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SVILUPPO DI UNA PROCEDURA SPERIMENTALE PER CARATTERIZZARE IL CEMENTO OSSEO ACRILICO

DEVELOPMENT OF AN EXPERIMENTAL PROCEDURE TO TEST ACRYLIC BONE CEMENT

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RIASSUNTO

Attraverso il pioneristico esperimento di Charney nel 1960 [1], il cemento osseo polimetilmetacrilato (PMMA) diventò il più diffuso materiale di fissaggio, per protesizzazione totale dei giunti articolari. Assicura un'ottima stabilità delle protesi in poco tempo dopo la polimerizzazione. Tra i vari tipi di protesizzazione cementata (spalla, gomito, anca ginocchio e caviglia) la sostituzione totale d'anca (Total Hip Replacement THR) è l'intervento più frequente [2].

Il cemento osseo crea un legame meccanico tra la componente protesica ed il tessuto osseo circostante. La sopravvivenza a lungo termine della sostituzione articolare dipende dalle proprietà meccaniche del cemento. Per questo motivo, prima di introdurre un nuovo modello di PMMA nella pratica clinica, il materiale deve soddisfare i requisiti descritti nella ISO 58333

Comunque, risultati clinici dimostrano che le prove meccaniche richiesti dalla normativa ISO non predicono le prestazioni a lungo termine del cemento [3]. L'inconsistenza degli attuali test di validazione pre-clinica è legata alla limitazione dei protocolli definiti per le prove meccaniche statiche, i.e. prove a compressione e flessione. Infatti, prove meccaniche dinamiche potrebbero essere maggiormente rappresentative delle condizioni di carico causate dalle attività fisiologiche quotidiane del paziente [4].

Numerosi studi sono stati pubblicati in passato, riportando proprietà dinamiche (fatica, resistenza a frattura, propagazione delle crepe a fatica) di diversi cementi ossei [5]. Comunque la variabilità tra protocolli di prova e risultati rende impossibile identificare un valido metodo di predizione a lungo termine delle proprietà dei cementi. Esempi di questa variabilità sono i seguenti [5]:

- tenacità a frattura; da 1.03 a 2.32 $MPa*m^{1/2}$

- propagazione della cricca a fatica (valori delle costanti di Paris C e n); C varia da $4.03*10^{-8}$ a $9.5*10^{-4}$, e n varia da 4.71 a 9.77.

Per questa ragione lo scopo del presente progetto è stato quello di identificare una procedura sperimentale per la validazione pre-clinica del cemento osseo acrilico. L'assunzione principale fatta all'interno di questo progetto è stata quella di realizzare una completa caratterizzazione meccanica di tre cementi ossei commerciali e di confrontare i risultati ottenuti con informazioni provenienti da protocolli fisiologici *in vitro*. In fine, dopo aver confrontato tutte le informazioni ottenute dagli esperimenti con risultati clinici dei tre cementi ossei scelti (Cemex RX, Surgical Simplex P and CMW1), è stato identificato il protocollo di prova il protocollo di prova che ha mostrato le predizioni più accurate.

Il lavoro presentato in questa tesi è stato sviluppato nel Laboratorio di Tecnologia Medica del'Istituto Ortopedico Rizzoli (Bologna, Italia).

La prima parte del progetto (Capitolo 1) è dedicata alle prove condotte secondo lo standard ISO 5833. Il cemento osseo selezionato è stato testato in termini di proprietà a compressione e a flessione e i risultati ottenuti sono stati paragonati con quelli forniti dal produttore e quelli trovati in letteratura. Lo scopo è stato quello di acquisire le informazioni di base relative allo standard utilizzato.

La prima serie di prove meccaniche è stata condotta in accordo con il protocollo interno LTM. Sono state analizzate (Capitolo 2) le proprietà dinamiche i.e., la resistenza a fatica, la resistenza alla propagazione delle crepe e la resistenza a frattura, di un cemento osseo acrilico (Cemex RX). La metodologia presentata è stata applicata in una seconda fase del lavoro, dedicata al confronto dei tre cementi selezionati e all'identificazione di quale tra i protocolli presentati sia maggiormente predittivo delle prestazioni a lungo termine del cemento osseo (Capitolo 3).

Il passo successivo del progetto è stato quello di caratterizzare tre cementi commerciali usando un protocollo fisiologico per simulare le attività più critiche in termini di carico di fatica (salita e discesa delle scale, entrata ed uscita dalla macchina, entrate ed uscita dalla vasca da bagno e inciampo) (Capitolo 4). Per

controllare la stabilità dello stelo protesico sono stati misurati i micromovimenti durante la prova. L'analisi della qualità del mantello di cemento, dopo una simulazione di 24 anni di attività del paziente, ha permessola verifica del protocollo per la predizione delle prestazioni a lungo termine del cemento osseo.

È stato sviluppato un protocollo che simulasse le condizioni di polimerizzazione presenti in sala operatoria, allo scopo di verificare l'influenza del pretrattamento dello stelo femorale e dei metodi di miscela del cemento, sulla resistenza meccanica del mantello di cemento. Durante le prove la temperatura e il corrispondente tempo di polimerizzazione sono stati monitorati in differenti punti. Provini, estratti dal mantello, sono stati sottoposti a prove di flessione o fatica. Il Capitolo 5 riporta i risultati dello studio sul preriscaldamento dello stelo femorale ed i suoi effetti sulla vita del mantello di cemento sottoposto a fatica, mentre nel Capitolo 6 è stato discusso l'effetto combinato del preriscaldamento e del metodo di miscela del cemento sulle prestazioni a fatica ed a flessione.

Una applicazione pratica del progetto di validazione dei metodi di prova, uno studio preliminare sulla formulazione di un nuovo cemento, è stata svolta presso Leeds University (UK). I dettagli di questa applicazione sono riportati nell'Appendica A. Una serie di prove meccaniche sono state eseguite su PMMA addizionato con quattro diverse concentrazione di glass flakes, e con due diverse dimensioni di glass flakes. Anche l'influenza della miscelazione sotto vuoto è stata analizzata. In totale, includendo i gruppi di controllo, 18 gruppi sono stati testati a compressione (ISO 5833) e alla resistenza alla frattura per doppia torsione

In conclusione, le informazioni ottenute dagli standard ISO indicano il cemento CMW1 come avente migliori proprietà meccaniche. Al contrario, dalla prove di fatica e le simulazioni fisiologiche *in vitro*, il CMW1 risulta essere il cemento a maggior rischio di fallimento, rispetto alle altre due formulazioni selezionate. Questi risultati sono in accordo con i dati clinici. Conseguentemente, i due test presentati si sono dimostrati capaci di predire la sopravvivenza delle protesi cementate relativamente alla formulazione di cemento osseo usata.

1. Charnley, J., *Surgery of the hip-joint: present and future developments*. Br Med J, 1960. **1**(5176): p. 821-6.
2. Finerman, G.A.M., et al., *Total Hip Arhroplasty Outcomes*. 1998, New York: Churchill Livingstone Inc.
3. Nilsen, A.R. and M. Wiig, *Total hip arthroplasty with Boneloc:Loosening in 102/157 cases after 0.5-3 years*. Acta Orthopaedica, 1996. **67**(1): p. 57-59.
4. NIH, *Total Hip Joint Replacement*. NIH Consens Statement 1994 Sep 12-14; 12(5): 1-31, 1994.
5. Lewis, G., *Properties of acrylic bone cement: State of the art review*. J. Appl. Biomater., 1997. **38**: p. 155-182.

SUMMARY

Through the pioneering experiment of Charnley in 1960 [1], PMMA bone cement became the most widely utilized fixing material in total joint replacements. It assures an optimal stability of the prosthesis in short time after polymerization. Among all types of cemented joint replacements, i.e. shoulder, elbow, hip, knee and ankle, the Total Hip Replacement (THR) is the most frequent intervention [2].

As bone cement creates a mechanical bond between the prosthetics components and surrounding bone tissue, the long-term survival of cemented joint replacement depends on mechanical properties of the cement. In fact, before introducing new PMMA bone cement into clinical use, the formulation must comply with the ISO 58333 standard requirements.

However, clinical outcomes demonstrate that the requested ISO standardized mechanical tests do not predict the long-term performance of the cement [3]. The irrelevance of current pre-clinical validation is due to the limitation of defined protocols to static mechanical test, i.e. compressive and bending test. In fact, dynamic mechanical testing would be more relevant to the loading condition caused by physiological daily activity of the patient [4].

Numerous studies have been published in the past, reporting dynamic (fatigue, fracture toughness, fatigue crack propagation) properties of different bone cements [5]. However, the variability among testing protocols and results makes it impossible to identify a valid method to predict long-term outcome of the cement. Examples of this variability are as fallows [5]:

- fracture toughness; 1.03 to 2.32 $MPa*m^{1/2}$
- fatigue crack propagation constants (values of Paris constants *C* and *n*); with *C* varying from $4.03*10^{-8}$ to $9.5*10^{-4}$, and *n* changing from 4.71 to 9.77.

For this reason, the aim of presented project was to identify an experimental procedure for pre-clinical validation of acrylic bone cement. The main assumption of the project was to perform complete mechanical characterization of three commercially available bone cements and to confront obtained results with data from an *in vitro* physiological protocol. Finally, after comparing all collected data from the experimental testing with clinical outcome of the three chosen bone cements (Cemex RX, Surgical Simplex P and CMW1), the testing protocol leading to the most accurate predictions has been identified.

The work presented within this thesis was carried out in Laboratorio di Tecnologia Medica of Istituto Ortopedico Rizzoli (Bologna, Italy).

The first part of the project **(Chapter 1)** is dedicated to the tests conducted in accordance to the ISO 5833 standard. The selected bone cements have been tested in terms of compressive and bending properties and obtained data have been compared with those provided by manufactures and found in the literature. The purpose was to acquire basic information according to the standard.

The first series of mechanical tests in accordance to the internal LTM protocol have been performed. Dynamic properties i.e. the fatigue strength, the resistance to crack propagation and the fracture toughness, of an acrylic bone cement (Cemex-RX) where investigated **(Chapter 2)**. Presented methodology has been applied in later part of this work, dedicated to the comparison of three selected cements and identification, which of three applied protocols is the most predictive for long-term performance of bone cement **(Chapter 3)**.

Next step of the project was to characterize three commercially available bone cements using a physiological protocol to simulate the most critical activities in terms of fatigue loading (stair climbing and stair descending, car entry and car exit, bathtub entry and bathtub exit, and stumbling) **(Chapter 4)**. To monitor stem stability, micromotions were measured during the test. Analysis of the quality of the cement mantle after simulation of 24 years of a patient's activities permitted the verification of a protocol, to predict the long-term performance of bone cement.

To verify the influence of stem pretreatment and cement mixing methods on mechanical strength of the cement mantle, a protocol simulating the surgical curing conditions has been developed. During curing, temperature and corresponding time were monitored at different locations. Specimens, extracted from the mantles, underwent bending or fatigue tests. **Chapter 5** reports results of the study on the effect of stem preheating on the fatigue life of cement mantle, while in **Chapter 6** an effect of both, stem preheating and mixing method on bending and fatigue performance of cement has been discussed.

As a practical application of the project on validation of testing methods, a preliminary study on developing a new cement formulation was carried out at Leeds University (UK), the details of which are reported in **Appendix A**. A series of mechanical tests were performed on PMMA with addition of four different glass flakes concentration, and with two different flake sizes. The influence of vacuum mixing has been investigated. In total, including reference groups (or control groups/samples), 18 groups were tested for compression (ISO 5833) and double-torsion fracture toughness.

To conclude, data obtained from standard ISO test shows the best mechanical properties for CMW1 bone cement. While, from complex fracture characterization and physiological *in vitro* simulation, the CMW1 results as cement with the highest failure risk, respect to two others selected formulations, which is in accordance with the clinical data. Consequently, those two tests are able to predict the survival of a cemented prosthesis in dependence on used bone cement formulation.

1. Charnley, J., *Surgery of the hip-joint: present and future developments.* Br Med J, 1960. **1**(5176): p. 821-6.
2. Finerman, G.A.M., et al., *Total Hip Arhroplasty Outcomes*. 1998, New York: Churchill Livingstone Inc.
3. Nilsen, A.R. and M. Wiig, *Total hip arthroplasty with Boneloc:Loosening in 102/157 cases after 0.5-3 years.* Acta Orthopaedica, 1996. 67 (1): p. 57-59.
4. NIH, *Total Hip Joint Replacement.* NIH Consens Statement 1994 Sep 12-14; 12(5): 1-31, 1994.
5. Lewis, G., *Properties of acrylic bone cement: State of the art review.* J. Appl. Biomater., 1997. 38: p. 155-182.

I INTRODUCTION

1.1 PMMA based bone cement

The majority of bone cements currently available on the market are based on poly(methyl methacrylate) (PMMA), where the monomer of methyl mathacrylate (MMA) is an ester of methacrylic acid.

Studies on methacrylic acids began more than 80 years ago in Tübingen (Germany), when Otto Röhm was given the topic of "polymerization products of acrylic acid" for his thesis. Later, based on his research, he founded a company (Röhm and Haas) for the development of acrylates [1]. Following, the establishment of a large number of technical synthesis techniques for MMA (by 1928), a new application was found for it in denture production. In 1935 Bauer patented this technique.

In 1936 the company Kulzer had discovered that mixing the PMMA powder with MMA liquid produces a dough, which became stiff if benzoyl peroxide (BPO) is added and the mixture is heated to 100^{o}C. In this way the first clinical use of PMMA mixture (Paladon 65) was developed for close cranial defects in humans. Prefabricated plates of PMMA, made under laboratory conditions, were adjusting by surgeons during the surgery [1].

Since chemists found that the polymerization process of MMA occurs at room temperature if a co-initiator is added, the companies Degussa and Kulzer established a protocol for the chemical production of PMMA bone cements in 1943. They used tertiary aromatic amines as the co-initiator. Thus, the defined procedure is valid until today, and it should be considered as the birth of PMMA based bone cement.

Upon the last 60 years about 70 types of bone cements have been produced.

Some of them have already been withdrawn from the market, others are used only in certain countries or play a minor role in clinical use. They can differ from each other by the chemical composition of the base mixture i.e. polymers molecular weight and concentration of accelerator and/or initiator. Moreover, they differ in the included additives e.g. barium sulfate or zirconium dioxide (as radiopaque medium), Na-fluoride, antibiotics, antiblastics, ethylene-oxide (sterilization), chlorophyllin (dye) or mechanically reinforcing particles (carbon fibers, glass fibers) [2] [3, 4]. Each change in composition of final bone cement mixture will influence its viscosity, working time, setting and in effect mechanical properties of the polymerized bone cement bulk [5-8].

Nowadays, PMMA based bone cements are widely used in surgery for the augmentation of fractured tissue (vertebroplasty and kyphoplasty) and dentistry, but more frequently as a fixing material that provides transmission of mechanical loading from the prosthesis to the bone. Generally, the application of cemented prosthesis is recommended when tissue surrounding an implant is too fragile/weak to support the load generated during physiological activity of the patient, e.g. patients with osteoporosis [9, 10].

1.2 Biocompatibility

The reaction of the tissue to PMMA bone cement, was the essential question just after Charnley developed his implantation technique. The extensive study of Hullinger [11] proved the biocompatibility of hardened PMMA. Also, Lehmann and Jenny [12] in their study with cell cultures have shown that PMMA did not cause any cytotoxic reactions. Further studies have shown, that cell reaction to PMMA is associated with particle size and it is not a specific immune response [10, 13]. However, the investigation of biocompatibility is not part of the scope of this thesis.

1.3 Cemented Total Joint Replacements

The PMMA based bone cement is widely used in Total Joint Replacements (TJR). Annually, over 1 mln of implantation procedures is performed worldwide, considering all types of joint replacements. More than 50% of the total TJR are the procedures of total hip arthroplasty [14]. Second, less numerous but also very common reconstructive procedure is total knee arthroplasty, followed by replacements of the ankle and shoulder.

The survival of joint reconstruction depends on many factors (infections, wearing, aseptic loosening, dislocations, fractures). Critical factors responsible for failure of the prosthesis can differ in dependence on type of the joint, e.g., wearing in knee replacements or implant design in ankle replacements. However, for the most frequently reconstructed joint, i.e. the hip, aseptic loosening results as the most critical factor leading to the revision [15, 16]. For that reason, this study is dedicated to problems related with cemented total hip arthroplasty.

1.4 Total Hip Arthroplasty: indication for surgery

The hip joint is one of the most severely loaded joints in the human body, designed for many different types of movement. It consists of the head of the femur, which is shaped like a ball; and a part of the pelvic bone called the acetabulum, which looks like a hollow or socket (Fig.1).

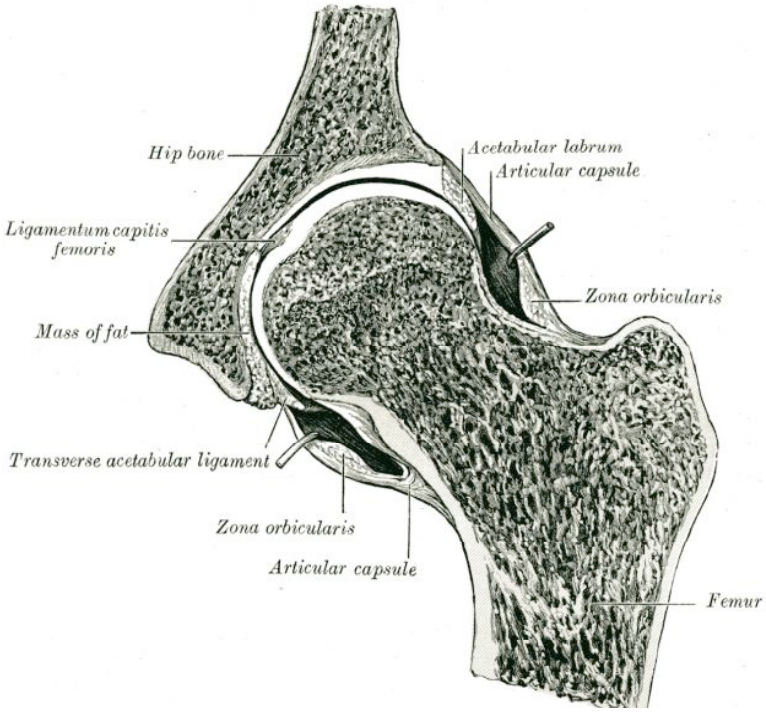

Fig.1 Section of the hip joint.

In a healthy hip joint, a layer of cartilage lies between the head of the femur and the acetabulum. The cartilage keeps the bony surfaces from grinding against each other, and allows the head of the femur to rotate in different directions inside the socket formed by the acetabulum. This is the natural range of motion, as well as the ability of the hip permit to support the weight of the upper body, but these can be gradually lost when the hip joint deteriorates. The prostheses that are used in hip replacement surgery are intended to restore as much of the functioning of to the hip joint as possible. The level of function in the hip after the surgery depends in part on the reason for the damage to the joint.

Disorders and conditions that may lead to the need for hip replacement surgery include [9]:

- Osteoarthritis (OA). Osteoarthritis is a disorder in which the cartilage in the joints of the body gradually breaks down, allowing the surfaces of the bones to rub directly and wear against each other (FIG). Eventually the patient experiences swelling, pain, inflammation, and an increasing loss of mobility.

OA effects appear most often in adults over the age of 45, and is thought to result from a combination of wear and tear on the joint, lifestyle, and genetic factors.

- Rheumatoid arthritis (RA). Rheumatoid arthritis is a disease that begins earlier in life than OA and affects the whole body. Its symptoms are caused by the immune system's attack on the body's own cells and tissues.
- Trauma. Damage to the hip joint from a fall, automobile accident, or workplace or athletic injury may trigger the process of cartilage breakdown in the hip joint.
- Avascular necrosis. Avascular necrosis, which is also called osteonecrosis, is a disorder caused by the loss of blood supply to bone tissue. Bone starved for blood supply becomes weak and eventually collapses. The most common reasons for loss of blood supply include trauma, the use of steroid medications, certain blood disorders, and alcoholism.
- Ankylosing spondylitis (AS). Ankylosing spondylitis is a less common form of arthritis that primarily affects the bones in the spine and pelvis. These bones gradually fuse together when the body replaces inflamed tendons or ligaments with new bone instead of elastic connective tissue.

1.5 Cemented Total Hip Arthroplasty: cementing techniques

The first surgery to anchor the femoral head prosthesis in the femur with auto-polymerizing PMMA was successfully performed by Charnley in 1958 [17]. In 1962 he introduced a new technique of total hip joint replacement using a stainless steel ball mounted on a stem that was inserted into the bone to replace the femoral head. A high-density polyethylene socket was fitted into the acetabular side of the joint. Both parts of the Charnley prosthesis fixed to their respective sides of the joint with an acrylic polymer cement. Soon, his totally innovative surgical method using modular implants found many enthusiasts among surgeons and researchers. More recent

developments include the use of cobalt chrome or titanium alloys or ceramic materials in place of stainless steel.

