Tanner, K.E., Wang, J.-S., Kjellson, F. and Lidgren, L. (2010) *Comparison of two methods of fatigue testing bone cement.* Acta Biomaterialia, 6 (3). pp. 943-952. ISSN 1742-7061

Comparison of Two Methods of Fatigue Testing Bone Cement

K.E. Tanner[1,2], Jian-Sheng Wang[2], Fred Kjellson[2] and Lars Lidgren[2]

[1]Departments of Mechanical and of Civil Engineering, University of Glasgow, Glasgow, G12 8QQ, UK

[2]Department of Orthopaedics, Lund University, Lund S-22185, SWEDEN

Corresponding author:
Professor K.E. Tanner
Departments of Mechanical and of Civil Engineering,
James Watt South Building
University of Glasgow
Glasgow
G12 8QQ
UK
Phone: +44 141 330 3733
Fax: +44 141 330 4343
e-mail: E.Tanner@eng.gla.ac.uk

ABSTRACT

Two different methods have been used to fatigue test four bone cements. Each method has been used previously, but the results have not been compared. One method tests at least 10 samples over a single stress range in tension only and uses Weibull analysis to calculate the median number of cycles to failure and the Weibull modulus. The second test regime uses fewer specimens at various stress levels tested in fully reversed tension-compression, and generates a stress versus number of cycles to failure (S-N) or Wöhler curve. Data from specimens where the fracture surface contains pores greater than 1mm across is rejected. The single stress level test is quicker to perform however, provides only tensile fatigue data, but the material tested includes pores, thus more physiological cement is tested. The multiple stress level testing regime uses combined tension and compression loading and multiple stress levels, thus more physiological loading, but excludes specimens where the defects are greater than 1mm across, so is less representative of cement *in vivo*. The fatigue lives between the cements were up to a factor 15 different for the single stress level tension only tests, while they were only a factor of 2 different in the fully reversed tension-compression testing.

The single stress level results are more effected by surface flaws, thus the differences found using the multiple stress levels are more indicative of differences in the fatigue lives of the cements. However, the single stress level tests are quicker, so are useful for initial screening.

Keywords: Bone cement, fatigue, Wöhler analysis, Weibull analysis, biomechanics.

INTRODUCTION

Fatigue failure of bone cement is considered to be a precipitating factor in the aseptic loosening of cemented joint replacements. Failure of cement has three effects, firstly, it reduces the ability of the cement mantle to provide uniform load transfer from the implant to the supporting bone [1], thus altering the biomechanics of the implant - supporting bone system. Secondly, fracture of the cement leads to the production of wear particles of cement and opacifier which both directly increase bone resorption [2,3] and increase the production of polyethylene wear particles which have also been shown to increase bone resorption [4]. Thirdly, the failure of the cement allows wear particles to track from the implant-cement interface to the cement-bone interface. All these mechanisms combine to accelerate implant loosening and thus eventually to implant revision. Approximately 75% of hip revision surgery is due to aseptic loosening [5], costing in the 1990s an average of US$ 21,224 per revision [6]. Thus investigation of the fatigue behaviour must be an essential component of pre-clinical assessment of new bone cements.

However, various methods have been described to perform fatigue testing of bone cement and to compare the fatigue lives of different cements. Two of the more common methods are fatigue testing over a single stress range of at least 10 samples, using minimal exclusion criteria, followed by Weibull statistical analysis to compare the mean fatigue lives. The second method is to develop a complete S-N or Wöhler curve by testing a smaller number of specimens at each of a series of stress levels [7]. From this data, both the mean number of cycles to failure at each stress level and the regression line for the each cement, calculated using the logarithm to base 10 of the number of cycles to failure, can be compared.

The first of these methods, single stress level tension only fatigue testing was used by Harper and Bonfield [8]. They used half size ISO 527 specimens, that is specimens 75 mm long and nominally 3.5mm thick with a gauge section 25mm long and 5mm wide. Their testing was performed between 0.3 and 22MPa tension only in air at room temperature. They compared the fatigue lives of 10 different cements mixed at atmospheric pressure but polymerised under pressure and used Weibull statistics for comparison. They found a huge range in the median fatigue lives ranging from 164 cycles to failure for Boneloc®, through to 27,892 for Palacos R and 26,667 for Simplex P, and for these last two cements the long fatigue lives matched the reported good clinical outcome with a low risk for revision [5]. Johnson *et al.* [9] used cylindrical cross-section specimens and a slightly lower stress range of 0.3 to 20MPa to show that the fatigue life increased when the test frequency was increased or when tested in water at 24˚C, while increasing the temperature to 37˚C decreased the fatigue life. Dunne *et al.* [10] investigated the relationship between porosity and fatigue properties and found that reducing the mixing pressure greatly improved the mean fatigue strength. Both Harper and Bonfield [8] and Dunne *et al.* [10] tested and analysed the data from every specimen.Jeffers *et al.* [12] similarly used tension-tension fatigue with flat test specimen, but using four stress levels, at 20, 15, 11, and 7 MPa with a constant R ratio of 0.1, that is the minimum stress was 10% of the maximum stress and produced an S-N curve.

In comparison to these flat dumbbell specimens Lewis [15] and Lewis *et al.* [16] used cylindrical dumbbells to ASTM 2118 [7]. Their specimens were aged and tested in air at 22˚C, only data from specimens with surface flaws or internal pores less 0.25mm in diameter was included. Lewis [15] applied fully reversed tension-compression at ±15MPa and found that both vacuum mixing and increasing the test frequency increased the fatigue life. Lewis & Janna [18] investigated the impact of the cross-sectional shape on the fatigue life outcome. Two specimen types were used, flat dumbbell specimens to ASTM D-638-01 Type IV which were compared to circular specimens to F2118-01a. These gave specimens with the same nominal cross-sectional area, but different surface areas. Three cements were tested at ±15 MPa and at a frequency of 5 Hz, the circular cross-section specimens had longer fatigue lives than the rectangular cross-section specimens.

Thus two major types of tests and specimens have been used, rectangular cross-section and a single load regime and circular cross-section at multiple stress levels. The first of these test regimes requires fewer specimens and thus less time to complete the tests, but the question remains whether information is lost by not going through the full ASTM F2118 test regime at multiple stress levels.

Recently Refobacin® Bone Cement R and Refobacin® Plus Bone Cement have been developed as to be equivalent to Refobacin Palacos® R and Palamed® G respectively. These new cements are generally equivalent to the previous formulations, although with minor changes in the colourant used to differentiate the cement from the surrounding bone. Dall *et al.* [19] using static strength tests, such as impact, compression, bending and tension tests have found no significant mechanical differences between these cements, although they did see differences in the handling behaviour [20]. However, it is not clear whether any influence will be seen on the fatigue life.

