4D measures of migration as a safety prediction of hip and knee implants: advances in evaluating implant fixation

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General introduction and outline of this thesis

Joint replacement surgery by total hip and total knee arthroplasty (THA and TKA) are among the most performed interventions worldwide (1, 2). The Dutch Arthroplasty Register (LROI) reported a total of 33,248 THAs and a total of 25,859 TKAs performed in 2019 (3). A further increase in these numbers is expected in the future due to aging of the population and a growing number of people with obesity (3). The trend projection suggests an estimated increase in the Netherlands of 140% by 2030 (4, 5). Both THA and TKA are generally considered successful treatments, however 'treatment success' can be interpreted in different ways. Traditionally, outcome is evaluated by objective measurements such as implant survival and revision rates (6). However, in the last decade a shift has occurred towards subjective patient-perceived outcome measures addressing what is most relevant for patients (7).

Subjective outcome measures

Although joint replacement surgery is highly effective in improving health-related quality-of-life at group level, this is not the case on an individual level (8). Up to 30% of joint replacement patients are dissatisfied with the results after surgery and persistent pain is reported in 9% of THA patients and in 20% of TKA patients at long-term follow-up (9-11). Patient-reported outcome measures (PROMs) is the general term used for a variety of self-reported questionnaires which allow researchers to quantify a wide selection of outcome variables like pain, satisfaction, quality of life, and function. Although these PROMs are considered by some to give a good representation of patients' satisfaction and functional gain, one should be aware that they only present the perceived outcome of the pre-, intra-, and postoperative complexity of joint replacement surgery (12). Hence, objective measurements next to PROMs are imperative to evaluate treatment success.

Objective outcome measures

Objective outcome measures after THA and TKA are regularly based on survival and revision rates. According to the Dutch Arthroplasty Register (LROI) in 2019, a total of 2787 THAs revisions were performed with exchange of both or only the femur or acetabular component. In 2019 the overall revision TKA numbers were 1685 revisions of both or only the femur or tibial component. Aseptic loosening was the major cause of revision; accounting for 37.8% of THA and 28.9% of TKA revisions (3). Looking at other joint registries, on average 5 to 10 percent of the patients require revision surgery within 10 years after implantation. Aseptic loosening accounts for the greatest proportion, approximately 40%, of the revision surgeries and is therefore the main threat for implant longevity (13-15). Quantifying implant fixation to anticipate aseptic loosening is an ongoing challenge in follow-up care of joint replacement. Identifying unstable implants prone to failure also permits innovation of novel interventions to prevent progression to gross loosening thereby possibly averting revision surgery.

Aseptic loosening

The exact underlying mechanism of aseptic loosening is still under debate and yet not fully understood (16). The debate has mostly focused on the hypothesis of particle disease, which is based on retrieval studies of failed implants and histological studies of periprosthetic tissue showing wear particles (polyethylene-, cement- or metal particles) and abundant macrophages and giant cells in this tissue. This theory postulates that wear particles generate a proinflammatory state resulting in periprosthetic osteolysis and ultimately implant loosening (17-19). However, as wear particles slowly accumulate in time it cannot explain early cases of aseptic loosening. Hence, the early loosening theory was proposed (20, 21). While the particle disease states that loosening is induced by wear particles, the early loosening theory postulates that loosening is already initiated shorty after surgery by triggering factors such as a poor bony interlock (between the implant-bone, or bone-cement interface), poor bone quality (due to osteoporosis or rheumatoid arthritis), and resorption of a necrotic bone bed (due to surgical trauma or due to the heat from curing cement). Ultimately, the endpoint of both theories is identical; a proinflammatory state promoting osteoclast activity and inhibiting osteogenic activity of osteoblasts. As a result, bone resorption predominates at the implant-bone or bone-cement interface leading to bone defects and the formation of a fibrous-granulomatous interface tissue (22, 23). This interface tissue has negligible stiffness and does not provide a strong interlock, resulting in motion of the implant in relation to the bone (24, 25). After initial loosening, biomechanical factors such as implant design and magnitude of mechanical stress can lead to progression of loosening, resulting in increasing periprosthetic osteolysis and subsequent gross migration. For example, a femoral component with a long neck in a varus position is exposed to extra high torque loads. Aseptic loosening is a slow, continuous process, gradually causing clinical symptoms such as pain. By the time a fibrous tissue layer is visible on conventional radiographs, presented as a radiolucent line around the implant, the loosening process may already be at an advanced stage (26). However, it is possible to detect this loosening process as early as 1 to 2 years postoperatively by measuring implant migration with roentgen stereophotogrammetric analysis (RSA).