1.5.1 Bone preparation

Bone preparation is critical for long-term survivorship of both the cemented stem and the cup [9]. The aim is to provide a clean, stable bony bed for cement interdigitation into the remaining cancellous bone and to maintain stable interfaces between the implant and cement, and the cement and the bone. Most investigators would agree that a surgeon should remove all loose cancellous bone but leave the remaining dense bone nearest to the cortex to enhance interdigitation of the cement into the remaining bone. This increases the shear strength of the cement and gives the best contact of the cement mantle to the remaining bone stock. Reaming with cylindrical or tapered reamers in the femur is often performed to remove the loosest bone but should be done by hand to leave a residuum of cancellous bone. It is important not to ream away all cancellous bone, as this will leave a smooth inner cortex and decreases the ability for the cement to bond to the bone [9].

Some implant systems are designed to be reamer-less and all bone preparation is meant to be done by a broach. Broaching, which compacts the bone rather than removes it as a reamer does, is an important step in the femoral preparation. The broaches, which in many systems are also used for sizing and trialing of the femoral implant, create a reproducibly larger envelope of 2 mm to 3 mm circumferentially around the stem. This allows for a uniform thickness of the cement mantle around the stem. Aggressive broaching should be avoided to prevent denuding of the inner cortical bone. Plugging the femoral canal improves the ability to pressurize the cement and limits the size and extent of the cement column. This increases the uniformity of the cement column.

1.5.2 Lavage

Once the bony bed has been broached, the cancellous bone compacted, and the canal plugged, the bone must be cleaned. Pulsative lavage has been shown to be an effective means of removing further loose bone and fat content [18, 19]. This step has

been shown to increase penetration of cement into the bone and has been considered critical in achieving an adequate cement interdigitation.

Brushing the canal has not been shown to have any added value [18]. Once the bone has been cleaned, it should appear white, signifying that most blood and fat have been removed. Several authors believe that the bone should be dried to maintain this clean, white state [20]. This can be achieved by using either hypotensive anesthesia or dilute epinephrine, or hydrogen peroxide mixtures. Frequent and regular drying of the canal with sponges will keep the field clean and dry. The drier the bone, the better the interdigitation and microlock of the cement to the bone.

1.5.3 Cement mixing

The cement can be mixed once the bone preparation has occurred. It has been shown that certain mixing methods can decrease cement porosity and fume exposure and influence mechanical properties of the cement mantle (see chapter 5 and 6) [21-23]. Porosity reduction has been well documented to increase tensile and fatigue strength in the cement, increasing the cement's longevity (see chapter 5) [24, 25]. The newer mixing systems are more user-friendly than the older mixing systems that were uncomfortable to use.

1.5.4 Stem centralizers

Centralization has been shown to increase the likelihood of long-term success on the cemented femur. Both proximal and distal centralizers, which are now considered part of third-generation cement technique, are widely used as they have shown an increased ability to maintain a more uniform circumferential cement mantle around the stem [26]. Consistently placing the stem in the center of the cement mantle has been shown to be a basic goal of cement technique; centralizers are important to enable the surgeon to achieve a reliable stem location.

1.5.5 Cement delivery

Although digital packing of the cement has been associated with a good deal of voids and cement mantle defects, the use of a caulking gun and the concept of

retrograde filling of the canal have been instrumental in improving the cement technique [27, 28]. A surgeon must ensure that the tip of the cement gun is placed at the tip of the plug so that the cement column begins directly on the tip of the plug and then, with steady pressure on the handle, a surgeon should allow the cement column itself to gently force the gun's syringe back out of the bone.

It is important to avoid the common mistake of having the cement migrating proximally while it is being introduced around the syringe. Removing the syringe from this type of a cement column leaves a defect in the mantle. The timing of cement introduction depends upon the type of cement being used. The doughier (fast setting) cements must be introduced right away and sometimes cannot be used with a gun because of the resistance generated by the cement.

The lower viscosity cements must be placed later in their setting cycle to avoid the cement running out of the canal and leaving retained cement around the joint. The ideal time for cement introduction is when the cement is just becoming doughy with a dull appearance and not sticky. The cement guns consistently deliver cement at pressures that can decrease the chances of blood mixing with the cement at the bone-cement interfaces and have been shown to decrease the incidence of air voids.

1.5.5 Cement pressurization and stem insertion

Once the cement column has been applied, it should be pressurized to further increase interdigitation and microlock. This can be accomplished by placing the thumb over the top of the canal and manually pressurizing the cement or by applying a cone or disk to the cement gun to improve proximal pressurization. This method has been shown to generate pressures >30 mm Hg in the proximal cement mantle [18, 26, 29]. When the cement has been pressurized, the stem is ready to be inserted. It is essential that the stem be inserted accurately into the envelope, which had been created by the broach. Cement mantle thickness is important. Although the ideal thickness is the subject of debate, it has been shown that stems with a 2 mm to 5 mm medial mantle had the best outcome and that 3 mm to 4 mm cement mantles appear to have the best stress curves [30-32]. The stem should be centrally aligned in the canal. A stem introducer, which can control the version of the stem while it is being

introduced, is a helpful tool. The optimal time for stem insertion is when the cement is in a slightly doughy shape as this has been associated with the best cement penetration [33]. Gentle steady manual pressure should be applied with version controlled by an inserter. It is imperative to hold both the leg and implant in place while the cement cures to avoid the creation of cement voids. All excess cement can be removed at this time.

1.6 Long-term stability of cemented THA

Application of cemented THA improved incredibly the quality of patients' life upon the last few decades. Only in Sweden, between 1979-2006 for 256520 primary total hip arthroplasty up to 96% were cemented. Due to the developed research on PMMA material properties and studies on bone cement with antibiotic release, long-term survival increased significantly. Yearly revision rates for cemented hip implants decreased to 7% per year, while it is higher for uncemented prostheses (ca. 13%) [15].

Unfortunately, like all surgical intervention on the human body and insertion of artificial materials into it, hip prosthesis implantation brings many risks. There are two groups of complications that can occur after a THA [10, 14]:

- Early complications (within few weeks after primary THA) i.e., primary infections, fractures, nerve injuries, dislocations, deep vein thrombosis and pulmonary embolism and wound complication
- Late complications (more than 2 month after primary THA) i.e., deep/secondary infections, heterotopic ossification, aseptic loosening.

An important cause for failure of cemented THA is biologic loosening due to two factors. First, thermal necrosis of surrounding bone tissue, affecting blood circulation and increase predisposition to formation of fibrous membrane at the cement-bone interface [34]. Rising temperature of polymerizing bone cement registered in vivo is between 67-124^{0}C, depending on the formulation [35]. Second, is a chemical necrosis due to the release of an unreacted monomer (MMA) [36].

1.7 Aseptic loosening

Although, the most frequently complication for cemented THA is aseptic loosening. Following The Swedish Hip Registry, for 21 519 cases of first revisions (where 83.1% are cemented THA), reported between 1979-2006 in Sweden the 74% are caused by aseptic loosening [15].

There are many factors involved in aseptic loosening of cemented arthroplasty e.g., interfacial failure, bond failure, bone remodeling and cement failure, porosity and stem-cement fretting [37-39]. The primary failure mechanism of cement mantle in vivo is fatigue, which is derived by the application of dynamic, repeated loads during daily activity [40, 41]. In that way, PMMA debris inducted by mantle fragmentation and/or fretting at stem-cement interface can generate a biological reaction, which accelerates bone destruction [13].

Currently, there is only one consensus among researchers, that mechanical failure of the cement at any of three so called weak-link zones (implant-cement interface, cement mantle, cement-bone interface) is critical for long-term survival of cemented prosthesis [38, 40, 42, 43]. Hence, it is of great importance to test the mechanical properties of bone cements under standardized conditions.

1.8 Physical and mechanical properties of bone cement

To create uniform and reproducible testing bases for PMMA bone cements, in 1976 American Society for Testing and Materials (ASTM) began the establishment of a standard. Based on this, a shortly afterwards, the first version of ISO 5833/1 (1979) was developed. Nowadays, before introducing new bone cement into the market, it must comply with the present ISO 5833 standard, established in 2002.

However, upon the last few decades, some alternative testing protocols have been developed, so material scientists have a greater number of testing methods at theirs disposal. There are several static tests (compressive, bending, tensile) that can be performed in different environments (Ringer solution, buffered phosphate

solution, room or body temperature, etc.), or at different times after polymerization. In addition, dynamic tests are possible (e.g. tensile fatigue test, fatigue crack propagation, etc.), which predict the long-term resistance of the material, these require the application of 5-10 millions alternating loads with a frequency of 3-5Hz [44-46]. Unfortunately, possible variability of testing protocols, samples storage, data presentation amongst different research group makes the comparison of theirs results difficult [46].

Comparative studies of various bone cements that have been published in the past, frequently deal only with a few parameters. The study of new cement compared with well known old bone cement as a reference (e.g. Palacos R), is a very popular method, but often only highlights certain benefits of the chosen cement. For example, Kindt-Larson et al. [47] made a detailed comparison of Boneloc, newly developed bone cement, and four other bone cements available in U.S. market. From mechanical tests performed on Boneloc and other bone cements in accordance to ISO 5883, Boneloc performed best. But, following its clinical introduction , it had to be withdraw from the market after only 2 years of follow-up [48-50].

That example shows the other existing problem. Namely, that case characterization of new bone cement based only on ISO 5833 standards was insufficient and not predictive of clinical performance. To avoid such mistakes in the future, it is of great importance to create a basis for valid tests for all cements by revising the standards.

1.9 Weak points of current standards

Clinical outcome of cemented prostheses shows that existing standard tests established to characterize mechanical properties of PMMA bone cement are not able to predict long-term performance of the cemented implantation. This lack of relevance of pre-clinical validation tests is due to limitations of the standardized test to static loading conditions (ISO 5833), while cement mantle during normal daily activity of patients is subjected to complex cycling loading. In the literature dedicated

to bone cement mechanical characterization, a large-volume of data on dynamic performance, i.e fatigue limit, fatigue crack propagation, fracture toughness, can be found [46, 51]. However, the variability of protocols for determining those properties and treatment of the results does not permit the selection of a valid and relevant procedure for pre-clinical prediction of long-term performance of bone cement.

1.10 Aim

The aim of this project was to develop a testing protocol able to predict the long-term performance of an acrylic bone cement.

Therefore, three commercially available bone cements has been chosen in dependence on theirs clinical outcome. Afterward, a complete characterization of chosen bone cements was performed, in terms of:

- mechanical properties required by ISO 5833
- fracture characteristic: fatigue endurance limit, fatigue crack propagation and fracture toughness tests
- long-term physiological-like performance: an in vitro simulation of loading spectrum that replicates all critical physiological activities.

Finally, data were collected and compared with clinical outcome to identify the most predictive mechanical test for long-term performance of bone cement.

To investigate the influence of stem pretreatment and cement mixing method on mechanical cement mantle properties, an *in vitro* protocol for cement mantles molding had to be developed. Fatigue and bending properties of specimens retrieved from an *in vitro* cement mantle were investigated using one of selected bone cements (Surgical Simplex-P).

1.11 Bone cements investigated within the project

Referring to the availability of bone cement formulation and data regarding clinical outcome, three cement formulation (listed in table 1) have been chosen for entire project.

Table 2- Chemical composition of selected bone cements [1], where:
PMMA - poly(methylmethacrylate), **MMA** - methylmetacrylate **DmpT** - N,N-dimethyl-p-toluidine**,**
$BaSO_4$ - barium sulphate as opacifier **HQ** - hydroquinone as stabilizer, **BPO** - benzoyl peroxide

Trade name (manufacture)	Composition of polymer	Additives	Viscosity type
Cemex RX, (Tecres SpA, Sommacampagna, Italy)	polymer powder (40g): 88.25% PMMA, 3% styrene, 2.75% BPO monomer liquid (13.30g): 99.1% MMA, 0.9% DmpT and 75 ppm of HQ	9% $BaSO_4$	low
Surgical Simplex P[11], (Stryker-Howmedica, Howmedica International, Limerick, Ireland)	polymer powder (40g): 15% PMMA, 75% MMA-styrene copolymer 3% styrene, 1.5% BPO monomer liquid (18.79g): 97.4% MMA, 2.6% DmpT and 80 ppm of HQ	10% $BaSO_4$	medium
CMW1, (DePuy Internationa Ltd., Blackpool,UK)	polymer powder (40g): 88.85% PMMA, 2.05% BPO monomer liquid (18.37g): 99.18% MMA, 082% DmpT and 25 ppm of HQ	9.1% $BaSO_4$	high

First two cement types (Cemex-RX and Simplex-P) have a documented extremely positive clinical outcome [52, 53]. They were chosen to represent a successful cement types in this study. Including two cement types having comparable clinical outcome enable assessing if the *in vitro* protocol yielded consistent results.

The third cement type (CMW1) has a negative clinical outcome [52, 54]. It was chosen to represent a cement type with poor performance in this study. Including this cement type in the study enabled assessing, in comparison against the other two

types, the ability of the *in vitro* protocol to discriminate between cement types having different clinical outcome.

In order to minimize the influence of additional ingredients (e.g. antibiotics or different radio-opacifiers), all bone cements chosen included $BaSO_4$ as the only additive.

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II CHARACTERIZATION OF STATIC MECHANICAL PROPERTIES (ISO 5833): A COMPARATIVE STUDY ON THREE COMMERCIAL BONE CEMENTS

2.1 Introduction

The bone cements, before being introduced to the clinical use must comply within present ISO 5833 (2002) standards. Several studies comparing mechanical properties obtained in accordance to ISO standards for various bone cements have been published in the past [1]. However, even though ISO 5833 obliges, users often have great difficulty in reproducing the specifications on the material properties given by differ researchers and/or manufacturer. The variability of obtained results can be due to the factors like storage temperature of cement formulation prior to mixing and mixing method and manual skills of the user.

The purpose of this study was to acquire necessary skills to guarantee reproducibility of specimens' fabrication in later steps of the whole project. For this reason a series of mechanical tests based on ISO 5833 was performed. Three bone cements selected for this project have been compared in terms of compressive and bending properties.

2.2 Material and methods

Three commercial bone cements were investigated: Cemex RX, Surgical Simplex P and CMW1. All bone cements were storied at least for 24h in 23^0C prior to mixing process. Two testing group were performed, first for compressive test, and second four-point bending test. For both compressive and bending cement formulation were mixed in air.

Specimens preparation, aging and test environment condition were in accordance with ISO 5833 (2002). In total for each cement formulation 12 specimens for compression and 12 for bending test were exanimate. The Chauvenet's criterion has been applied to exclude the outliers.

2.3 Results

Obtained results from compressive test and four-point bending have been presented adequately in Table1 and Table2.

Table 1- Compressive mechanical properties of three commercial bone cements. Relevance with the literature: * Kühn K.D. [1], **Hansen, D.; Jensen, J. S., [2]

	Ultimate compressive strength (MPa)			
	Cemex-RX	Surgical Simplex-P	CMW1	ISO limit
AV	103	98	86	70
SD	1.5	2.8	2.5	-
Ref. AV	92.2*	100**	87**	-

Table 2- Results of four-point bending test and correspondence with data from literature. Relevance with the literature: *Baleani et al., [3], **Weber et al., [4], *** Hansen, D.; Jensen, J. S., [2], **** Kühn K.D., [1]

	Ultimate bending strength (MPa)				**Elastic modulus (MPa)**			
	Cemex-RX	Surgical Simplex-P	CMW1	ISO limit	Cemex-RX	Surgical Simplex-P	CMW-1	ISO limit
AV	58	53	64	50	2503	2460	3027	1800
SD	3.6	5.1	7.2	-	111	135	19	-
Ref. AV	60*	52.7**	64***	-	2441****	2290**	2700***	-

2.4 Discussion

The purpose of this study was to acquire necessary skills to guarantee reproducibility of specimen fabrication in later steps of the whole project. For this reason a series of mechanical tests based on ISO 5833 was performed. Three bone cements selected for this project have been compared in terms of compressive and bending properties.

Obtained results are in correspondence with data found in literature. Existing small differences between our results and previously published data can be due to differences in bone cement storage, mixing time or environment (polymerization of acrylic cements is extremely sensitive even to negligible variation of mentioned factors). The results obtained through testing protocol defined in ISO 5833 standards, indicated CMW1 as the cement type with the best bending strength, comparing with two other cement types. This observation is opposite to clinical outcomes [5]. That experiment confirms the hypothesis that additional testing methods need to be defined in ISO standards to validate pre-clinically new cement brands.

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III FRACTURE PROPERTIES OF AN ACRYLIC BONE CEMENT

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3.1 Abstract

This study investigated experimentally the fracture properties, i.e., the fatigue strength, the resistance to crack propagation and the fracture toughness, of an acrylic bone cement (Cemex RX). The mean endurance limit was determined following the staircase method. The endurance limit was estimated at 9.2 MPa. The fatigue crack propagation rate was measured according to the ASTM E647 standard. The equation of the line fitting the crack growth per cycle (da/dN) versus the stress-intensity factor range (delta K), in a log-log graph, was used to calculate the empirical constants of Paris' law for the selected bone cement: a/dN (m/cycle) = 3.56 x 10 (-7) x delta K (MPa x m1/2) 5.79. This power-law relationship described well (R2 = 0.96) the growth rate in the stable crack growth region, i.e., in the mid delta K range. The fracture toughness K(IC) of the bone cement was determined according to the ASTM E399 standard. The K(IC) mean value was 1.38 MPa x m1/2. These experimental results provide the set of necessary inputs for numerical studies aimed to investigate the damage accumulation process in the mantle fixing cemented prostheses.

Keywords

Biomaterials – Cement – Fracture properties – Fatigue - Fracture toughness

3.2 Introduction

Polymethylmethacrylate (PMMA) based bone cement is the most common, commercially available material used in the orthopaedic field to fix cemented prostheses to the hosting bone. The use of PMMA assures an optimal implant stability after the surgical session which should be guaranteed for the entire implant life.

Clinical data from Swedish Total Hip Replacement Register show that aseptic loosening has caused nearly 60% of the failures in cemented implants during the last 26 years [1]. Many causes may contribute to the complex phenomenon which causes implant loosening. Among others, one of the potential causes for aseptic loosening is the long-term mechanical performance of the cement mantle. It has to transfers loads, generated during daily activities, from the implant to the periprosthetic tissues. Therefore, in vivo the cement mantle undergoes complex cyclic loadings. These loads cause cyclical stresses which may crumble the cement mantle [2, 3], promoting loosening of the prosthetic component [4-12].

The long-term behaviour of the cement mantle depends on the mechanical properties of the bone cement and how it is stressed in vivo [5, 13-16]. The former are characteristics of the materials itself, generally referred to as fracture properties [17]. However, the stress levels within the cement mantle are affected by prosthesis design, mantle thickness and quality, and support of the bone tissue surrounding the implant [9, 18-22]. The prosthesis-cement mantle-bone system can be investigated by means of Finite Element Models (FEMs). FEMs are used to calculate the stress within the mantle and to predict the fatigue damage under simulated physiological conditions [6, 10, 23-25]. These studies require the knowledge of the fracture properties of the bone cement.

Although there are many reports about the mechanical characteristics of bone cement [14, 26-31], a complete characterisation of the fracture properties of a commercial bone cement is missing. The aim of this study is to determine all the fracture properties, that are the fatigue strength, the resistance to crack propagation and the fracture toughness, of a PMMA based radiopaque bone cement.

3.3 Materials and methods

3.3.1 Materials and specimens preparation

Cemex RX (Tecres, Verona, Italy) was selected for this study. It is a PMMA based bone cement. A percentage of 9% barium sulphate was present in this formulation to assure the required radiopacity, as in most of the commercially available formulations of bone cements. The bone cement was mixed at a temperature of 23±1°C and at a relative humidity falling in the range of 40-60%, in agreement to ISO 5833 recommendations. The bone cement was mixed in air and, once reached the doughing time, the dough was poured into the moulds to cast the specimens of defined dimensions (see Figure 1). After 1h of polymerization specimens were stored in saline solution at 37°C for 14 days before testing. Prior to testing both sides of each specimen were polished using 800-grid sand paper to adjust the thickness to the desired value, with an accuracy of 0.1 mm. Before testing, specimens were X-ray checked, rejecting all ones with macro-porosity (pore diameter>1 mm) in the working region [17, 32]. Since this inspection was not possible for the 10 mm thick specimens, the fracture surface was examined after testing: if a macro-porosity was found on the crack surface, the specimen was discarded [31]. All the specimens were tested in air at 23±1°C on a material testing machine (MTS Mini Bionix 858, MTS System Corp., Minneapolis, MN). The frequency of cyclic loading was set to 4 Hz.

3.3.2 Fatigue testing

Fatigue tests were performed on dog-bone like specimens. The dimensions and geometry of the specimen were chosen in agreement to ISO 527-2. Working part dimensions were: length (l) 80mm, width (w) 10 mm, and thickness (t) 4 mm (figure 1).