In this study these four cements have been tested using both fully reversed tension compression on cylindrical specimens and in tension only on rectangular cross-section specimens in saline at 37˚C and the results have been compared. To clarify the differences found, density measurements, fractography and radiography have been performed.

MATERIALS AND METHODS

Four bone cements (Table 1) were tested, namely Refobacin® Bone Cement R andRefobacin® Plus Bone Cement (Biomet Cementing Technologies, Sjöbo, Sweden), and Refobacin Palacos® R and Palamed® G (manufactured by Kulzer). All these cements are based on poly(methylmethacrylate with methylacrylate co-polymer). These cements contain zirconium dioxide as an opacifier and gentamicin antibiotic in the powder phase. (Table 1)

Table 1. Composition of the four bone cements tested (Manufacturer's data).

		Refobacin® Bone Cement R	Refobacin® Palacos R	Refobacin® Plus Bone Cement	Palamed® G
Powder (40.8/44.9 g)	Poly(methyl acrylate, methyl methacrylate)	33.6 g	33.6 g	38.3 g	38.3 g
	Gentamicin sulphate	0.8 g	0.8 g	0.9 g	0.9 g
	Zirconium dioxide	6.1 g	6.1 g	5.3 g	5.3 g
	Benzoyl peroxide	0.3 g	0.3 g	0.4 g	0.4 g
	Chlorophyll	-	+	-	+
Monomer (20 ml)	Methyl methacrylate	18.4 g	18.4 g	18.4 g	18.4 g
	N,N-dimethyl-p-toluidine	0.4 g	0.4 g	0.4 g	0.4 g
	Chlorophyll	+	+	+	+
Total mass		59.6g	59.6g	63.7g	63.7g
Powder to Liquid ratio /g ml^{-1}		2.04	2.04	2.245	2.245
Wt% Gentamicin sulphate		1.3%	1.3%	1.4%	1.4%
Wt% zirconium dioxide		10.2%	10.2%	8.3%	8.3%

It should be noted that 18.8g of liquid monomer is 20ml of liquid.

The studies were performed in two laboratories and the results were blind between the laboratories until the combined analysis was performed for this study. In all cases the cements were prepared in the manufacturer's recommended manner. The cements were stored and mixed at room temperature. All the bone cements were vacuum-mixed in Optivac® mixing systems (Biomet Cementing Technologies AB, Sjöbo, Sweden) and two minutes after the start of mixing were injected into the moulds. Two types of fatigue testing were performed.

Single Stress Level Tension-Tension Fatigue Tests

For the single stress level tension only tests half-size ISO 527 flat dumbbell specimens, nominally 4mm thick with a gauge section 25mm long and 5mm wide were directly moulded in polytetrafluoroethylene (PTFE) moulds, giving single stress level rectangular (SSR) specimens Table 2). After 20 to 30 minutes under a pressure of 820MPa the specimens were removed from the mould and were examined for pores against a strong light and specimens containing visible pores (>1.0mm diameter) were excluded from the study. The SSR specimens were loaded under force control between 0.3 and 22 MPa at 2 Hz using sinusoidal loading in tension-tension as described by Harper and Bonfield [8] and others. Testing was performed using an Instron 8511.20 Load frame with an MTS controller running MTS Teststar II® software. The number of cycles to failure was recorded and the data from all tested specimens was included. A minimum of 11 and up to 31 specimens of each cement were tested. The Weibull number was calculated using eqn 1:

$$\text{Weibull number} = \ln(\ln(1 - \ln(1 - \text{probability of failure}))) \quad (1)$$

where the probability of failure was calculated using Bernard's correction. A Weibull model of the natural logarithm of number of cycles to failure versus the Weibull number was used to calculate the mean number of cycles to failure and to display the data.

TABLE 2 Comparison of test specimens

	Single Stress Level rectangular SSR specimens	Multiple stress level cylindrical MSC specimens
Standard Used	ASTM	ISO
Cross section	Rectangular – 4mm × 5mm Circumference = 18mm Cross-sectional area = 20mm^2	Circular – diameter 5mm Circumference = 15.7mm Cross-sectional area = 19.6mm^2
Gauge section	Length 25mm Surface area 450mm^2	Length 10mm surface area 157mm^2
Manufacturing pressure	820MPa	Yes but not quantified
Machined before testing	No	Yes from rods of cement

Multiple Stress Range Fully Reversed Tension-Compression Fatigue Tests

To generate the stress-number of cycles or Wöhler curve, the cement, mixed as before, was injected into 10mm diameter cylindrical stainless steel moulds which were pressurized for a few minutes. The mould was then placed in an incubator at 37˚C for at least one hour to allow setting and polymerization of the cement, prior to specimen removal from the moulds. After a minimum of 24 hours at 37˚C in air the specimens were machined into cylindrical dumbbells according to ATSM F2118-03 [7], giving specimens with a nominal 5mm diameter by 10mm long gauge length with 8mm diameter gripping shoulders, giving multiple stress level cylindrical (MSC) specimens (Table 2). Specimens were radiographed to exclude those with pores greater than 1mm in diameter, compared to the pore size of 1.7mm determined by Cristofolini *et al.* [22] to give a 50% chance of initiating specimen fracture. Testing was performed at 5 Hz in fully reversed tension-compression at ±10.0, ±12.5, ±15.0, ±20.0 or ±30.0 MPa maximum stress and were tested to failure or 5 million load cycles, the run-out value given by ASTM F2118 [7]. Eight specimens were tested per stress level. If a pore greater than 1mm across was visible on the fracture surface, the data was rejected and the specimen replaced. The S-N or Wöhler curve was generated by plotting the logarithm to base 10 of the number of cycles to failure against the maximum applied stress.

For both fatigue test regimes all testing was performed at 37˚C in phosphate buffered saline (PBS) on specimens that had been aged for between 1 and 6 weeks in PBS at 37˚C, the aging time range suggested by Lewis and Austin [21]. Both types of specimens were held in MTS immersible axial-torsion manually tightened stainless steel grips irrigated with a continuous flow of PBS at 37˚C throughout the testing (Figure 1).