RSA

RSA is a highly accurate stereo X-ray technique for the assessment of 3D movement between two rigid bodies, for example movement of an implant relative to the bone. The use of X-rays to determine the 3D position of an object in space dates back to the time X-rays were discovered (27). Modern utilization of RSA is based on the work of Göran Selvik, a Swedish mathematician and anatomist, who described the technique in his thesis in 1972 (28). Over time this technique improved due to the introduction of digital radiographs and software measurements thereby reducing the time for analysis significantly (29, 30). In order to measure movement of an implant in relation to the bone, small X-ray opaque tantalum markers are attached onto the implant by the manufacturer and during surgery markers are placed into the bone surrounding the implant thereby creating two rigid bodies. A typical modern RSA setup consists of two synchronized X-ray tubes, a calibration box, which holds markers at accurately known positions, and a radiograph detector. The patient is positioned in between the X-ray tubes and the calibration box, producing two plain, stereo radiographs showing the implant of interest, the bone markers and the calibration box markers. With the help of software, the 3D positions of the X-ray tubes are reconstructed from the projected calibration box markers on the two digital radiographs. Subsequently, the 3D positions of the markers on the implant and in the bone can be reconstructed, producing a 3D RSA scene. By fitting the rigid body of the reference bone markers of all following RSA scenes onto the postoperative RSA scene, the migration overtime of the implant relative to the bone can be calculated (31, 32). Measuring migration over time with RSA has an accuracy between 0.05 and 0.5 mm for translations and between 0.15 and 1.15° for rotations (32). Compared to conventional radiographs, which have an accuracy between 5 and 12 mm for translations, the accuracy of RSA is 10-20 fold better (33). The attachment of markers (i.e. marker-based RSA) onto the implant poses some issues; the marker-based implants are more expensive in comparison to their conventional counterparts and the attached markers may jeopardize its strength and could also act as local stress risers. In order to overcome these problems, a method was developed that does not require any markers on the implant: model-based RSA (MB-RSA) (30, 34). MB-RSA uses CAD models or models from reversed engineering instead of markers on the implant. The 3D virtual surface models are "matched" on the radiographs by minimizing the difference between the virtual projection of the model with the actual projection as it appears in a radiograph.

Clinical implication

Due to its high accuracy, migration as measured with RSA, has shown to be able to predict future long-term (10 years) loosening of THA and TKA based on early follow-up (1-2 years) (24, 25, 35-37). Furthermore, combining early RSA migration data with survival studies using meta-regression analyses revealed that early migration of both acetabular cups in THA and tibial components in TKA is associated with late revision (38, 39). Using meta-regression analyses thresholds values for early migration were established, thereby providing an upper limit of acceptable early migration, above which implants are at risk for future failure. The Dutch Orthopaedic Association (NOV) adopted RSA as an early qualitative tool as part of a phased introduction of newly designed implants. For that matter, RSA exposes only a small number of patients during a relatively short period of time to a potential poor "new" implant design (40). In 2013, the International Organization for Standardization (ISO) published a standard protocol for early clinical studies, providing requirements for the clinical assessment of migration of implants with RSA. By performing and reporting results in a standardized manner, comparison of RSA studies is more straightforward and will enhance its applicability as a qualitative tool in a phased introduction of novel implants (41).