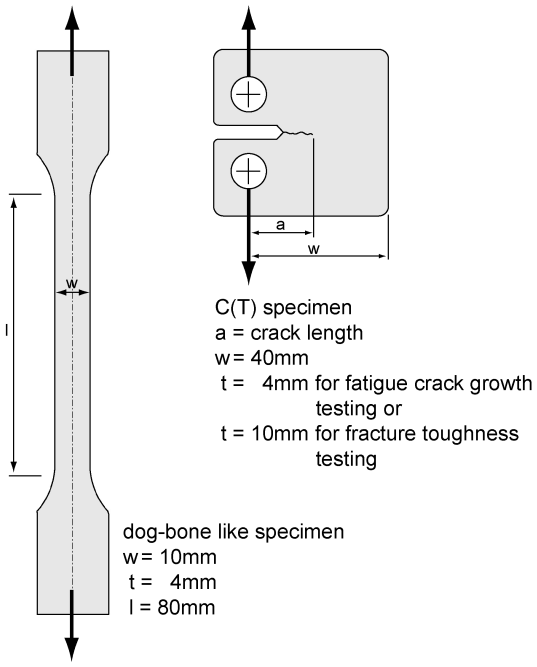

Fig.1 The dimensions of the dog-bone like specimen and the C(T) specimen. t indicates the thickness of the specimen.

Fatigue testing were performed at selected load levels until specimen fracture or runout (test completed). Runout was fixed at 10 million cycles. Preliminary testing were performed above the rough estimated endurance limit. This series continued decreasing the load level until a specimen did not fail during the test, i.e. reached 10 million cycles. At this point the up-and down scheme of the staircase method started and continued until 15 specimens were tested in the failure-not failure region. The collected data were used to determine the median endurance limit [33].

3.3.3 Fatigue crack propagation testing

The crack propagation rate was measured according to a method based on ASTM E647. Standard compact-type (C(T)) specimens were moulded. Specimen dimensions were: width (w) 40 mm, and thickness (t) 4 mm (figure 1).

A razorblade was used to produce a pre-crack in the specimen notch before subjecting the specimen to cyclic loading. A sinusoidal tensile load between 0 and 60 N was applied. Before testing, Krak Gages (Mod. B20CE, Rumul, Switzerland) were attached to both sides of the specimen to allow the measurement of the crack length (a) during the test. The number of load cycles

(N) was recorded at each crack length increment of 0.4±0.1mm. Five test repetitions were performed. A linear regression was used to fit the data, plotted in a log-log graph of the crack growth per cycle (da/dN) versus the stress-intensity factor range (ΔK). The regression equation was used to calculate the empirical constants C and n of the Paris' law ($da/dN = C*(\Delta K)^n$). This power-law relationship describes the growth rate in the stable crack growth region of the log-log graph, referred to as region II [33].

3.3.4 Fracture toughness testing

The fracture toughness was determined according to a method based on ASTM E399. Specimen dimensions were: width (w) 10 mm, and thickness (t) 10 mm (figure 1). Preliminary, the specimens were pre-cracked by applying a cyclic load. To maintain the pre-crack growth rate in the order of 10^{-3} mm/cycle, four decreasing load levels were chosen. The crack length was monitored by means of an extensometer attached to the specimen mouth. Pre-cracking was stopped when the a/W ratio fell in the range of 0.45-0.55. Then the specimen was preloaded with 100 N and subjected to a monotonic tensile test at a crosshead rate of 10 mm/min. The load and the corresponding crack opening were recorded throughout the test to calculate the critical stress intensity value, K_{IC}, according to the ASTM standard. Experimental series continued until five valid specimens were tested.

3.4 Results

3.4.1 Fatigue testing

15 specimens were tested in the failure-not failure region. Six specimens completed the test. As runout was the less frequent event, its occurrence was used to estimate the mean endurance limit. The specimen fraction not-failed at 360N was 60%, at 370N was 40%, while all specimens failed at 380N. On the basis of these experimental data, the mean endurance limit was estimated to 9.2MPa.

3.4.2 Fatigue crack propagation testing

A set of fatigue crack growth data versus stress-intensity range was collected for each specimen. All the five sets are plotted in Figure 2 together with the regression line.

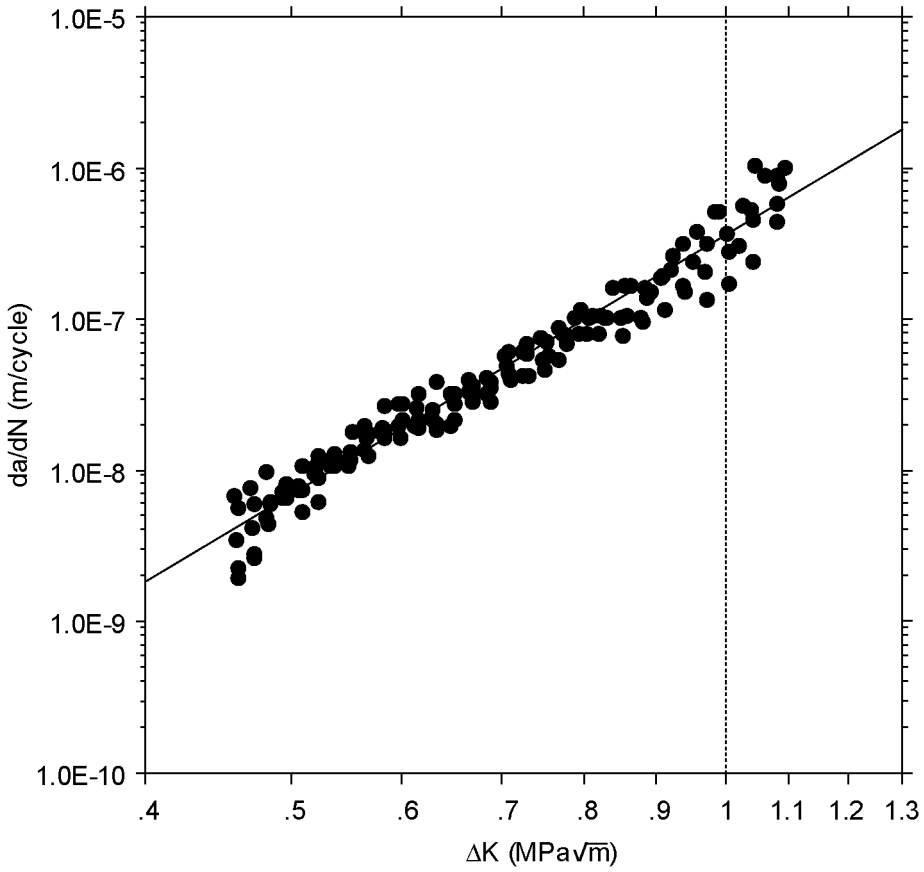

Fig.2 A linear line fitting the fatigue crack growth data for the investigated bone cement.

The coefficient of determination was R^2=0.96. From the equation of the regression line the constants C and n of the Paris' law were calculate: C=3.56*10^{-} 7 (m/cyclex(MPa * m–)$^{-n}$); n=5.79.

3.4.3 Fracture toughness testing

Seven C(T) specimens were tested. Two of these were excluded since a macro-porosity was found on the fracture surface, and therefore the K_{IC} value was not calculated from the experimental data. The K_{IC} mean value calculated for the five valid specimens was 1.38 MPa x m1/2. The coefficient of variation for K_{IC} of these five specimens was 3.6%.

3.5 Discussion

This study aimed to assess the fracture properties of a commercial, PMMA base, bone cement. The fracture properties characterise the material behaviour

under cyclic loads. These data are necessary as input parameters in FEMs investigating the damaging process in the cement mantle due to load generated during physiological activities.

The fracture properties of a bone cement may depend on chemical formulation of the material [34-37]. on the procedure to mould the specimen (i.e. on the final quality of the specimen) [38-42], and on the testing procedure [17, 43, 44]. The first consideration would require that this study should be performed for each cement formulation whose mechanical behaviour is going to be modelled in a FEM. Considering the great number of bone cement brands currently available on the market for orthopaedic applications [37], this approach is not possible. The bone cement investigated in this study was selected as 'representative' of a standard PMMA based bone cement. This formulation contains barium sulphate as radiopacifier, the most common compound added to gain material radiopacity. Barium sulphate, together with benzoyl peroxide (a polymerisation catalyser), N-N dimethyl-p-toludine (a polymerisation accelerator), and hydroquinone (a MMA stabiliser), is generally present in the bone cement formulation [37]. Referring to the quality of the specimens, all three procedures considered the specimen inspection and a rejection criterion: specimens showing macro-porosities were rejected, in agreement with that proposed by other authors [17, 31, 45]. Similarly the specimens were seasoned for 14 days before testing to assure the complete polymerisation of the material [46-48]. Last, the experimental procedures used in this study were preliminary validated [31, 32] and/or were already used by other authors to determine some of the fracture properties of a bone cement [49, 50].

On the basis of this rationale, few data reported in the literature can be compared with the present one. To the authors' knowledge, no data have been published about the crack growth rate for the investigated bone specimen. In a previous study, an estimation of 9.7 MPa for the endurance limit was reported [51]. However in that study the stress value of the slope part of the Wöhler curve corresponding to 2 million cycles was assumed as a rough prediction of the endurance limit. In this study the mean endurance limit was estimated defining the runout at 10 million cycles, therefore at a higher fatigue life. This may explain the difference of 5% between the two estimated mean endurance limits. Another study reported fatigue data for the same bone cement tested at higher stress levels

[52]. In that study the endurance limit was estimated to 12.9 MPa, although the authors stated that their procedure might overestimate the real value. Also the calculated fracture toughness was 33% lower than that reported for the same formulation by Lewis et al. [53]. In this study a fatigue-cracked C(T) specimen was tested while in the cited study the fracture toughness was determined using Chevron-notched short rod specimen obtained machining the slot but no fatigue pre-crack was reported. Therefore, the difference may be due both to the effective shape of the crack tip [31] and to the different experimental procedures [43].

Considering different cement formulations, the results found in the present study are in agreement with those reported for a not commercial bone cement, similar to the present one except for the barium percentage [54]. Not considering the important effect of the cement formulation on its fracture properties, it can be highlighted that the fracture properties measured in this study were within the range reported in the literature for PMMA based cements both for the endurance limit [27, 55] and for the fracture toughness [31, 35, 56-61], although none of the cited studies considered all the fracture properties of the bone cement.

In conclusion, the fracture properties of a PMMA base bone cement were experimentally determined. These properties are necessary inputs for any numerical studies aimed to investigate the damage accumulation process in mantles fixing cemented prostheses.

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IV FRACTURE PROPERTIES COMPARISON OF THREE COMMERCIAL BONE CEMENTS

To be submitted: *J. Appl. Biomat.*

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4.1 Abstract

The long-term endurance of the cement mantle depends on the mechanical properties of the bone cement and how it is stressed in vivo. In spite of presence of many reports describing the mechanical characteristics of bone cement, predicting their long-term performance under physiological loading condition is difficult. Existing mandatory standardized material testing protocols for bone cement (ISO 5833) only consider simple static test (bending, compression), while under physiological condition a cycling loading is applied to the cement mantle. Thus, it is necessary to define additional standardized mechanical tests for pre-clinical validation of bone cements. This study was aimed to rank three selected cement types, having diverse (well known) clinical outcome, in terms of their fracture properties (fatigue endurance limit, fatigue crack propagation and fracture toughness). The fracture properties of thee cement types were successfully determined. No significant difference was found between Simplex-P and Cemex-RX,

while CMW1 demonstrated poorer fracture resistance. Obtained data were in agreement with data found in the literature and with the clinical outcome. Proposed testing protocol, to study crack nucleation and propagation within the bone cement, can be applied to rank differ cement types according to their clinical performance. Furthermore, presented procedures can be applied to validate pre-clinically new cement formulations. New cement formulation can be compared in terms of fracture properties with other bone cements with known clinical outcome.

4.2 Inroduction

Polymethylmethacrylate (PMMA) based bone cement is the most common, commercially available material used in the orthopaedic field to fix cemented prostheses to the hosting bone. The use of PMMA assures optimal implant stability after the surgical session, which should be guaranteed for the entire implant life.

According to The Swedish Hip Registry, following 21519 cases of first revisions, where 83% are cemented THA (reported between 1979-2006 in Sweden), 74% were caused by aseptic loosening [1]. Many factors may contribute to the complex phenomenon, which causes implant loosening [2-6]. In particular, the mechanical failure of cement mantle is critical for long-term survival of cemented prosthesis [7-9]. Hence, it is necessary to validate pre-clinically mechanical properties of bone cements before introducing them into clinical use.

Although there are many reports about the mechanical characteristics of bone cement [10-13], predicting their long-term performance under physiological loading condition is difficult. Existing mandatory standardized material testing protocols for bone cement (ISO 5833:2002) only consider simple static test (bending, compression), while during normal daily activities the implantation is subjected not to a single load, but to a spectrum of loading cycles [14-16]. However, ISO 5833:2002 does not oblige manufacturers to characterize fatigue properties of bone cements.

Boneloc and CMW3 are examples of bone cement that were introduced to clinical practice after successfully passing all tests described in the ISO5833. Despite this,

Boneloc exhibited a dramatic failure rate (as high as 60% after 0.5-3 years, [17-19]). Similarly, CMW3 had a higher failure rate than most cements in use (as high as 17% at ten years [20, 21]). Such disasters are clear evidence of the inadequacy of existing standards.

Numerous studies were performed over last three decades to characterize fatigue performance of bone cement formulations [22]. However, due to variability between testing protocols and treatment of the results, it is difficult to indicate a method providing the results in agreement with clinical long-term follow-up. For example, in some studies cement types having extremely good clinical performance (Palacos-R) demonstrate lower fatigue life comparing with other cement types, clinically less successful [10, 23]. Therefore, it is necessary to define additional standardized mechanical tests for pre-clinical validation of bone cements.

The aim of this study was to rank three selected cement types, having diverse (well known) clinical outcome, in terms of their complex fracture properties (fatigue endurance limit, fatigue crack propagation and fracture toughness). For that purpose chosen cement types were tested according to previously validated protocol [24-26]. To assess predictability of the testing protocol, obtained results were compared with the clinical outcome.

4.3 Material and mathods

4.3.1 Cement type selection

Three commercial PMMA based bone cements (listed in Table 1) were selected for this study. Selection of cements types was based on their clinical outcome:

- The firs two cement types (Cemex-RX and Simplex-P) have a documented extremely positive clinical outcome [27, 28]. They were chosen to represent a successful cement types in this study.
- The third cement type (CMW1) has a negative clinical outcome [20, 27]. It was chosen to represent a cement type with poor performance in this study. Including this cement type in the study enabled assessing, in comparison

against the other two types, the ability of the *in vitro* protocol to discriminate between cement types having different clinical outcome.

In order to minimize the influence of additional ingredients (e.g. antibiotics or different radio-opacifiers), all bone cements chosen included $BaSO_4$ as the only additive.

Table1- Chemical composition of selected bone cements [29], where: **PMMA**- poly(methylmethacrylate), **MMA** - methylmetacrylate **DmpT** - N,N-dimethyl-p-toluidine **, $BaSO_4$** - barium sulphate as opacifier **HQ** - hydroquinone as stabilizer, **BPO** - benzoyl peroxide

Acronym used in the paper	Composition of polymer	Additives	Trade name (manufacture)	Viscosity type
CMW1	polymer powder (40g): 88.85% PMMA, 2.05% BPO monomer liquid (18.37g): 99.18% MMA, 082% DmpT and 25 ppm of HQ	9.1% $BaSO_4$	CMW1, (DePuy International Ltd., Blackpool,UK)	high
Simplex-P	polymer powder (40g): 15% PMMA, 75% MMA-styrene copolymer 3% styrene, 1.5% BPO monomer liquid (18.79g): 97.4% MMA, 2.6% DmpT and 80 ppm of HQ	10% $BaSO_4$	Surgical Simplex-P (Stryker-Howmedica, Limerick, Ireland)	medium
Cemex-RX	polymer powder (40g): 88.25% PMMA, 3% styrene, 2.75% BPO monomer liquid (13.30g): 99.1% MMA, 0.9% DmpT and 75 ppm of HQ	9% $BaSO_4$	Cemex RX (Tecres SpA, Sommacampagna, Italy)	low

4.3.2 Specimen preparation

All bone cements were mixed at temperature of 23±1°C and relative humidity falling in the range of 40-60%, in agreement to ISO 5833 recommendations. They were mixed in air and, once reached the doughing time, the dough was poured into the moulds to cast the specimens of defined dimensions (see Figure 1). After 1h of polymerization specimens were stored in PBS solution at 37°C for 14 days before testing. Prior to testing both sides of each specimen were polished using 800-grid sand paper to adjust the thickness to the desired value, with an accuracy of 0.1 mm. Before testing, specimens were X-ray checked, rejecting all ones with macro-porosity (pore diameter >1 mm) in

the working region [25]. Since this inspection was not possible for the 10 mm thick specimens, the fracture surface was examined after testing: if a macro-porosity was found on the crack surface, the specimen was discarded [24]. All the specimens were tested in air at 23±1°C on a material testing machine (MTS Mini Bionix 858, MTS System Corp., Minneapolis, MN). The frequency of cyclic loading was set to 4 Hz.

The Cemex-RX specimens belonged to previously published study [26], but were prepared and tested in the same manner as other two cement types.

4.3.3 Fatigue testing

Fatigue tests were performed on dog-bone like specimens. The dimensions and geometry of the specimen were chosen in agreement to ISO 527-2. Working part dimensions were: length (l) 80mm, width (w) 10 mm, and thickness (t) 4 mm (Fig.1).

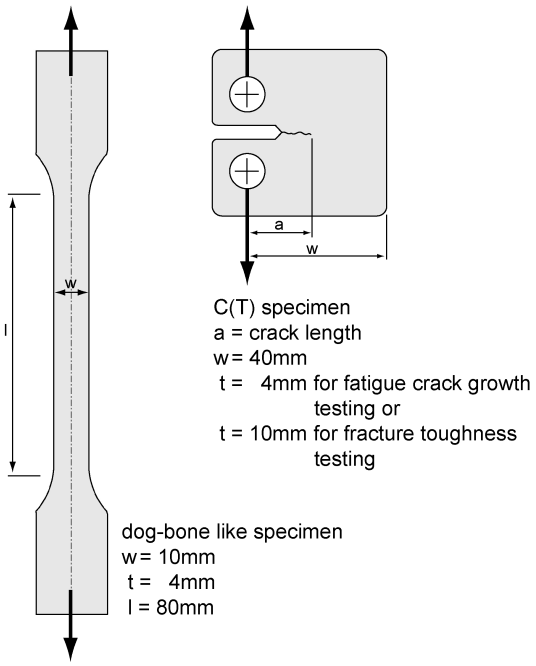

Fig.1 The dimensions of the dog-bone like specimen and the C(T) specimen. t indicates the thickness of the specimen.

Fatigue testing were performed at selected load levels until specimen fracture or runout (test completed). Runout was fixed at 10 million cycles. Preliminary testing were performed above the rough estimated endurance limit. This series continued decreasing

the load level until a specimen did not fail during the test, i.e. reached 10 million cycles. At this point the up-and down scheme of the staircase method started and continued until 15 specimens were tested in the failure-not failure region. The collected data were used to determine the mean endurance limit [30].

4.3.4 Fatigue crack propagation testing

The crack propagation rate was measured according to a method based on ASTM E647. Standard compact-type (C(T)) specimens were moulded. Specimen dimensions were: width (w) 40 mm, and thickness (t) 4 mm (Fig.1).

A razorblade was used to produce a pre-crack in the specimen notch before subjecting the specimen to cyclic loading. A sinusoidal tensile load between 0 and 60 N was applied. Before testing, Krak Gages (Mod. B20CE, Rumul, Switzerland) were attached to both sides of the specimen to allow the measurement of the crack length (a) during the test. The number of load cycles (N) was recorded at each crack length increment of 0.4±0.1mm. Five test repetitions were performed. A linear regression was used to fit the data, plotted in a log-log graph of the crack growth per cycle (da/dN) versus the stress-intensity factor range (ΔK). The regression equation was used to calculate the empirical constants C and n of the Paris' law ($da/dN = C*(\Delta K)^n$). This power-law relationship describes the growth rate in the stable crack growth region of the log-log graph, referred to as region II [30].

4.3.5 Fracture toughness testing

The fracture toughness was determined according to a method based on ASTM E399. Specimen dimensions were: width (w) 10 mm, and thickness (t) 10 mm (figure 1). Preliminary, the specimens were pre-cracked by applying a cyclic load. To maintain the pre-crack growth rate in the order of 10^{-3} mm/cycle, four decreasing load levels were chosen. The crack length was monitored by means of an extensometer attached to the specimen mouth. Pre-cracking was stopped when the a/W ratio fell in the range of 0.45-0.55. Then the specimen was preloaded with 100 N and subjected to a monotonic tensile test at a crosshead rate of 10 mm/min. The load and the corresponding crack opening were recorded throughout the test to calculate the critical stress intensity value, K_{IC},

according to the ASTM standard. Experimental series continued until five valid specimens were tested.

4.4 Results

4.4.1 Fatigue testing

15 specimens were for all cement types. The mean endurance limit estimated on the basis of experimental data was: 9.2MPa for Cemex-RX, 9.1MPa for Surgical Simplex-P and 8.4MPa for CMW1. The differences between cement types were rather of small significance (ANOVA test, $p=0.03$). No significance was observed between Cemex-RX and Simplex-P (Scheffe's test, $p>0.05$), while for CMW1 the mean endurance limit was decidedly lower (Scheffe's test, $p=0.04$-0.048).