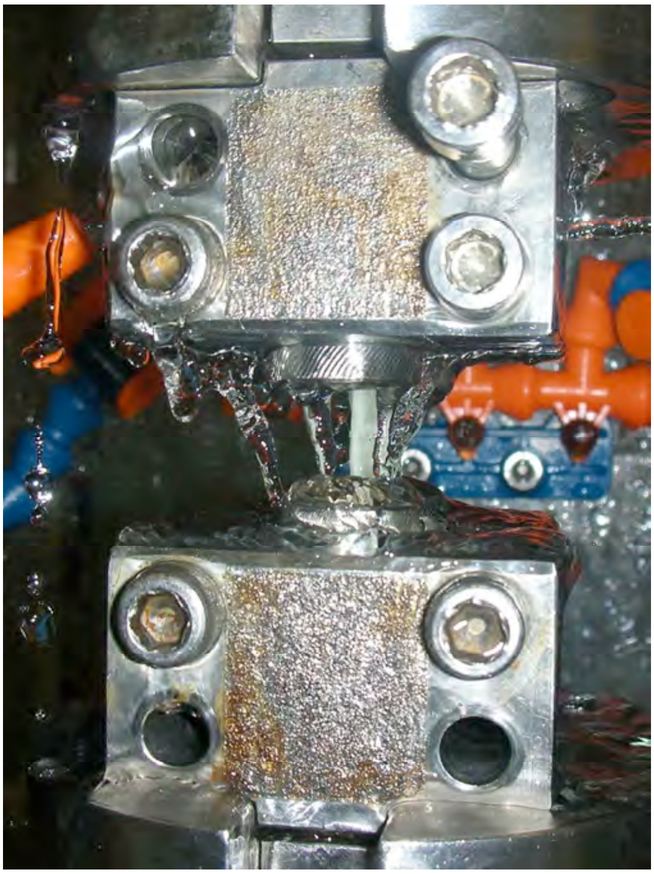


Figure 1 Close up of a test specimen showing the flowing PBS fully covering the specimen

Physical Characterisation

After the fatigue testing and data analysis specimens were selected for physical characterization. In all cases specimens which had failed at close to the median number of stress cycles were chosen for analysis. From the SSR six were chosen. For the MSC specimens two subjected to each of ±10MPa, ±15MPa and ±30MPa stress levels were chosen again giving a total of six specimens. The physical characterization consisted of radiographic analysis of the included pores, surface roughness of the surfaces of the gauge lengths, density measurements of the gauge region and Scanning Electron Micrography (SEM) of the fracture surfaces.

Radiographic Analysis

Six specimens per group, that is cement and test method were radiographed at 50V and 16mAs to give an indication of the number of pores and their size. Radiography was performed using a Diacom system thus providing digital data In the gauge region only the number and size of the pores were estimated.

Surface Roughness

The surface roughness of six specimens from each from each set of test specimens was measured using a Perthometer M4P (Mikromess AB, Järfalla, Sweden) along the length of the specimen, thus perpendicular to the fracture surface. The SSR specimens were measured on one flat and one profiled side, over a distance of 8mm near fracture surface, for each specimen three measurements were taken per surface per specimen. For the MSC specimens the measurements were taken at six positions around the specimen, again the measurements taken over a distance of 8mm near fracture surface.

Density Measurement

To consider the effect of the different pressurization regimes the density of six specimens per cement for each test regime was measured using a AE 260 (Mettler Instrument Corporation, Greifencee, Switzerland) density measurement kit based on Archimedes' principal. The gripping shoulders were sawn off the gauge section and the density of the gauge section alone was measured. Specimen density was calculated using equation 2:

$$\rho = \frac{m_a \times \rho_{water}}{m_a - m_w}$$

where m_a is mass of the specimen in air, m_w is mass of the specimen when suspended in water and ρ_{water} is the density of water, 0.99681 Mg m^{-3} at 26°C.

Electron Microscopy

Scanning Electron Microscopy (SEM) was performed on the fracture surfaces of specimens which had failed close to the mean fatigue life for that batch of specimens, using a JOEL JSM700F SEM. Prior to imaging the specimens were coated with gold. For SSR specimens, one specimen of each cement was examined. For the MSC specimens SEM was performed on specimens from the highest and lowest applied stress levels to consider any effects produced by the stress levels and thus the number of cycles to failure.

Statistical Analysis

The ANOVA Post Hoc Bonferroni/Dunn test was used to compare the number of cycles to failure at each individual stress level and for all bone cements, as well as to compare the Ra values and densities of the different specimens.

RESULTS

Fatigue Testing

The results from the SSR testing are shown in Figure 2 plotting ln(number of cycles to failure) against the Weibull number. The median number of cycles to failure calculated from this graph for each cement are shown in Table 2. It can be seen that all four cements showed high correlation, with the R^2 value being 0.95 or higher. The gradients, that is the Weibull moduli, and the median number of cycles to failure for Refobacin Palacos® R and Refobacin® Bone Cement R are extremely close. The Refobacin® Plus Bone Cement had the higher Weibull modulus and underwent a greater median number of cycles to failure than Palamed® G. However, using a Mann Whitney U test to compare these two sets of data showed that the differences are not statistically significantly. The highest Weibull modulus, that is the lowest range of fatigue lives was seen for the Refobacin® Plus Bone Cement. For the Refobacin Palacos® R and Refobacin® Bone Cement R the median fatigue lives are a factor of 11-12 less than that for Palamed® G and a factor of 13-15 less than that for Refobacin® Plus Bone Cement.

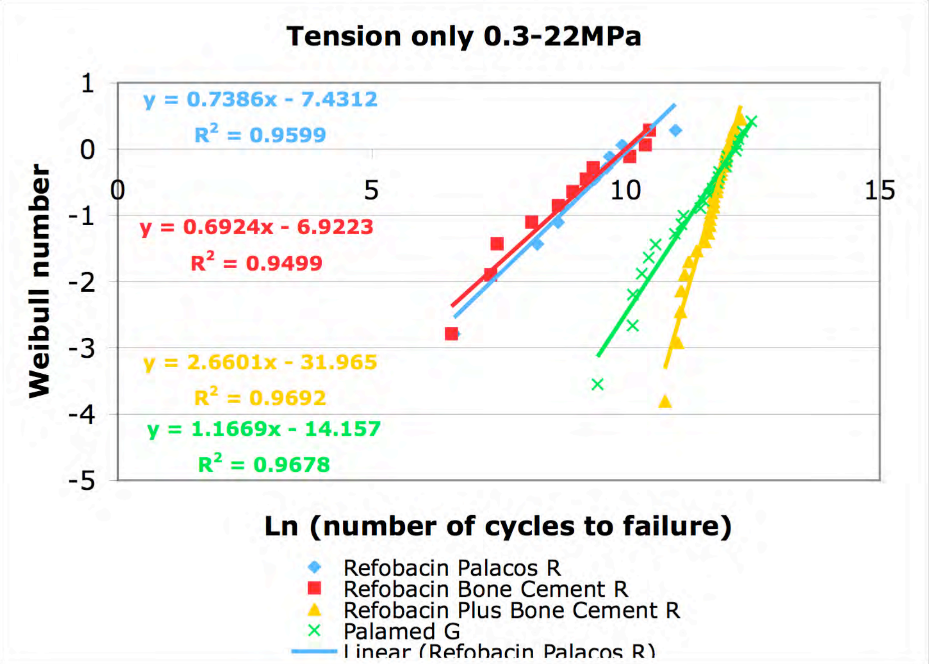


Figure 2 ln(number of cycles to failure) against the Weibull number for the four different bone cements, Refobacin® Palacos R ◆, Refobacin® Bone Cement R ■, Refobacin® Plus Bone Cement R ▲ and Palamed G ×

