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Challenges of pre-clinical testing in orthopedic implant development

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ABSTRACT

The market for orthopedic implants is growing rapidly with the increasing prevalence of orthopedic diseases in an aging society. Different designs and materials have been developed over the years and have, in general, shown excellent results in pre-clinical testing. However, there have been incidences of serious complications when novel implants or materials are put into clinical use, with some well-known cases being metallosis in patients implanted with metal-on-metal hip replacements and osteolysis from polyethylene wear debris generated in hip and knee joint replacements. Unforeseen factors related to new designs, materials and surgical techniques can lead to different outcomes for pre-clinical testing and clinical use. While often an excellent indicator of a device's performance in clinical settings, pre-clinical testing does sometime fail to predict critical flaws in implant development. This article aims to explore the gaps in the current approach to testing. The ISO international standard of pre-clinical testing should be modified to more adequately capture actual clinical use of the implant and simulate daily activities. This article will also introduce modern methods for implant development, such as FEM, 3D printing and computer-aided orthopedic surgery, which can be widely applied to improve pre-clinical testing procedures and reduce the incidence of surgical malalignment by analyzing biomechanical performance, planning surgical procedure and providing surgical guide.

1. Introduction

In 2018 alone, revenue from the sale of orthopedic implants was approximately USD 51.2 billion, with joint replacements accounting for 37% of this [1]. Joint replacement is a reliable and cost-effective surgical intervention generally used to treat debilitating joint pain, often as a result of osteoarthritis, rheumatism, avascular necrosis, or trauma. The survival rates of primary hip and knee replacements have been reported at 93% and 94% respectively after 14 years implantation [2].

The Food and Drug Administration (FDA) imposes strict regulations on the development and marketing of orthopedic implants, with the requirements been commensurate to the risk to human health [3]. As class III medical devices, such implants require clinical trials prior to being placed on the market. Phase I clinical trials evaluate the safety of the device in a limited number of patients, while Phase II trials determine the efficacy of the proposed implant in comparison to the currently accepted standard of care. For a manufacturer to market a new implant in the United States, substantial equivalence to a similar implant previously cleared by FDA can be established through the 510(k) regulatory pathway [4]. Mechanical performance data are also typically provided as a part of the 510(k) submission. However, despite being granted the necessary market clearance and having a full suite of performance data to support the functionality of the implant, the clinical success of the implant is still highly dependent on the material, design, and surgical alignment. Even with progressive developments in implant designs and materials, there is still a persistent issue of unacceptable failure rates [5,6].

In the past 60 years, there has been tremendous progress with the development of novel materials that show excellent biocompatibility: first generation (bioinert materials), second generation (bioactive and biodegradable materials), third generation (biological adaptive materials) [7]. Each generation represents an evolution of the properties of the materials involved and allows the implants to be used with a wider range of orthopedic diseases, but implant failure remains a persistent concern [8]. When a joint prosthesis fails it is primarily because of material wear and fatigue, which often produces wear debris resulting in osteolysis and loosening of the prosthesis [9]. Oxidative degradation is also a common failure mode for polymeric materials, particularly for

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cross-linked polyethylene which is often used as an implant liner [10].

The key concept in the design of any medical device is that it must be safe and effective for its intended use. Considering hip joint replacements as an example, anatomical joint designs have been introduced in recent years which can accommodate larger head diameters, but these larger heads have been reported to produce greater wear and corrosion [11]. Similarly, a dual-taper stem design, which added an extra tapered junction between the neck and the stem, has been proposed to better conform to the natural anatomy of the bone, but also increases the risk of moderate to severe corrosion [12]. An alternative to using anatomical designs is to cement the prosthesis in place. Cemented fixation provides immediate stability postoperatively, but the foreign material can lead to adverse biological reactions and subsequent implant loosening [13]. To mitigate some of the causes of implant loosening, femoral stems have been produced with a variety of surface features and coatings. Manufacturers have also introduced different lengths for the femoral stem. Shorter stems have been shown to improve load transmission, preserve the femoral bone stock and allow for minimally invasive surgical procedures [14,15]. Another measure introduced by manufacturers was to increase the diameter of the head to improve implant stability, which for metal-on-metal prostheses led to the generation of metallic debris from mechanical and corrosive wear. The metallic particulates disrupted bone ingrowth and soft tissue attachment, ultimately causing aseptic loosening which subsequently required revision surgery [5,6]. This is a clear example of where a critical flaw in the implant design did not show during pre-clinical testing, and was so devastating on the market that the devices had to be recalled. Although the design of prostheses and materials are constantly improving, there are still unforeseeable risks with introducing new concepts to the market [16,17].