4.4.2 Fatigue crack propagation testing

A set of fatigue crack growth data versus stress-intensity range was collected for each cement type. All data sets are plotted in Fig.2 together with the regression lines.

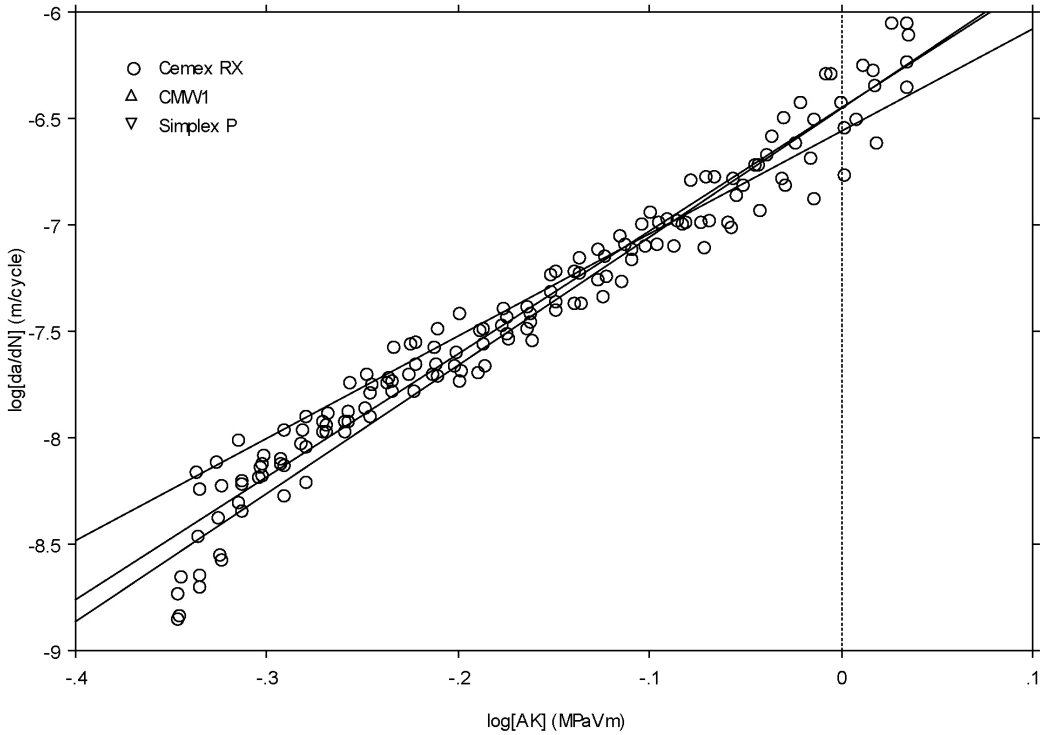

Fig.2 A linear line fitting the fatigue crack growth data for the investigated bone cements.

The estimated coefficients of determination, R^2, calculated for the Cemex-RX, the Simplex-P and the CMW1were 0.96, 0.94 and 0.90, respectively.

Insignificant difference was found in the crack growth rate regression slope and intercept of the Cemex RX versus Simplex P (t-test, $p>0.05$). While, the CMW1 was statistically different (t-test, $p<0.001$) when compared with the slope values calculated for the Cemex-RX and Simplex-P bone cement. From the equation of the regression line the constants C and n of the Paris' law were calculate (Table 2):

Table 2- Fatigue crack propagation rate results: values of Paris constants C and n.

Cement type	C	n
Cemex-RX	3.55E-07	5.77
Simplex-P	3.52E-07	6.02
CMW1	2.74E-07	4.81

No statistically significant difference was found in the crack growth rate regression intercept of the Cemex-RX and Simplex-P versus CMW1 (t-test, $p>0.05$).

4.4.3 Fracture toughness testing

The C(T) samples were tested to obtain five valid specimens for each cement type. The K_{IC} mean value calculated for the five valid specimens was 1.38+/-0.05, 1.39+/-0.03 and 1.31+/-0.06 MPa x m1/2 for Cemex-RX, Simplex-P and CMW1 respectively. The negligible difference was found between Cemex-RX, Simplex-P and CMW1 (ANOVA test, $p=0.05$).

4.5 Discussion

The long-term behaviour of the cement mantle depends on the mechanical properties of the bone cement and how it is stressed in vivo [14-16]. Although, there are many reports describing the mechanical characteristics of bone cement [10-13, 24], predicting their long-term performance under physiological loading condition is difficult. Existing mandatory standardized material testing protocols for bone cement (ISO 5833) only consider simple static test (bending, compression), while under

physiological condition a cycling loading is applied to the cement mantle [14-16]. Thus, it is necessary to define additional standardized mechanical tests for pre-clinical validation of bone cements. This study was aimed to rank three selected cement types, having diverse (well known) clinical outcome, in terms of their fracture properties (fatigue endurance limit, fatigue crack propagation and fracture toughness).

Cement types used in this study were selected regarding their clinical outcome: Cemex-RX and Simplex-P were chosen because of their positive clinical performance [27, 28], while CMW1 has documented poor long-term in vivo survival [20, 27]. The experimental procedures used in this study were preliminary validated [24-26]. Referring to the quality of the specimens, all three procedures considered the specimen inspection and a rejection criterion: specimens showing macro-porosities were rejected, in agreement with that proposed by other authors [24, 25].

No statistical differences have been found between Cemex-RX and Simplex-P in their fracture properties. This observation is in agreement with the positive clinical follow-up of both cement [21, 27, 28] and wit previously published mechanical data [10, 11, 24, 31]. On the other hand, CMW1 demonstrated poorer clinical survivorship [21, 27, 28] and fracture properties [10, 23].

Obtained results confirm study of Harper et al. [10], where differ cement types were ranked, using fatigue testing protocol. In fact in, in this study has been found that Simplex-P has significantly better fatigue performance than the CMW1. Additionally, they proved that Boneloc (having dramatic failure rate in clinical follow-up), has the lowest fatigue resistance comparing with all cement types. However, the method proposed by Harper et al. considered fatigue testing performed under stress control, using sinusoidal loading in tension-tension, with only single upper stress level of 22MPa. In consequence, only Weibull mean number of stress cycles to fracture was determined (for single stress level). In theirs study, no range of cyclic stress was defined, which can be applied to the material without causing fatigue failure for certain fatigue lifetime. Conversely, in this study the mean endurance limit was estimated, defining the runout at 10 million cycles (simulating 10 years of gait cycles).

In conclusion, the fracture properties of thee cement types were experimentally determined. Obtained data are agreement with data found in the literature and with the clinical outcome. Proposed testing protocol, aimed to study crack nucleation and propagation within the bone cement, can effectively different rank cement types according to their clinical performance. Furthermore, presented procedures can be applied to validate pre-clinically new cement formulations. A new cement can be compared in terms of fracture properties with other bone cements with known clinical outcome.

4.6 Acknowledgement

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V EFFECT OF LONG-TERM PHYSIOLOGICAL ACTIVITY ON THE LONG-TERM STEM STABILITY OF CEMENTED HIP ARTHROPLASTY: *IN VITRO* COMPARISON OF THREE COMMERCIAL BONE CEMENTS

Submitted to: ***ImechE Part H: J. Engineering in Medicine***

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5.1 Abstract

Long-term endurance of the cement mantle is fundamental for the survival of cemented hip prostheses. Current protocols to characterize bone cements are unsuitable to predict the actual clinical outcome. The aim of this study was to assess if it is possible to rank cement types having diverse clinical outcome, by using a simplified *in vitro* physiological test. Composite femurs were implanted with identical stems (Lubinus-SPII), using different commercial cement types: CMW1 to represent cement with poor clinical outcome; Simplex-P and Cemex-RX to represent cements with a positive clinical outcome. Implanted femurs were subjected to a validated protocol that simulated a demanding but physiological loading spectrum. Inducible micromotions and permanent migrations were recorded throughout the test. After test completion, the cement mantles were sectioned and inspected with dye-penetrants to quantify the fatigue-induced

cracks. Micromotions did not differ significantly between cement types (possibly because a successful prosthesis was chosen, that is very stable in the host bone). Significant differences were observed in terms of cement cracks: CMW1 induced significantly more numerous and larger cracks than Simplex-P and Cemex-RX; no difference was observed between Simplex-P and Cemex-RX. This indicates that this protocol: (i) can discriminate between "good" and "bad" cements, (ii) yields consistent results when comparable cements are tested. Therefore, the proposed protocol overcomes the limitations of existing standardized material tests for bone cements. New cements can be assessed in comparison with other cements with known (positive/negative) clinical outcome, tested with the same protocol.

Keywords: cemented hip prostheses; acrylic bone cement; long-term stability; fatigue testing; physiological loading; pre-clinical validation; aseptic loosening of the stem

5.2 Introduction

The most frequent cause for revision of cemented Total Hip Arthroplasty (THA) is aseptic loosening. According to the Swedish Hip Registry, following 21519 cases of first revisions, where 83% were cemented THA, 74% were caused by aseptic loosening [1]. There are many factors involved in aseptic loosening of cemented arthroplasty, e.g., cement-bone and cement-stem interfacial failure, cement failure and bone remodelling [2-4]. The consensus amongst researchers is that mechanical failure of cement is critical for long-term survival of cemented prostheses [4-6]. The main factor causing fracture of bone cement is its inadequate mechanical resistance to physiological loading [7]. It has been shown that the primary failure mechanism of the cement mantle *in vivo* is fatigue, driven by the application of repeated loads during daily activity [2, 6]. Hence, it is necessary to validate pre-clinically mechanical properties of bone cements before introducing them into clinical use.

While there are many reports defining the mechanical material properties of different bone cements [8], predicting their long-term performance in a real patient, under physiological loading condition is difficult. Existing mandatory

standardized material testing protocols for bone cement (ISO 5833:2002) only consider simple static tests (bending, compression), while, under physiological conditions complex dynamic loading is applied to the cement mantle [7, 9, 10]. Moreover, during normal daily activities the implantation is subjected not to a single load, but to a spectrum of loading cycles [2, 6]. However, ISO 5833 does not oblige manufacturers to characterize fatigue properties of bone cements. The ASTM F2118-03 standard describes a constant amplitude force controlled fatigue test. However, even such a test (i) does not include a variable loading spectrum, (ii) is based on a simplified specimen geometry, which is not representative of a real cement mantle in hip arthroplasty.

Boneloc and CMW3 are examples of bone cement that were introduced to clinical practice after successfully passing all tests described in the ISO5833. Despite this, Boneloc exhibited a dramatic failure rate (as high as 60% after 0.5-3 years, [11-13]). Similarly, CMW3 had a higher failure rate than most cements in use (as high as 17% at ten years [14, 15]). Such disasters are clear evidence of the inadequacy of existing standards.

Events associated with implant failure are stem micromotion, and cracks disrupting the cement mantle [6, 16, 17]. Additionally, adverse biological reactions are expected in bone in relation to PMMA debris induced by mantle failure [4, 5, 18], with accelerated bone destruction. Therefore, presence of the crack is an indicator that the cement mantle is being damaged, and potentially can indicate eventual loosening of the prosthesis. Therefore, simulation of long-term physiological loading conditions and subsequent investigation of the damage within the cement mantle could be an indicator for quality of bone cement formulation. This would enable: (i) taking into account a variable loading spectrum; (ii) investigating failure of cement when it is prepared, delivered and shaped similar to the actual clinical application.

While long-term stability of different hip stems have been assessed *in vitro* [9, 10, 19], the mechanism of failure of different cement types has not been fully explained, when cement is used for fixing a hip stem.

The aim of this study was to assess if it is possible to rank different cement types having diverse (known) clinical outcome, by using a simplified *in vitro*

physiological testing protocol. For this purpose, three cement types with documented clinical performance where used to implant *in vitro* the same stem type, which was assumed as a golden standard. A previously validated physiological protocol [7, 9, 10, 19] was used, where a range of activities were simulated to replicate the most critical scenario in terms of fatigue. *In vitro* results obtained for cement mantle damage and implant stability were compared with the clinical outcome of the three types of bone cement chosen.

5.3 Materials and methods

5.3.1 Bone cement selection

Selection of cements types was based on their clinical outcome. To study how bone cement formulation can affect long-term stability of the cemented implant three bone cements types were chosen (Table 1):

- The first cement type (CMW1) has a negative clinical outcome [14, 20]. It was chosen to represent a cement type with poor performance in this study. Including this cement type in the study enabled assessing, in comparison against the other two types, the ability of the *in vitro* protocol to discriminate between cement types having different clinical outcome.
- The last two cement types (Cemex-RX and Simplex-P) have a documented extremely positive clinical outcome [20, 21]. They were chosen to represent a successful cement types in this study. Including two cement types having comparable clinical outcome enable assessing if the *in vitro* protocol yielded consistent results.

In order to minimize the influence of additional ingredients (e.g. antibiotics or different radio-opacifiers), all bone cements chosen included $BaSO_4$ as the only additive.

Table 1 – Chemical composition of selected bone cements [22], where: PMMA - poly(methylmethacrylate), MMA - methylmetacrylate DmpT - N,N-dimethyl-p-toluidine, $BaSO_4$ - barium sulphate as opacifier HQ - hydroquinone as stabilizer, BPO - benzoyl peroxide.

Acronym used in the paper	Composition of polymer	Additives	Trade name (manufacture)	Viscosity type
CMW1	polymer powder (40g): 88.85% PMMA, 2.05% BPO monomer liquid (18.37g): 99.18% MMA, 082% DmpT and 25 ppm of HQ	9.1% $BaSO_4$	CMW1, (DePuy International Ltd., Blackpool,UK)	high
Simplex-P	polymer powder (40g): 15% PMMA, 75% MMA-styrene copolymer 3% styrene, 1.5% BPO monomer liquid (18.79g): 97.4% MMA, 2.6% DmpT and 80 ppm of HQ	10% $BaSO_4$	Surgical Simplex-P (Stryker-Howmedica, Limerick, Ireland)	medium
Cemex-RX	polymer powder (40g): 88.25% PMMA, 3% styrene, 2.75% BPO monomer liquid (13.30g): 99.1% MMA, 0.9% DmpT and 75 ppm of HQ	9% $BaSO_4$	Cemex RX (Tecres SpA, Sommacampagna, Italy)	low

5.3.2 Preparation of the specimens

The Lubinus-SPII stem (150mm, Waldemar-Link, Hamburg, Germany) was used for all *in vitro* implants. This stem is in clinical use from more than 30 years and demonstrates positive outcome when properly implanted [1]. To minimize variability between samples, composite femurs (Mod. 3103, Pacific Research Labs, Vashon Island, WA, USA) were used, as they keep the same stiffness properties as human bones [23] and are suitable for long-term simulations [9, 19, 24]. Previous research [25] has demonstrated that the stability of the prosthesis and the sensitivity to the stem design are of the same order of magnitude in synthetic and human femurs.

An anatomic reference system was established [25, 26] to assist in maintaining consistent implantation, and increase repeatability during specimen

preparation and testing. A skilled surgeon prepared all femurs them following the manufacturers' instructions for the Lubinus-SPII stem. Femoral necks were consistently resected using an adjustable jig to guide the blade. Additional reference measurements allowed the surgeon to rasp the canal and position the stem with a reproducibility better than 0.5mm: the position of the reference points marked on the stem was measured with respect to the neck-resection plane; moreover, cement gap and stem insertion depth were measured with a Vernier caliper during insertion. Canal preparation resulted in removal of most of the polyurethane foam simulating spongy bone.

To standardize cement preparation conditions, all bone cements were stored at 23^0C for at least 24h before implantation, and were prepared in a controlled environment (23±1°C, 40-60% relative humidity). The cements were mixed according to the manufacturer's recommendations. For consistencey, they were all mixed using a standardized mixing and delivery system (Optivac, Scandimed, Sjobo, Sweden). CMW1 was mixed at atmospheric pressure, while Cemex-RX and Simplex-P were vacuum-mixed (-0.8 bar). All cements were injected in a retrograde fashion prior to stem insertion.

For CMW1 and Simplex-P six specimens were prepared for each cement type. Specimens implanted with Cemex-RX belonged to a previous study [9, 10], but were prepared and tested in an identical fashion to the other specimens. All implants were X-rayed to document implant alignment, and exclude the presence of significant voids that could bias the test.

To allow cement seasoning, implanted femurs were stored in air at 37°C for at least 1 week prior to mechanical testing (as recommended in ASTM F2118-03).

5.3.3 The load history and testing setup

The load history and testing setup have been extensively validated [9, 10, 19]. As the focus was on the most demanding patients, a severe load history was simulated that replicated 24 years of activity of a subject [9]. As walking has been shown to be less detrimental than other tasks [27, 28], only stair-climbing and more severe motor tasks were included. All the most relevant activities from a fatigue point of view were included in the accelerated test (Table 2), for a total of 1000348 cycles. A body weight (BW) of 550 N was fixed. This is suitable for the

small size composite femurs ([29], personal communication) and was used in similar investigations [9, 19]. A mixed "day" module was constructed, by alternating activities, because a sequence effect was suspected. The "day" was replicated cyclically, including one stumbling event every seven "days". More details can be found elsewhere [9]. The test frequency was relatively low (0.75Hz), preserving physiological conditions, allowing the cement to undergo the same creep experienced during patient activity, and preventing adiabatic heating. The tests ran for 15 days on the testing machine.

Table 2 – Activities in the *in vitro* simulated physiological loading (load values and frequency of occurrence). The load components were based on the literature so as to replicate the most critical scenario for the axial and torsional stability [9].

	Axial force (compression)	Bending moment (frontal plane)	Axial torque (intra-rotation)	Cycles/simulated day
ACTIVITY	**% BW**	**% BWm**	**% BWm**	**N**
Stairs up	370	4.66	4.60	54
Stairs down	404	5.09	4.40	54
Bath tub entry	498	6.27	6.19	1
Bath tub exit	498	6.27	6.19	1
Car entry	587	7.40	6.34	2
Car exit	534	6.73	5.16	2
Stumbling	807	10.71	7.01	weekly

The specimens were mounted on a biaxial testing machine (858-MiniBionix, MTS, Minneapolis, MN, USA) with a system of constraints (two perpendicular hinges, and two horizontal bearings, Fig. 1) that avoided any additional load components.

The prosthetic neck was potted in a steel box that allowed positioning the antero-posterior tilting hinge in a consistent position with respect to the femoral axis. The machine applied cyclic loads (replicating the different activities, Table 2), consisting of an axial force and a torque (generated by the biaxial actuator), and a bending moment (generated by the controlled offset of the proximal hinge).

Tests were carried out in air at room temperature 23 ± 2^{0}C.

5.3.4 Micromotion measurement

The implanted femurs were equipped with five displacement transducers (overall accuracy: better than 2.3micron [19, 30]):

- Four linear variable-displacement transducers (LVDTs) (D5/40AW with S7M conditioner, RDP, Wolverhampton, UK) were mounted following a validated protocol [19, 30]. This included (Fig.1): drilling 3.5mm transcortical holes, inserting a custom designed LVDT support in the cement at 0.5mm from the stem-cement interface, and inserting the spherical probe of the LVDT in a 1mm hole that was precision-drilled in the stem surface. This allowed direct measurment of the stem-cement interface micromotion (without artifacts due to strain gradients within the bone and/or cement). LVDT1, LVDT2 and LVDT3 measured micromotion in the direction of rotation on the medial aspect, respectively: close to the calcar, at mid-stem, and close to the stem tip. LVDT4 measured axial micromotions at the anterior side, close to the stem tip in the CMW1 and Simplex-P specimens; in the previous study on the Cemex-RX [9, 10], LVDT4 measured rotational micromotions (identical to LVDT1-3).
- A single-arm extensometer (Mod. 632.06-H20, MTS, Minneapolis, MN, USA) was mounted proximally (on the greater trochanter), to measure the axial motion of the stem with respect to the bone.

