the immediate post-operative reference RSA exam needed to measure one year migration is not trivial.

An alternative RSA-measured metric is inducible displacement: the elastic displacement of an implant relative to the bone in response to an external load. Inducible displacement requires only a one time visit where unloaded and loaded exams are taken at the same appointment. Although inducible displacement has had limited adoption historically, this measurement can provide data about the stability of the implant-bone interface, with or without bone cement, at independent time points post-operatively. As cyclic loading is common in daily activities such as walking, the evaluation of instantaneous motion is relevant to long term fixation. Previous studies have investigated the relationship between migration and inducible displacement in small, short-term studies, reporting variable findings of weak or non-existent correlations (Fukuoka et al. 2000, Hilding et al. 1995, Regner et al. 2000, Toksvig-Larsen et al. 1998, Uvehammer and Karrholm 2001).

The objectives of this study were two-fold. The first objective was to examine the influence of both patient and implant factors on inducible displacements of tibial components over a ten-year post-operative period to determine what factors influence inducible displacement and specifically to compare cemented and uncemented fixation. The second objective was to investigate if inducible displacement is related to implant migration in the context of using inducible displacement as a screening tool in place of migration assessments. The analyses examined the association of inducible displacement with short- and long-term migration, and migration between one and two years, as well as classification as continuous or stable migration.

4.2 Methods

Unloaded (supine) and loaded (single-leg stance) RSA exams at the same visit were prospectively collected on primary TKA recipients to measure inducible displacement. All subjects had been enrolled in RSA migration studies and had tantalum markers inserted intra-operatively between 2002 – 2015 at a single institution (Halifax Infirmary, Halifax, Nova Scotia). Inducible displacements were measured at follow-up visits at 6 months, 1, 2, 3, or 10 years from surgery. For single-leg stance exams, subjects were instructed to weight-bear fully on the operated leg but were allowed to toe-touch with the opposite leg and hold a handrail for balance (Figure 4.1).

Figure 4.1. Loaded (single-leg stance) pose RSA exam for inducible displacement.

Inclusion criteria were subjects receiving a knee arthroplasty for a primary diagnosis of osteoarthritis. Exclusion criteria included: revision total knee replacements, revision for any reason, revision components used in a primary TKA case, and technical problems with RSA analysis (insufficient markers visible, condition number > 150, or RBE > 0.35) (Valstar et al. 2005).

Details of the equipment used for RSA data collection are provided in the supplementary data (Appendix B). Marker-based analysis was used in all cases, with maximum total point motion (MTPM) calculated for standardized locations to reduce variation by implant design (Nilsson et al. 1991).

4.2.1 Statistics

To investigate the influence of patient and implant factors on inducible displacement, the primary outcome of interest was implant motion measured as maximum total point motion (MTPM), the vector length of the standardized point at the periphery of the tibial baseplate which moved the most (Ryd et al. 1995). Log(MTPM) was used because of the inherent non-normal distribution of the vector length (Astephen et al. 2010, Pijls et al. 2012). The following variables were included in the analysis: age, sex, body mass index (BMI in kg/m^2), smoking status, implant fixation (cemented or uncemented), implant size (estimated tibial baseplate area in cm^2) and time of exam (months from date of surgery). Multiple regression models were fitted to examine the influence of the patient and implant factors on inducible displacements.

To examine the relationships between inducible displacement and migration, two investigations were performed. First, migration (calculated from the immediate post-operative reference exam) and inducible displacement assessments were compared for individual knee replacements performed at the same follow-up visit at any post-operative time. Migration-inducible displacement pairs were analyzed separately by time frame: initial migration within the first post-operative year (to allow for osseointegration of uncemented components and migration to stabilize), from one to three years post-operatively (midterm migration, representing the post-stabilization period), and at ten years from the time of surgery (late migration). Correlation coefficients were calculated and multiple regression models were fitted with migration as the dependent variable and inducible displacement, and patient and implant factors as the independent variables. Implant motion was quantified as MTPM for both migration and inducible displacement.

The second investigation of inducible displacement and migration compared inducible displacement within the first post-operative year to the change in migration from one to two years, since continuous migration of more than 0.2 mm during this period has been shown to be predictive of risk for later loosening (Ryd et al. 1995). As before, migration and inducible displacement was calculated as MTPM and multiple regression models fitted to determine the influence of inducible displacement, and patient and implant factors on the change in migration from one to two years. Additionally, each case was classified as stable or continuously migrating (one to two year change of more than 0.2 mm) and inducible displacements compared for continuously migrating and stable groups (*t*-test, using log(MTPM)). Finally, a logistic regression model was fitted to examine the influence of inducible displacement and patient and implant variables on classification as stable or continuously migrating.

Subgroup analyses were performed for all investigations on uncemented females, uncemented males, cemented females, and cemented males. The influence of implant design was also investigated in subgroup analyses. Significance was set at $p < 0.05$ for all analyses.

4.3 Results

4.3.1 Subjects

Overall, four hundred and seventy-two primary total knee replacements were recruited. Subjects with revision components used in a primary case were excluded (n=16). A total of fourteen revisions were performed (2 for aseptic loosening, 5 due to infection, 1 peri-prosthetic fracture, 1 due to avascular necrosis, 3 due to instability, and 2 due to pain; range of time to revision 1 week to 4.7 years). Ten subjects were excluded due to unacceptable RSA errors for migration or inducible displacement results.

Two hundred and eighty-six inducible displacement exams were available for 274 knees in 249 patients. Six implant designs (three cemented and three uncemented) were included (Table 4.1). Simplex P cement (Stryker, Mahwah, NJ, USA) was used for all cemented components. Three knees had assessments performed at both one and two years post-operatively; only the one year exam is included in the analysis. Twelve knees were evaluated at two visits three years and ten years from the date of surgery, providing longitudinal inducible displacement data on a small subset (Figure 4.2). All other knees were evaluated at one time.

Table 4.1. Subject demographics by fixation (cemented and uncemented) and by implant design. Short implant name in bold. Insert types: medial pivot (MP), posterior stabilized (PS), cruciate retaining (CR), and cruciate stabilized (CS). *Indicates posterior cruciate ligament (PCL) resected.

Implant Design	**Insert**	**n**	**Age** (years) mean (SD)	**BMI** (kg/m2) mean (SD)	**Female:Male** (%Female)	**Non-Smokers: Smokers** (%Smokers)
All Implants		274	63 (8)	33.1 (6.1)	181:93 (66%)	244:26 (9%)
All Cemented Implants		193	63 (8.3)	33.4 (6.3)	132:61 (68%)	179:12 (6%)
Advance® (Wright Medical Technology, Inc., Arlington, TN)	MP*, PS*	38	62 (7.8)	33.8 (6.7)	26:12 (68%)	36:2 (5%)
NexGen® (Zimmer, Warsaw, IN)	PS*	22	64 (7)	32.5 (5.4)	13:9 (59%)	21:1 (5%)
Triathlon® (Stryker, Mahwah, NJ)	PS*, CR, CS	133	64 (8.7)	33.8 (6.7)	93:40 (70%)	122:9 (7%)
All Uncemented Implants		81	63 (7.3)	32.3 (5.5)	49:32 (60%)	65:14 (17%)
Trabecular Metal™ (**TM**) **Monoblock** (Zimmer, Warsaw, IN)	PS*, CR	46	64 (7.8)	31.8 (5.5)	30:16 (65%)	37:9 (20%)
Triathlon® **PA**®-Coated (Stryker, Mahwah, NJ)	PS*, CR, CS	19	62 (6.7)	34.7 (4.8)	11:8 (58%)	15:2 (11%)
Trabecular Metal™ (**TM**) **Modular** (Zimmer, Warsaw, IN)	PS*	16	62 (6.9)	30.9 (5.8)	8:8 (50%)	13:3 (19%)

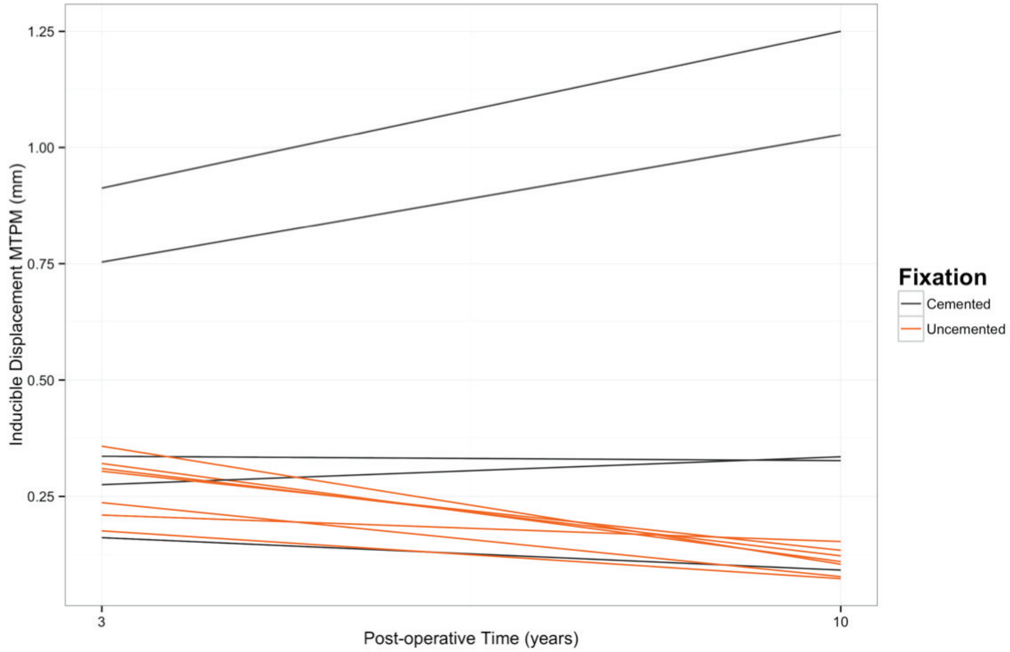


Figure 4.2. Inducible displacements (MTPM) for individual subjects measured at multiple visits, demonstrating change in inducible displacement over time (n = 12).

4.3.2 Inducible Displacement in Revised Cases

Of the fourteen TKA who were revised, inducible displacement exams were available for ten cases. The knees that were revised for reasons unrelated to mechanical loosening had median MTPM inducible displacements of 0.16 mm (range 0.08 to 0.40 mm) at one or two years post-operatively (median inducible displacement of 0.21 mm for four cemented cases, 0.11 mm for four uncemented cases).

Inducible displacement results were available for one case revised for aseptic loosening after 11.5 months; inducible displacement just prior to revision was 1.70 mm MTPM (uncemented TM Modular implant). The single case revised at 14 months due to a peri-prosthetic fracture had inducible displacement of 1.54 mm MTPM at 12 months (uncemented Triathlon PA).

All revised cases are excluded from the following analyses unless otherwise noted.

4.3.3 Influence of Subject and Implant Factors on Inducible Displacements

The interaction of time and fixation was significant in analysis of the complete dataset ($p=0.02$), therefore early inducible displacements (visit date 0.5 to 3 years from the date of surgery) and late inducible displacements (10 years) were analyzed separately (Appendix E). Within the early follow-ups group, time was not a significant factor, confirming the appropriateness of grouping visits at 3 years or earlier.

Inducible displacements were significantly higher for uncemented implants compared to cemented implants at early visits (within the first three post-operative years, $p < 0.001$), but significantly lower for uncemented implants at late follow-ups ($p < 0.001$, Figure 4.3). Implant designs were not evenly distributed between follow-up visit time points (Table 4.2, Figure 4.4).

Regression analysis of all tibial components at both the early and late time points showed that except for fixation, no subject or other implant factors were significant for the magnitude of inducible displacement (supplementary data, Appendix E). When analyzing subgroups divided by fixation, sex, and time point, higher BMI was associated with higher inducible displacement of uncemented males in the early post-operative period (p = 0.004). No patient or implant variables were significant for any other subgroup (supplementary data, Appendix E). The inducible displacements were significantly different by implant design for uncemented components with the TM Modular group having higher early inducible displacements and the Triathlon PA group lower inducible displacements (Figure 4.4). For cemented implants at the late time point, the NexGen implants had significantly higher inducible displacements (Figure 4.4).