Apart from the design of the implant itself, improper surgical technique is also one of the primary causes of revision [9]. Of particular concern is improper alignment of the prosthesis, which can arise from frontal misalignment, sagittal overstuffing or mispositioning, axial malrotation, poor bone fixation, inappropriate constraints or ligamentous balance, and an inappropriate level of joint spacing [18]. One of the prerequisites of a successful total knee arthroplasty (TKA) is restoration of neutral knee alignment by placing the femur in external rotation to make the flexion gap symmetrical and conform to the extension gap [19]. However, malalignment is the primary cause of revision for TKA, accounting for approximately 20% of failures, followed by aseptic loosening and instability [20]. Therefore, improving the design of the implants alone will not resolve many of the complications experienced, it is also necessary to standardize surgical techniques to reduce the occurrence of early failure. The development of computer-assisted orthopedic surgery (CAOS), including image registration and robotic-assisted navigation systems, has improved surgical accuracy and precision [21]. Wider adoption of CAOS in the future may help to standardized procedures and prolong the survivorship of implants.

Pre-clinical testing is performed in accordance with the relevant international standards (ISO, ASTM, etc.) and national regulations, but such methods still cannot adequately simulate in vivo performance when an implant is placed under diverse situations, such as variations in daily activities due to the cultural and regional demands and atypical malalignment. In recent years considerable resources have been put towards evaluating novel implant designs and materials in an effort to improve clinical outcomes [22]. Extensive testing and evaluation are performed in the pre-market phase, typically consisting of mechanical testing such as fatigue and wear studies [23–26], but clinical failure stills persist. The following examples discuss various causes of implant failure and aspects that need to be considered during the design and development stages in order to improve patient outcomes.

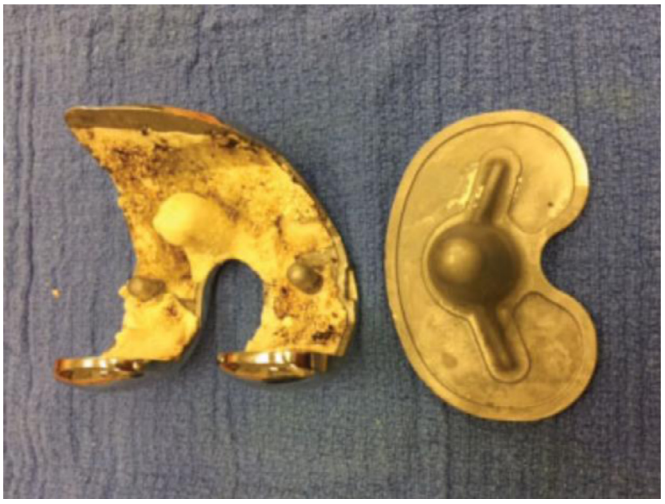

Figure 1. [28] Cement adhering to the femoral component but not the tibial component.

1.1. Implant design

New prostheses introduced to the market are often iterations of existing designs, such as the Attune® (DePuy Synthes, Warsaw, IN) TKA prosthesis being a modified version of the Press Fit Condylar [PFC] Sigma® (DePuy Synthes) prosthesis. Some of the advantages of Attune prosthesis, as promoted by DePuy Synthes, are increased conformity between the femoral component and polyethylene insert with a gradual femoral radius, an s-curve design of the cam and post for gradual femoral rollback and stability, and an improved polyethylene insert locking mechanism [27]. However, clinical complications associated with the Attune prosthesis are well documented. It has been reported that patients present with pain on weight bearing, effusion, and decreased range of motion (ROM) within 2 years after surgery. Radiographic evaluation has shown loosening of the tibial components in 13% of implants (2 of 15 knees evaluated) [28] (Fig. 1). Tibial component loosening is a rare complication of cemented TKA at short-term follow-up, but may appear due to the increased constraint of cement fixation, insufficient cement used, and limited rotational stabilizers (i.e. smooth surfaces on tibial fixation surface). Also, the roughness factor on the fixed bearing is only 60, versus 220 for the previous generation Sigma system (DePuy Synthes). The increased constraint of the tibial insert may contribute to higher loads at the implant-cement and cement-bone interfaces, which may contribute to loosening [28]. In addition, the surface of the tibial component has rounded edges and fewer insets for cement interdigitation relative to the previous designs.