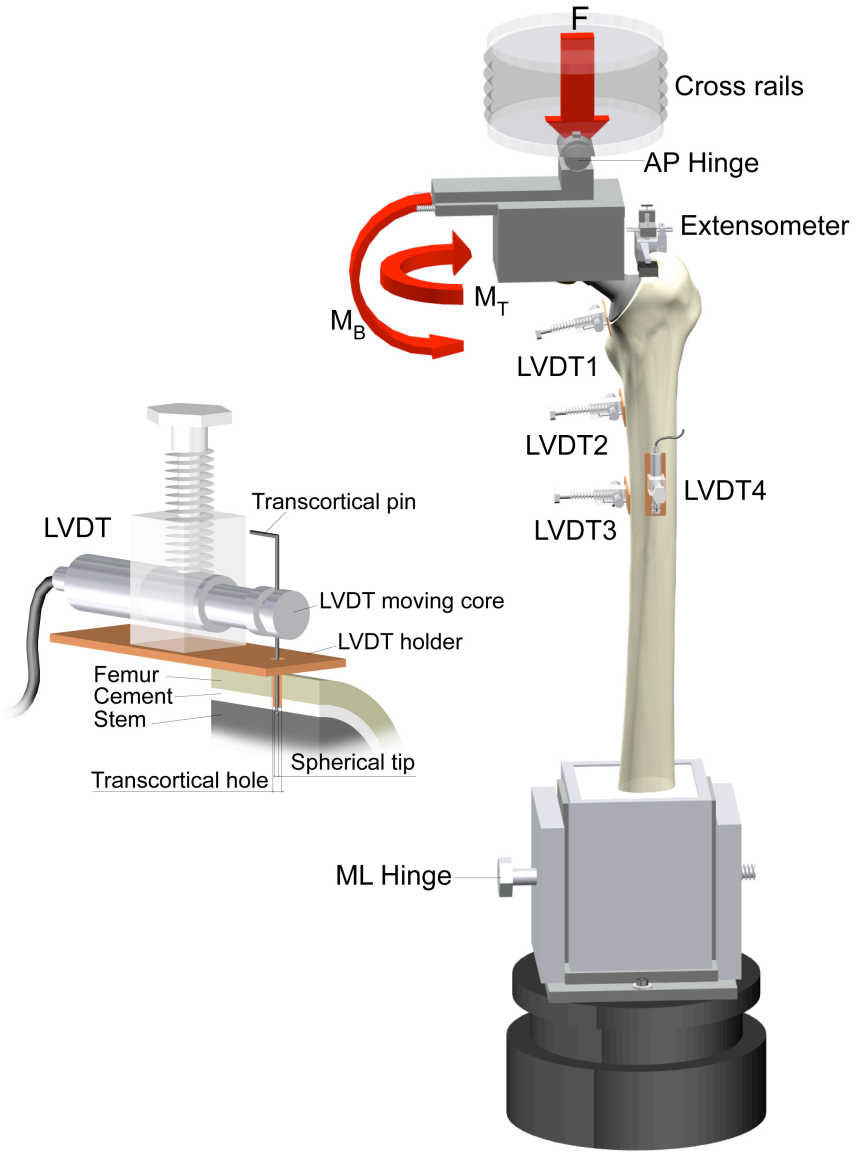

Fig. 1 – *In vitro* setup with represented position of the transducers: LVDT1 (proximal, medial), LVDT2 (mid stem, medial) and LVDT3 (stem tip, medial) are recording stem-cement interface micromotions in the direction of rotation. The single arm extensometer (mounted on the greater trochanter) and LVDT4 (same level as LVDT3, anterior) are recording micromotions in the longitudinal direction. The direction of the axial force F, torsional moment M_T and bending moment M_B are indicated. Left: detailed illustration of the LVDT mounted to measure micromotions close to the stem-cement interface: a transcortical hole of 3.5mm was drilled, so that the LVDT frame could be fixed at 0.5mm from the stem-cement interface, while the probe was inserted in a 1mm hole drilled in the stem.

All transducers, were recorded throughout the test to obtain: (i) the inducible micromotion for each loading cycle (i.e., the amount of relative motion that is recovered after load release); (ii) the permanent migration (i.e., the non-recoverable relative slippage at the interface which is not recovered, and which accumulates cycle after cycle). For each specimen and each sensor, data were processed to obtain [9, 19]: the total permanent migration of the stem from the

beginning to the end of the test, and the 95th percentile of the inducible motion all over the mechanical test (95th percentile values were chosen so as to discard occasional higher peaks, which are not representative of the average trend).

5.3.5 Cement mantle inspection for fatigue damage

At the end of the mechanical testing the specimens were opened with two longitudinal cuts, so as to extract the stem. Cuts were placed on the medial and lateral faces, following a previously described protocol [19]. This caused a loss of approximately 1mm of cement for subsequent inspection.

The stem-cement interface was inspected under an optical microscope, both in its original condition, and with the aid of dye penetrants to highlight cracks. Specimens were subsequently reassembled, and bone-cement constructs were sectioned transversely every 6.5 mm with a diamond blade (MDP200, Remet, Bologna, Italy) on a water-cooled disk-saw (TR60, Remet, Bologna, Italy). The cut surface was polished with silicon-carbide-paper (Hermes-P600, Stone-Boss, New York, USA) on a rotating polishing machine (D-2000, Exakt-Aparatebau, Norderstedt, Germany). Both faces of each slice were prepared with dye-penetrants (AVIO-B spray, Rotvel, American gas&chemical Company, Northwale, NJ, USA). Images were acquired digitally using a flatbed scanner (Perfection V750-Pro, Epson, Long Beach, USA) with optical resolution of 4800 dpi (1pixel=5.3micron). They were subsequently processed with a semi-automated custom-written software that allowed:

- Measurement of the cement mantle area
- Measurement of the cement mantle thickness
- Measurement of cracks longer than 0.05mm
- Counting and recording the position of cracks
- Recording the presence of voids and defects

Two indicators were considered to quantify the fatigue damage of the cement mantles: number of cracks per volume unit (NC/V), and the crack area per volume unit (CA/V) [10].

5.36 Statistical analysis

The criterion of Peirce was applied to screen for doubtful data [31, 32].

To evaluate the significance of differences of inducible micromotions and permanent migrations due to the cement type and to measurement position, a nonparametric Kruskal-Wallis test was applied. When a significant effect was observed ($p<0.05$), pairs of cement types were compared separately on each sensor (nonparametric multiple comparison [33]).

To evaluate the significance of differences in terms of cement damage due to the cement type and to the position (along and around the stem), a nonparametric Kruskal-Wallis test was applied. When a significant effect was observed ($p<0.05$), pairs of cement types were compared separately at each level/region of the cement mantle (nonparametric multiple comparison [33]).

5.4 Results

5.4.1 Inducible and permanent micromotions

None of the stems were visibly loose following tests. Inducible micromotions (Fig. 2) varied significantly between measurement locations (Kruskal-Wallis test, $p<0.001$). In the rotational direction (LVDT1, LVDT2, LVDT3) inducible motions were generally smaller than 1 micron, close to the accuracy of measurement system. Similarly, the axial inducible motions measured by LVDT 4 were of the order of 1 micron. Axial inducible motions from the extensometer were significantly larger (multiple comparison test [33], $p<0.001$). No significant difference has been detected between cement types, at any of the measurement positions (Kruskal-Wallis test, $p=0.26$-0.99).

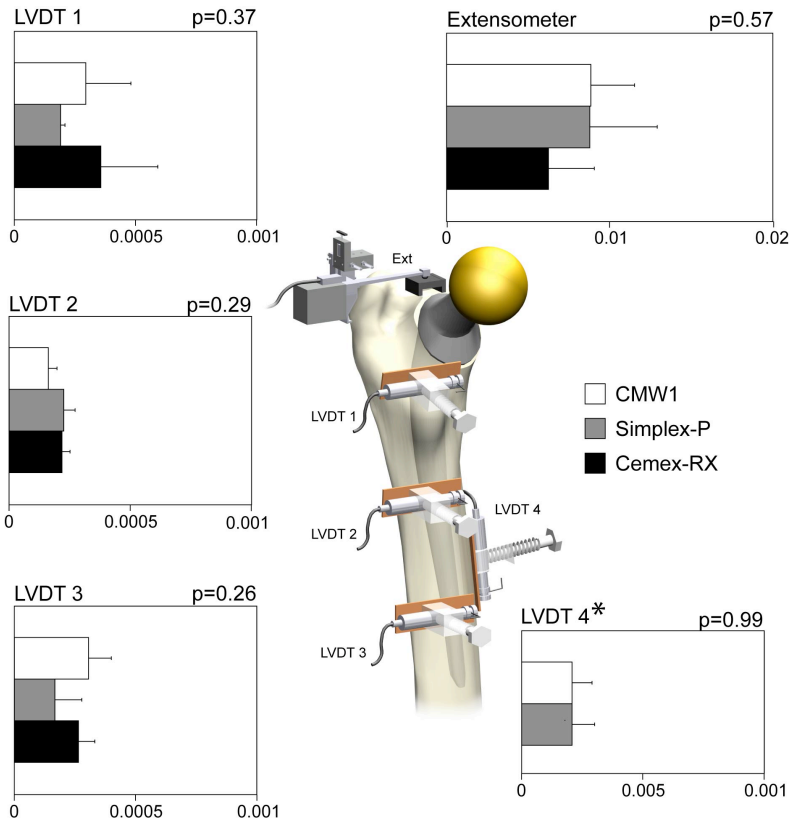

Fig. 2 – Inducible micromotions (mm) at the five measurement location (absolute value of the 95th percentile). Average value and standard deviation between specimens are reported for the three cement types. P-values (Kruskal-Wallis test) are reported for each sensor.
LVDT4*: for Cemex-RX the motions were measured in rotational direction. Thus, comparison is possible only between Simplex-P and CMW1.

Permanent migrations (Fig. 3) varied significantly between measurement locations (Kruskal-Wallis test, $p<0.001$). Axial permanent migrations from the extensometer were significantly larger (multiple comparison test [33], $p<0.05$). The difference between cement types was not significant for all measurement locations (Kruskal-Wallis test, p=0.19-0.99).

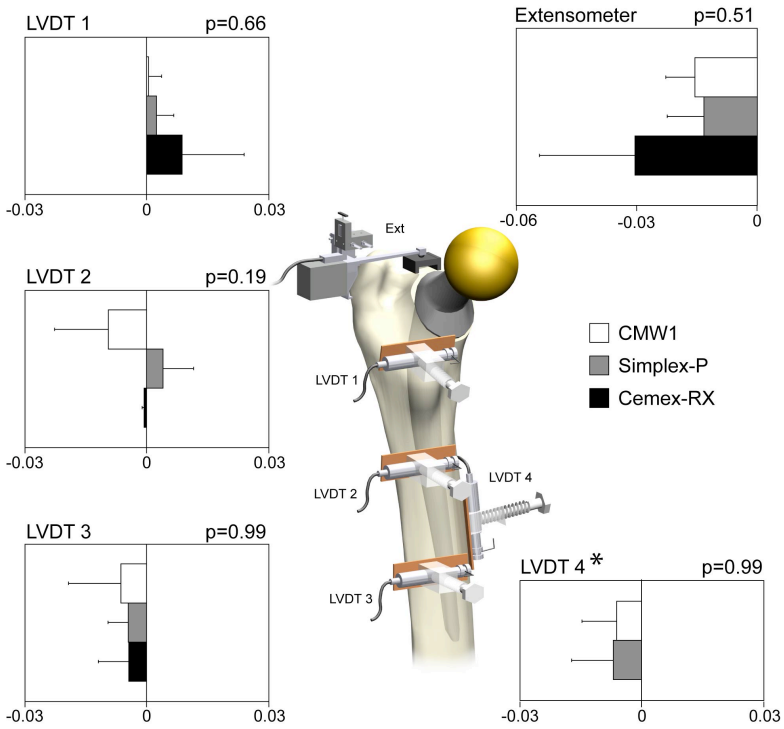

Fig. 3 – Permanent migrations (mm) at five measurement locations; average and standard deviation between specimens for the three cement types. P-values (Kruskal-Wallis test) are reported for each sensor.

LVDT4*: for Cemex-RX the motions were measured in rotational direction. Thus, comparison is possible only between Simplex-P and CMW1.

5.4.2 Fatigue damage in the cement mantle

The entire cement inspection was successfully applied to all specimens. No evidence of fretting damage was found in the cement mantles, or on the stem surface after extraction of the stem.

Only in few cases some crack propagated across the thickness of the cement mantle: such cracks were mainly localized in regions where the cement mantle was extremely thin (<0.5mm) or near large air inclusions (>2mm); they did not seem to be correlated with a specific cement type (mostly proximally). Cracks in the distal regions were more numerous, but much shorter than those in the proximal region.

Both the number of cracks per volume unit (NC/V, Fig. 4), and the crack area per volume unit (CA/V, Fig. 5) varied along the stem, with the highest value at the distal level (multiple comparison test, $p<0.001$ when all cement types were

pooled). Analyzing damage of the cement around the stem, both NC/V and CA/V were larger within the medial and lateral regions than in the anterior and posterior regions (multiple comparison test [33], $p<0.001$ when all cement types were pooled).

The cement type was a significant factor for the number of cracks per volume unit (NC/V, Fig. 4) both in total (Kruskal-Wallis test, $p=0.013$), and in the single regions along the stem and around the stem (Table 3): the largest effect was in the distal part, and on the medial and lateral sides. When the cement types were compared with each other, the NC/V for CMW1 was significantly higher than the other two cement types when the entire mantle was considered, but also in most regions (Table 3). Conversely, no statistically significant difference existed between Simplex-P and Cemex-RX (Table 3).

Table 3 – Statistical analysis performed on number of cracks per cement volume (NC/V). The nonparametric multiple comparison [33] was applied only if Kruskal-Wallis yielded a significant result ($p<0.05$).

		Overall effect of cement types (Kruskal-Wallis test)	Paired comparison (nonparametric multiple comparisons)		
			CMW1 vs Cemex-RX	CMW1 vs Cemex-RX	Simplex-P vs Cemex-RX
Whole specimen		p=0.013	p=0.008	p=0.008	p=0.43
Along the stem	**Proximal**	p=0.031	p=0.014	p=0.017	p=0.49
	Intermediate	p=0.014	p=0.004	p=0.019	p=0.52
	Distal	p=0.013	p=0.004	p=0.021	p=0.45
Around the stem	**Anterior**	p=0.15	n.a.	n.a.	n.a.
	Medial	p=0.012	p=0.007	p=0.009	p=0.47
	Posterior	p=0.56	n.a.	n.a.	n.a.
	Lateral	p=0.014	p=0.005	p=0.014	p=0.61

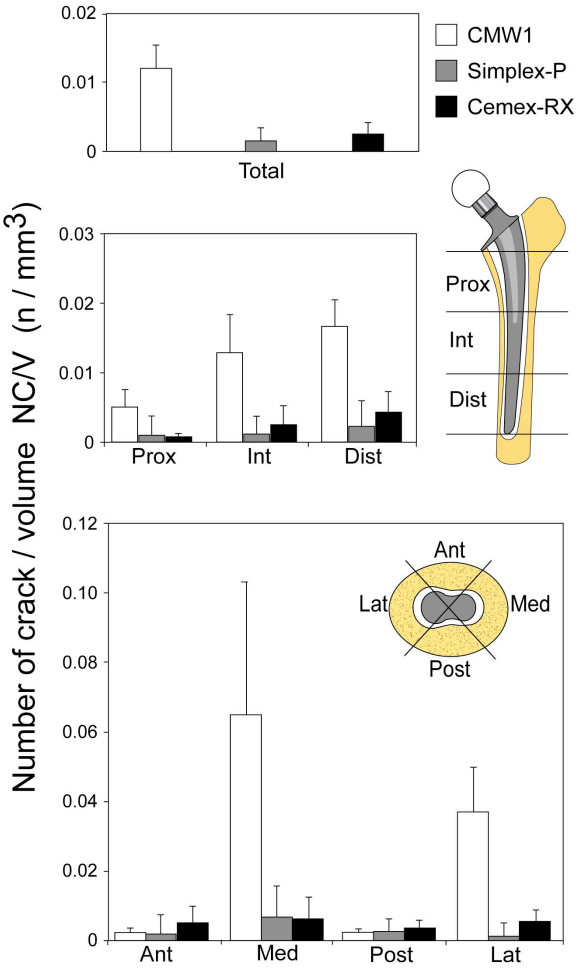

Fig. 4 – Comparison of cement damage between three types of bone cement. The number of crack per cubic millimeter of bone cement (mean and standard deviation) is shown for whole specimen (top), as well as in dependence on location along the stem (middle) and around the stem (bottom).

The cement type was a significant factor for the crack area per volume unit (CA/V, Fig. 5) both in total (Kruskal-Wallis test, p=0.012), and in the single regions along the stem and around the stem (Table 4): the largest effect was at the intermediate level along the stem, and on the medial and lateral sides. When the cement types were compared with each other, the CA/V for CMW1 was significantly higher than the other two types when the entire mantle was considered, but also in several other regions (Table 4). Conversely, no statistically significant difference existed between Simplex-P and Cemex-RX (Table 3).

Table 4 – Statistical analysis performed on crack area per unit volume of bone cement (CA/V). The nonparametric multiple comparison [33] was applied only if Kruskal-Wallis yielded a significant result ($p<0.05$).

		Overall effect of cement types (Kruskal-Wallis test)	Paired comparison (nonparametric multiple comparisons)		
			CMW1 vs Cemex-RX	CMW1 vs Cemex-RX	Simplex-P vs Cemex-RX
Whole specimen		p=0.012	p=0.013	p=0.005	p=0.32
Along the stem	**Proximal**	p=0.15	n.a.	n.a.	n.a.
	Intermediate	p=0.005	p=0.005	p=0.003	p=0.32
	Distal	p=0.13	n.a.	n.a.	n.a.
Around the stem	**Anterior**	p=0.055	n.a.	n.a.	n.a.
	Medial	p=0.011	p=0.003	p=0.018	p=0.52
	Posterior	p=0.27	n.a.	n.a.	n.a.
	Lateral	p=0.014	p=0.015	p=0.006	p=0.31

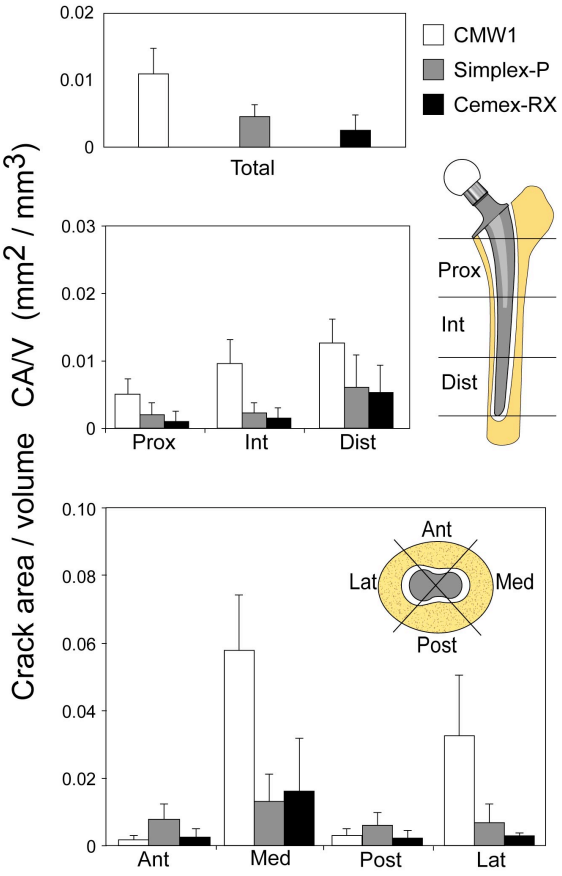

Fig. 5 – Comparison of cement damage between three types of bone cement. The crack area per cubic millimeter of bone cement (mean and standard deviation) is shown for whole specimen (top), as well as in dependence on location along the stem (middle) and around the stem (bottom).

5.5 Discussion

Long-term endurance of the cement mantle is a key factor for the survival of cemented hip prostheses. Current protocols to characterize acrylic bone cements appear unsuitable to predict the actual clinical outcome of bone cements [11-13, 15]. The mechanical properties of bone cement have been investigated extensively in the past, using various testing methods [8]. In spite of that, no consensus was reached on the relationship between laboratory tests and clinical performance [21]. The aim of this study was assess if it is possible to rank different cement types having diverse clinical outcome, by using a simplified *in vitro* physiological testing protocol.

Three cement types with documented clinical performance where used to

implant *in vitro* the same stem type (Lubinus-SPII): CMW1 was chosen because of its sub-optimal clinical performance [14, 20]; two more cements (Simplex-P and Cemex-RX) were chose because of their positive clinical follow-up [20, 21]. A validated *in vitro* protocol [7, 9, 10, 19] was used to load the implants with a physiological loading spectrum. Statistically significant differences were found between the cement having a poor and positive clinical outcome in terms of cracks in the cement mantle. This confirms the ability of the proposed protocol to discriminate between "good" and "bad" cements. At the same time, no significant difference was found between the two cements having a similar (positive) clinical follow-up. This confirms the robustness of the method, and the consistency of the results provided.

To the Authors' knowledge, the mechanical properties of bone cements in the past have never been addressed using this kind of *in vitro* simulation of the physiological loading conditions. The results found in this study for these three types of bone cements are in full agreement with the clinical experience with the same cement types [14, 20, 21]. The present results are also in agreement with the fatigue tests of the Cemex-RX [34], and of the Simplex-P [35]At the same time, the poorer fatigue properties found for CMW1 [35]agree with the present findings. Conversely, the present study contradicts the results of static tests for the CMW1 [22]: although it met the requirements set by the ISO 5833 standard, it exhibited a poorer performance when used to fix a hip stem both *in vitro* (present study) and clinically [14, 20].

Some of the observations of the present study are in agreement with past experience with this type of *in vitro* test. In fact, micromotions were rather consistent with a previously presented study [9]: inducible micromotions were in all cases close to the sensitivity of the measurement method (microns), hence almost insignificant; similarly, the permanent migrations were negligible. These observations are in accordance with previously published *in vitro* studies on Lubinus-SPII stem [19, 24, 36]. Also clinically, the Lubinus-SPII demonstrates a good survivorship [1], with a revision rate of 4 % after 10 years. The good long-term stability of the stem used in this study can explain the scarce sensitivity of micromotions to the cement type.

Differences between cement types became evident, when the damage of

cement mantles was quantified. The cracking pattern was similar for all cement types: (i) along the stem, the cement damage increased in the distal direction; (ii) around the stem, the most extensive cement damage was observed in the medial and lateral regions. This pattern corresponds to stress distribution measured *in vitro* [37, 38] and estimated with finite element models [39] for the Lubinus-SPII.