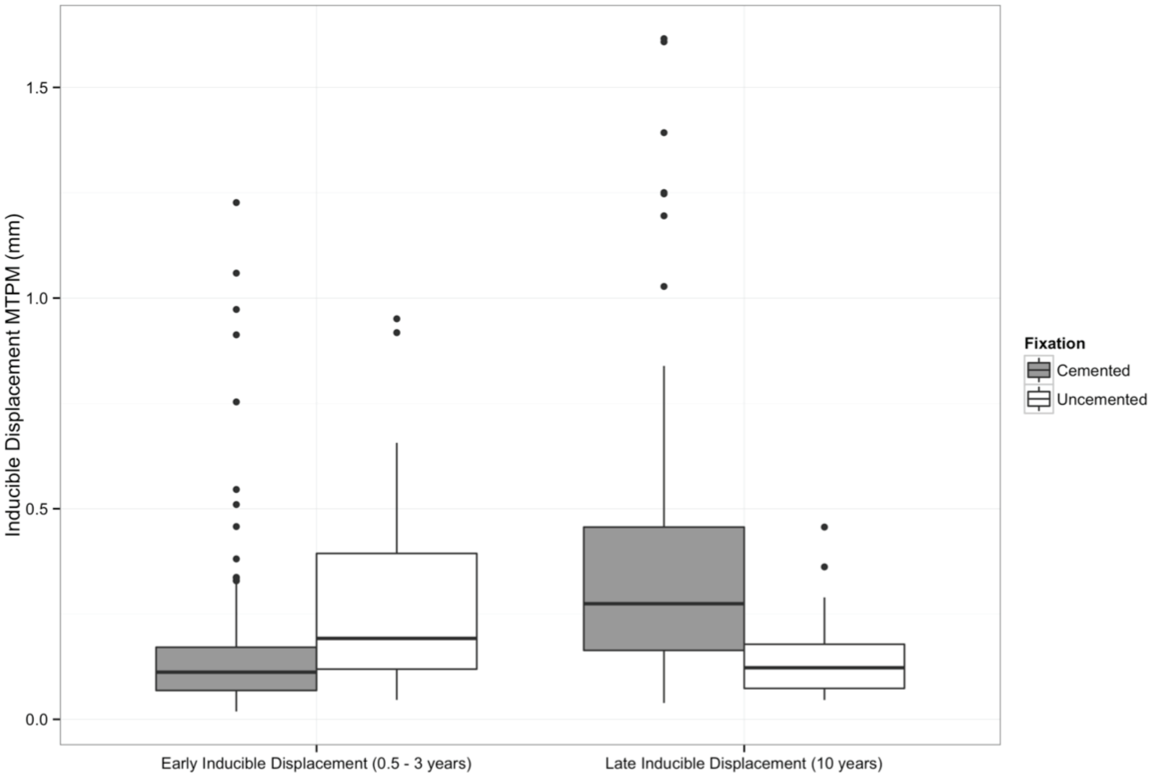


Figure 4.3. Inducible displacements (MTPM) by implant fixation at early and late follow-up visits.

Table 4.2. Inducible displacement (MTPM, mm) for early and late visits by fixation group and implant design group.

	n	mean	SD	median	min	max
Early Inducible Displacement (0.5 - 3 years post-operatively)						
Uncemented	**67**	**0.27**	**0.21**	**0.19**	**0.05**	**0.95**
TM Modular	19	0.46	0.25	0.54	0.05	0.95
TM Monoblock	32	0.23	0.14	0.18	0.06	0.60
Triathlon PA	16	0.14	0.13	0.10	0.05	0.54
Cemented	**142**	**0.16**	**0.19**	**0.11**	**0.02**	**1.23**
Advance	3	0.22	0.10	0.16	0.16	0.34
NexGen	6	0.47	0.31	0.39	0.19	0.91
Triathlon	133	0.15	0.17	0.11	0.02	1.23
Late Inducible Displacement (10 years post-operatively)						
Uncemented	**21**	**0.15**	**0.11**	**0.12**	**0.05**	**0.46**
TM Monoblock	21	0.15	0.11	0.12	0.05	0.46
Cemented	**56**	**0.40**	**0.39**	**0.27**	**0.04**	**1.62**
Advance	37	0.31	0.30	0.25	0.04	1.62
NexGen	19	0.59	0.48	0.41	0.06	1.61

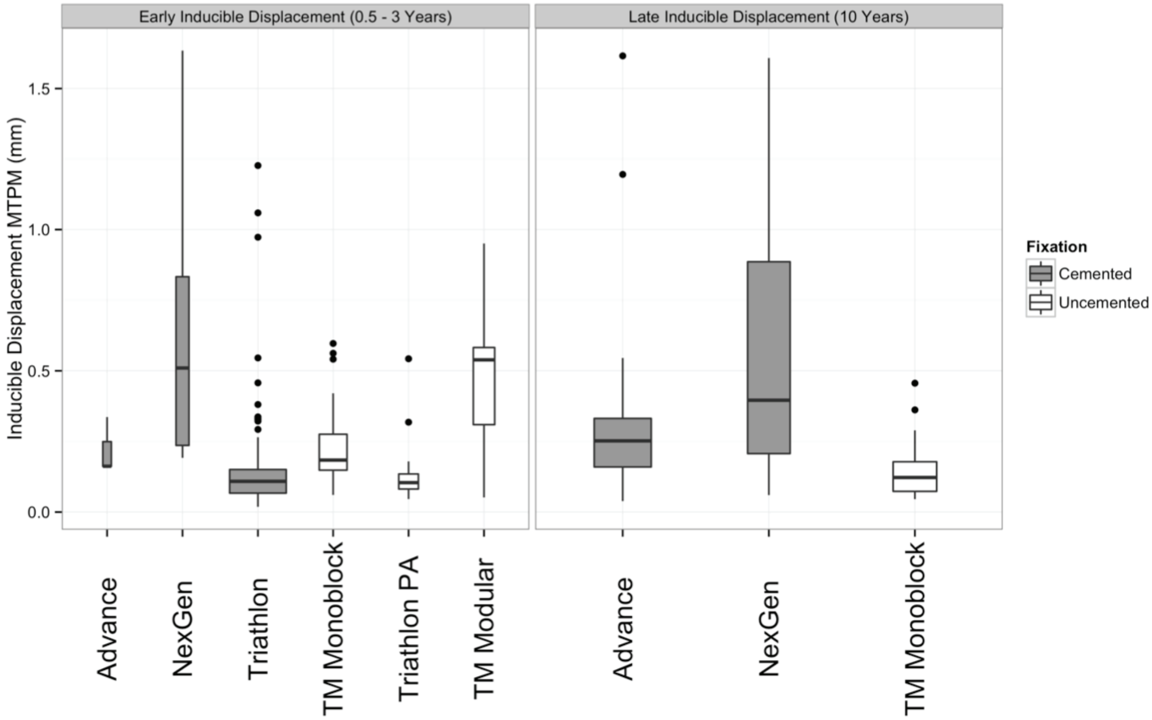


Figure 4.4. Early and Late inducible displacement by prosthesis. Width of boxplots scaled by square root(n) to indicate differences in sample sizes.

4.3.4 Association between Migration and Inducible Displacement

4.3.2.1 Migration and Inducible Displacements at the same post-operative time

Two hundred and seventy pairs of migration and inducible displacement assessments made at the same follow-up visit were available for 259 knees in 237 patients in the three time periods representing initial, mid, and late migration (Figure 4.5). Eleven knees were assessed on two occasions; three knees were evaluated at 1 and 2 years and eight knees at 3 and 10 years post-operatively.

Overall, correlations between migration and inducible displacement were significant but not strong when analyzing all tibial components at all times ($r = 0.41$, $p < 0.001$, Table 4.3). Correlations were greatest for uncemented tibial components in the first post-operative year (Table 4.3). At late follow-ups, correlation between migration and inducible displacement was significant for cemented components, but not uncemented components, reversing the relationship seen in the first post-operative year (Table 4.3).

The regression model found that inducible displacement was a significant predictor for migration ($p < 0.001$). The interaction of fixation and the three time frames representing initial, midterm, and late migration was also significant ($p = 0.023$). Therefore, further regression analyses were performed separately by time frame in addition to fixation and sex. For assessments within the first post-operative year, inducible displacement was a significant predictor of migration in the following cases (with additional significant variables noted): for all implants ($p<0.001$; fixation was also significant, $p<0.001$), for all uncemented components ($p<0.001$; age also significant, $p=0.03$), for uncemented components in males ($p = 0.01$) and for cemented components in females ($p=0.02$; tibia area also significant, $p = 0.02$). For midterm results, inducible displacement was a significant predictor of migration for all implants ($p=0.01$; fixation $p<0.01$) and all cemented components ($p=0.01$) but not for uncemented components or any subgroups by sex. At late follow-ups, inducible displacement was not a significant predictor of migration for any group. See supplementary data (Appendix E) for complete results.

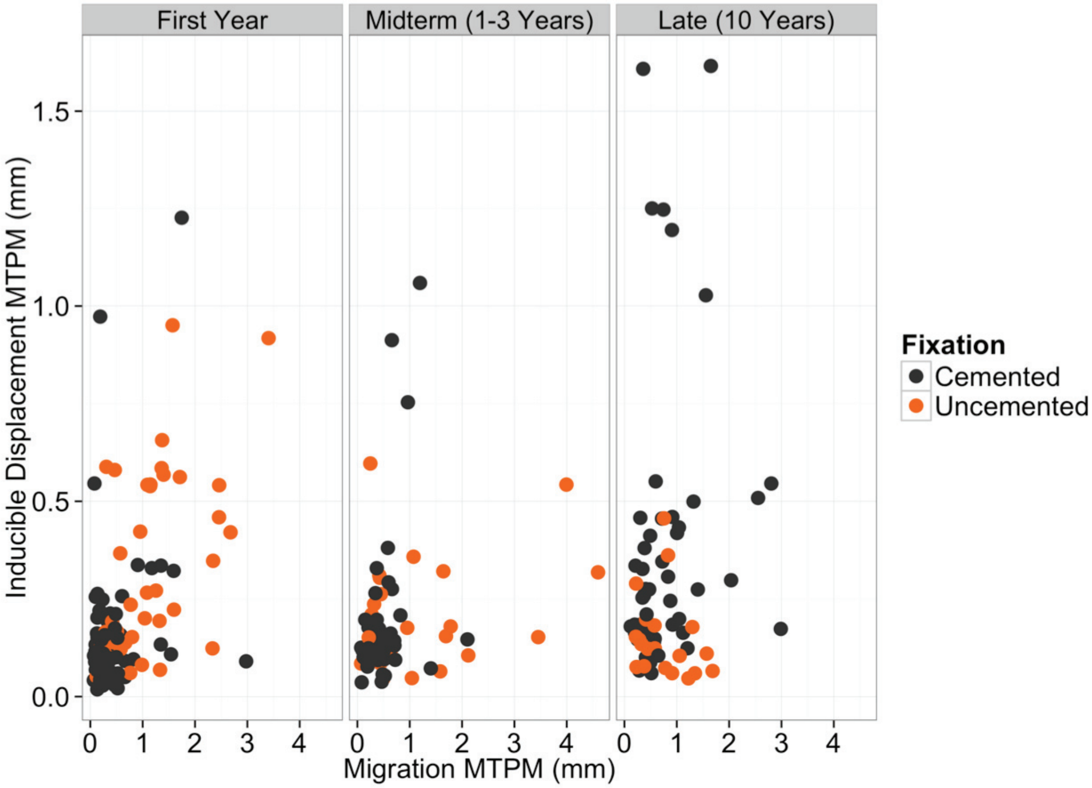


Figure 4.5. Migration and inducible displacement for matched knees and visit date, separated by initial follow-up (0.5 – 1 years post-surgery), midterm follow-up (>1 – 3 years post-surgery) and late follow-up (10 years post-surgery).

Table 4.3. Correlations between migration (log(MTPM)) and inducible displacement (log(MTPM)) at the same visit for all cases and grouped by follow-up time frame, fixation, and sex.

Group	n	Pearson correlation coefficient	p-value
***All follow-up visit periods**, all implants*	270	**0.41**	**<0.001**
First post-operative year			
All implants	131	**0.51**	**<0.001**
Uncemented implants	40	**0.58**	**<0.001**
Females	24	**0.57**	**<0.01**
Males	16	**0.60**	**0.01**
Cemented implants	91	**0.22**	**0.03**
Females	62	**0.32**	**0.01**
Males	29	-0.01	0.94
Midterm (2-3 years post-operatively)			
All implants	69	**0.28**	**0.02**
Uncemented implants	27	0.18	0.40
Females	15	0.32	0.30
Males	12	-0.06	0.80
Cemented implants	42	**0.36**	**0.02**
Females	27	0.35	0.07
Males	15	0.44	0.10
Late (10 years post-operatively)			
All implants	70	0.15	0.20
Uncemented implants	20	-0.30	0.20
Females	12	-0.38	0.23
Males	8	-0.66	0.07
Cemented implants	50	**0.32**	**0.02**
Females	34	0.23	0.19
Males	16	0.41	0.11

4.3.2.2 One Year Inducible Displacement and Change in Migration from One to Two Years

One hundred and twenty-two tibial components had migration measured from one to two years and inducible displacements collected within the first post-operative year (Figure 4.6). Overall, the correlation between inducible displacement and change in migration was significant, but not strong (r = 0.32, p <0.001, Table 4.4). When analyzed by subgroups, the correlation remained for uncemented components, but not cemented components nor subgroups of uncemented or cemented components by sex (Table 4.4).

Including the first year inducible displacement and subject and implant factors in a regression model predicting the change in migration from one to two years found that only inducible displacement was significant ($p<0.001$) when analyzing all tibial components. For uncemented males, inducible displacement was a significant predictor of the change in migration ($p=0.04$). For all other subgroups, no variables were significantly associated with the change in migration from one to two years (supplementary data, Appendix E).

When individual cases were classified as either continuously migrating (change in migration of greater than 0.2 mm) or stable (less than or equal to 0.2 mm), inducible displacement (at 0.5 – 1 years) was significantly higher for continuously migrating components ($p = 0.001$, Table 4.5). When analyzed separately by fixation, continuously migrating uncemented components had significantly greater inducible displacements, but cemented components did not (Table 4.5).