Another complication of the Attune prosthesis is related to the tibial component stem being located more posterior to the stem than the PFC Sigma prosthesis [29] (Fig. 2). Although the prosthesis may be placed in accordance with the recommended surgical procedure, the posterior stem is designed into the prosthesis and has been shown to increase the risk of injury to the posterior tibial cortex, causing subsequent pain and periprosthetic fracture [29].

However, DePuy Synthes appear to have recently acknowledged some of the shortcomings of the Attune prosthesis and introduced new design features, which they are terming Attune S+™ Technology [27]. Four disconnected pockets for cement integration have been placed on the underside of the tibial plate (termed Macrolock) and the bone interface has been given a rougher surface (termed Microblast) to assist with bone integration. The efficacy of these new design features still needs further clinical evidence before been proven to improve long-term clinical outcomes.

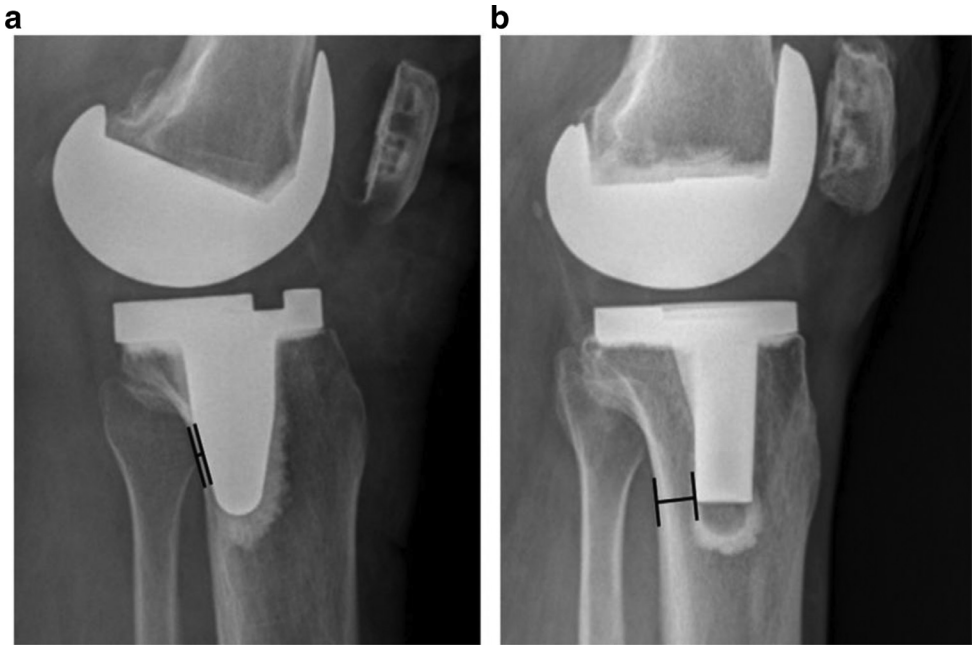

Figure 2. [29] Radiographic measurement of the minimal distance between the tibial component stem and posterior tibial cortex. (a) Attune. (b) PFC.