The MSC data for all four cements is presented in an S-N (stress - number of cycles to failure) or Wöhler graph in Figure 3. Again the fatigue behaviour for Refobacin® Palacos and Refobacin® Bone Cement R are nearly identical, but in these tests Palamed® G also shows similar results. The only cement to show an increased fatigue life is Refobacin® Plus Bone Cement and the difference in this test regime is a factor of approximately 2 over the entire stress range tested. When the individual stress levels are considered the differences range from, at ±30MPa, between Palamed® G having a factor of approximately 1.4 greater fatigue life than Refobacin Palacos® R or Refobacin® Bone Cement R and Refobacin® Plus Bone Cement having approximately 2.0 greater fatigue life than Refobacin Palacos® R or Refobacin® Bone Cement R. At ±12.5MPa, Refobacin® Plus Bone Cement had a fatigue life over 5 times greater than Refobacin Palacos® R and a factor of 2.8 greater fatigue life than either Refobacin® Bone Cement R or Palmed® G. At ±10 MPa none of the Palamed® G specimens survived to 5 million cycles while one of the Refobacin Palacos® R, three of the Refobacin® Bone Cement R and five of the eight Refobacin® Plus Bone Cement were still intact after 5 million load cycles. Thus Refobacin® Plus Bone Cement had a fatigue life between 1.7 and 5 times greater than the other three cements depending on stress level.

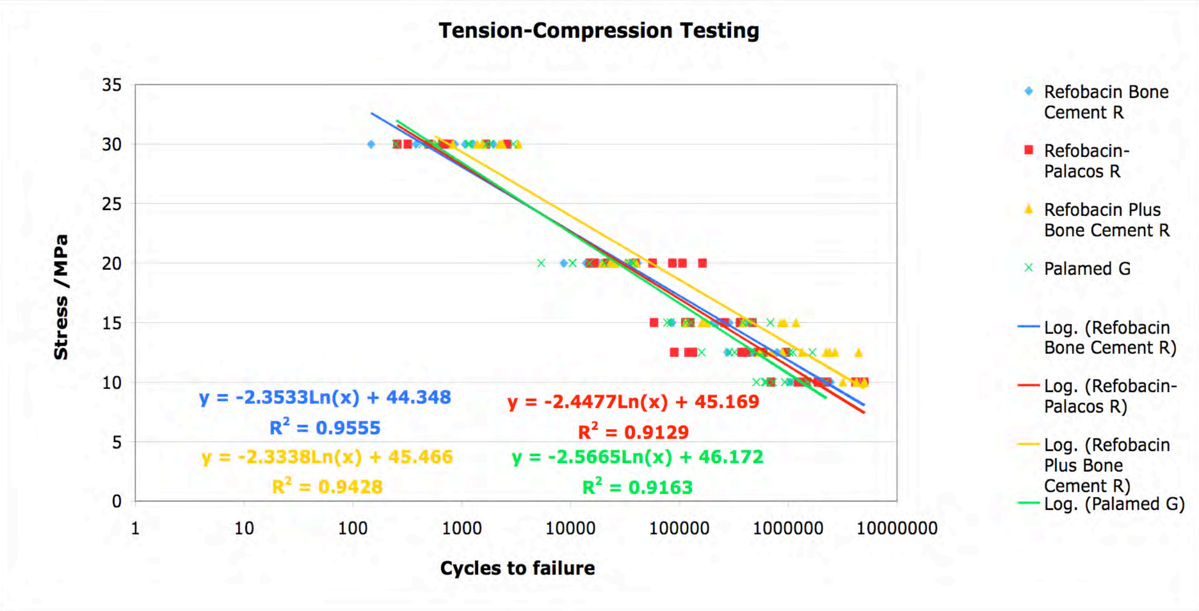


Figure 3 Stress vs number of cycles to failure for the four different bone cements Refobacin® Palacos R ◆, Refobacin® Bone Cement R ■, Refobacin® Plus Bone Cement R ▲ and Palamed G ×

Statistical analysis using One Way ANOVA Post Hoc showed no differences at ±30MPa, ±20MPa, ±15MPa between any of the cements. However at ±12.5MPa and ±10MPa Refobacin® Plus Bone Cement had statistically longer fatigue lives than any of the other three cements. When the five stress levels were combined and a Two Way ANOVA Post Hoc test was performed again Refobacin® Plus Bone Cement statistically had a longer fatigue life than any of the other three cements with no differences between the other three cements.

Physical Characterisation

To consider the reasons for these relative differences in the fatigue lives in these test the specimens were characterized physically.

Roughness

The SSR specimens are moulded with a rectangular cross-section, so have sharp corners ,also due to the interaction with the mould surfaces have rougher surfaces, thus a greater potential for crack initiating surface defects, while the MSC specimens have been machined down from moulded specimens and thus would be expected to have smoother surfaces. The values for various sides of the MSC specimens were compared and found not to be significantly different so these data were combined. The Ra values for both shapes of specimens are shown in Table 3. No significant differences can be found between Refobacin Palacos® and Refobacin® Bone Cement or between Palamed G and Refobacin® Plus Bone Cement whether as SSR or MSC specimens. When comparing the shape of specimens the SSR shape shows a trend of higher roughness compared to the cylindrical specimens (Table 3, p=0.06). Furthermore, Refobacin Palacos® and Refobacin® Bone Cement show higher roughness than Palamed G and Refobacin® Plus Bone Cement (p<0.05).

TABLE 3 Range and median cycles to failure for the bone cements tested using ISO 527 dumbbell specimens loaded between 0.3 and 22MPa.

Cement	Minimum number of cycles to failure	Maximum number of cycles to failure	Median number of cycles to failure
Refobacin® Bone Cement R	711	35142	9827
Refobacin® Palacos R	748	58527	8710
Refobacin® Plus Bone Cement	47515	211922	130010
Palamed® G	12647	261364	107209

However, due to the stylus deflection test method used, differences in roughness were measured on the submillimeter scale while micro and macropores, that is in the range 0.25 to 2.0mm deep, on the surface of the specimens were not included in the roughness data. For the SSR specimens, obvious pores were visible on the surface of the specimens while minimal such pores were seen on the MSC specimens.

Density measurements

The density measurements (Table 4) show that there are no significant differences in density between the two different specimen types for any of the cements and therefore the density data of the two specimen types were combined. ANOVA showed that there were differences between the four cements with a higher density of 1.273±0.007Mg m^{-3} found for Refobacin® Palacos R compared with 1.251±0.012Mg m^{-3} to 1.259±0.011Mg m^{-3} for the other three cements.

TABLE 4 Roughness values and densities of the specimens used for the Weibull and the Wöhler analysis, n=6 specimens and 6 measurements per specimen for all sets of data with the rectangular cross-section specimens measured three times on each surface.