Due to many simplifications necessary to carry out such a complex *in vitro* simulation, the present study has some limitations:

- The Lubinus-SPII stem has been proposed as a golden standard by several research groups and by a large European Project [24, 37, 39]. However, the fact that this stem has an excellent long-term stability both *in vitro* and clinically makes it less sensitive to poorer bone cements. This can probably explain why differences in terms of inducible micromotions and permanent migrations were not significant in this study. However, to predict implant long-term outcome, it has been recommended to use simultaneously different indicators (both implant micromotions, and cement damage) [10, 40]. In fact, the cement damage indicators were capable of discriminating the different cement types investigated in this study.
- Composite femurs: The use of these bone models as a benchmark for comparative pre-clinical testing has been established in a large European Project [24, 41], as they keep the same stiffness properties as human bones [23] while allowing a significant reduction of the specimen variability compared to human bones. This type of composite bone can also withstand very severe cyclic loading, such as in this case [7, 19, 24, 36]. Previous research [10, 19, 24, 25, 36] has demonstrated that the stability of the prosthesis and the sensitivity to the stem design are of the same order of magnitude in synthetic and human femurs. It must be taken in consideration, that some of characteristics of composite femurs differ from those of human bone (e.g. porosity). Therefore, the damage induced in the cement mantle cannot be analysed in terms of crack type (e.g. originating from the stem-cement interface, the cement-bone interface, the cement bulk). In fact, while cement-polyurethane foam bonding is guaranteed [10, 19], the morphology of such interface differs from the interdigitated

cement-bone interface in real bone [42].

- Curing/testing environment: it is commonly known, that mechanical properties of bone cement can be influenced by the presence of liquids around the cement mantle, e.g. physiological electrolytes, blood. It has been shown that such effect does not significantly compromise the results yielded by this test, both in terms of micromotions, and cement damage [9, 10]. Therefore, it does not represent a limitation, furthermore as the results are comparative (rather than absolute) any minor bias introduced is consistent throughout all samples tested.
- Set up: In order to use a robust and reproducible setup, no muscle groups were included, while the correct resultant hip joint force was applied. In fact, inclusion of any of the muscle groups affects the stress in the cement mantle around a debonded stem by less than 11% [43]. Moreover, no-muscle-simulation leads to stress overestimation with respect to a full-muscle one [43, 44], thus yielding a worst-case scenario simulation.

It must be noted that, despite all the simplifications above, the applied protocol is highly clinically relevant. In fact, this protocol: (i) is capable of discriminating between successful and unsuccessful implants [7, 9]; (ii) it produces results that are in agreement with previous study [10].

In conclusion, on the one hand, this study confirmed that existing material testing protocols are inadequate for bone cements. At the same time, this study has proven that it is possible to test bone cements pre-clinically, by using a complex *in vitro* physiological simulation. In fact, the procedure proposed can successfully rank different cement types according to their actual clinical performance. Therefore, the proposed method can be used to test bone cements pre-clinically: poor cements can be discarded based on the amount of cement damage they produce *in vitro* in the cement mantle. New cements can be assessed in comparison with the results reported with the same test by other cements with known (positive or negative) clinical outcome.

5.6 Acknowledgements

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VI EFFECT OF STEM PREHEATING ON THE FATIGUE BEHAVIOUR OF BONE CEMENT AROUND HIP PROSTHESES

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6.1 Abstract

Tensile fatigue behaviour of bone cement specimens obtained from cement mantles moulded in vitro, simulating the surgical scenario, was investigated. The effect of stem preheating before its insertion into the cement dough, on specimen fatigue life was studied.

A commercial bone cement was selected for this study. Bone cement mixing was conducted in air, following the manufacturer instructions, and injected simulating the clinical practice. Two conditions were considered: stem maintained at environmental temperature (23°C); and stem preheated to 45°C. Four repetitions of the whole procedure were performed for each condition obtaining a total of 32 specimens. All specimens underwent fatigue testing (stress ratio=0, maximum tensile stress =15MPa) until failure.

Both two-parameter and three-parameter Weibull distributions were initially used to analysis the fatigue life dataset. However, the two-parameter distribution was chosen for both groups on the basis of the coefficient of determination used to test the goodness-of-fit.

Stem preheating seems to have a negligible effect on fatigue behaviour of the studied bone cement in the low range of fatigue life (up to 10^4). However,

above this cycle number, stem preheating seems to reduce the probability of failure. These findings were discussed in the text.

Keywords:

Cemented prostheses - Bone cement - Mechanical behaviour - Fatigue life - Stem preheating

List of notations

C.I. confidence interval

i failure order number, assigned to a cycles to failure value after all the values were arranged in ascending order of magnitude

$F(n_i)$ median rank of the order i failure

G sample size of a group

m shape parameter of the Weibull distribution

n number of cycles to failure or fatigue life

N_a scale parameter of the Weibull distribution

n_i number of cycles to failure with order number i

N_0 location parameter of the Weibull distribution

R^2 coefficient of determination

6.2 Introduction

Polymethylmethacrylate based bone cement is the material used to fix cemented arthroplasty. The long-term survival of cemented implants depends on the fatigue strength of the bone cement mantle, which assures the implant stability. In fact, cemented arthroplasties are subjected to dynamic loads during normal physiological activity, which may promote a damage accumulation process in the cement mantle [1-3].

To reduce the risk of fatigue failure, the stress field within the cement mantle has to be reduced as much as possible. Among others, one important factor for the long-term failure risk is the quality of the bone cement making the mantle in vivo [4-6]. Great efforts have been done to assure the integrity of the mantle.

Cementing techniques have been improved over the years to reduce or delete stress raisers in the cement mantles [7-9]. Therefore the clinical practice has been applying improved cementing techniques, which may consider accurate canal preparation, intramedullary bone plugs, retrograde injection and/or cement pressurization [10-13]. However, these methods cannot eliminate all defects at the stem-cement interface due to stem insertion and/or the polymerisation process [5, 14, 15].

During the last decade, a modified technique has been investigated to improve stem-cement interface integrity. In 1996, Bishop et al. found that preheating the stem up to 44°C, prior to insertion, significantly reduces the porosity at the stem-cement interface [16]. Subsequently, other groups have demonstrated that stem preheating improves both the static strength of the bone cement making the mantle and the shear strength of the stem-cement interface [17, 18]. However, until now there are no data available in the literature about the effect of stem preheating on the fatigue behaviour of the cement itself.

The aim of this study was to instigate the effect of stem preheating on the fatigue behaviour of bone cement used for cemented prostheses.

6.3 Materials and methods

6.3.1 Materials and specimens fabrication

Commercially available bone cement (Surgical Simplex-P, Stryker-Howmedica, Howmedica International, Limerick, Ireland) was used to study the effect of stem preheating on fatigue behaviour of the cement mantle. The bone cement was mixed at a temperature of 23±1°C and a relative humidity in the range of 40-60%, in agreement with ISO 5833 recommendations.

An experimental protocol was designed to simulate the surgical procedure of inserting a prosthetic stem into the femoral cavity. A mould was manufactured to replicate the dimensions of a typical femoral diaphysis and a CrCo-stem was used to replicate the prosthesis [15]. The mould was made of HDPE to simulate the thermal characteristics (thermal conductivity) of wet and fresh cortical bone tissue [19]. The dimensions of stem and inner cavity of the mould allowed the moulding of a cement mantle with a constant thickness of 4.0 mm.

To investigate the effect of stem preheating on the fatigue performance of the bone cement making the mantle, two stem temperatures were considered: the first was 23°C (surgical room temperature); the second temperature was raised up to 45°C [16, 17]. After mixing, the doughy bone cement was injected into the mould and the stem was inserted. Stem insertion rate was set to 30 mm/s, to replicate the clinical procedure [15]. The whole procedure was performed within 5 min. One hour after beginning the bone cement mixing, the stem was removed and the cement mantle was extracted from the mould. One double-bell specimen for fatigue tensile testing was machined from each of the four sides. The final dimensions of the specimen were defined in agreement with ISO 527-2 (specimen type 1-A).

The surface of each specimen (originally located on the external surface of the mantle) was polished with 800-grit sand paper to adjust the thickness to the desired value (4.0 mm) with an accuracy of 0.1 mm. Eight mantles were moulded (four with each stem temperature) to obtain a total of 32 specimens.

Specimens were stored in a phosphate buffered saline solution at 37^0C for 14 days before testing. Each specimen underwent fatigue testing in a temperature controlled environment chamber maintained at 37^0C. During the test, the narrow part of the specimen was immersed in a physiological solution. Cyclic tensile stress between 0 and 15 MPa was applied to all specimens, using a material testing machine (Mini Bionix 858 MTS System Corp., Minneapolis, MN). Tests were stopped at specimen failure, obtaining a complete set of fatigue data.

Fatigue data, i.e. number of cycles to failure, were analysed using the Weibull distribution. Since it is not known a-priori, which form of Weibull distribution is the most appropriate to fit the experimental data, both two-parameter and three-parameter Weibull distributions were considered to fit the fatigue-life dataset. Regression analyses were performed: the linear least squares method was used for the two-parameter distribution; an iterative minimisation method of the sum of the squared residuals was used to estimate the 3 parameters of the three-parameter distribution. In both cases Bernard's formula, $F(n_i)=(i-0.3)/(G+0.4)$, was used to assign a median rank to each failure. The coefficient of determination (R^2) was used as a goodness-of-fit test to compare the two Weibull distributions [20].

6.4 Results

All specimens failed in the narrow part. Hence, 16 valid values of cycles to failure were collected for each group. The two datasets are plotted in Figure 1.

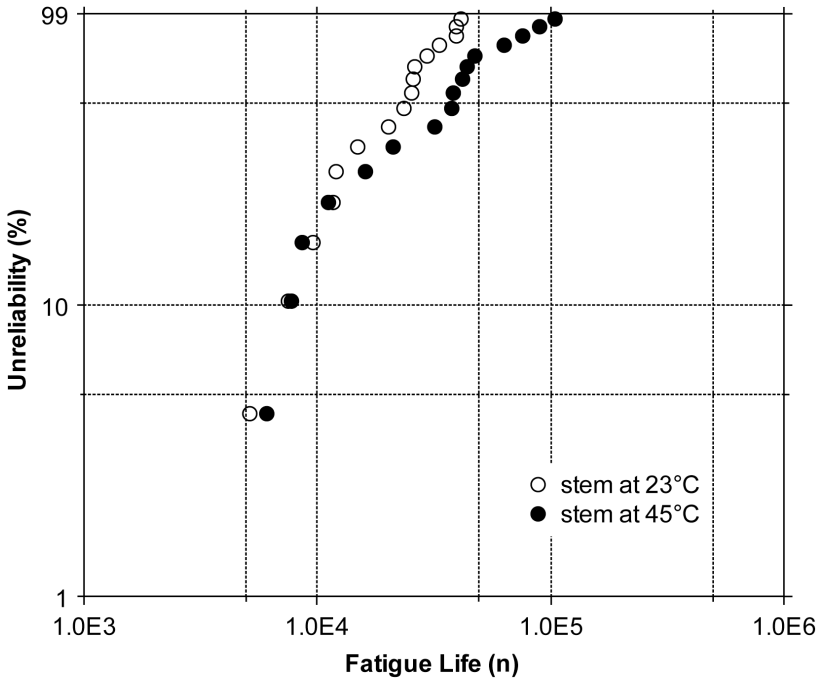

Figure 1: The estimated median ranks plotted versus the fatigue life.

Estimations of the Weibull parameters, both for the two-parameter and the three-parameter distribution, are given in Table 1.

Table 1: Parameters calculated for the two-parameter and thee-parameter Weibull distributions for the two groups.

Configuration	**Model**	**Shape parameter m**	**Scale parameter Na**	**Location parameter N_0**	**Coefficient of determination R^2**
Cement moulded inserting the stem at 23°C	Weibull 2-parameter	1.85	$2.60x10^4$	0	0.97
	Weibull 3-parameter	1.38	$2.22x10^4$	$3.4x10^3$	0.97
Cement moulded inserting the stem at 45°C	Weibull 2-parameter	1.26	$4.48x10^4$	0	0.95
	Weibull 3-parameter	1.03	$4.00x10^4$	$3.4x10^3$	0.96

The R^2 values were similar for the two-parameter and the three-parameter distribution, for both groups. Considering also that none of the two datasets showed a clear downward curvature (Figure 1), the two-parameter distribution was chosen for both groups. The reliability functions are shown in Figure 2.

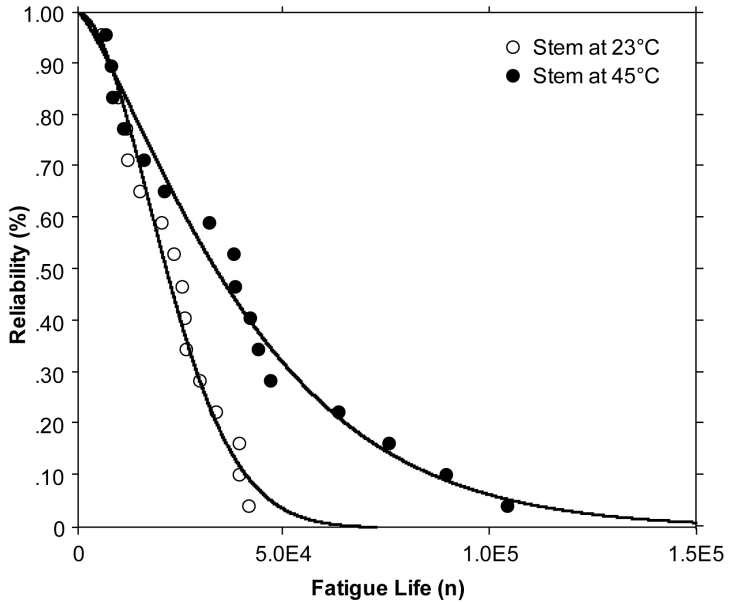

Figure 2: Reliability curves calculated for the two groups using the two-parameter Weibull model.

The reliability values for the two groups were comparable at a low range of fatigue cycles (up to 10^4). Above this value, the two estimated curves diverged. Cement specimens moulded with the stem at 23°C and at 45°C demonstrated 10% (95%C.I. 2% -24%) and 40% (95%C.I. 24%-56%) reliability at 4.1×10^4 cycles, respectively. For the 45°C group, 10% reliability (95%C.I. 3%-24%) was estimated at 8.6×10^4 cycles.

6.5 Discussion

The aim of this study was to investigate the effect of stem preheating on the fatigue behaviour of the bone cement making the mantle of cemented prostheses. The data, collected for one commercial bone cement mixed in air, showed an increased fatigue life for specimens obtained from mantles moulded inserting a preheated stem in comparison with those moulded without preheating the stem.

However the improvement was not general but limited to the higher range of cycles to failure, while no effect was found on short fatigue life.

This finding can be explained considering that the porosity affects fatigue life of bone cements [6, 21-24]. Stem preheating decreases the porosity within the bone cement, especially at the stem-cement interface [16, 17, 19]. Therefore, it would be expected that stem preheating, decreasing bone cement porosity, would increase cement fatigue life. However, the effect of this technique is limited to porosities generated during the final curing process. In fact, stem preheating reverses the curing direction in the cement mantle, reducing pore generation associated with the shrinkage process [5, 16]. Stem preheating has no effect on pores generated during cement mixing or injection. If these defects are present within the material, then the positive effect of stem preheating will be minimised or deleted. The defects created during mixing or injection may be larger in size than those generated during curing [25-27]. Since the stress raiser effect of a pore is related to its size [6, 28, 29], the reduction of small pores when large pores are present would have no significant effect on the risk of crack nucleation, which causes the fatigue failure of the specimen. In these cases fatigue life will be shorter and insensitive to stem preheating, explaining the negligible effect of stem preheating found in the specimens failed at a low number of cycles.

There are a few limitations in this study.

The first limitation is that one commercial bone cement, mixed in air, was tested. The results cannot be generalised to bone cements with different formulation and/or mixed using different procedures.

The second limitation is that a simplified experimental procedure was used to mould the bone cement specimens. This simplified procedure was required to obtain flat specimens with a constant thickness. Additionally, the procedure was developed to assure experimental repeatability. The use of the proximal parts of human or animal femora would have prevented a high repeatability, due to differences in the local anatomy and tissue density, and made impossible the moulding of regular flat specimen.

The third limitation is the small sample size of each group. Increasing the sample size, more information could have been collected about the failure

distribution. This would have corresponded to a more accurate reliability estimation. However, the aim of this study was to verify if any difference exists in the fatigue life of a bone cement moulded with stems maintained at different temperatures before their insertion. The chosen sample size, selected to guarantee the recommendations of the minimum number of specimen (11) to be tested in fatigue series [30], showed a difference in fatigue behaviour between the two groups.

In conclusion, stem preheating seems to be a technique, which could improve the fatigue strength of bone cement. This improvement has been found for one commercial bone cement mixed in air. Therefore, it remains to be investigated if this technique is feasible for other cement brands and/or different mixing techniques.

6.6 Acknowledgments

The authors thank Stryker-Howmedica for bone cement donation and Caroline Öhman for the help in preparing the manuscript.

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VII VACUUM MIXING AND STEM PRE-HEATING IMPROVE MECHANICAL PERFORMANCE OF THE BONE CEMENT MANTLE

Manuscript submitted to: ***Journal of Bone and Joint Surgery***

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7.1 Abstract

Tensile fatigue behaviour was investigated for bone cement specimens obtained from cement mantles moulded in vitro, simulating the surgical scenario. The effect of stem preheating, before its insertion into the cement dough, on specimen fatigue life was studied.

A commercial bone cement was selected for this study. Bone cement mixing was conducted in air, following the manufacturer instructions, and injected simulating the clinical practice. Two condition were considered: stem maintained at environmental temperature (23°C) and stem preheated to 45°C. Four repetitions of the whole procedure were performed for each group obtaining a total of 32 specimens. All specimens underwent fatigue testing (stress ratio=0, maximum tensile stress =15MPa) until failure.

Both two-parameter and three-parameter Weibull distributions were initially used to analysis the fatigue life dataset. However, the two-parameter distribution was chosen for both group on the basis of the coefficient of determination used to test the goodness-of-fit.

Stem preheating seems to have a negligible effect on fatigue behaviour of the studied bone cement in the low range of fatigue life (up to 10^5). However, above this cycle number, stem preheating seems to reduce the probability of failure. These findings were discussed in the text.

Keywords:
Cemented prostheses, Bone cement, Mechanical behaviour, Fatigue life, Stem preheating

7.2 Introduction

Long-term clinical outcomes show that aseptic loosening is the main cause of failure (60%) of cemented hip prostheses [1].

Polymethylmethacrylate (PMMA) based bone cement is commonly used as fixing material for cemented prosthesis. While a cement mantle assures an optimal post-operatively implant stability [2], it may mechanically fail in a long-term perspective, being one potential cause of aseptic loosening. Therefore, long-term survival of cemented arthroplasties depends also on the mechanical strength of the bone cement used for fixing the implant components to the hosting bone [3-5]. Several reports have shown that long-term survival of cemented implants is also dependent of the stem-cement interface quality[6-10]. In fact, investigations on cement mantles retrieved during prosthesis revisions proved that the porosities found in the bone cement was of critical importance for crack initiation [9, 11-14].

The overall amount of porosity within the cement mantle is influenced by different factors: cement formulation, mixing method, injection technique, implant surface properties [6, 8, 10, 15, 16]. Large efforts have been made to optimise cement formulations [17-20], to improve mixing and/or injection procedures[21-26], to select the best implant surface morphology [27-30]. Despite these efforts, some degree of porosity is still observable in bone cement mantles [31-34]. Some authors have suggested to reduce the porosity by thermally influencing the polymerization of bone cement, preheating the stem before its insertion into the medullar canal [6, 35]. Pre-heating the stem at 44-45°C generated an increase in bone cement static strength [36] and strength of the

implant-cement interface [10, 29]. However, the influence of stem pre-heating on fatigue behaviour of the bone cement, which is the most important factor for its long-term performance [11, 12, 37], has not yet been investigated. Additionally, it has to be verified if stem pre-heating gives any advantages also for vacuum mixed bone cement.

The aim of this work was two-fold: (1) to verify the effect of stem pre-heating on porosities and mechanical behaviour (static and fatigue strength) of manually mixed bone cement obtained under curing conditions simulating the surgical scenario, and (2) to verify if any effect is still observable in vacuum mixed bone cement. Since the temperature of polymerisation may cause bone necrosis, the effect of stem pre-heating and mixing method on the curing process of the bone cement was also investigated.

7.3 Material and methods

7.3.1 Materials and bone cement mantle moulding

Surgical Simplex-P (Stryker-Howmedica, Howmedica International, Limerick, Ireland) bone cement was selected for this study.