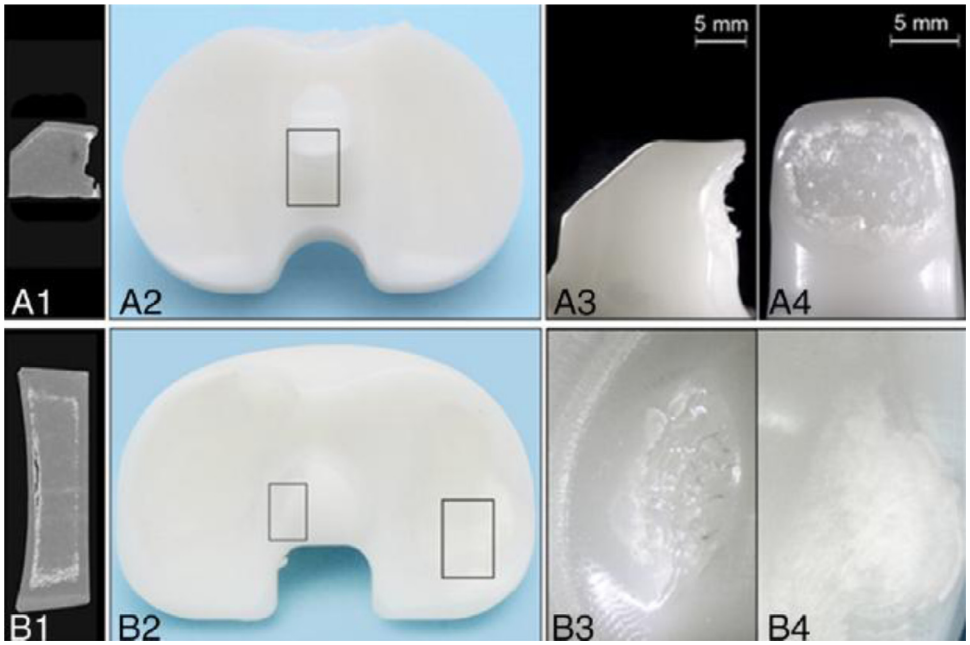

Figure 3. [30] Oxidation of X3 material.

1.2. Material failure

Osteolysis and prosthesis loosening caused by the generation of wear debris are the primary causes of implant failure [9]. Highly cross-linked polyethylene was introduced to reduce wearing and improve fatigue resistance through cross-linking, but the free radicals generated in the process lead to oxidative degradation over time [10].

X3^{TM} Highly Crosslinked Polyethylene was introduced in 2005 as an annealed polyethylene variant for improved wear resistance and mechanical performance. Wear testing of Triathlon CR tibial inserts has shown that, after 5 million cycles, inserts made of conventional UHMWPE had a wear volume of $98.6 \pm 6.1\,mm^3$ while inserts made of X3 had a wear volume of $26.8 \pm 1.3\,mm^3$, representing a 68% decrease [26]. However, oxidation of the X3 PE material has been a problematic issue ever since its introduction (Fig. 3), but it has also been reported that the X3 material exhibits significantly less oxidation than the previous generation of remelted highly cross-linked polyethylene [30–32]. Oxidation in the intercondylar region leads to rapid material degradation, resulting in the generation of particulate debris which has the potential to induce a localized tissue response.

1.3. Surgical alignment

Accurate rotational alignment of the tibial and femoral component is critical in total knee replacements and plays an important role in loading the underlying bone. Malalignment has been asso-