Cement	Ra of rectangular specimens /µm	Ra of cylindrical specimens /µm	Density of rectangular specimens /Mg m^{-3}	Density of cylindrical specimens /Mg m^{-3}
Refobacin® Bone Cement R	4.61 ± 0.53	3.58 ± 2.28	1.254 ± 0.011	1.263 ± 0.009
Refobacin® Palacos R	4.61 ± 0.91	4.05 ± 2.09	1.269 ± 0.008	1.276 ± 0.002
Refobacin® Plus Bone Cement	3.40 ± 1.06	2.51 ± 0.45	1.255 ± 0.002	1.247 ± 0.018
Palamed® G	3.20 ± 0.56	2.78 ± 1.01	1.256 ± 0.001	1.253 ± 0.018
Statistical differences using ANOVA	p<0.01	P=0.36	P<0.005	P<0.01

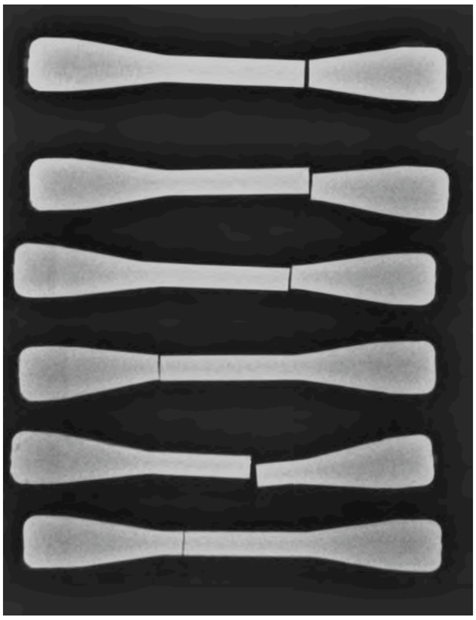
Radiography

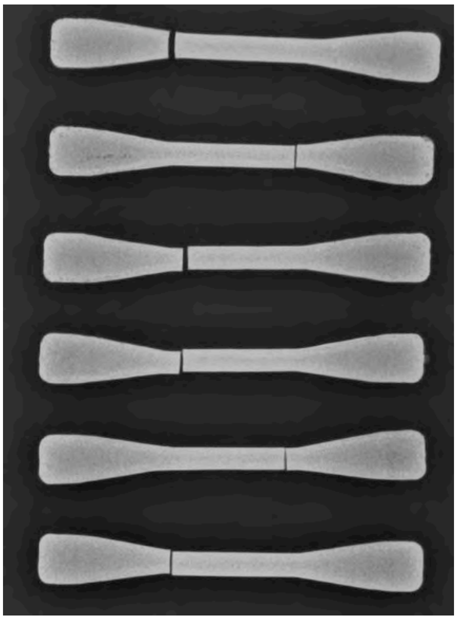
Radiographs of the specimens (Figure 4) show the range of pores found through the specimens. For the SSR specimens, the gauge sections of Refobacin® Bone Cement R (Figure 4a) and Refobacin® Palacos R (Figure 4b) show more small and defuse pores (less than 0.5 mm diameter) compared to the gauge sections of Refobacin® Plus Bone Cement (Figure 4c) and Palamed® G (Figure 4d). Also for the Refobacin® Bone Cement and Refobacin® Palacos R there are more pores on the edges of the specimens than the other two cements. Through all these specimens the gauge sections had fewer pores than the ends of the specimens. The radiographic density is reduced in the dumbbell ends, but these sections are only used for gripping, so are not relevant to the fatigue life. For the MSC specimens a few larger pores (around 0.5 to

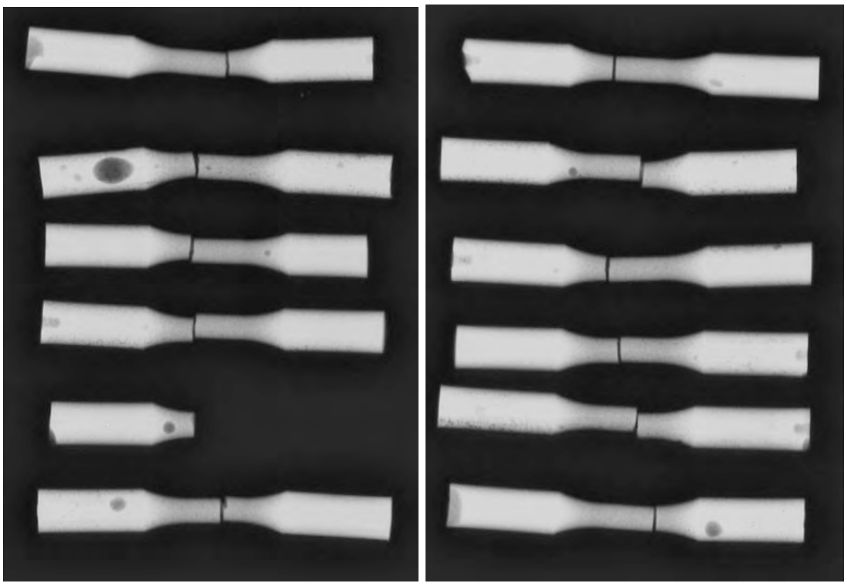
0.8 mm diameter) were seen in all the specimens, but no differences in number or size of pores could be seen between any of the four cements.