Logistic regression found that inducible displacement alone was a significant predictor ($p = 0.025$) of classification as a continuous migrator when accounting for age, sex, and BMI. When separated by fixation, again inducible displacement alone was significant for uncemented components ($p = 0.022$), but no variables were significant for cemented components. When analyzing separately by fixation and sex, no variables were significant (supplementary data, Appendix E).

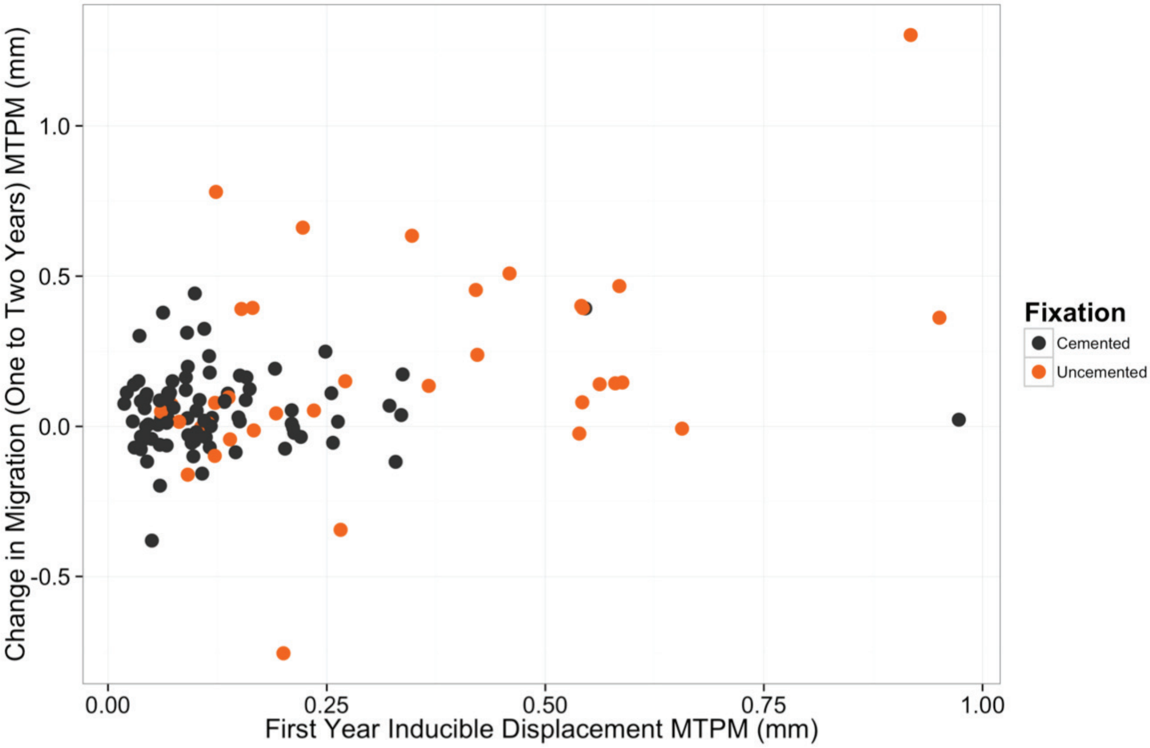


Figure 4.6. Inducible displacement in the first post-operative year (0.5 – 1 year) and change in migration from one to two years.

Table 4.4. Correlations between change in migration from one to two years (MTPM) and inducible displacement (MTPM; log(MTPM) used in correlation calculation) within the first year.

Group	**n**	**Pearson correlation coefficient**	**p-value**
All implants	122	**0.32**	**<0.001**
Uncemented implants	36	**0.37**	**0.03**
Females	22	0.35	0.10
Males	14	0.44	0.10
Cemented implants	86	0.10	0.40
Females	58	0.00	1.00
Males	28	0.28	0.20

Table 4.5. Inducible Displacements (MTPM in mm) in the first post-operative year for implants classified as Stable or Continuously Migrating from change in migration from one to two years post-operatively. p-value for difference in inducible displacement by classification (*t*-test using log(MTPM)).

	Classification	n	mean	SD	median	min	max	p-value
All Tibial Components	Stable	101	0.16	0.16	0.11	0.02	0.97	**0.001**
(17% Cont. Migr.)	Cont. Migr.	21	0.34	0.27	0.25	0.04	0.95	
Uncemented	Stable	23	0.27	0.20	0.19	0.06	0.66	**0.02**
(36% Cont. Migr.)	Cont. Migr.	13	0.45	0.27	0.42	0.12	0.95	
Uncemented Females	Stable	14	0.27	0.18	0.22	0.09	0.59	0.10
(36% Cont. Migr.)	Cont. Migr.	8	0.46	0.26	0.50	0.12	0.95	
Uncemented Males	Stable	9	0.26	0.24	0.12	0.06	0.66	0.10
(36% Cont. Migr.)	Cont. Migr.	5	0.43	0.30	0.42	0.17	0.92	
Cemented	Stable	78	0.12	0.13	0.10	0.02	0.97	0.50
(9% Cont. Migr.)	Cont. Migr.	8	0.16	0.17	0.10	0.04	0.55	
Cemented Females	Stable	52	0.13	0.15	0.10	0.02	0.97	0.90
(10% Cont. Migr.)	Cont. Migr.	6	0.11	0.07	0.10	0.04	0.25	
Cemented Males	Stable	26	0.10	0.06	0.09	0.02	0.26	0.50
(7% Cont. Migr.)	Cont. Migr.	2	0.32	0.32	0.32	0.10	0.55	

Cont. Migr. = Continuously Migrating

4.4 Discussion

Inducible displacements of cemented and uncemented tibial components were significantly different between fixation groups at early and late follow-up times. Our data, which showed significantly lower late inducible displacement for uncemented components compared to cemented components, suggest successful long-term fixation is achievable without cement and that long-term cemented fixation may not be completely stable. Higher inducible displacement of cemented components at the late follow-up suggests that mechanisms such as stress-shielding, fibrous tissue membrane formation, or cement delamination may have compromised the implant-cement-bone interfaces or underlying bone stock (Huiskes 1993, Linder 1994).

While the sample sizes of repeated inducible displacements on the same knee were too small for statistical analysis, the twelve individual cases measured at three and ten years post-operatively demonstrated consistent results with the above conclusions, showing some increasing inducible displacement over time for cemented components but lower late inducible displacement for uncemented components.

For early inducible displacements, cemented components had significantly lower motion compared to components with uncemented fixation, but with a number of outlying cases. The significance of higher earlier inducible displacement for uncemented components is less generalizable as it may be influenced by one implant design (TM Modular), which also has a high proportion of continuously migrating components, and may be at greater risk of poor survivorship (Chapter 2). Excluding the TM Modular group reduces the mean early inducible displacement of uncemented components from 0.27 mm to 0.20 mm MTPM, but is still statistically significantly higher than for the cemented components. Patient factors were not significant in predicting inducible displacement.

Comparing migration and inducible displacement showed varied results. Migration and inducible displacement assessments made on the same knees at the same follow-up visits had the greatest correlation for uncemented implants in the first post-operative year. In contrast, at late visits, only cemented components demonstrated correlated migrations and inducible displacements, further supporting the concept that long-term cemented fixation is susceptible to degenerative processes. As migrations were always calculated from the immediate post-operative reference exam, a higher late migration in an uncemented component may be attributable to high initial migration but without a change in migration long-term. The low inducible displacements for the uncemented components at 10 years supports the concept of stable fixation after high initial migration followed by osseointegration.

Inducible displacement was a significant predictor of migration in the first year and midterm periods, along with implant fixation and a number of demographic factors (age, tibia area, and BMI, depending on the subgroups). This contrasts with the finding of an almost complete lack of subject factors significantly influencing inducible displacement, suggesting inducible displacement is reflecting a separate aspect of implant fixation from migration.

The absence or presence of continuous migration in the second post-operative year is currently the best indicator of risk for later mechanical loosening (Ryd et al. 1995). When comparing inducible displacement to this change in migration, assessments made within the first post-operative year were used because this would be most valuable from the perspective of early screening of implant designs or individual patients. The logistical advantages of inducible displacements compared to migration in assessing implant fixation are clear; it eliminates the need for repeated serial RSA exams, and especially the immediate post-operative reference exam which can be challenging from both an institutional and patient perspective. The finding that inducible displacement was significantly associated with the change in migration between one and two years post-operatively, as well as significantly higher inducible displacement for tibial components classified as continuously migrating, indicates that there is potential to use inducible displacement as a screening tool. The correlation between inducible displacement and change in migration from one to two years was greatest for uncemented tibial components, which included the TM Modular implant that has a 50% incidence of continuous migrators. The limitation of the continuous migration metric is that it is itself a surrogate measure of long-term fixation.

The challenge with comparing inducible displacement and migration is that they are likely capturing different mechanisms which are inconsistent by both time and fixation method. The timeline for osseointegration of uncemented tibial components is generally believed to be on the order of the first few months post-operatively, although possibly sooner (Engh et al. 1987, Matsuda et al. 1999, Moucha et al. 2006, Toksvig-Larsen et al. 1998). As all of our subjects were evaluated a minimum of 6 months post-operatively, it is expected that sufficient time for osseointegration had elapsed in the majority of cases. Indeed, repeated measurements of inducible displacement at 6 weeks and 1 year postoperatively have been found to be consistent for both uncemented and cemented components (Toksvig-Larsen et al. 1998) and of similar magnitude at 2 months and 12 months post-operatively(Regner et al. 2000). Additionally, Regner et al. (2000) found that 1 year inducible displacement correlated with 5 year migration of uncemented implants, concluding that the status of the interface is determined in the first post-operative year.

Our findings are in agreement with previous studies that have also found significant but not strong correlations between migration and inducible displacement (Fukuoka et al. 2000, Regner et al. 2000, Toksvig-Larsen et al. 1998, Uvehammer and Karrholm 2001). The finding of significantly higher inducible displacements for continuously migrating implants has been previously reported with a similar magnitude(Ryd et al. 1999).

The varying implant designs and sample sizes available at the different time points are a limitation of this study. Only a single uncemented implant design was available for long-term follow-ups so the promising results seen with the TM Monoblock implant may not be generalizable to all uncemented designs as the relatively low modulus of this implant design may preferentially reduce stress shielding (Minoda et al. 2010). Additionally, only single leg stance was used to load the knee. This pose was selected as the simplest to implement although other poses such as torque tests may elicit higher inducible displacements. As with most stress tests, single leg stance loads the joint through muscle contraction to stabilize the knee in addition to load to the mass of the subject. This makes normalization by body mass unreliable and likely contributes to inter-patient variability, but does provide a physiologically relevant load for each patient, similar to what is experienced during the stance phase of gait.

Potentially, the most valuable use of inducible displacement would be screening uncemented implant designs in the first post-operative year to identify failure to achieve adequate osseointegration without needing to wait until 2 years post-operatively to measure continuous migration. This may, in fact, be what is seen with the TM Modular implants group in this study. The significantly higher migration between one and two years (Chapter 2) as well as a high proportion of continuous migrators suggests that this implant design is leading to inferior biological fixation. A compelling case study is the study patient who had a TM Modular component revised after 11.5 months for aseptic loosening with significant migration and inducible displacement of 1.7 mm MTPM just prior to one year. She was a bilateral study subject with a successful TM Monoblock component in the other knee. This suggests that patient factors such as poor bone quality were not the driving cause of aseptic loosening in this case.

For cemented implants the value of inducible displacements may be at late visits, capturing a compromised interface between the implant and cement or cement and bone, or the bone itself.

As a clinical tool, inducible displacement may have a role in evaluating clinically challenging cases such as determining if an implant in a symptomatic patient is loose. Developments in markerless RSA may make this feasible even in individuals without bone markers inserted intra-operatively (Seehaus et al. 2012, Stentz-Olesen et al. 2017).

In uncemented components, inducible displacement may be an indicator of the elusive “biological potential” of bone that permits bone in-growth, in combination with a suitable surface and loading environment. The dynamic nature of osseointegration makes it difficult to predict or assess with static measures such as bone mineral density. While some studies have shown an association between migration and bone mineral density (Andersen et al. 2017), others have found an inverse relationship between pre-operative bone strength and implant migration (Moritz et al. 2011), suggesting that bone content alone is not the best predictor of future beneficial remodeling processes. Current tools to quantify active bone in-growth are limited.

The inducible displacement outcomes found in this study are promising in terms of providing enhanced evaluation of implant fixation above implant migration alone, but the case is not currently definitive for using them in place of migration assessments. One of the limitations of this study is that only one case of aseptic loosening was available for study. Comparing inducible displacement to continuous migration as a surrogate for long term fixation increases the uncertainty in the assessment compared to using a definite endpoint of revision.

The demonstration of increasing migration of cemented tibial components at late follow-up is a novel finding that lends support to the continued investment in studying uncemented fixation options.

4.5 Conclusions

Inducible displacement assessments measured with RSA are a promising tool for early determination of osseointegration, especially for uncemented tibial components. Overall, inducible displacement is more sensitive to implant fixation than patient factors, showing differing trends for cemented and uncemented fixation over time. The correlation between inducible displacement and migration was greatest for uncemented components in the early post-operative period. Investigating the effectiveness of inducible displacements in identifying failure to achieve adequate early fixation is worth pursuing because of the potential for extremely short time frames and possible application to symptomatic patients.