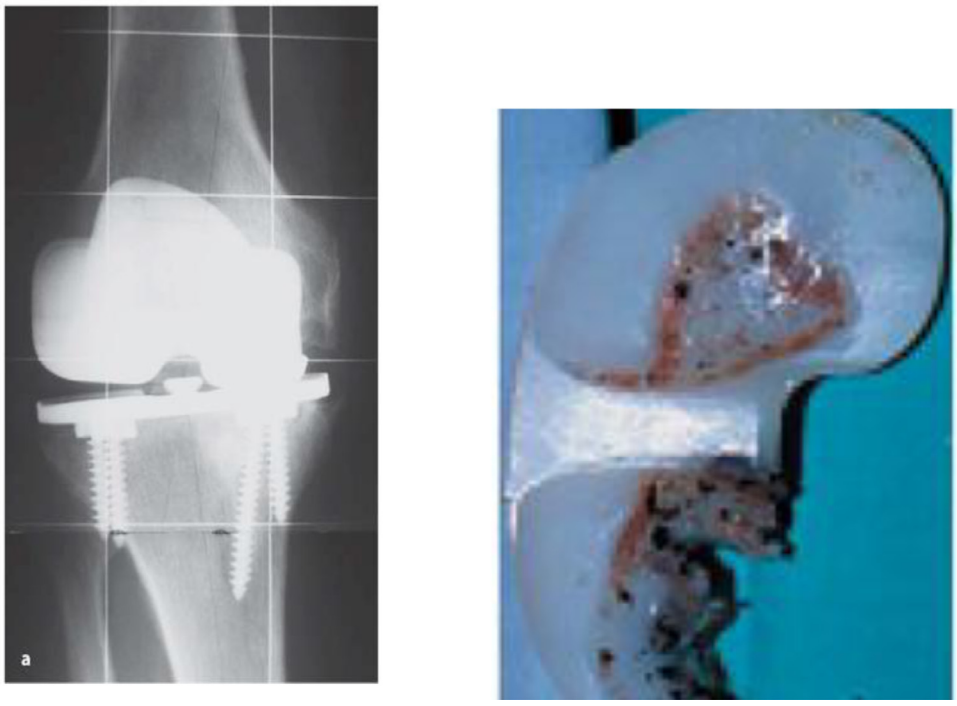

Figure 4. [34] Rotational malalignment of knee joint.

ciated with bone fractures and implant loosening in both metal-backed and all-polymer tibial components [33]. Hofmann et al. [34] reported on a typical example of joint malalignment where the knee was placed at a 9° varus angle during implantation but increased to 14° post-operatively. In this case, improper alignment led to increased loading of the medial side which caused full thickness wearing of the tibial insert (Fig. 4). Cheng et al. [35,36] demonstrated that malalignment also has a considerable influence on the biomechanics of the knee joint and the improper loading patterns can lead to implant failure, but mobile tibial bearings had a relatively better outcome than fixed bearings. Therefore, achieving correct frontal alignment and soft tissue balance is crucial for long-term success.

2. Discussion

Regardless of the quantity and quality of testing performed on a prosthesis, clinical complications arising from material wear and fatigue are still frequently reported. Implant failure may be caused by numerous sources that are difficult to anticipate during the development stages or pre-clinical testing, such as flaws in the manufacturing process, improper surgical technique or strenuous activities by the patient. Inevitable differences between the in-vivo and in-vitro environment may also limit how well laboratory analysis can predict how an implant will operate in situ.

Large and very large femoral heads in metal-on-metal (MoM) hip replacements were introduced to mimic anatomical conditions, but these larger heads also acted to increase the lever arm of the joint, leading to high friction during certain movements. Suddenly the tapered interface between femoral head and stem exhibited issues with corrosion on a previously unknown scale. It was speculated that due to the higher mechanical loading with larger heads, the tapered connection became less forgiving with respect to assembly conditions, contamination, and manufacturing tolerances [37]. Since the pre-clinical testing of these bearings was very successful and no major complications had been found [38], the unsatisfactory clinical outcome could not be anticipated. In such cases it is important to understand why the prosthesis behaved so differently when placed inside a patient.

The current ISO standard (ISO 14242) for simulator wear testing of total hip replacements (THRs) recommends loading and motion parameters that represent a standard walking cycle for correctly positioned prostheses with no degradation of the materials [39]. It does not consider many aspects of the highly variable in vivo kinematics and biomechanics, such as during squatting and climbing stairs. Gait studies have revealed that the hip joint may subjected to elevated loads up to eight times body weight when stumbling which are not captured during standard testing, and retrieval studies have demonstrated that UHMWPE cups experience edge loading and impingement in vivo [40,41].

A key difference between in-vitro and in-vivo performance is the release and accumulation of ions [42]. During laboratory testing, at a specific point in time, the test serum is extracted and the ion content measured with a mass spectrometer. The serum is then replaced and the simulation performed again. This method does not adequately address the accumulation and metabolism of ions over time. In vivo, the metal ion concentration is a function of ion production, distribution and accumulation in the body, and subsequent excretion by the kidneys.