a) Refobacin® Bone Cement R

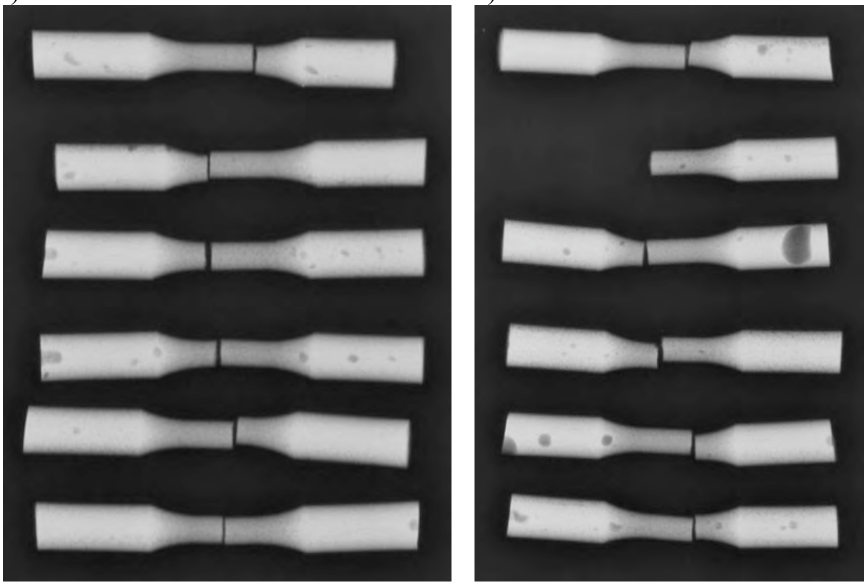

b) Refobacin® Palacos R,


c) Refobacin® Plus Bone Cement


d) Palamed G



e) Refobacin® Bone Cement R f) Refobacin® Palacos R



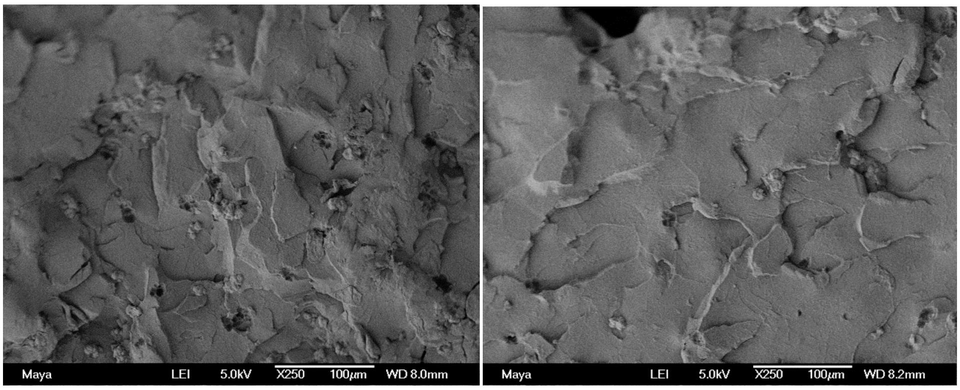
g) Refobacin® Plus Bone Cement h) Palamed G

Figure 4 Radiographs of fractured rectangular a) Refobacin® Bone Cement R, b) Refobacin® Palacos R, c) Refobacin® Plus Bone Cement, d) Palamed® G, and circular e) Refobacin® Bone Cement R, f) Refobacin® Palacos R, g) Refobacin® Plus Bone Cement, h) Palamed® G cross sectional specimens used for the single stress level and multiple stress level tests respectively

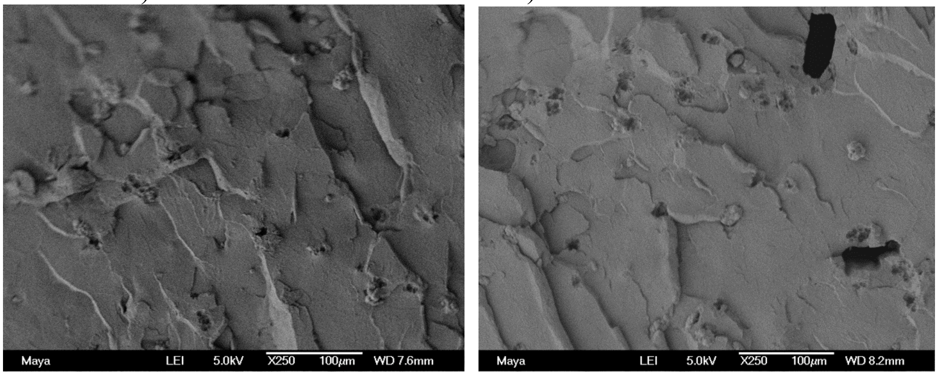
Scanning Electron Microscopy-Fractography

The Scanning Electron Micrographs are shown in Figures 5 to 6. At low magnification (not shown) pores of varying sizes are seen in the fracture surfaces of the SSR specimens whereas the more uniform fracture surfaces of the MSC specimens indicate the selective removal of specimens with pores greater than 1mm in diameter from the groups. There are no substantial differences in the fracture surfaces in different cements for either fatigue method. A few pores about 500 µm can be found in all the cements. The topography of fracture surface from some low stress level (±10 MPa) showed some uneven surfaces, while the surface of high stress level (±30 MPa) appeared fairly smooth.

At higher magnification the fracture surfaces from the SSR specimens (Figure 5) look fairly flat in the form of a series of interconnecting flat zones, with a few pores up to 50µm across and some smaller pores visible. Some opacifier particles are visible in all the fracture surfaces. The fracture surface from the MSC specimens (Figure 6 a and c) was undulating in low stress level (±10 MPa) for Refobacin® Bone Cement R and Refobacin® Palacos R. The fracture line appears to be passing over the original polymer beads with both positives and negatives of the beads visible on the surface. However, at the high stress level (±30 MPa) in both these cement (Figure 6 b and d) a series of flat sections are seen similar to the results seen in the rectangular specimens shown in Figure 5. However, the fracture surface from Refobacin® Plus Bone Cement and Palamed G were quite similar, both cements showed smooth surfaces at low and high stress levels (Figure 6 e to h). On all the surfaces of Figure 5 and 6 zirconium dioxide opacifier particles and the negative impressions, where they were present on the opposing surface, can be seen although it does appear that there are more on the surfaces where the crack appears to have tracked around the edge of the pre-polymerised polymer beads than where the crack has progressed through the pre-polymerised polymer beads.