Inducible displacement

The evaluation of implants using RSA has primarily focused on the migration of the implant over a period of time, i.e. comparing the postoperative relative position of the implant in relation to the host bone, versus the position of the implant 1 or 2 years later. However, another approach is to instantly measure migration, i.e. comparing the relative position of the implant in a loaded and an unloaded situation. Thereby inducing a displacement on the implant. Inducible displacement is a tool to evaluate implant fixation on a specific moment in time, instead of assessing fixation by measuring migration longitudinally. The first publications describing inducible displacement dates back to the late 1980s, while most research was published in the 1990s (42). Although inducible is promising in theory, the number of publications addressing inducible displacement declined in the 2000s. The latter was probably related to uncertainty about the underlying mechanism of inducible displacement, inconsistent results and the lack of a distinct loading protocol. In theory, inducible displacement can take place within the implant itself (i.e. implant elasticity), as movement or deformation within the fixation interface (implant-bone, implant-cement, cement-bone), or as an elastic deformation within the bone (43, 44). Research on inducible displacement has focussed on TKA and several loading protocols have been employed to generate a displacement. These so-called stress tests have commonly included weight-bearing on the affected limb (single-leg stance, step-up and step-down, squatting) and weight-bearing with a torque applied at the foot to induce a rotatory stress. A number of studies have found significant, albeit weak correlations between inducible displacement and migration (44-48). However, today it is still unclear which approach of inducing a force onto an implant is effective and foremost how much inducible displacement is acceptable and thus can be used as a threshold value to predict the risk of future loosening of an implant.

Advances in measuring implant migration

Migration analysis of implants as measured with RSA has led to several milestones for implant safety in patient care. The association of early migration with late failure has led to the implantation of migration analysis as part of a phased introduction of implants to the market. Another success is the definition of thresholds values for acceptable early migration, it is important to judge these values in time in relation to each other, meaning is a "plateau phase" reached. The latter can be used as a benchmark in a phased introduction of new implants. Also, evaluation of early migration provided more insight into the loosening process and resulted in the early loosening theory of aseptic loosening. Furthermore, ISO guidelines will enhance conformity of RSA studies performed worldwide thereby enhancing developments. However, there are still some advances to be realized. Thresholds values for acceptable early migration are yet only available for acetabular cups in THA and for tibial components in TKA, however not for femoral stems in THA. Moreover, little is known about the migration patterns of distinct implants designs and characteristics. Additionally, RSA studies addressing long-term migration patterns are scarce. What is more, inducible displacement has great potential but needs resurgence.

AIM AND OUTLINE OF THIS THESIS

The overall aim of this thesis is to examine the influence of implant factors on fixation of both THA and TKA, measured as both migration over time and inducible displacement, and quantified by RSA. Within this aim, areas of focus are examining migration patterns of both cemented and cementless femoral stems in THA, determining the effect of mobile-bearings in TKA on migration and survival, and considering how inducible displacement has potential for clinical applications of evaluating implant fixation.

The first part of this thesis concerns femoral stems in THA. In **Chapter 2** the migration of a cementless femoral stem with a long, conical design (Mallory-Head Porous), with up to 25 years of follow-up, is described and compared among different bioactive coatings (i.e. hydroxyapatite, fluorapatite, uncoated). The same Malloy-Head Porous stem is subsequently compared to the Taperloc stem with a flat wedged design. For this purpose, a randomized controlled trial described in **Chapter 3**, was performed comparing the migration and functional outcome of these two cementless stems with different design rationale. **Chapter 4** presents the results of a randomized controlled trial comparing two different types of bone cement (Palacos R + G and Refobacin bone cement R) in a stem with a shaped-closed design (Stanmore). To establish thresholds for acceptable early migration, a systematic review on the association between early migration and late aseptic revision of stems is included in **Chapter 5**.

The second part of this thesis concerns TKA. In **Chapter 6** the migration and functional outcome of four different TKA designs (high-flexion and conventional, either with a mobile-bearing or fixed-bearing) are compared in a randomized controlled trial. The effect of bearing type on implant survival is elaborated in a systematic review between mobile-bearing and fixed-bearing TKA and described in **Chapter 7**.

The third part of this thesis comprises an experimental study investigating approaches to instantly detect loosening in TKA. In **Chapter 8** an *in vitro* study is presented testing different methods to induce a measurable displacement in an artificially created loose implant.

Finally, **Chapter 9** summarizes the studies described in this thesis with a general discussion and final conclusions.

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