Chapter 5

DISCUSSION, CONCLUSIONS AND FUTURE WORK

5.1 Summary of Findings

The overall aim of this work was to examine the influence of patient and implant factors on two measures of implant fixation in TKA quantified with RSA, namely tibial component migration and inducible displacement. Within this aim, areas of focus were examining the differences between cemented and uncemented fixation, determining the effect of analyzing female and male subjects separately, and considering what RSA-based measures have potential for clinical application of evaluating patients post-operatively.

In the first paper (Chapter 2), cemented fixation was associated with significantly lower MTPM migration at one year compared to uncemented fixation, but equivalent change in migration from one to two years. This suggested that uncemented implants undergo a period of initial settling which does not prevent achieving stable fixation by one year post-operatively.

Longitudinal data analysis was used to investigate the influence of patient and implant factors on overall migration in the second paper (Chapter 3). Uncemented tibial components had higher magnitudes of migration in the first two post-operative years, and in female patients this difference was even more pronounced. Cemented fixation was not different by sex.

For uncemented tibial components, the effect of smoking was reversed for women and men. In women, smoking was associated with higher magnitude migration, while in men smokers had lower migration compared to non-smokers. This finding was tempered by the relatively small proportion of smokers. Additionally for uncemented tibial components in women, increasing age, especially above age 60, was linked to higher magnitude migration. For cemented components, the only significant factor was tibial component area, with larger sizes associated with greater migration.

The third paper (Chapter 4) investigated the utility of inducible displacement data from single leg stance as an alternative assessment method to migration data.
Inducible displacement was significantly different for cemented and uncemented components but not sensitive to patient factors. The correlation between migration and inducible displacement was greatest for uncemented components in the first year post-operatively. Inducible displacements were significantly higher for continuous migrators as well, especially for uncemented components.

5.2 Overall Findings

Cemented versus uncemented fixation in TKA remains a lingering debate. Part of what leaves this question open to so much dispute is how much uncertainty there is around how both of these procedures actually work in the dynamic and unique environments of individual patients. Registries and retrieval studies point to gaps in knowledge around mechanisms of fixation and failure in TKA, especially in regard to issues of reactions to wear particles, stress shielding, and peri-operative tissue differentiation. Because implant-bone interfaces are so difficult to study directly, we rely on surrogate measures of fixation and success. The current findings may suggest favoring uncemented designs, as uncemented fixation demonstrated minimal motion after 10 years with inducible displacement results.

The question of bone quality in women is another enduring discussion that ties in directly with the cemented versus uncemented debate. What we have seen in this research is an apparent bias against using uncemented fixation in women (women received uncemented components 29% of the time while men received them 48% of the time). At first glance, this might seem justified based on the higher initial migration of uncemented components in women. However, stabilization was equivalent between women and men; both groups showed consistent migration from one to two years post-operatively. This implies that while uncemented components in females have greater degree of settling, potentially due to lower bone mineral density or compromised structural integrity secondary to post-menopausal bone changes, this does not translate into a difference in osseointegration. This supposition is supported by the finding that age is a significant predictor of overall migration in females with uncemented components, especially over the age of 60, but there is no effect of age in males. Uncemented components in both females and males appear to achieve equivalent fixation once the period of initial settling is over. This brings into question the definition of "better" migration. These data suggest that the magnitude of migration in the initial period is irrelevant in well-fixed implants. If we are to consider a refined one year threshold of migration for uncemented implants that differs from cemented thresholds, we should perhaps consider different definitions of acceptable early migration in women and men as well.

If female patients (or any patient with lower pre-operative bone strength) are perhaps more susceptible to surgical bone damage, leading to high initial migration in uncemented cases as damaged bone is resorbed, there is a question of what happens in similar cases with cemented fixation. While in uncemented fixation, it appears that the biological activity is not compromised in women as they achieve the same stability of implant fixation after one year, what happens to damaged bone in cemented cases? It is unclear if the mechanical interlock created by bone cement could be compromised due to damaged trabeculae or if the bone healing and remodeling process could be impaired by the presence of bone cement.

The risk is that not using uncemented TKA in women without true justification is possibly unintentionally leading to inferior long-term outcomes in women because we have seen excellent long-term fixation in both sexes with uncemented components and perhaps evidence of slow degenerative processes with cemented fixation.

5.3 Research Limitations

Although a single dataset was used for all three papers, not all of the subjects are represented in all of the papers. Notably, no inducible displacement data was collected on the uncemented Advance Biofoam subjects, nor the subjects recruited in Perth. This may have contributed to the lack of influence of smoking in the inducible displacement analysis as a number of smokers had Biofoam components.

Ironically, one of the limitations of this research was the lack of failures due to mechanical loosening. Of the more than 470 primary TKA cases recruited, only three knees were revised due to aseptic loosening or peri-prosthetic fracture, all within less than a year, and representing less than 1% of the study population. The end result was that although we could not build a model to predict failure, we did have an opportunity to investigate the factors that influence a diversity of implant micromotions that seem to all represent stable fixation.

The exception from stable fixation in these findings is the small group of 19 subjects with the TM Modular implant. Both migration and inducible displacement data suggest that the TM Modular components may be at risk of a higher revision rate than the other implant designs. While mean MTPM migration at one year of 1.5 mm put this implant design in the "at risk" classification (Pijls et al. 2012), the 50% proportion of continuously migrating components between 1 to 2 years is concerning. Based on the findings of Ryd et al (1995), continuous migration leads to revision in 20% of cases. For the TM Modular group, this translates into an expected 1 –2 cases that will be revised for mechanical loosening, which has in fact already happened for 1 subject. Mean inducible displacement in the first year for the TM Modular cohort was 0.46 mm±0.25 excluding the revised case; 0.59±0.26 for continuously migrating tibial components, and 0.45±0.20 for not continuously migrating components. If the inducible displacement of the revised component measured prior to revision surgery (1.7 mm) is included, this raises the mean inducible displacement to 0.52 mm. In contrast, the other uncemented implant designs had mean inducible displacement of 0.20 mm in the first year. The apparently negative outcomes of the TM Modular implant design are in contrast to the consistently positive results of the TM Monoblock implant despite the fact that both employ trabecular metal. They differ in incorporation of the polyethylene component via a solid baseplate and locking mechanism for the TM Modular implant as opposed to the polyethylene being directly molded into the trabecular metal for the TM Monoblock design, conferring a low modulus construct (Henricson et al. 2008). Orthopaedics unfortunately has multiple examples of apparently innocuous implant design changes leading to inferior outcomes (Valstar et al. 2012). While the TM Modular implant may be an example of negative design changes, implant fixation in the remaining 134 uncemented cases does not appear to be inferior to cemented fixation.

5.4 General Discussion

The cemented versus uncemented debate will continue and may take a while to shift as registry data currently provides perhaps the best information about long-term performance but at the cost of long lead times. It seems from our findings that cement functions as a normalizer in TKA – by removing the outliers, we eliminate both worse and better outcomes. Bone cement can fill in the gaps left by imperfect bone cuts and in fill around compromised bone from both necrosis and a lack of osseointegration; but as a purely mechanical solution in a mechanical and biological environment, cementing is ignoring half of the potential solution to implant fixation. The advantage of a mechanical solution is that it is more reliable if not necessarily better, but it is also susceptible to mechanical failure, especially in the long term. The challenge with uncemented fixation is to eliminate the early failures where initial fixation is not achieved in order to shift the outcomes to more positive results. By using cemented fixation, we are perhaps sacrificing superiority for reliability and reducing the risk of inferiority. At the end of the day, a patient's outcome may be related to his or her risk tolerance. The goals of research and phased innovation are to reduce the risk to the patient to the lowest possible level.

The implant itself is only part of the equation in a stable fixation solution. Demographic differences in patients are vast and despite this, most implants for TKA are intended for use in any patient. Women and men are biologically different, but perhaps more importantly, individuals are different. Acknowledging sex-based differences is one step towards recognizing individual differences. But even acknowledging sex-based differences is a big first step, and one that medicine hasn't completely committed to. Sex-based bias in biomedical research starts at a cellular level, where most basic cell research is contacted on exclusively in male cell lines, and animal models have also been predominantly male (Beery and Zucker 2011, McCarthy 2015). In clinical trials, less than one quarter of participants are reported to be female, despite 80% of drugs recalled by the FDA due to unanticipated effects in female patients (Heinrich 2001, Keitt 2013, Novicoff and Saleh 2011). In regard to total knee arthroplasty for osteoarthritis, sex and gender differences influence the entire spectrum of the disease and treatment from incidence and disease progression to access to care and surgical outcomes. While women have a significantly higher prevalence of osteoarthritis, have worse symptoms, and greater disability, the unmet need for arthroplasty for women is 4 times that of men (Hawker et al. 2000). Research using standardized patients with moderate OA has revealed a bias against recommending TKA to women, with men with the same presentation being 22 times more likely to have TKA recommended by an orthopaedic surgeon (Borkhoff et al. 2008). This bias may contribute to both the unmet need for arthroplasty in women and the status of women as having TKA at a later stage in the disease process with consequently poor functional outcomes because while their improvement may be equal to men, they are starting from a worse function state (Parsley et al. 2010). When confronted with the numbers it is hard to not feel discouraged by the disparities between the sexes. These differences are even greater for minority groups and are also influenced by socioeconomic class (Collins et al. 2016). The recognition of this issue is growing and federal granting agencies in Canada and US require consideration of sex and gender in all funded research studies (CIHR 2017, Clayton and Collins 2014, Johnson et al. 2009, Keitt 2013).

Critics have argued against the cost of increasing sample sizes to permit sub analyses by sex. Perhaps the more important question is if we can afford not to. The cost of a 50% (or less) increase in sample size is surely less than the cost of a recall to the manufacturer, let alone the cost to the patients. If sample sizes are a concern, perhaps we should only test on women. Based purely the numbers, to have the biggest impact, TKA should be designed and optimized for women, and then modified if necessary for the special case of a male patient. It is a difficult balance: to acknowledge difference while treating everyone equally. The key concept with equality is that it doesn't necessarily mean the same. In some cases, refusing to acknowledge difference is as detrimental as treating someone sub-optimally because of it.

When evaluating implants in any patient, the question remains: what does "good" implant fixation look like when measured with RSA and how early in the post-operative period can we quantify it? The literature to date has told us that very high initial migration in the first year is negative, but only on a mean group level (Pijls and Nelissen 2016, Pijls et al. 2012). On an individual level, the change in migration from one to two years is above 0.2 mm in all implants that are revised, but only 20% of these continuous migrators go on to loosen mechanically (Ryd et al. 1995). What is notable about the historical data are the differences in the patient demographics as well as the implants. In fact there is no overlap between the implant designs used in the studies by Pijls et al and Ryd el al and those included in the current research. This supports on-going research using RSA for TKA. As we continue to evaluate implant designs in changing patients, there are four potential applications of RSA data for joint arthroplasty:

1. Screening of new implant designs or surgical techniques as part of phased innovation where small samples of patients are monitored closed by measuring RSA migration, hopefully prior to general release of a new product.
2. Routine monitoring of arthroplasty patients, where all patients receive beads intra-operatively and have RSA radiographs in place of standard radiographs at proscribed post-operative periods in order to quantify implant fixation on an individual level.
3. Aiding in the diagnosis of symptomatic patients with painful joint replacements without a clear underlying cause.
4. Answering more fundamental research questions such as testing the effectiveness of medications such as bisphosphonates, attempting to understand the relationship between implant alignment and migration, or testing surgical innovations such as "refixation"

where the damaged tissue around a loose implant is removed and replaced without removing the implant itself (de Poorter et al. 2008).

While the case for use of RSA in routine monitoring may not currently be realized, the application of RSA to screening new implant designs, researching questions of implant interfaces, and possibly application in evaluating symptomatic patients are easily defendable and warrant further study.

5.5 Future Work

The importance of RSA for screening implant designs is undeniable and future work to refine the thresholds for "safe" implants would be valuable. In an ideal scenario, a living version of Pijls el al (2012) analysis would be regularly updated with matched results from RSA and registry data as they become available. This could be expanded to include patient demographics in addition to implant factors and ideally would consider additional RSA metrics beyond one year MTPM migration such as individual translations and rotations (Gudnason et al. 2017), longitudinal data, and inducible displacements. Statistical techniques, such as longitudinal data analysis, to help us better model our data and to provide predictive models are an important area of development as well.

Is there still potential for better implant designs or should we focus on improving surgical techniques with the current proven designs? I would make the argument that there is still room for technological improvement within implant designs and it is worth pursuing for a number of reasons. Dissatisfaction, changing demographics, especially obesity, and changing expectations are all reasons to continue to improve implant designs. Secondly, the technologies that may allow improvements in implant design to be realized are now becoming feasible and they include additive manufacturing processes and robotic surgery. The main reasons these two technologies may be revolutionary are that they eliminate geometric limitations that have previously been in place due to saw cuts and that they are suited to moving towards patient-specific approaches. Thirdly, one of the existing challenges with uptake of RSA is the specialized equipment required, but new research developments in markerless solutions, may reduce this challenge (Seehaus et al. 2012, Stentz-Olesen et al. 2017). Markerless methods may come at a cost of reduced precision, but this compromise may be acceptable with increased sample sizes. The final justification to continue implant design development is that the orthopaedic research community is poised to enable the international collaborations that will allow the necessary sample sizes to accommodate less precise but more accessible techniques as well as examination of increasingly granular levels of patient and implant characteristic groups.