The bone cement was mixed at a temperature of 23±1°C and at a relative humidity in the range of 40-60%, in agreement with ISO 5833 recommendations. To investigate the effect of stem pre-heating on porosity distribution and mechanical properties, bone cement mantles were moulded following two procedures: the former required the insertion of the stem at 23°C (room temperature), the latter was similar to the previous one except for the stem temperature, set to 45°C (temperature level selected following Bishop's and Iesaka's reports [6, 10]. For both moulding procedures, two mixing methods were used: vacuum mixing (VM), with a nominal vacuum level of 0.8 bar [25, 38, 39], and air mixing (AM). The VM was performed using an commercial mixing system (Opivac®, Biomet Cementing Technologies AB, Sjöbo, Sweden) [25]. The AM was performed in the same manner, except that the vacuum pump was not connected to the mixer. Once the doughy bone cement was ready (3 min form starting mixing), it was injected into a custom made mould designed to simulate the surgical curing condition.

The shape and dimensions of the mould, hereinafter called pseudofemur, were chosen to replicate those of a typical femoral diaphysis [40]. The pseudofemur consisted of a parallelepiped made of high density polyethylene. This material has a value of thermal conductivity similar to that of wet and fresh cortical bone tissue, which is in the range of 0.42-0.88 W/mK [14, 41]. The pseudofemur had an inner cavity, with a square cross-section, slightly tapered along its axis. The thickness of the mould wall ranged from 3.5 mm proximally to 5.0 mm distally to simulate the cortical wall of a femur metaphysis and diaphysis, respectively. A polished Co-alloy stem, with a square cross-section and tapered along its axis with the same angle as the inner cavity of the pseudofemur, simulated the prosthetic stem. The design of the mould ensured that the stem was aligned centrally allowing overflow of cement in excess. The square cross-sectional model was used instead of a real human shaped femur to obtain a cement mantle with four flat surfaces. The dimensions of the stem and the inner cavity were selected to obtain two different thicknesses of cement mantles: 3.3 mm, selected to extract four strips from the mantle for bending test in agreement with ISO 5833 recommendations; 4.0 mm, selected to extract four double-bell specimens from the mantle for tensile fatigue tests in agreement with ISO 527-2 (specimen type 1-A). Both values fall in the range 2-5 mm which is indicated as the standard cement mantle thickness [42]. Stem insertion rate was set to 30 mm/s, to replicate the clinical procedure [40].

7.3.2 Monitoring the curing process

To assess the influence of stem preheating on temperature distribution, three thermocouples were inserted 1-1.5 mm into the bone cement mantle, and three more were inserted into the pseudofemur, 0.5-1.0 mm from the pseudofemur-cement interface **(Fig.1).**

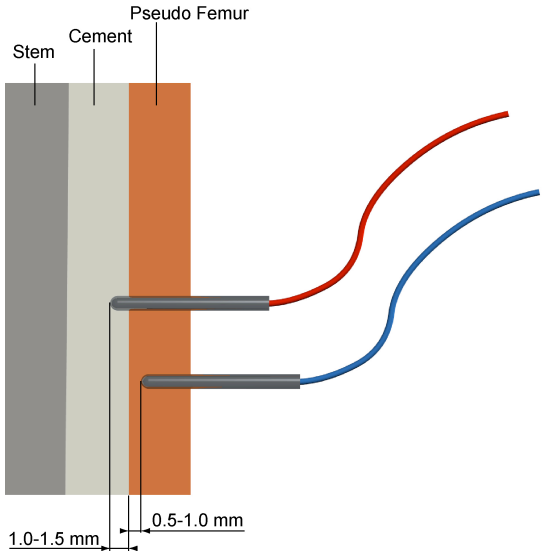

Fig.1 Location of the thermocouple into the bone cement mantle (upper thermocouple) and into the pseudofemur closer the pseudofemur-cement interface (lower thermocouple).

The thermocouples were inserted on three levels along he axis of the pseudofemur: proximal (P), mid-stem (M) and distal (D). Data from thermocouples were registered using an acquisition device (AD 6B11, Analogue Device, Norwood, USA) controlled by a laptop (LabView, National Instruments, Texas, USA). The accuracy of the whole system was better than 1°C. The polymerization time (t_{pol}) was defined as the time between mixing start and the maximum temperature of polymerization (T_{max}). The time values were rounded to the closest 10 sec.

7.3.3 Specimens extraction

One hour after bone cement mixing, the stem was removed and the cement mantle was extracted from the pseudofemur. Each cement mantle was machined to obtain a strip **(Fig.2a)** or a double-bell **(Fig.2b)** specimen from each of the four sides.

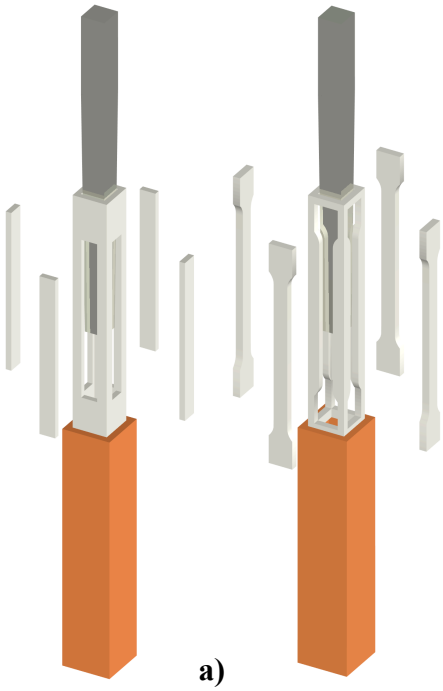

Fig.2 Scheme of extraction of bone cement specimens from mantle: a) strip specimens; b) double-bell specimens.

The surface of each specimen (originally located on the external surface of the mantle) was polished with 800-grit sand paper to adjust the thickness to the desired value (3.3 or 4.0 mm) with an accuracy of 0.1 mm. Specimens were stored in a phosphate buffered saline solution at 37^0C until testing.

7.3.4 Bending test

Two days after curing the bone cement strips underwent bending test in agreement with the ISO 5833 standard. For each configuration, 12 specimens obtained from three cement mantle (i.e. three repetitions of the whole moulding procedure) were tested. For comparison 12 specimens, moulded according to the ISO 5833 recommendations, were tested. Tests were performed on a material testing machine (Mini Bionix 858, MTS, Minneapolis, MN). The bending strength and elastic modulus were calculated following the standard recommendations.

7.3.5 Fatigue test

Two weeks after curing the double-bell specimens underwent fatigue test. A material testing machine (Mini Bionix 858, MTS, Minneapolis, MN) was used to stress the specimen from about 0 up to 15 MPa. For each configuration, 16 specimens obtained from four cement mantles (i.e. four repetitions of the whole

moulding procedure) were tested until failure. Tests were performed in saline solution maintained at 37°C. For comparison 16 directly-moulded specimens were tested. The latter (control group) were checked before testing to assure the absence of macro-porosities (pores>1.0 mm) in the narrow part of the specimen [43] while no exclusion criterion was applied prior to testing for the sample obtained from cement mantles, as the effective strength of the bone cement forming the mantle had to be investigate. The fatigue data were analysed using the two-parameter Weibull distribution. The method of linear least squares was used to estimate the Weibull parameters. The Weibull mean value was calculated for each group.

7.3.6 Porosity analysis

All specimens, tested in bending, underwent this analysis. Of each strip, the surface, which formed the stem-cement interface (S-C I), and one of the lateral surfaces, which represented the cement mantle cross section (CS), were analysed for porosities. After the bending tests, the specimens were glued back together and sprayed with dye-penetrant (AVIO-B spray, Rotvel, American Gas & Chemical Company, NJ USA). The specimen surfaces were scanned with a flatbed scanner with an optical resolution of 2400 DPI (HP ScanJet 5590, Hewlett-Packard Development Company, Palo Alto, USA). The porosities were assessed by analysing the digital images using an image analysis software (Matlab 6.5, The MathWorks Inc, Natick, USA). The porosity was expressed by area percentage.

7.3.7 Statistical analysis procedure

All data about curing process, bending test and surface analysis were analysed for outliers by applying the Chauvenet criterion. Afterwards, the experimental data was statistically analysed using an analysis of variance (ANOVA) and post hoc analysis (Scheffe's test).

The differences in mean log fatigue life and the significance between all groups was compared using a non-parametric method (Kruskal-Wallis test) and a nonparametric multiple comparison test.

7.4 Results

7.4.1 Curing process

Two values out of 168 were excluded by the Chauvenet's criterion (both T_{max} and its respective t_{pol} measured by a thermocouple located in the bone cement mantle). Since these two values were different from those measured at the same depth at the other two levels of the same cement mantle, it was assumed that they were caused by an error in positioning the thermocouple into the cement mantle.

Both stem temperature and mixing method affected the curing process of the bone cement, although the former had a greater effect than the latter. Raised stem temperature led to an increase in T_{max} (Scheffe's test P=0.001) and a decrease in t_{pol} (Scheffe's test P=0.001) within the bone cement. T_{max} increased by 30% (61.7°C vs 47.5°C) while the whole curing process was shortened by 16% (7 min 40sec vs 9min 10sec).

Although, both T_{max} and t_{pol} seemed to decrease when cement was vacuum mixed (43.1°C vs 47.5°C and 8min 40sec vs 9min 10sec), these differences were not statistically significant (Scheffe's test P=0.65 for T_{max}; Scheffe's test P=0.62 for t_{pol}).

When stem preheating was combined with vacuum mixing, an increase in T_{max} within the bone cement was observed (Scheffe's test P=0.01) together with a shorter t_{pol} (Scheffe's test P<0.001). T_{max} increased by 21% within the bone cement (58.5°C vs 47.5°C) while the whole curing process was shortened by 20% (7min 10sec vs 9min 10sec).

The above described effects on T_{max} were smaller within the pseudofemur: the maximum significant increase was of 5°C measured both when the stem was pre-heated and when the stem pre-heating was associated with vacuum mixing. However in general the maximum temperature was lower than 45°C except for 7 values (four values equal to 46°C, two to 47°C and one to 48°C).

7.4.2 Bending strength

The bending behaviour of the bone cement specimens extracted from cement mantles moulded simulating the clinical scenario or according to the ISO standard for mechanical characterization of the material are showed in figure 3. Four specimens were excluded by the Chauvenet's criterion (two specimens extracted from a mantle of the group 23°C VM, the other two extracted from a mantle of the group 45°C VM). All these four outliers showed a large defect on the fracture surface.

The statistical analysis of the five groups showed some effects of stem preheating and vacuum mixing both on the bending modulus (ANOVA $P<0.001$) and on the bending strength (ANOVA $P=0.003$) **(Fig.3)**.

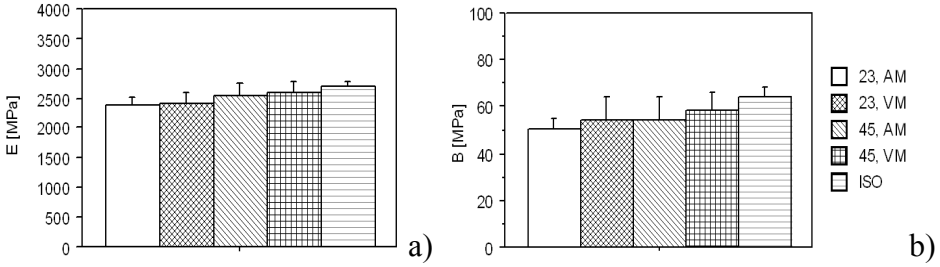

Fig3. Static bending properties (average values) of bone cement for the different groups: a) elastic modulus, b) beding strength.

Post-hoc analysis showed significant difference in bending modulus between the control group (ISO) and bone cement moulded with the stem at 23°C both mixed in air (Scheffe's test, $P=0.003$) and mixed under vacuum (Scheffe's test, $P=0.005$). Similarly findings were found for the bending strength, although a significant difference was found only between the control group (ISO) and bone cement moulded with the stem at 23°C mixed in air (Scheffe's test, $P=0.008$).

7.4.3 Fatigue strength

All the specimens except four (two specimens extracted from a mantle of the group 23°C VM, the other two extracted from a mantle of the group 45°C VM) failed in the narrow part of the specimen. Only these specimens were considered in the statistical analysis. A summary of fatigue life is shown in **Fig.4**.

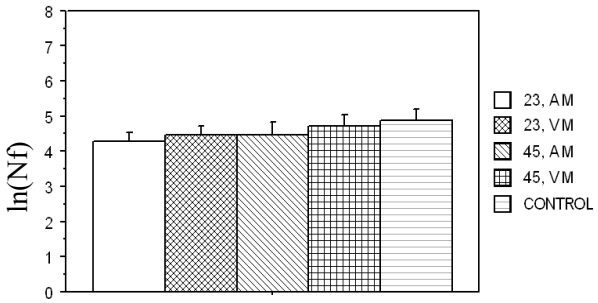

Fig. 4. Fatigue life (average values) for the five groups.

The statistical analysis of the fatigue life (lnNf) calculated for the five groups showed significant effects of stem preheating and vacuum mixing (Kruskal-Wallis $P<0.001$). The non-parametric multiple comparison test showed significant increase between the following pairs: control group (ISO) vs 23°C AM, control group (ISO) vs 23°C VM, control group (ISO) vs 45°C AM, 45°C VM vs 23°C AM. Therefore, the highest fatigue life was observed for specimens moulded according to the standardized protocol. However this value was not significant different from that of the bone cement mixed under vacuum and moulded with the stem at 45°C.

7.4.4 Porosity

All data were split into two groups depending on the analysed surface: Cross Section and Stem-Cement Interface **(Fig.5).**

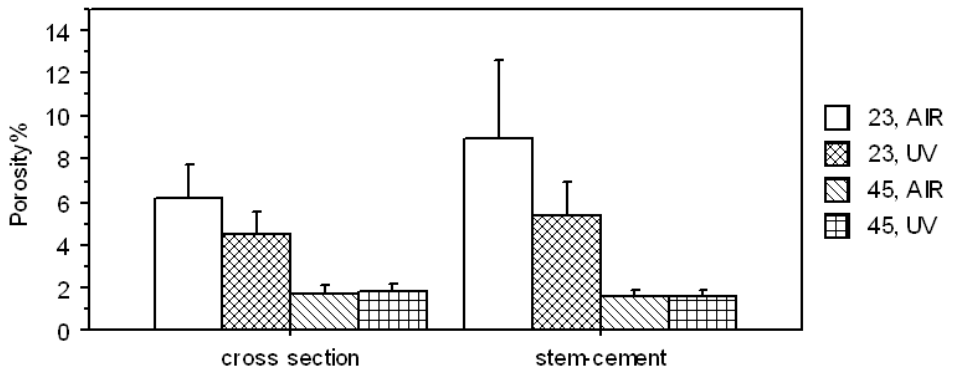

Fig 5. Porosity observed within the bone cement at different locations.

On both those surfaces, both stem preheating and mixing method had significant influence of overall porosity fraction (ANOVA $P<0.001$ in all cases). Considering the 23°C AM moulding condition as reference, on CS surfaces the porosity was reduced by 28% using vacuum mixing and by 71% preheating of the stem, while similar reduction (74%) was found combining the two techniques. These reduction were more marked on the S-CI: 40% using vacuum mixing, 82% preheating of the stem, and 82% also when both techniques were used.

7.5 DISCUSSION

This study investigated both the effect of bone cement vacuum mixing and of pre-heating the stem, before its insertion into the diaphyseal femoral canal, on the bone cement mantle quality in a simulated surgical scenario.

This study has several limitations. The experimental procedure, used to simulate the clinical scenarios, is based on several simplifications such as plastic material to simulate bone tissue, flat cement-pseudofemur interface, geometrical shape of the whole stem-cement-pseudofemur system. All these simplification were necessary to assure test repeatability, allowing the extraction of flat specimens from moulded cement mantles for mechanical testing. Additionally only a specific configuration was considered (metallic stem made of Co-alloy, polished stem surface) using one bone cement brand and one preheating temperature. These choices were necessary because of the number of samples required to reach the necessary sample size and to limit the time of test/analysis.

Despite these limitations, this study demonstrated that stem preheating and vacuum mixing have some marked effects on the cement mantle.

The reduction of curing process duration found when pre-heating the stem before its insertion, which is in agreement with data reported in literature [36, 44], confirms the accelerating effect of heat on the bone cement polymerisation. It has to be highlighted that the reduction in the curing process length is limited to the phase after the stem insertion, since it is the stem temperature that accelerates the chemical reaction. This acceleration increases maximum temperature within the bone cement, near the cement-bone interface, which has previously been reported (Iesaka et al [10] detected a rise of 6°C, i.e. 13%). The higher increase found in

this study (30%) may be explained by the different location of the thermocouples within the cement mantle in comparison with the referred study (deeper into the bone cement at the stem level and not below its distal tip). Despite this increase within the mantle, only a slight effect of stem pre-heating on the maximum temperature value (increases in the range 1-5°C) was measured within the pseudofemur near the interface with the cement. This might be caused by the poor thermal conductivity of the polymethylmethacrylate (i.e. heat does not easily escapes from the cement mass) and the thermal characteristic of the whole stem-cement-pseudofemur system. These findings are in agreement with the small differences found by Bishop et al. [6] in the temperature peak measured half way through the femoral cortex for the two different stem temperatures selected also in this study. Vacuum mixing had a smaller and different effect on the curing process. Indeed, mixing cement under the described vacuum level seems to slightly shorten the curing process, and also decrease the maximum temperature value measured within the pseudofemur. These results are in agreement with the findings of Rahman et al. [45], obtained for the same bone cement using similar vacuum level (environmental pressure and vacuum level of 0.7 Bar). When stem preheating is used together with vacuum mixing, a combination of the two previously-described effects was observed: the maximum temperature within the bone cement slightly decreased while the curing process was further shortened in comparison with the values measured preheating the stem alone, indicative of a synergic effect of the two technique on the curing process.

Both techniques have a positive effect on cement porosity but they act in different ways. Vacuum mixing decreases porosities produced during mixing [26, 38] while it can not eliminate porosities generated during cement injection, stem insertion and polymerization [46-48]. Conversely, stem preheating has no effect on the whole procedure of cement mixture handling but it affects the curing once the dough is in situ. It has been demonstrated that, increasing the stem above 43°C (which is the case in this study), curing is initiated at the stem-cement interface [44]. The reversed curing (i.e. from the stem towards the bone) eliminates the shrinkage-induced porosities at the stem-cement interface [10, 29]. The results of this study are in agreement with findings reported in the literature [6, 46]. as the highest reduction of porosity at the stem-cement interface was found when the

stem was pre-heated, while the vacuum mixing can reduce the porosities within the mantle (40%) but it was less effective at the stem-cement interface (28%).

It has been experimentally demonstrated that decreased porosity increases fatigue life of bone cement specimen [8, 48-50]. In fact, pores act as stress concentrators and therefore promote fatigue crack nucleation [10, 51]. This explains the present findings. Both vacuum mixing and stem preheating decrease the cement porosity and therefore increase its fatigue strength. The maximum increase was measured when the two techniques were associated. In this case fatigue life of cement extracted from the mantle was comparable to that measured on the specimen directly moulded (control). There are no other reports referring to the effect of stem preheating on the fatigue behaviour of the cement itself. Conversely, since stem preheating was supposed to decrease the porosity at the stem-cement interface, the mechanical behaviour of this interface has been investigated [10, 29]. However, the static or fatigue strength of this interface is not directly correlated with the fatigue strength of the material itself but it is affected by the characteristics of the stem-cement interface (mechanical interlock, micro or macro gap) which may affect its progressive debonding.

The mechanical effect of pores, although less marked, has been reported for the static behaviour of the material [38]. In fact, negligible improvement was found in the present study on bending behaviour of bone cement with reduced porosity. This is consistent with the report of Fognani et al. [36] who found a significant increased bending strength only with stem preheated at 55°. That temperature was not considered in this study since increasing the stem temperature would increase also curing temperature and therefore the associated biological risk

It is debated if porosity within the bone cement is clinically relevant. However a different point of view must be considered, i.e. the stress distribution within the bone cement. This is clinically relevant since its determine the long-term behaviour of the cement mantle [52-54]. Different parameters (prosthesis design, implant surface morphology, bone cement quality, mantle thickness, bone-cement interface integrity) affect the stress level within the cement mantle. The proposed technique seems effective in improving the quality of the bone cement.

Therefore, it could be a step towards a reduction of the highest stress within the bone cement, which has great effect on its damage accumulation process.

In conclusion, stem preheating had significant effects on the quality of bone cement making the mantle. For the investigated cement brand, the cement porosity decreased and its fatigue strength was improved significantly. This effect was greater when stem preheating was associated with vacuum mixing. Although curing temperatures also increased, it seems like that the increment within the bone near the cement interface would be small with little or negligible biological effect. However only further clinical study can confirm this conclusion.

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VIII CONCLUSIONS

The aim of this study was to identify a predictable mechanical experimental method for pre-clinical validation acrylic bone cement. Hence, three commercially available bone cements (Cemex RX, Surgical Simplex P, and CMW1) were chosen on the basis of the clinical outcome. They were investigated of in terms of: (i) mechanical properties required by ISO 5833, (ii) complex fracture characteristic: fatigue endurance limit, fatigue crack propagation and fracture toughness tests and (iii) long-term physiological-like performance: an in vitro simulation of loading spectrum that replicates all critical physiological activities. Finally, data were collected and compared with clinical outcome to identify the most predictive mechanical test for long-term performance of bone cement.