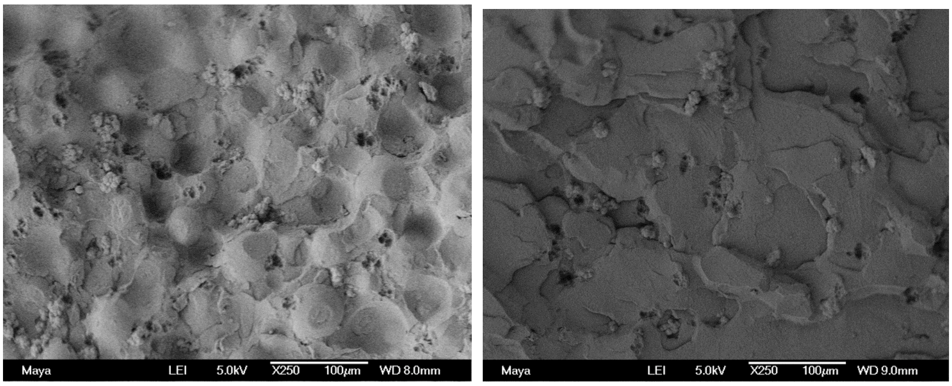


a) Refobacin® Bone Cement R b) Refobacin® Palacos R

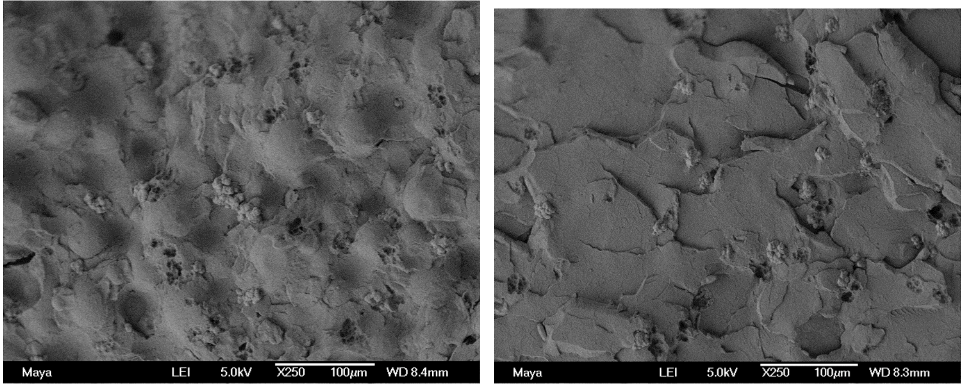


c) Refobacin® Plus Bone Cement d) Palamed® G

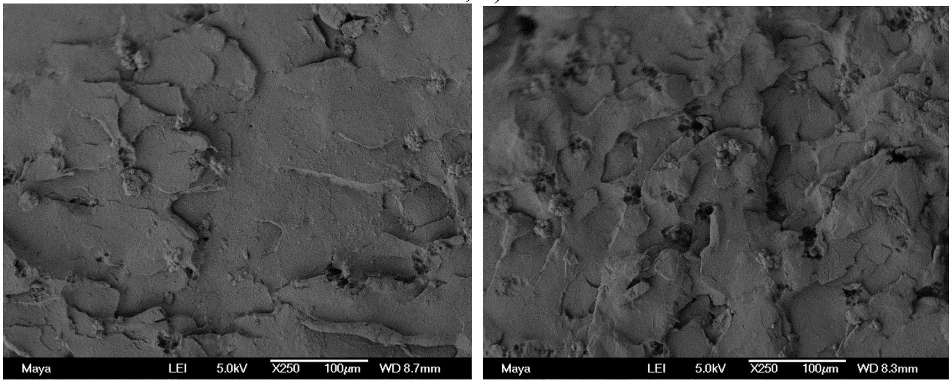
Figure 5 Higher magnification scanning electron micrographs of rectangular cross sectional specimens of a) Refobacin® Bone Cement R, b) Refobacin® Palacos R, c) Refobacin® Plus Bone Cement, d) Palamed® G. All scale bars = 100µm.



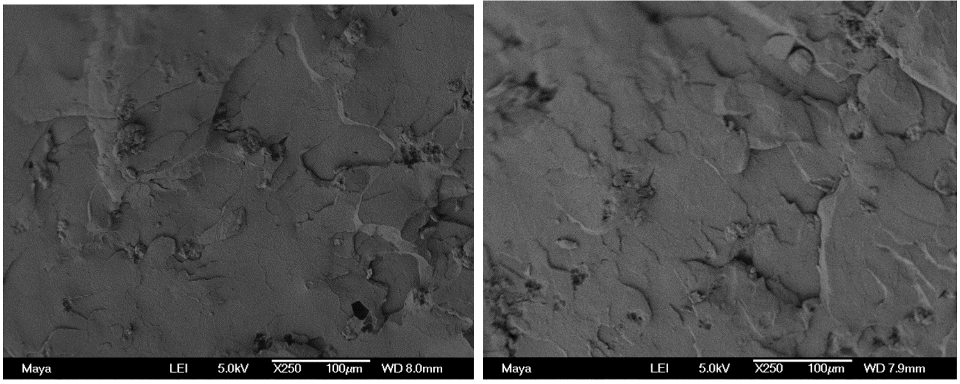
a) Refobacin® Bone Cement R tested at ±10MPa, b) Refobacin® Bone Cement R tested at ±30MPa



c) Refobacin® Palacos R tested at ±10MPa, d) Refobacin® Palacos R tested at ±30MPa,



e) Refobacin® Plus Bone Cement tested at ±10MPa, f) Refobacin® Plus Bone Cement tested at ±30MPa,



g) Palamed G tested at ±10MPa and h) Palamed G tested at ±30MPa

Figure 6 Higher magnification scanning electron micrographs of rectangular cross sectional specimens of a) Refobacin® Bone Cement R tested at ±10MPa, b) Refobacin® Bone Cement R tested at ±30MPa, c) Refobacin® Palacos R tested at ±10MPa, d) Refobacin® Palacos R tested at ±30MPa, e) Refobacin® Plus Bone Cement tested at ±10MPa, f) Refobacin® Plus Bone Cement tested at ±30MPa, g) Palamed® G tested at ±10MPa and h) Palamed® G tested at ±30MPa. All scale bars = 100μm

DISCUSSION

Both methods of testing show an increase in the fatigue life for Refobacin® Plus Bone Cement compared to Refobacin® Bone Cement and Refobacin Palacos® R. These are different formulation cements with Refobacin® Plus Bone Cement and Palamed® G having a higher powder-to-liquid ratio and lower zirconium dioxide content than the other pair of cements (Table 1). The antibiotic content is similar in the four cements and although these levels of antibiotic are clinically effective [23,24] they are not thought to significantly affect the mechanical properties of the cement [22,25]. Only the SSR specimens indicate an increase in the fatigue life for Palamed® G compared to Refobacin® Bone Cement R and Refobacin Palacos® R and no significant difference between Refobacin® Plus Bone Cement and Palamed® G. The Wöhler analysis using the MSC specimens shows an increase over all the stress levels for Refobacin® Plus Bone Cement compared to the Refobacin® Bone Cement R and Refobacin Palacos® R, with no substantial differences seen between the Palamed® G and the other two cements. Furthermore the SSR tests show a factor of 11-15 difference in the mean fatigue lives between the cements whereas the MSC data showed an factor of 2 difference over all the stress levels combined and a maximum factor of 5 difference at the lowest stress level.

The decreased fatigue lives for the higher zirconium dioxide content and lower powder to liquid ratio cements may have various causes. Reduction in the fatigue life with increased opacifier content has been reported [25] as the particles act as stress concentrators in the cement therefore either initiating or propagating cracks. Furthermore, when the opacifier accumulates at the surface of the pre-polymerised beads and the specimen is loaded at low stress levels, instead of the crack front propagating through the specimen and passing through the original polymer beads and through the *in situ* polymerized monomer, as happens with the Refobacin® Plus Bone Cement and Palamed® G, the crack tip follows the interface between the original polymer beads and the *in situ* polymerized monomer. This behaviour is due to a combination of the agglomeration of the opacifier particles on the surface of the original polymer beads [26], thus generating a zone of weakness, and by the *in situ* polymerized monomer having a lower molecular weight and thus lower strength. Increased opacifier allows more agglomeration at the bead surfaces and with more *in situ* polymerized monomer, both the *in situ* polymerized monomer and the interface between the beads will be weaker. At lower stress levels the reduced crack velocity allows the crack front to be deflected through the weaker regions.