The goals of RSA researchers will hopefully align with collaborative initiatives such as The Canadian RSA Network (http://www.canadianrsanetwork.com). Going forward, we can work towards creating infrastructure and policies that will facilitate this collaboration. Consideration must be made to obtaining appropriate and well documented consent from patients to use data in international collaborative research projects while protecting patient privacy absolutely. We need to consider as many demographic factors as is reasonable, perhaps even quantifying smoking status (Salandy et al. 2016), and design linkable databases that will allow us to incorporate other data such as joint kinematics and kinetics and biomarker data. We also need to work towards international standards for identifying implant components accurately, considering model numbers and versions as well as all of the relevant material, manufacturing, sterilization, and dimensional data. This will hopefully be done through barcodes (Campion et al. 2014) which can improve data quality and have additional benefits such as secondary use for inventory management and data submission to national registries.

As data becomes the world's most valuable resource (Economist 2017), it is our responsibility to use this data to provide patients with the most robust and applicable evidence possible.

Appendix A

Ethics Approvals and Funding Details for Research Protocols

- "A Prospective Randomized Trial using Roentgen Stereophotogrammetric Analysis of the Advance Medial Pivot Knee"
    - Local ethics approval numbers: CDHA-RS/2001-213*
    - ClinicalTrials.gov identifier: **NCT00405470**
    - Source of funding: Wright Medical Technologies
- "A Prospective Randomized Controlled Trial using Roentgen Stereophotogrammetric Analysis (RSA) of a Trabecular Metal Mesh Tibial Monoblock Knee Arthroplasty Component"
    - Local ethics approval numbers: CDHA-RS/2002-096*
    - ClinicalTrials.gov identifier: **NCT00405379**
    - Source of funding: Zimmer
- "A Prospective RCT using Roentgen Stereophotogrammetric Analysis (RSA) and DEXA to Evaluate Fixation of Periapatite coated Triathlon Total Knee Arthroplasty Components"
    - Local ethics approval numbers: CDHA-RS/2009-039*, 1020606§, Referenence Number 293 (Protocol TRI-DC-06)†
    - ClinicalTrials.gov identifier: **NCT01180582**
    - Source of funding: Stryker
- "A Prospective RCT using Roentgen Stereophotogrammetric Analysis (RSA) to Evaluate Fixation of the Biofoam Advance Total Knee Arthroplasty Components with and without Screw Augmentation"
    - Local ethics approval numbers: CDHA-RS/2007-250*, 1020650§
    - ClinicalTrials.gov identifier: **NCT00657956**
    - Source of funding: Wright Medical Technologies

- “Randomized Control Trial Using Radiostereometric Analysis (RSA) to Compare the Fixation of the Trabecular Metal Monoblock and the Trabecular Metal Modular Total Knee Arthroplasties”
    - Local ethics approval numbers: CDHA-RS/2011-010*, 1000199§
    - ClinicalTrials.gov identifier: NCT01180595
    - Sources of funding: Zimmer, ACOA/AIF
- “A ten year evaluation of implant fixation in four total knee replacement designs using radiostereometric analysis”
    - Local ethics approval numbers: CDHA-RS/2015-229*, 1018407§
    - ClinicalTrials.gov identifier: N/A
    - Sources of funding: NSHARF
- “Development of a Clinical Diagnostic System for Assessing Orthopaedic Implant Stability”
    - Local ethics approval numbers: CDHA-RS/2010-388*, 1020265§
    - ClinicalTrials.gov identifier: N/A
    - Sources of funding: ACOA/AIF
- “Randomized Control Trial using RSA to Compare the OtisMed Customfit Total Knee Replacement Procedure with Computer Assisted Surgery”
    - Local ethics approval numbers: CDHA-RS/2011-296*, 1005885§
    - ClinicalTrials.gov identifier: NCT01262430
    - Sources of funding: Stryker

*Capital District Health Authority Research Ethics Board (Halifax, Nova Scotia, Canada)
§Nova Scotia Health Authority Research Ethics Board
(Halifax, Nova Scotia, Canada) (note: name change from Capital District Health Authority Research Ethics Board (effective April 1, 2015) but the same institution)
†St John of God Health Care Ethics Committee (Subiaco, Perth, Western Australia, Australia)

Appendix B

RSA Technical Details: Equipment and Precision

Calibration Boxes and x-ray tube orientation

- Halifax, 2002-2003
    - biplanar calibration box (Tilly Medical Products AB, Lund, Sweden), 90° between beams (anterior-posterior and lateral-medial)
- Halifax, 2003 – March 2008 and September 2009 – July 2010
    - uniplanar calibration box (Halifax Carbon Box, MEDIS medical imaging systems BV, Leiden, The Netherlands), 1.6 m from calibration box to x-ray heads, beams angled 20° from the vertical (40° between beams).
- Halifax, March 2008 – August 2009
    - uniplanar calibration box (HBI Box003 Halifax, Halifax Biomedical Inc., Mabou, Nova Scotia, Canada), beams angled 30° from vertical (60° between beams)
- Perth, 2009-2010
    - uniplanar calibration box (Perth Carbon Box, MEDIS medical imaging systems BV, Leiden, The Netherlands), and x-ray beams angled 20º from the vertical.
- Halifax, 2010 – present
    - uniplanar calibration box (HBI Box007 Halifax, Halifax Biomedical Inc., Mabou, Nova Scotia, Canada), beams angled 30° from vertical (60° between beams)

X-ray Heads

- Halifax, 2002 – 2008
    - one fixed x-ray head (Model Ultranet-SA, GE Medical Systems, Monza, Italy)

  - one portable x-ray head (Model 46-194759G1, General Electric Company, Milwaukee, WI, USA)
- Halifax, 2008 - present
  - two ceiling mounted x-ray tubes (Rad92, Varian Medical Systems, Salt Lake City, UT, USA)
- Perth, 2009-2010
  - one ceiling mounted tube (Toshiba DST-100A, Japan)
  - one portable x-ray machine (GE Medical Systems AMX4 XFMR, Milwaukee, WI, USA)

Detectors

- Halifax, 2002-2008 and September 2009 – July 2010
  - AFGA-Gevaert NV CRMD4.0 cassettes (35 x 43 cm) (Mortsel, Belgium) scanned with AGFA-Gevaert NV CR85-X digitizer (Mortsel, Belgium) producing images with a spatial resolution of 6 pixels/mm and greyscale resolution of 12 bits/pixel.
- Halifax, March 2008 – August 2009
  - IDC X1590 DR SYSTEM X4C digital detectors (Imaging Dynamics Company Ltd., Calgary, Alberta, Canada), 43 x 43 cm, pixel size 108 microns^2,
- Perth, 2009-2010
  - Kodak GP Storage Phosphor System 35x43 cm cassettes (Carestream Health, Inc., Rochester, NY, USA) with Kodak Directview CR850 System digitizer (Carestream Health, Inc., Rochester, NY, USA) producing images with a spatial resolution of 5.8 pixels/mm and a 12-bit grayscale resolution.
- Halifax, 2010 – present
  - CXDI-55C digital detectors (Canon Inc., Tokyo, Japan), 35 x 43 cm (2,208 x 2,688 pixels), pixel size 160 microns^2, greyscale resolution of 12 bits/pixel

RSA Software

- RSA-CMS, Version 4.3, MEDIS medical imaging systems BV, Leiden, The Netherlands (2002-2004)
- Model-based RSA (Version 3.21, Medis specials b.v., Leiden, The Netherlands)
- Model-based RSA (Version 3.32, Version 3.4, RSA*core*, Leiden, The Netherlands)

RSA Analysis Support

- Halifax Biomedical Inc. (Mabou, NS, Canada)

RSA beads

- Tantalum RSA marker beads (0.8 mm in diameter; Wennbergs Finmek AB, Gunnilse, Sweden) (2002-2004)
- Tantalum RSA marker beads (1.0 mm in diameter; Halifax Biomedical Inc., Mabou, NS, Canada)

RSA Precision

Table 1. RSA Precision calculated from 267 double exams. Anatomical directions for reported translations and rotations as follows. X translation: medial (+) / lateral (-); y translation: superior (+) / inferior (-); z translation: anterior (+) / posterior (-); x rotation: anterior tilt (+)

	mean	SD	**Precision** (1.96*SD)[1]
Translations (mm)			
x	0.00	0.04	**0.08**
y	0.00	0.04	**0.07**
z	0.01	0.08	**0.15**
Rotations (degrees)			
Rx	0.00	0.16	**0.31**
Ry	0.00	0.09	**0.17**
Rz	0.00	0.07	**0.14**
MTPM (mm)	0.13	0.07	**0.14**

[1] ISO 16087:2013 Implants for surgery -- Roentgen stereophotogrammetric analysis for the assessment of migration of orthopaedic implants

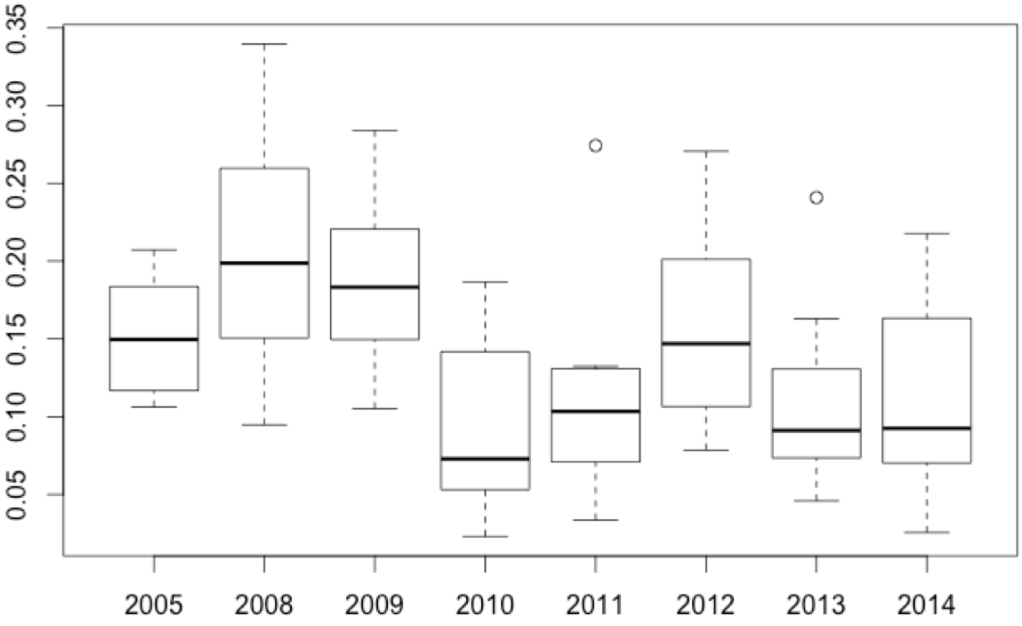


Figure 1. MTPM Double Exams by year of surgery.
Note: double exams were not collected prior to 2005. Phantom testing during this period calculated translational precision as 0.07 mm (Bohm et al. 2003).Boxes enclose the interquartile range (25th – 75th percentile) with the middle line indicating the median, the whiskers showing the min and max values unless there are outliers, represented by the circles, which exceed 1.5 x the interquartile range.

Multiple comparison testing found that the difference by year with the lowest p-value was 2008 to 2010 (p = 0.06). All p-values were not significant.

Appendix C

Supplementary Data for Chapter 2

Revised Cases

Of the fourteen revised cases, three cases were revised for reasons related to mechanical loosening (two due to aseptic loosening and one due to a peri-prosthetic fracture). Tibial component migrations at the last available follow-up for each of these cases were: 6.7 mm MTPM at 11.5 months (uncemented component, aseptic loosening), 7.0 mm MTPM at 6 months (cemented component, aseptic loosening), and 12 mm MTPM at 12 months (uncemented component, tibial plateau fracture).

Of the remaining eleven cases revised for pain, infection, instability, or avascular necrosis, eight were cemented and three were uncemented. One and two year migration data was available for five of these cases. Mean MTPM migration at one year was 1.44 mm for the cemented implants (n=2) and 0.55 mm for the uncemented cases (n=3). Mean change in migration from one to two years was 0.34 mm for the cemented components and -0.11 mm for the uncemented components.