The results obtained through testing protocol defined in ISO 5833 standards, indicated CMW1 as the cement type with the best bending strength, comparing with two other cement types. This observation is opposite to clinical follow-up. That experiment confirmed the hypothesis that additional testing methods need to be defined in ISO standards to validate pre-clinically new cement brands.

The fracture properties of thee cement types were successfully determined. No significant difference was found between Simplex-P and Cemex-RX, while CMW1 demonstrated poorer fracture resistance. Obtained data were in agreement with data found in the literature and with the clinical outcome. Proposed testing protocol, to study crack nucleation and propagation within the bone cement, can be applied to rank differ cement types according to their clinical performance. Furthermore, presented procedures can be applied to validate pre-clinically new cement formulations. New cement formulation can be compared in terms of fracture properties with other bone cements with known clinical outcome.

Physiological testing protocol was applied successfully. Inducible

micromotions and permanent migrations were recorded throughout the test. After test completion, the cement mantles were sectioned and inspected with dye-penetrants to quantify the fatigue-induced cracks. Micromotions did not differ significantly between cement types (possibly because a successful prosthesis was chosen, that is very stable in the host bone). Significant differences were observed in terms of cement cracks: CMW1 induced significantly more numerous and larger cracks than Simplex-P and Cemex-RX; no difference was observed between Simplex-P and Cemex-RX. This indicates that this protocol: (i) can discriminate between "good" and "bad" cements, (ii) yields consistent results when comparable cements are tested. Therefore, the proposed protocol overcomes the limitations of existing standardized material tests for bone cements. New cements can be assessed in comparison with other cements with known (positive/negative) clinical outcome, tested with the same protocol.

Tensile fatigue behaviour was investigated for bone cement specimens obtained from cement mantles moulded in vitro, simulating the surgical scenario. The effect of stem preheating, before its insertion into the cement dough, on specimen fatigue life was studied. A commercial bone cement was selected for this study. Bone cement mixing was conducted in air, following the manufacturer instructions, and injected simulating the clinical practice. Two condition were considered: stem maintained at environmental temperature (23°C) and stem preheated to 45°C. Four repetitions of the whole procedure were performed for each group obtaining a total of 32 specimens. All specimens underwent fatigue testing (stress ratio=0, maximum tensile stress =15MPa) until failure. Both two-parameter and three-parameter Weibull distributions were initially used to analysis the fatigue life dataset. However, the two-parameter distribution was chosen for both group on the basis of the coefficient of determination used to test the goodness-of-fit. Stem preheating seems to have a negligible effect on fatigue behaviour of the studied bone cement in the low range of fatigue life (up to 10^5). However, above this cycle number, stem preheating seems to reduce the probability of failure. These findings were discussed in the text.

APPENDIX A

THE COMPRESSIVE PROPERTIES AND FRACTURE TOUGHNESS OF PMMA BASED ACRYLIC RESIN REINFORCED WITH MILLED AND MICRONISED GLASS FLAKES

To be submitted*: J. Dental Materials*

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9.1 Introduction

The poly(methyl methacrylate) (PMMA) based bone cement is a material widely used in orthopedics. PMMA is low cost, easy to manipulate as an accurate fitting material anchoring components in total joint replacement and for bone tissue augmentation. Moreover, PMMA based bone cement in its bulk polymerised form, demonstrates optimal biocompatibility with the host bone tissue [11, 34]. Despite these favorable characteristics, the clinical outcome only for cemented hip prosthesis shows that after 10 and 20 years from primary implantation respectively 7% and 21% need to be revised. The principal cause of

revisions is aseptic loosening (60%), which can be due to mechanical failure of cement layer. Long term success depends upon implant surgical technique, implant design and bone cement properties.

Given that, *in vivo* bone cement is subjected to cyclical loading, it is of great importance to improve mechanical strength and ability to resist fracture of the material. Over last 20 years, many studies were performed to improve mechanical properties of PMMA based bone cement mostly changing chemical formulation but also using reinforcing additives. Kim et al (1994, 1996) have reported that addition of wire coil into the bone cement can significantly improve its mechanical resistance in a simulated dynamic compression-compression tests. However, no further information have been published about in vivo performance of wire coil filled bone cement. Another innovative application in bone cement reinforcement has been presented by Koth et al (2006, 2006). His studies proved that tensile and fracture properties of unfilled bone cement can be improved by the addition of short titanium fibers, however, appear to be largely dependent on the orientation of the fibres in the polymer matrix [10]. On the other hand, addition of metal fillers could increase wear debris and in effect cause loosening of an implant.

Franklin *et al*. recently investigated an innovative application of glass flakes for denture base reinforcement [8]. Low-cost micronised flakes available as a commercial reinforcing additive were mixed to a denture base acrylic material in concentrations of 5, 10 and 20%. Higher concentrations appeared to have a deleterious effect on the viscosity of the compound. Initial results indicated that the addition of glass flakes increased the fracture toughness of the base material by 52-69%. In addition, the mixing procedure was not altered by the inclusion of the reinforcing agent as this was added to the polymer powder prior to polymerisation.

Moreover, glass flake as a filler or reinforcer demonstrates in polymer systems demonstrates many benefits e.g., improves wear and abrasion resistance, reduces shrinkage of curing polymer, improves impact strength. That characteristics appears to be optimal for applications of glass flakes in orthopedics. Nevertheless, the influence of particle size distribution (e.g. milled or micronised) and the effect of the additive on the porosity of the polymer were

not jet studied. An expansion of this initial evaluation is required prior to the recommendation of using glass flakes to reinforce PMMA based bone cement.

The aim of this study was to evaluate the compressive properties and fracture toughness of reinforced PMMA acrylic resin with glass flakes additives of different particle size distributions (milled and micronised) and concentrations.

9.2 Materials and methods

9.2.1 Preparation of reinforced acrylic specimens

Commercially available PMMA acrylic material was selected as the control material and the medium to be reinforced with glass flakes. The material was a composite of PMMA-powder and MMA-monomer, without radiopacifier. A ratio of 3 PMMA : 2 MMA (wt/wt) mixture preparation was used in all cases. Untreated micronised and milled glass flakes (GF) of modified 'C' composition (Glassflake Ltd, Leeds, UK) were used as the reinforcing additives.

The micronised GF (product code GF002) were disk-like shaped, nominally 1.3-2.3 μm thick and 88% had a diameter <50μm. The milled GF (product code GF200M) were of similar thickness with 65% having a 50-300μm diameter and 25% having a diameter <50μm. Based on previous investigations [8], four concentrations of glass flake were tested: 1, 2, 5 and 10% by total mass of the PMMA mixture. The GF were introduced into PMMA powder prior to mixing to avoid the presence of agglomerated flake particles.

The acrylic resin was mixed in a temperature controlled environment at 23ºC. In a proportional of cases, a vacuum mixing system was used to assess the effects of the mixing procedure on the mechanical properties of the denture base. A mixing phase of 90 seconds was employed, followed by 60 seconds rest as the polymer entered the dough phase. The resin was then introduced into moulds that were closed and compressed to ensure a maximal fill. The samples were allowed to cure for 24h.

For each compressive test group, eight reinforced acrylic samples (H 12mm, Ø 6mm) were generated according to ISO5833. Since compressive test had to be

performed 24h after mixing, six specimens were used for compression tests and two were assigned for microCT assessments.

For double torsion tests, specimens of dimensions 75mm x 35mm x 4mm were prepared in a manner previous outlined [8]. In all cases a longitudinal 90° groove of 1mm depth was milled along the central axis of the specimen face. To initiate the crack within the longitudinal groove, a 3mm notch was created at the end of each specimen. In summary, for each test group five specimens were prepared.

9.2.2 Mechanical Testing

Specimens prepared for compression tests were positioned centrally between two parallel steel endplates on a materials testing machine (Lloyd instruments, Fareham Hampshire UK) attached to a personal computer running a compression program to control the experimental conditions. In accordance with ISO5833, a single point compressive load was applied to the upper endplate in stroke control at 20mm/min.

The double-torsion test has been defined in the literature as the most technique-sensitive of the fracture toughness testing methods and provides most indicative properties of dental composites [9]. The concept of double-torsion test is generally defined as a test of geometry whose stress intensity factor is constant along the propagation of the crack.

For the double torsion tests, all samples were placed in a custom-made rig with the grooved surface on the underside positioned centrally between stationary rollers (Ø=3mm) spaced 20mm apart (Figure 1). A compressive load was applied at 1mm/min evenly through two connected steel spheres (Ø=3mm) positioned equidistant from the notched surface of the test specimen. The crack propagation force was defined as the peak load causing failure. Fracture toughness was calculated using a previously defined equation [8, 17].

Fig. 1. Experimental apparatus for the double torsion tests.

9.2.3 Micro-CT assessment

Micro-CT scans were performed using a micro-CT system (μCT80, Scanco Medical AG, Bassersdorf, Switzerland) to evaluate the porosity of the specimens. Spatial resolution was set at 148μm (114mA, 70kV). In all cases, a large volume of interest was chosen for each specimen (>95% of the total specimen) and values for the porosity were calculated using a computer protocol calibrated to a hydroxyapatite phantom.

9.2.4 Statistical Analysis

Mechanical data generated for each test group were compared using repeated measures analysis of variance (ANOVA) and Fisher exact test (alpha = 0.05) test for fracture toughness. Significance was accepted at $P<0.05$. Mean porosity values were calculated for the different GF additives, concentrations and mixing procedure.

9.3 Results

9.3.1 Compressive testing

- Results from the compression tests are presented in Fig.1and 2.

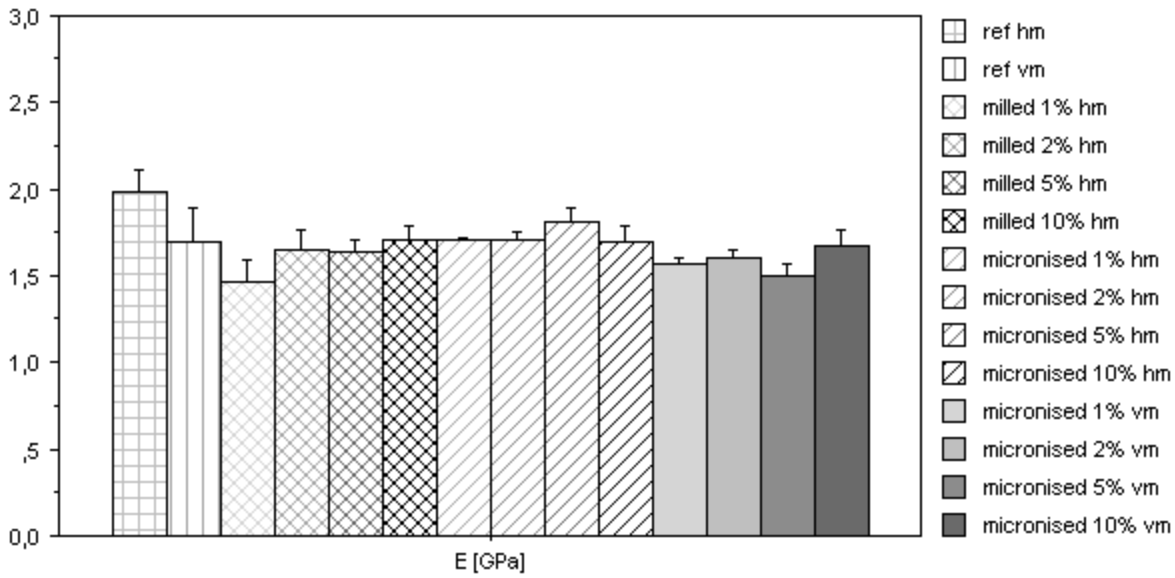

Fig. 1- Elastic modulus of the PMMA reinforced with micronised and milled glass flakes (for both glass flakes types four differ concentration was shown).

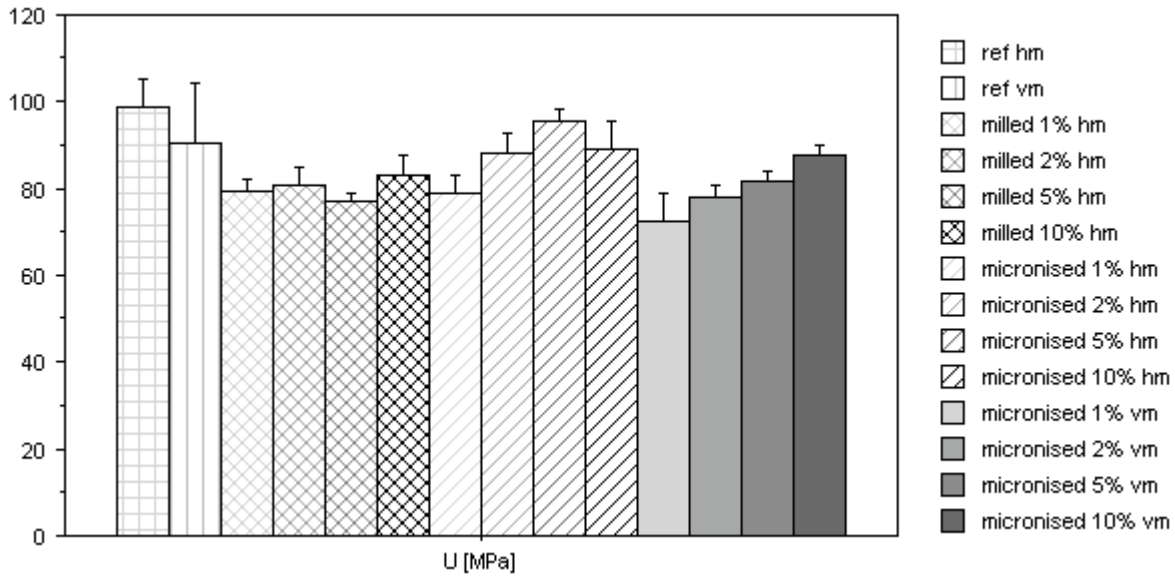

Fig. 2- Compressive strength of the PMMA reinforced with micronised and milled glass flakes (for both glass flakes types four differ concentration was shown).

- The mixing method appeared to have a significant effect on the mechanical properties of the composite. The hand mixing procedure significantly increased the elastic modulus (Fisher's exact test, P<0.001) and compressive strength (Fisher's exact test, P=0.013) in comparison to vacuum mixing.
- The addition of milled or micronised glass flakes significantly reduced the elastic modulus and compressive strength in comparison to the base composite (Fisher's exact test, P<0.001) . Milled glass flakes produced the greater reduction in elastic modulus (Fisher's exact test, P=0.0014) and compressive strength (Fisher's exact test, P=0.015) in comparison to the micronised glass flake additions.
- However, in comparisons including the control group the concentration of glass flakes appeared to have no significant effect on the reduction in modulus or compressive strength.
- In comparisons excluding the control group, a positive correlation was found between the proportion of glass flake additions and the elastic modulus and compressive strength. (i.e. increasing proportions of glass flake additions resulted in an increase in elastic modulus and compressive strength)

9.3.2 Fracture toughness

- The mean fracture toughness (Kic) is shown for the different cement sets in Fig. 3.

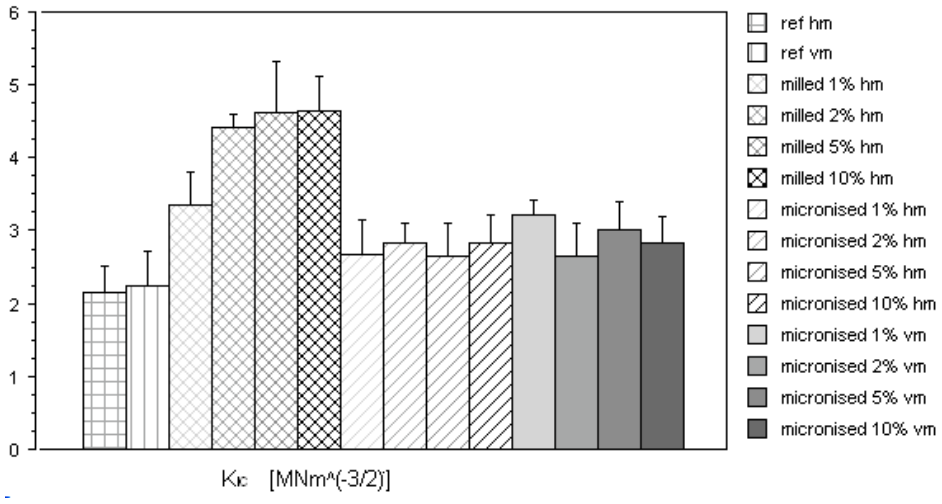

Fig. 3- Fracture toughness values for the PMMA reinforced with micronised and milled glass flakes (for both glass flakes types four differ concentration was shown).

- Micronised and milled glass flake additions significantly increased the fracture toughness in comparison to the base composite (Fisher's exact test, $P<0.001$). The milled flake additions had the greatest effect on Kic.
- No significant difference in Kic was found between the hand and vacuum mixing procedures (ANOVA test, $P=0.25$), although the vacuum mixing procedure provided a lower spread in Kic values (ANOVA test, $P=0.11$ for vacuum mixing and $P=0.88$ for hand mixing).
- All concentrations of glass flake additions increased Kic. The proportion of glass flake additions had the greatest influence on Kic in comparison to the mixing procedure or the type of glass flake (milled or micronised).

9.3.3 Porosity

- The mean porosity of the samples was 4.81% ±2.64%.
- No significant correlation was found between porosity and the mixing procedure, the type of glass flake addition or the concentration of flake additive.
- The variation in the porosity is thought to have been introduced through both the mixing and preparation of the samples which led to pores of various dimensions

9.4 Discussion

Although poly (methyl methacrylate) has become a standard material for use as a denture base, improvements to the strength characteristics are required to reduce the risks of fracture and its associated complications. Previously, various particulates and fibers have been added to PMMA denture base with the aim of improving the mechanical properties, although most have failed to provide significant improvements or have introduced considerable complicity to the mixing procedure. In this study, the mechanical properties and porosity of PMMA based denture acrylic material reinforced with two type of glass flake of varying quantities were investigated to evaluate the suitability of using glass flake as a reinforcing agent.

Reinforcement of the PMMA acrylic resin with milled and micronised glass flakes of various quantity did not appear to provide significant improvements to the compressive strength or elastic modulus of the base material. Moreover, the mechanical properties decreased when mixed under vacuum pressure. It is possible that the decline in mechanical behaviour is partially due to monomer suction from the mixture. A reduction in the amount of monomer creates shorter polymer chains and hence a final PMMA material that is less resistant to failure. This is in agreement with previously published studies that demonstrated a reduction in the monomer to powder ratio when using a vacuum mixing procedure [36, 37].

As K_{ic} is described as a function of the load and dimensions [8, 17], the crack should propagate with constant load at a constant displacement rate. In our test series, the constant load proved more difficult to define as the load during crack propagation did not remain stable. In a number of samples, a sudden decrease in load was observed after the maximum load was achieved, reducing the stress intensity factor and creating a saw-tooth profile (Figure 3). This load-deformation profile was consistent across samples within each testing group and is possibly due to the presence of voids in the specimens. In these cases, an average value was calculated to determine the constant load for calculating the fracture toughness.

Additions of milled and micronised glass flakes of all concentrations generated significant increases in the fracture toughness of the composite. Milled GF provided the greatest improvement. Vacuum mixing appeared to provide more consistent improvements, although the maximum improvement in K_{ic} were found with composites that were generated through the hand mixing procedure. These differences in fracture toughness improvement, however, did not appear to be related to the porosity of the material. Further work is now required to evaluate the interaction between the glass flake additive and the base material to determine the key factors influencing the fracture toughness of the composite.

An important consideration in reinforcing denture base material with particulates is the effect on the processing and the additional equipment required. In this study, the addition of glass flakes to the acrylic powder did not alter the formulation process or require any specialist mixing equipment, although it

should be noted that the mixture required constant stirring to avoid the amalgamation or settling of the glass flakes.

In addition to improving the mechanical properties of the denture base, the aesthetic characteristics are an important consideration when attempting to modify the composite material. Previously, this has prohibited the routine use of reinforcing agents despite the improvements seen in the mechanical behaviour [19]. The aesthetic implications of adding glass flakes to PMMA have previously been considered and were reported to generate a grainy or sparkly appearance depending on the surface finish and the way the light reflected on the material. The effect of different size distribution, however, was not evaluated in this study and should be considered before the routine use of glass flakes as a reinforcing agent can be recommended.

9.5 Conclusions

- No improvement of the compressive strength and elastic modulus was observed for PMMA with the addition of glass flakes. In addition, the concentration or size of the glass flake particulates appeared to have no significant effect of the mechanical properties.
- Vacuum mixing may reduce the mechanical compressive properties of PMMA.
- Fracture toughness of PMMA resin can be significantly improved by the addition of milled glass flakes. The maximum increase in fracture toughness was obtained for milled glass flake of 5% or 10% concentration.
- No significant effect of mixing method on fracture toughness was observed, although vacuum mixing appeared to provide more consistent improvements irrespective of glass flake size or concentration.
- The porosity of the composite did not appear to be affected by the mixing process. Milled glass flakes generated lower porosity in comparison to micronised flake additions.
- Glass flakes can be added to PMMA denture base without any significant alterations to the processing procedure and further work is now required.

9.6 References

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