Another drawback of in vitro testing is that it is difficult to factor in conditions outside of the control of the recommended surgical procedure, such as malalignment, infection, and variations in surgical technique. Between April 1 2003, and Dec 31 2013, of the 623,253 primary joint replacements performed in England and Wales 2705 required subsequent revision [43]. Similarly, Cochran et al. [44] found that rates of re-infection after treatment for infection following TKA can be as high as 19%. The positioning of the femoral component or tibial tray may vary between procedures and surgeons, which was not considered during the standard test. However, with the introduction of precision-guided techniques, such as patient-specific guided instruments and CASO, it is anticipated that surgical procedures will become more standardized, which will help to minimize implant malalignment and ensure the test conditions mimic the actual conditions during surgery.

In general, pre-clinical testing is good for evaluating ideal the functionality of a prosthesis, but often cannot predict complications, some of which are critical, that may arise when placed in vivo.

3. Future prospects

Osteolysis and malalignment are the primary factors affecting the survivorship of implants, and are related to the implant materials and design in terms of wear, fatigue and surgical technique. Progressive advancements in materials have helped to prolong the lifetime of implants, while computer-assisted techniques, such as 3D printed custom designs and CAOS, could help to reduce malalignment. Similarly, computational power and the complexity and accuracy of computer model are currently the main limitations of using finite element method (FEM) for pre-clinical testing, but it is foreseeable that FEM will eventually replace the need for physical testing.

3.1. 3D printing and CAOS

Going forward, the design and testing of orthopedic implants should consider individual variations such as the specific indication, anticipated daily activities (can vary from country to country) and physiological conditions. While such variations are difficult to design into a standard prosthesis, 3D printing can overcome this setback and also open up a much wider field of application. 3D printing is already actively used for treating orthopedic diseases, and has been proven effective for preoperative planning, producing personalized implants, and producing patient-specific instrumentation [45–47]. The greatest limitations with the 3D printing technology available today are the cost of production and the quality of the implant at long term follow-up. Combining 3D printing with CAOS, patient-specific implants could be designed from medical scans and fabricated by 3D printing, and the positioning could be confirmed using state-of-the-art navigation and robotic systems. In order to improve the clinical outcomes of surgical malalignment, 3D printing and CAOS may be considered for wider application in orthopedic surgery.

3.2. FEM with materials and design

The influence of the active internal environment should also be taken into consideration when designing implants and choosing materials for construction. Finite element method (FEM) is a well-established technique for evaluating the mechanical and material properties of prosthetic joints [48,49] and numerous models have been validated with results that are comparable to in vitro test data [24–26]. Wang et al. [26] demonstrated that the wear contours on a tibial insert produced by a finite element model are very similar to those produced by a knee simulator under the same loading conditions. The key advantages of FEM are low cost and the speed with which results can be generated. By altering the inputs to the model, the software readily allows the user to modify the implant design, materials and conditions under which it is loaded. It is speculated FEM will be crucially applied in the development of the orthopedic implants in the future by replacing some of the current pre-clinical testing.

3.3. Testing standard for malposition

Pre-clinical testing is generally performed in accordance with either the relevant ISO or ASTM standards, and the choice of standard generally depends on the institute performing the testing and the intended market. But the test methods described in these standards are not interchangeable and the differences can have a drastic effect on the results. For example, Wang et al. [24] demonstrated clear variations in the input motion curves for a knee joint in accordance with ISO 14243 and ASTM F3141. Consequently, the results for anterior-posterior (AP) translation, internal-external (IE) rotation, contact area, contact force, wear depth and wear distribution were different. It is difficult to determine which standard more closely resembles in vivo conditions, but these results do highlight that consensus is needed in order to address this obvious gap. In addition, the accuracy of implant positioning is typically under the direct control of the surgeon, but unintentional misalignment is still prevalent at post-operative follow-up. It is therefore recommended that a standard test method for surgical malalignment be taken into consideration when running pre-clinical testing.

4. Conclusion

This manuscript analyzed some of the current challenges facing pre-clinical testing in orthopedic implant development. The discussion focused on the three main factors that determine whether an implant succeeds or fails; design, materials and surgical malalignment. While any product testing for gaining market approval must be conducted in accordance with the relevant standards, there are cases where clear differences exist between the ISO and ASTM standards for the same test. It is recommended that advanced techniques such as FEM, 3D printing and CAOS be extensively used in the development of orthopedic implants going forward.

Declaration of Competing Interests

None declared.

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Ethical approval

Not required.

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