Regression Results

Table C.1 Regression results for the effect of fixation, sex, age and BMI on one year MTPM migration and change in migration from one to two years (MTPM) for all tibial components and for cemented and uncemented implants separately.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
One Year Migration (log(MTPM) as outcome variable)					
All tibial components (cemented and uncemented)					
Fixation	0.790	0.083	0.626	0.954	**0.000**
Sex	0.097	0.084	-0.068	0.263	0.246
Age	0.008	0.005	-0.002	0.019	0.133
BMI	0.008	0.007	-0.006	0.022	0.289
$r^2_{adj} = 0.20$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Uncemented Tibial Components					
Sex	0.199	0.139	-0.076	0.475	0.155
Age	0.019	0.011	-0.002	0.040	0.072
BMI	0.025	0.014	-0.003	0.054	0.079
Implant: Biofoam + Screws	-0.081	0.243	-0.562	0.400	0.740
Implant: TMModular	0.460	0.271	-0.076	0.996	0.092
Implant: TMMonoblock	-0.119	0.207	-0.529	0.291	0.566
Implant: Triathlon PA	-0.118	0.224	-0.562	0.325	0.599
$r^2_{adj} = 0.08$					
Cemented Tibial Components					
Sex	-0.003	0.104	-0.208	0.203	0.979
Age	0.002	0.006	-0.010	0.014	0.758
BMI	-0.002	0.008	-0.018	0.014	0.818
Implant: Advance	0.159	0.111	-0.059	0.377	0.153
Implant**: NexGen**	0.308	0.143	0.027	0.589	**0.032**
$r^2_{adj} = 0.01$					
Change in Migration One to Two Years (MTPM as outcome variable)					
All tibial components (cemented and uncemented)					
Fixation	0.014	0.025	-0.036	0.064	0.589
Sex	-0.012	0.026	-0.062	0.039	0.649
Age	0.001	0.002	-0.002	0.004	0.490
BMI	0.003	0.002	-0.001	0.008	0.139
$r^2_{adj} = 0.00$					
Uncemented Tibial Components					
Sex	-0.034	0.047	-0.126	0.059	0.473
Age	0.001	0.004	-0.006	0.008	0.713
BMI	-0.002	0.005	-0.011	0.008	0.687
Prosthesis: Biofoam + Screws	-0.019	0.082	-0.180	0.143	0.819
Implant**: TMModular**	0.286	0.091	0.106	0.466	**0.002**
Implant: TMMonoblock	0.009	0.070	-0.129	0.147	0.896
Implant: Triathlon PA	-0.069	0.075	-0.218	0.080	0.363
$r^2_{adj} = 0.08$					
Cemented Tibial					
Sex	-0.006	0.029	-0.063	0.050	0.826
Age	0.001	0.002	-0.002	0.005	0.391
BMI	0.003	0.002	-0.001	0.008	0.141
Implant: Advance	-0.001	0.030	-0.061	0.059	0.962
Implant**: NexGen**	0.084	0.039	0.007	0.161	**0.033**
$r^2_{adj} = 0.01$					

*CI = 95% confidence interval

Appendix D

Supplementary Data for Chapter 3

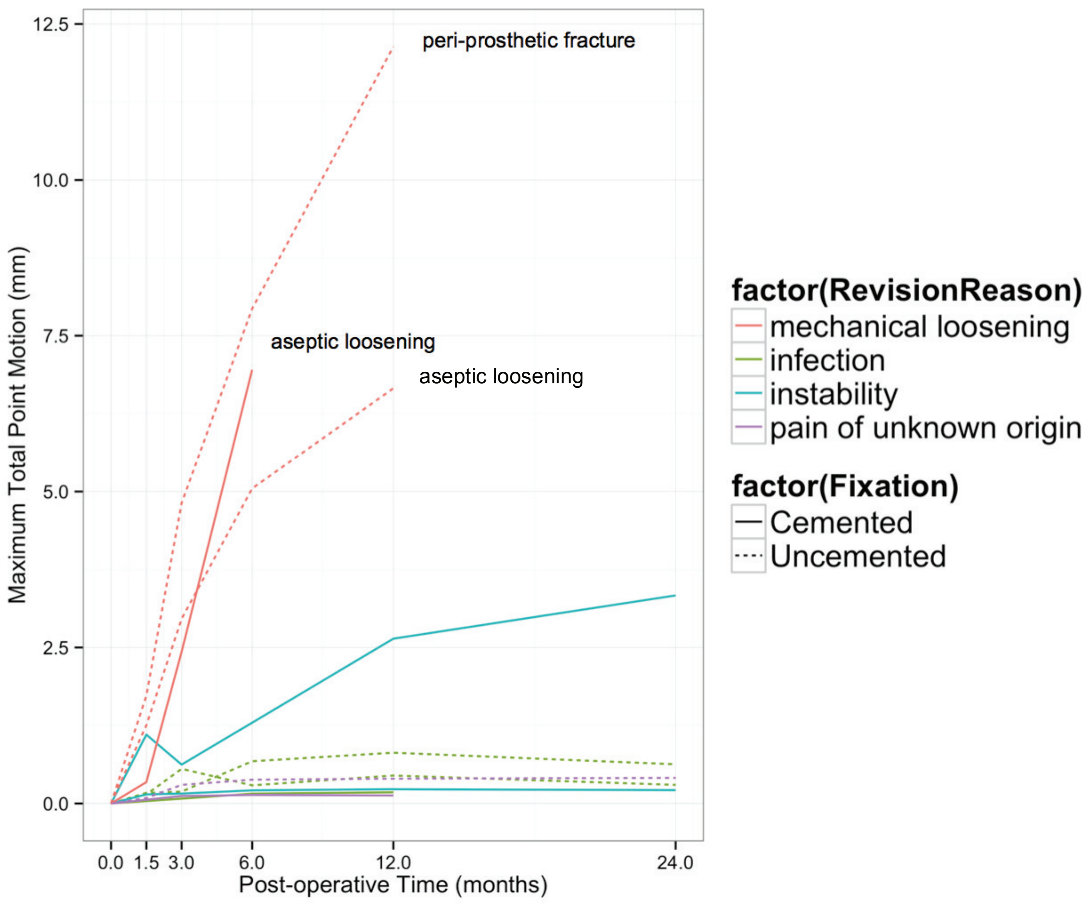


Figure D.1. Longitudinal migration for revised cases

Table D.1 Longitudinal data analysis results for the effect of fixation, age and BMI, tibial component area, and smoking status on individual translations and rotations in Uncemented Females.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
x translation					
Age	0.004	0.004	-0.005	0.012	0.378
BMI	0.004	0.004	-0.004	0.011	0.312
Tibial Component Area	-0.012	0.010	-0.031	0.006	0.198
Smoking Status	0.101	0.064	-0.025	0.226	0.115
y translation					
Age	-0.013	0.010	-0.032	0.006	0.181
BMI	-0.010	0.010	-0.029	0.010	0.335
Tibial Component Area	-0.007	0.024	-0.054	0.039	0.759
Smoking Status	-0.377	0.230	-0.827	0.074	0.101
z translation					
Age	0.004	0.005	-0.006	0.014	0.428
BMI	0.002	0.009	-0.016	0.021	0.816
Tibial Component Area	-0.011	0.022	-0.054	0.033	0.636
Smoking Status	-0.201	0.197	-0.586	0.184	0.306
x rotation					
Age	-0.012	0.017	-0.045	0.021	0.481
BMI	-0.032	0.028	-0.088	0.023	0.254
Tibial Component Area	-0.016	0.068	-0.150	0.117	0.809
Smoking Status	-0.192	0.196	-0.576	0.193	0.329
y rotation					
Age	0.004	0.010	-0.015	0.023	0.706
BMI	0.003	0.015	-0.027	0.033	0.844
Tibial Component Area	0.024	0.038	-0.051	0.099	0.528
Smoking Status	-0.192	0.172	-0.530	0.146	0.266
z rotation					
Age	-0.016	0.018	-0.051	0.020	0.395
BMI	0.002	0.017	-0.031	0.035	0.922
Tibial Component Area	0.013	0.037	-0.059	0.084	0.728
Smoking Status	-0.453	0.405	-1.246	0.340	0.262

*CI = 95% confidence interval

Table D.2 Longitudinal data analysis results for the effect of fixation, age and BMI, tibial component area, and smoking status on individual translations and rotations in Uncemented Males.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
x translation					
Age	-0.003	0.002	-0.007	0.001	0.190
BMI	-0.004	0.004	-0.012	0.004	0.306
Tibial Component Area	0.003	0.005	-0.008	0.014	0.600
Smoking Status	-0.009	0.033	-0.073	0.055	0.782
y translation					
Age	0.000	0.006	-0.012	0.012	0.995
BMI	0.000	0.008	-0.015	0.016	0.981
Tibial Component Area	0.001	0.015	-0.028	0.030	0.943
Smoking Status	0.052	0.100	-0.145	0.249	0.606
z translation					
Age	0.007	0.004	-0.002	0.016	0.117
BMI	0.006	0.008	-0.009	0.021	0.455
Tibial Component Area	-0.002	0.015	-0.030	0.027	0.910
Smoking Status	0.059	0.097	-0.132	0.249	0.548
x rotation					
Age	-0.003	0.014	-0.030	0.025	0.851
BMI	-0.035	0.031	-0.095	0.026	0.264
Tibial Component Area	-0.016	0.037	-0.089	0.058	0.675
Smoking Status	0.039	0.237	-0.426	0.504	0.870
y rotation					
Age	-0.010	0.007	-0.023	0.003	0.130
BMI	0.020	0.015	-0.009	0.050	0.177
Tibial Component Area	-0.011	0.013	-0.035	0.014	0.401
Smoking Status	-0.149	0.079	-0.304	0.006	0.060
z rotation					
Age	0.007	0.007	-0.006	0.020	0.281
BMI	-0.013	0.019	-0.050	0.023	0.477
Tibial Component Area	0.046	0.025	-0.003	0.095	0.064
Smoking Status	0.017	0.119	-0.218	0.251	0.890

*CI = 95% confidence interval

Table D.3 Longitudinal data analysis results for the effect of fixation, age and BMI, tibial component area, and smoking status on individual translations and rotations in Cemented Females.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
x translation					
Age	-0.001	0.002	-0.004	0.002	0.620
BMI	0.000	0.001	-0.003	0.002	0.952
Tibial Component Area	0.002	0.003	-0.004	0.008	0.604
Smoking Status	-0.025	0.028	-0.081	0.030	0.372
y translation					
Age	0.000	0.001	-0.002	0.002	0.883
BMI	0.000	0.001	-0.002	0.002	0.948
Tibial Component Area	0.005	0.003	-0.001	0.011	0.102
Smoking Status	-0.067	0.019	-0.105	-0.029	**0.001**
z translation					
Age	0.002	0.002	-0.003	0.006	0.469
BMI	-0.003	0.002	-0.008	0.001	0.128
Tibial Component Area	0.005	0.009	-0.012	0.022	0.581
Smoking Status	0.012	0.053	-0.091	0.116	0.819
x rotation					
Age	-0.003	0.004	-0.010	0.004	0.372
BMI	0.001	0.004	-0.007	0.009	0.815
Tibial Component Area	-0.008	0.011	-0.030	0.014	0.473
Smoking Status	0.003	0.105	-0.204	0.209	0.980
y rotation					
Age	0.000	0.002	-0.004	0.004	0.881
BMI	-0.003	0.002	-0.008	0.001	0.161
Tibial Component Area	0.005	0.006	-0.008	0.017	0.448
Smoking Status	-0.124	0.052	-0.225	-0.023	**0.016**
z rotation					
Age	0.005	0.003	0.000	0.010	0.069
BMI	0.005	0.003	0.000	0.010	0.060
Tibial Component Area	-0.001	0.007	-0.015	0.013	0.865
Smoking Status	-0.051	0.035	-0.119	0.018	0.147

*CI = 95% confidence interval

Table D.4 Longitudinal data analysis results for the effect of fixation, age and BMI, tibial component area, and smoking status on individual translations and rotations in Cemented Males.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
x translation					
Age	0.004	0.003	-0.001	0.009	0.152
BMI	-0.001	0.002	-0.005	0.004	0.714
Tibial Component Area	-0.005	0.005	-0.016	0.006	0.343
Smoking Status	-0.012	0.069	-0.148	0.123	0.857
y translation					
Age	0.001	0.001	-0.002	0.004	0.495
BMI	-0.001	0.002	-0.006	0.004	0.679
Tibial Component Area	-0.001	0.003	-0.007	0.005	0.685
Smoking Status	0.036	0.036	-0.034	0.107	0.314
z translation					
Age	0.002	0.002	-0.003	0.006	0.424
BMI	-0.003	0.003	-0.009	0.003	0.372
Tibial Component Area	-0.002	0.006	-0.014	0.010	0.754
Smoking Status	0.124	0.110	-0.093	0.340	0.263
x rotation					
Age	0.003	0.007	-0.010	0.016	0.658
BMI	-0.012	0.007	-0.027	0.002	0.101
Tibial Component Area	-0.016	0.014	-0.044	0.012	0.253
Smoking Status	0.295	0.094	0.110	0.480	**0.002**
y rotation					
Age	0.000	0.004	-0.007	0.008	0.900
BMI	-0.007	0.006	-0.019	0.005	0.259
Tibial Component Area	0.018	0.009	0.000	0.036	0.056
Smoking Status	-0.174	0.104	-0.379	0.030	0.095
z rotation					
Age	-0.007	0.004	-0.015	0.000	0.051
BMI	-0.007	0.005	-0.017	0.003	0.166
Tibial Component Area	0.000	0.007	-0.013	0.013	0.964
Smoking Status	0.005	0.090	-0.171	0.180	0.959

*CI = 95% confidence interval

Results with Sampled Bilateral Patients

Patients with two research knees were randomly sampled to select one knee per patient. Sample size of 381 knees in 381 patients.

Table D.5 Results of longitudinal data analysis for the influence of demographic variables on implant migration (MTPM) for tibial component groups for single knees per patient only. *Compare to Table 3.3*

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented, male and female) n = 381					
Follow-up Exam Time	0.003	0.000	0.003	0.004	0.000
Fixation	0.779	0.083	0.616	0.942	**0.000**
Sex	0.101	0.121	-0.137	0.338	0.406
Age	0.007	0.005	-0.004	0.017	0.208
BMI	0.005	0.007	-0.008	0.018	0.421
Tibial Component Area	0.014	0.014	-0.013	0.042	0.309
Smoking Status	-0.012	0.143	-0.291	0.267	0.933
Subgroup 1: Uncemented Tibial Components in Female Subjects					
Follow-up Exam Time	0.001	0.001	0.000	0.002	0.014
Age	0.036	0.014	0.008	0.064	**0.012**
BMI	0.011	0.016	-0.021	0.042	0.504
Tibial Component Area	-0.031	0.042	-0.113	0.050	0.450
Smoking Status	0.797	0.286	0.237	1.357	**0.005**
Subgroup 2: Uncemented Tibial Components in Male Subjects					
Follow-up Exam Time	0.002	0.001	0.001	0.003	0.008
Age	-0.004	0.014	-0.032	0.024	0.770
BMI	0.044	0.025	-0.005	0.093	0.080
Tibial Component Area	0.009	0.036	-0.062	0.079	0.812
Smoking Status	-0.611	0.241	-1.082	-0.139	**0.011**
Subgroup 3: Cemented Tibial Components in Female Subjects					
Follow-up Exam Time	0.004	0.001	0.003	0.005	0.000
Age	0.004	0.006	-0.009	0.016	0.576
BMI	-0.001	0.007	-0.015	0.013	0.892
Tibial Component Area	0.055	0.018	0.019	0.091	**0.003**
Smoking Status	-0.165	0.195	-0.546	0.217	0.398

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Subgroup 4: Cemented Tibial Components in Male Subjects					
Follow-up Exam Time	0.004	0.001	0.003	0.005	0.000
Age	-0.003	0.011	-0.025	0.019	0.777
BMI	-0.004	0.016	-0.036	0.027	0.790
Tibial Component Area	-0.003	0.022	-0.047	0.041	0.904
Smoking Status	0.138	0.235	-0.323	0.598	0.558

Independent variable: log(MTPM). Follow-up Exam Time is included in the model to account for the repeated measures and is significant as expected in all models since migration is not constant over time

*CI = 95% confidence interval, two-tailed

Appendix E

Supplementary Data for Chapter 4

Table E.1. Linear Regression results for Inducible Displacement (log(MTPM) as outcome variable)

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented) at all times					
Fixation	0.863	0.145	0.577	1.149	**0.000**
Sex	-0.049	0.149	-0.343	0.245	0.743
Age	0.000	0.007	-0.013	0.013	0.947
BMI	0.007	0.009	-0.010	0.024	0.421
Tibia Area	-0.007	0.018	-0.043	0.029	0.707
Smoking Status	0.070	0.169	-0.263	0.403	0.679
Months	0.009	0.001	0.007	0.012	**0.000**
Fixation:Months	-0.015	0.002	-0.020	-0.011	**0.000**
$r^2_{adj} = 0.19$					
Early Uncemented Tibial Components					
Sex	-0.180	0.255	-0.690	0.331	0.484
Age	0.019	0.013	-0.006	0.044	0.141
BMI	0.003	0.016	-0.030	0.036	0.870
Tibia Area	-0.036	0.035	-0.106	0.034	0.309
Smoking Status	0.171	0.237	-0.303	0.646	0.473
Prosthesis: TM Monoblock	-0.783	0.200	-1.185	-0.382	**0.000**
Prosthesis: Triathlon PA	-1.341	0.227	-1.796	-0.887	**0.000**
$r^2_{adj} = 0.36$					
Early Uncemented Tibial Components - Females					
Age	0.023	0.018	-0.013	0.059	0.203
BMI	-0.010	0.020	-0.051	0.030	0.612
Tibia Area	-0.031	0.052	-0.137	0.075	0.553
Smoking Status	0.403	0.327	-0.263	1.069	0.227
Prosthesis: TM Monoblock	-0.608	0.264	-1.146	-0.071	**0.028**
Prosthesis: Triathlon PA	-1.036	0.314	-1.676	-0.396	**0.002**
$r^2_{adj} = 0.17$					
Early Uncemented Tibial Components - Males					
Age	0.023	0.024	-0.027	0.072	0.353
BMI	0.119	0.036	0.043	0.195	**0.004**
Tibia Area	-0.065	0.063	-0.196	0.067	0.317
Smoking Status	-0.136	0.466	-1.106	0.833	0.773
$r^2_{adj} = 0.26$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Early Cemented Tibial Components					
Sex	0.187	0.234	-0.276	0.651	0.425
Age	-0.010	0.009	-0.027	0.008	0.277
BMI	0.011	0.011	-0.012	0.033	0.348
Tibia Area	0.039	0.027	-0.015	0.093	0.160
Smoking Status	-0.210	0.289	-0.782	0.362	0.469
$r^2_{adj} = -0.01$					
Early Cemented Tibial Components - Females					
Age	-0.008	0.011	-0.028	0.013	0.472
BMI	0.010	0.013	-0.016	0.036	0.438
Tibia Area	0.064	0.035	-0.006	0.134	0.072
Smoking Status	-0.302	0.388	-1.073	0.468	0.437
$r^2_{adj} = -0.01$					
Early Cemented Tibial Components - Males					
Age	-0.011	0.016	-0.044	0.022	0.516
BMI	0.010	0.025	-0.040	0.060	0.684
Tibia Area	0.000	0.046	-0.092	0.093	0.994
Smoking Status	-0.140	0.456	-1.059	0.779	0.760
$r^2_{adj} = -0.07$					
Late Uncemented Tibial Components					
Sex	0.822	0.399	-0.029	1.672	0.057
Age	-0.012	0.022	-0.058	0.034	0.576
BMI	-0.009	0.024	-0.059	0.041	0.710
Tibia Area	0.056	0.082	-0.120	0.232	0.509
Smoking Status	0.433	0.500	-0.633	1.500	0.400
$r^2_{adj} = 0.20$					
Late Uncemented Tibial Components - Females					
Age	0.000	0.045	-0.103	0.102	0.992
BMI	-0.009	0.034	-0.088	0.071	0.807
Tibia Area	0.076	0.150	-0.271	0.422	0.628
Smoking Status	0.332	0.849	-1.626	2.289	0.706
$r^2_{adj} = -0.26$					
Late Uncemented Tibial Components - Males					
Age	-0.030	0.012	-0.069	0.009	0.093
BMI	-0.013	0.019	-0.075	0.049	0.558
Tibia Area	0.112	0.061	-0.083	0.307	0.166
Smoking Status	-0.074	0.475	-1.586	1.438	0.886
$r^2_{adj} = 0.90$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Late Cemented Tibial Components					
Sex	-0.448	0.343	-1.137	0.241	0.197
Age	-0.009	0.019	-0.048	0.029	0.634
BMI	-0.020	0.026	-0.073	0.032	0.440
Tibia Area	-0.036	0.040	-0.116	0.045	0.379
Smoking Status	0.377	0.522	-0.673	1.426	0.474
Prosthesis: NexGen	0.505	0.246	0.011	0.998	**0.045**
$r^2_{adj} = 0.10$					
Late Cemented Tibial Components - Females					
Age	0.010	0.028	-0.045	0.066	0.721
BMI	-0.003	0.032	-0.066	0.061	0.937
Tibia Area	-0.052	0.053	-0.156	0.052	0.333
Smoking Status	0.700	0.762	-0.793	2.192	0.365
Prosthesis: NexGen	0.364	0.319	-0.260	0.988	0.262
$r^2_{adj} =- 0.03$					
Late Cemented Tibial Components - Males					
Age	-0.044	0.031	-0.105	0.018	0.192
BMI	-0.073	0.056	-0.183	0.038	0.223
Tibia Area	-0.008	0.061	-0.128	0.112	0.897
Smoking Status	-0.002	0.776	-1.522	1.518	0.998
Prosthesis: NexGen	1.161	0.406	0.366	1.956	**0.015**
$r^2_{adj} = -0.16$					

*CI = 95% confidence interval

Table E.2. Regression results for Migration (log(MTPM) as outcome variable) at matched time points for Inducible Displacement Exams.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented) at all times					
ID	0.929	0.202	0.533	1.326	**0.000**
Fixation	0.863	0.147	0.574	1.152	**0.000**
Sex	0.078	0.150	-0.217	0.372	0.605
Age	0.008	0.007	-0.004	0.021	0.199
BMI	0.008	0.009	-0.008	0.025	0.325
Tibia Area	-0.004	0.018	-0.040	0.032	0.821
Smoking Status	0.050	0.167	-0.279	0.379	0.766
Months	0.005	0.001	0.002	0.008	**0.000**
Fixation:Months	-0.005	0.002	-0.010	-0.001	**0.022**
$r^2_{adj} = 0.25$					
First Year - All Components					
ID	1.482	1.048	-4.583	-0.431	**0.018**
Fixation	0.783	0.347	0.795	2.168	**0.000**
Sex	0.235	0.220	-0.202	0.671	0.289
Age	0.003	0.009	-0.015	0.021	0.763
BMI	-0.004	0.012	-0.027	0.019	0.739
Tibia Area	0.055	0.285	-0.510	0.620	0.848
Smoking Status	0.032	0.028	-0.023	0.086	0.254
$r^2_{adj} = 0.34$					
First Year - Uncemented Tibial Components					
ID	2.028	0.474	1.062	2.993	**0.000**
Sex	0.274	0.377	-0.495	1.042	0.473
Age	0.042	0.018	0.005	0.080	**0.029**
BMI	0.017	0.023	-0.030	0.064	0.459
Tibia Area	0.050	0.058	-0.069	0.169	0.399
Smoking Status	0.497	0.341	-0.199	1.193	0.156
$r^2_{adj} = 0.35$					
First Year -Uncemented Tibial Components - Females					
ID	1.360	0.728	-0.169	2.889	0.078
Age	0.059	0.027	0.003	0.116	**0.040**
BMI	0.018	0.032	-0.049	0.086	0.573
Tibia Area	0.058	0.089	-0.128	0.244	0.521
Smoking Status	1.016	0.513	-0.061	2.093	0.063
$r^2_{adj} = 0.22$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
First Year -Uncemented Tibial Components - Males					
ID	3.682	1.019	1.333	6.032	**0.007**
Age	0.032	0.026	-0.028	0.092	0.251
BMI	-0.059	0.050	-0.174	0.056	0.270
Tibia Area	0.076	0.072	-0.090	0.242	0.324
Smoking Status	0.378	0.532	-0.850	1.606	0.498
$r^2_{adj} = 0.63$					
First Year -Cemented Tibial Components					
ID	0.952	0.479	0.000	1.904	**0.050**
Sex	0.281	0.271	-0.259	0.820	0.303
Age	-0.009	0.010	-0.030	0.012	0.383
BMI	-0.014	0.013	-0.040	0.013	0.319
Tibia Area	0.039	0.032	-0.025	0.102	0.229
Smoking Status	-0.444	0.483	-1.404	0.516	0.361
$r^2_{adj} = 0.01$					
First Year -Cemented Tibial Components - Females					
ID	1.185	0.491	0.201	2.169	**0.019**
Age	-0.003	0.012	-0.028	0.021	0.790
BMI	-0.014	0.015	-0.044	0.017	0.374
Tibia Area	0.090	0.038	0.015	0.166	**0.020**
Smoking Status	-1.064	0.777	-2.621	0.493	0.176
$r^2_{adj} = 0.12$					
First Year -Cemented Tibial Components - Males					
ID	-1.812	1.521	-4.959	1.335	0.246
Age	-0.022	0.020	-0.063	0.019	0.277
BMI	-0.027	0.027	-0.084	0.029	0.322
Tibia Area	-0.046	0.058	-0.166	0.073	0.428
Smoking Status	-0.125	0.634	-1.436	1.187	0.846
$r^2_{adj} = 0.03$					
Midterm - All Components					
ID	1.362	0.536	0.289	2.434	**0.014**
Fixation	0.548	0.214	0.120	0.975	**0.013**
Sex	0.015	0.340	-0.665	0.695	0.964
Age	0.009	0.013	-0.017	0.035	0.489
BMI	0.005	0.019	-0.033	0.043	0.805
Tibia Area	-0.064	0.041	-0.146	0.018	0.125
Smoking Status	0.216	0.292	-0.368	0.800	0.462
$r^2_{adj} = 0.16$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Midterm -Uncemented					
ID	1.008	1.371	-1.851	3.868	0.470
Sex	-0.627	0.577	-1.831	0.576	0.290
Age	-0.035	0.028	-0.094	0.023	0.218
BMI	0.030	0.042	-0.057	0.116	0.486
Tibia Area	-0.222	0.076	-0.382	-0.062	**0.009**
Smoking Status	0.342	0.533	-0.770	1.455	0.529
$r^2_{adj} = 0.27$					
Midterm -Uncemented Tibial Components - Females					
ID	-0.953	2.300	-6.581	4.674	0.693
Age	0.011	0.049	-0.109	0.130	0.834
BMI	0.013	0.039	-0.083	0.110	0.745
Tibia Area	-0.012	0.168	-0.421	0.398	0.947
Smoking Status	-0.007	0.928	-2.276	2.263	0.995
$r^2_{adj} = 0.25$					
Midterm-Uncemented Tibial Components - Males					
ID	-93.225	36.948	-252.199	65.749	0.128
Age	-0.364	0.142	-0.977	0.249	0.125
BMI	-0.386	0.130	-0.947	0.175	0.098
Tibia Area	1.291	0.613	-1.347	3.930	0.170
Smoking Status	-3.778	1.987	-12.327	4.771	0.198
$r^2 = 0.52$ **insufficient sample size for reliable results*					
Midterm -Cemented Tibial Components					
ID	1.560	0.533	0.477	2.642	**0.006**
Sex	0.362	0.378	-0.407	1.131	0.345
Age	0.023	0.013	-0.004	0.050	0.090
BMI	-0.003	0.019	-0.042	0.036	0.883
Tibia Area	0.003	0.046	-0.091	0.098	0.941
Smoking Status	0.365	0.330	-0.305	1.035	0.276
$r^2_{adj} = 0.13$					
Midterm -Cemented Tibial Components - Females					
ID	1.603	0.885	-0.243	3.448	0.085
Age	0.028	0.018	-0.009	0.066	0.130
BMI	0.005	0.024	-0.045	0.055	0.842
Tibia Area	0.021	0.080	-0.146	0.187	0.796
Smoking Status	0.246	0.505	-0.807	1.299	0.631
$r^2_{adj} = 0.05$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Midterm-Cemented Tibial Components - Males					
ID	1.869	0.780	0.105	3.633	**0.040**
Age	0.012	0.023	-0.041	0.065	0.609
BMI	-0.063	0.048	-0.173	0.046	0.223
Tibia Area	-0.008	0.065	-0.155	0.139	0.905
Smoking Status	0.803	0.614	-0.587	2.193	0.224
$r^2_{adj} = 0.11$					
Late Follow-up - All Components					
ID	0.453	0.271	-0.089	0.994	0.100
Fixation	0.153	0.208	-0.263	0.569	0.466
Sex	-0.135	0.252	-0.638	0.368	0.594
Age	0.021	0.014	-0.008	0.049	0.159
BMI	0.023	0.018	-0.014	0.060	0.219
Tibia Area	-0.006	0.031	-0.069	0.056	0.842
Smoking Status	-0.078	0.301	-0.679	0.524	0.796
$r^2_{adj} = -0.01$					
Late Follow-up -Uncemented					
ID	-1.293	1.944	-5.493	2.908	0.518
Sex	0.075	0.529	-1.068	1.219	0.889
Age	-0.001	0.027	-0.060	0.057	0.960
BMI	-0.007	0.031	-0.073	0.059	0.830
Tibia Area	-0.089	0.103	-0.310	0.133	0.403
Smoking Status	-0.028	0.628	-1.384	1.327	0.965
$r^2_{adj} = -0.07$					
Late Follow-up -Uncemented Tibial Components - Females					
ID	-0.953	2.300	-6.581	4.674	0.693
Age	0.011	0.049	-0.109	0.130	0.834
BMI	0.013	0.039	-0.083	0.110	0.745
Tibia Area	-0.012	0.168	-0.421	0.398	0.947
Smoking Status	-0.007	0.928	-2.276	2.263	0.995
$r^2_{adj} = -0.65$ **insufficient sample size for reliable results*					
Late Follow-up-Uncemented Tibial Components - Males					
ID	-93.225	36.948	-252.199	65.749	0.128
Age	-0.364	0.142	-0.977	0.249	0.125
BMI	-0.386	0.130	-0.947	0.175	0.098
Tibia Area	1.291	0.613	-1.347	3.930	0.170
Smoking Status	-3.778	1.987	-12.327	4.771	0.198
$r^2_{adj} = 0.66$ **insufficient sample size for reliable results*					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Late Follow-up -Cemented Tibial Components					
ID	0.478	0.281	-0.088	1.045	0.096
Sex	-0.158	0.329	-0.823	0.506	0.633
Age	0.026	0.018	-0.010	0.062	0.153
BMI	0.034	0.024	-0.015	0.083	0.167
Tibia Area	0.020	0.037	-0.056	0.095	0.602
Smoking Status	0.474	0.469	-0.471	1.420	0.317
$r^2_{adj} = 0.03$					
Late Follow-up -Cemented Tibial Components - Females					
ID	0.466	0.337	-0.226	1.158	0.178
Age	0.027	0.026	-0.025	0.080	0.298
BMI	0.042	0.029	-0.017	0.100	0.156
Tibia Area	0.042	0.049	-0.059	0.142	0.403
Smoking Status	0.205	0.636	-1.100	1.510	0.750
$r^2_{adj} = -0.05$					
Late Follow-up-Cemented Tibial Components - Males					
ID	0.336	0.550	-0.891	1.562	0.556
Age	-0.024	0.035	-0.103	0.054	0.506
BMI	-0.062	0.063	-0.202	0.077	0.342
Tibia Area	-0.038	0.069	-0.193	0.116	0.593
Smoking Status	1.468	0.848	-0.421	3.357	0.114
$r^2_{adj} = 0.10$					

*CI = 95% confidence interval

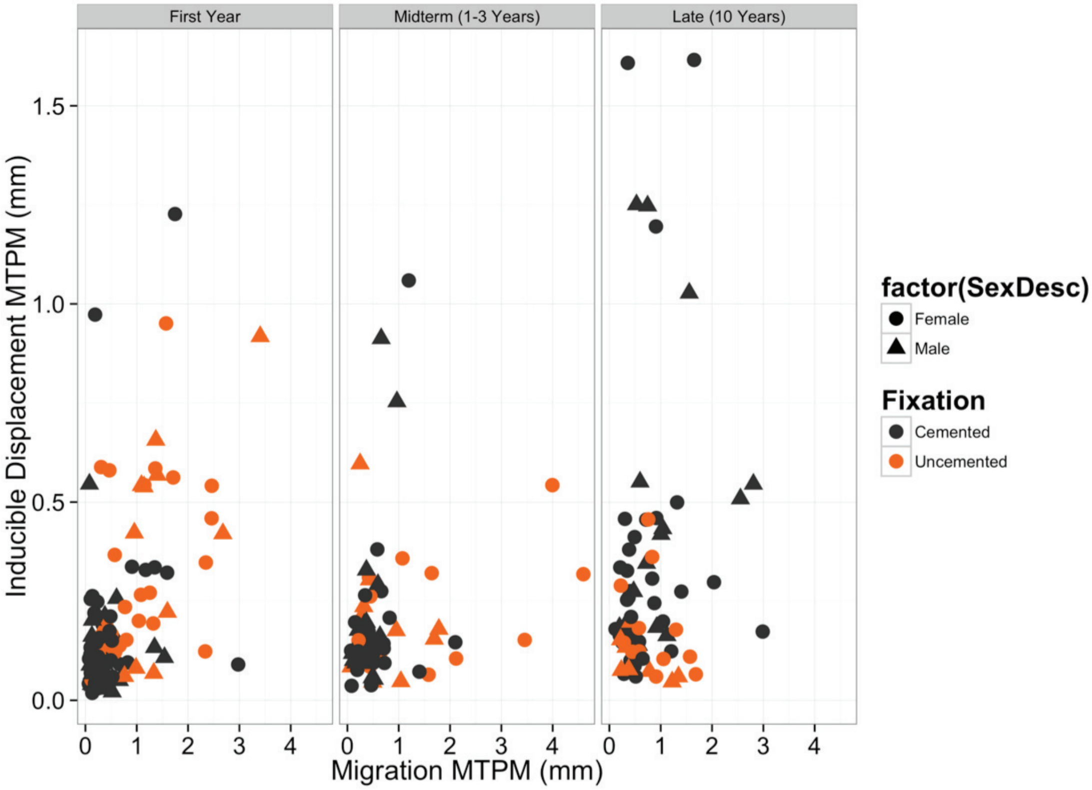


Figure E.1 Migration and inducible displacement for matched knees and visit date, separated by initial follow-up (0.5 – 1 years post-surgery), midterm follow-up (>1 – 3 years post-surgery) and late follow-up (10 years post-surgery) showing results by sex (alternate version of Figure 4.5)

Table E.3. Regression results for Change in Migration from One to Two Years (MTPM as outcome variable). Inducible Displacement exams within the first post-operative year.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented)					
ID	0.426	0.112	0.204	0.647	**0.000**
Fixation	0.009	0.050	-0.089	0.108	0.849
Sex	-0.041	0.062	-0.164	0.082	0.510
Age	0.001	0.003	-0.004	0.006	0.737
BMI	0.000	0.003	-0.006	0.006	0.986
Tibia Area	-0.004	0.008	-0.019	0.012	0.634
Smoking Status	0.109	0.079	-0.047	0.266	0.169
$r^2_{adj} = 0.13$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Uncemented Tibial Components					
ID	0.680	0.236	0.197	1.163	**0.007**
Sex	-0.081	0.184	-0.458	0.297	0.665
Age	0.007	0.009	-0.012	0.025	0.472
BMI	-0.004	0.011	-0.026	0.019	0.754
Tibia Area	-0.007	0.028	-0.064	0.050	0.806
Smoking Status	0.214	0.166	-0.126	0.553	0.208
$r^2_{adj} = 0.11$					
Uncemented Tibial Components - Females					
ID	0.391	0.331	-0.309	1.092	0.254
Age	0.012	0.012	-0.013	0.038	0.325
BMI	-0.003	0.014	-0.034	0.027	0.821
Tibia Area	0.003	0.039	-0.080	0.085	0.945
Smoking Status	0.421	0.230	-0.067	0.908	0.086
$r^2_{adj} = 0.06$					
Uncemented Tibial Components - Males					
ID	1.826	0.755	0.041	3.612	**0.046**
Age	0.001	0.017	-0.039	0.041	0.951
BMI	-0.056	0.036	-0.142	0.030	0.170
Tibia Area	-0.014	0.044	-0.119	0.091	0.760
Smoking Status	0.273	0.336	-0.520	1.067	0.442
$r^2_{adj} = 0.20$					
Cemented Tibial Components					
ID	0.098	0.114	-0.130	0.326	0.395
Sex	-0.004	0.049	-0.101	0.093	0.942
Age	0.000	0.002	-0.004	0.003	0.810
BMI	-0.001	0.002	-0.005	0.004	0.820
Tibia Area	0.000	0.006	-0.012	0.011	0.988
Smoking Status	-0.015	0.085	-0.185	0.154	0.857
$r^2_{adj} = -0.06$					
Cemented Tibial Components - Females					
ID	-0.005	0.122	-0.250	0.241	0.969
Age	0.000	0.002	-0.005	0.004	0.931
BMI	0.001	0.003	-0.004	0.006	0.676
Tibia Area	-0.004	0.007	-0.018	0.009	0.529
Smoking Status	-0.084	0.133	-0.351	0.182	0.528
$r^2_{adj} = -0.07$					

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Cemented Tibial Components - Males					
ID	0.542	0.304	-0.089	1.174	0.089
Age	0.001	0.004	-0.007	0.009	0.778
BMI	-0.004	0.005	-0.015	0.008	0.522
Tibia Area	0.005	0.012	-0.020	0.029	0.698
Smoking Status	0.029	0.127	-0.234	0.292	0.821
$r^2_{adj} = -0.01$					

Table E.4. Logistic Regression results for classification of change in migration from one to two years as continuous migration (MTPM > 0.2 mm). Inducible Displacement exams within the first post-operative year.

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
All tibial components (cemented and uncemented) at all times					
ID	3.015	1.341	0.510	5.909	**0.025**
Fixation	0.903	0.633	-0.380	2.141	0.154
Sex	-0.224	0.900	-2.009	1.561	0.804
Age	-0.016	0.036	-0.085	0.058	0.654
BMI	-0.038	0.049	-0.138	0.057	0.439
Tibia Area	0.687	0.995	-1.394	2.613	0.490
Smoking Status	-0.114	0.119	-0.357	0.114	0.339
Uncemented Tibial Components					
ID	5.539	2.423	1.421	11.069	**0.022**
Sex	1.060	1.405	-1.661	4.031	0.451
Age	0.072	0.070	-0.060	0.222	0.303
BMI	-0.120	0.111	-0.369	0.076	0.280
Tibia Area	1.910	1.322	-0.686	4.683	0.149
Smoking Status	0.056	0.204	-0.359	0.472	0.785
Uncemented Tibial Components - Females					
ID	4.663	3.026	-0.763	11.570	0.123
Age	0.084	0.090	-0.084	0.285	0.348
BMI	-0.110	0.134	-0.420	0.132	0.413
Tibia Area	3.512	2.024	0.024	8.639	0.083
Smoking Status	0.218	0.294	-0.356	0.862	0.458

	Estimate	Standard Error	Lower CI*	Upper CI*	p-value
Uncemented Tibial Components - Males					
ID	4.634	4.264	-2.977	15.082	0.277
Age	0.194	0.138	-0.044	0.548	0.162
BMI	-0.083	0.221	-0.589	0.345	0.707
Cemented Tibial Components					
ID	1.642	2.143	-3.738	5.841	0.444
Sex	0.450	0.870	-1.136	2.446	0.605
Age	-0.048	0.041	-0.133	0.035	0.237
BMI	-0.035	0.060	-0.158	0.082	0.555
Cemented Tibial Components - Females					
ID	-1.501	4.415	-13.907	4.302	0.734
Age	-0.017	0.051	-0.114	0.099	0.741
BMI	-0.002	0.065	-0.131	0.133	0.973
Cemented Tibial Components - Males					
ID	10.360	10.628	-3.386	57.275	0.330
Age	-0.088	0.133	-0.450	0.138	0.511
BMI	-0.339	0.337	-1.538	0.124	0.315

*CI = 95% confidence interval

Appendix F

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