Therefore two questions remain: why are the differences large with the SSR regime and less with the MSC regime and are the differences seen between these cements significant for the surgeon when choosing a cement for clinical applications. Harper and Bonfield [8] used the same SSR test regime, except that their aging and testing was performed in air at room temperature, and even excluding Boneloc® found a factor of 100 difference between the shortest and longest fatigue lives. Dunne *et al.* [10] using one cement and various mixing systems also in rectangular cross section specimens found a factor of 2.4 difference between the shortest and longest median fatigue lives calculated using Weibull statistics. Lewis and Janna [18] using both rectangular and circular cross-section specimens of three cements and two mixing methods in fully reversed tension-compression found a factor of 25 between the shortest and longest fatigue lives for rectangular specimens compared with a factor of 90 for the circular cross-section specimens, but always found that the circular specimens gave a longer fatigue life. They concluded that rectangular test specimens rather than circular cross-section should be used as these are more likely to exclude poor cements. However, all these authors performed their testing in air at room temperature without the plasticising effect of liquid immersion [9] which presumably occurred with both sets of specimens in this study. Also Lewis and Janna [18] did not age at physiological temperature and they found significant differences in the amount of residual non polymerised monomer in the cements, which should have been minimised in our studies by the identical ageing at 37˚C.

Considering why our two test regimes found a factor of only 2 with one the MSC regime and over 10 with the SSR leads to consideration of the specimens and the test regimes. All the cements were mixed in a similar manner and were aged in PBS at 37˚C for 1 to 6 weeks so should be as polymerised as cement in clinical use. However, the radiographic and SEM analysis of the specimens shows that the SSR specimens of Refobacin® Bone Cement R and Refobacin

Palacos® R had more pores than SSR specimens of Refobacin® Plus Bone Cement and Palamed® G produced in the same manner or any of the MSC specimens therefore the lower fatigue lives for these specimens is only to be expected. There was a trend for lower density in these specimens although the differences were not statistically significant. In the case of the MSC specimens were excluded from the data analysis where there were pores greater than 1mm across, while for the SSR specimens pores were allowed that are obvious in the radiographs, but were not visible when light was shone through the specimens prior to testing. It can be seen from the radiographs that for the MSC specimens the porosities were similar between all the cement whereas for the SSR specimens Refobacin® Bone Cement R and Refobacin Palacos® R were more porous and would therefore be expected to fail earlier. Therefore the MSC specimens are testing more similar materials than the SSR specimens due to the preparation methods and exclusion criteria used. Secondly, the SSR specimens had a factor of three greater surface area and rougher surfaces than the MSC specimens and the roughness difference was greater for Refobacin® Bone Cement R and Refobacin Palacos® R than Refobacin® Plus Bone Cement and Palamed® G. Therefore the cements with more inclusions, thus probably lower fracture toughness, although this toughness has not been measured, had more crack initiators on the larger surface area, thus again it is to be expected that with the rectangular cross-section specimens the differences in the fatigue lives would be greater than with the circular cross-sectional specimens. Finally, the SSR specimens undergo tension only so, although it was not measured in these studies, the dynamic creep would be expected to be greater than in the fully reversed tension-compression testing of the circular cross-section specimens [27]. Failure due to tensile creep in polymers is accelerated by the addition of non-bonded filler particles [28], thus in the cements with more non-bonded fillers, that is more radiopacifier, creep failure will be accelerated. Thus the substantially greater differences between the cements seen in the tension only tests compared to the fully reversed multi stress level tests are probably more to do with extrinsic than intrinsic factors. Secondly they are not loading the specimens over the range of stresses to which they are subjected *in vivo*.

Which of these tests is more clinically relevant is a more difficult question to answer. Failure of bone cement has been reported as more common in areas of cement that are mainly in tension, thus indicating the tension only testing is clinically relevant. However cement *in vivo* is loaded in both tension and compression and at a range of stress levels thus the multi-level testing can be considered to be more relevant. *In vivo* bone cement will contain pores of various sizes including those over 1mm in diameter so the exclusion of specimens containing pores greater than 1mm may be considered to be non-physiological. Cristofolini *et al*. [22] showed that less than 10% of 1.1mm diameter pores initiated failure cracks whereas 50% of 1.7mm diameter initiated the cracks that lead to specimen failure. *In vivo* cement will conform to the newly cut surfaces of the supporting cancellous bone and thus have substantially rougher surfaces than the machined specimens tested here in fully reversed tension-compression. The final consideration is the time to perform each test, the fully reversed tension-compression requires either 32 or 40 acceptable tests for each cement, depending on the number of stress levels considered, and that cements which fail through pores need to be replaced in the test regime. Whereas Weibull statistics requires a minimum of 10 specimens be tested, although more are advisable, and the rejection of the specimens takes place before testing, so all specimens entering the test regime will provide acceptable data points. Therefore the fully reversed tension-compression testing requires approximately three times as many specimens. Although the tests at ±30MPa will take less than 1 hour including initial stabilisation time those that run through to 5 million cycles take over 11 days per specimen, so the total testing time is substantially longer with the fully reversed tension-compression regime.

In this study it appears that due to the exclusion criteria commonly used for tension only fatigue testing the specimens subjected to the fully reversed tension-compression testing were more similar specimens than those subjected to the tension only testing thus indicating that the difference of a factor of 2 in the fatigue life is probably nearer what will occur *in vivo* than the factors of over 10 seen with the tension only test specimens.

CONCLUSIONS

The testing regime does alter the differences seen between these four bone cements, although the ranking remains the same. The S-N or Wöhler analysis with fully reversed tension-compression testing gives data throughout the stress spectra to which cement is exposed *in vivo*, while the single stress level tension only Weibull analysis investigates the repeatability of the cement. The tension only testing on rectangular specimens gives greater differences between the cements than fully reversed tension-compression on circular cross-section specimens. These increased differences are due to both the differences in the porosity seen in the rectangular specimens, increased crack initiation points on the larger surfaces of the rectangular specimens due to increased surface roughness and finally increases in the opacifier content leads to earlier failure in tension only testing than in fully reversed testing.

Acknowledgements

The fatigue testing was performed as part of two separate studies for Biomet Bone Cement Division, Sjöbo, Sweden. The authors are grateful for their permission to combine this data with our own additional physical characterization of the cements and further data analysis in this paper. The further analysis was funded by Stiftelsen för bistånd åt rönelsehindrade i Skåne, the Swedish Medical Research Council (9509) and the Faculty of Medicine, Lund University. The authors would also like to thank Larsson Mekaniska in Bjärred (Sweden) for the use of the profilometer to measure Ra values and Philippe Wagner, statistician in NKO, in the Medical Faculty, Lund University for the advice on the statistical analysis.

REFERENCES

1 Harrigan TP, Kareh JA, O'Connor DA, Burke DW, Harris WH. A finite element study of the initiation of failure of fixation in cemented total hip components. J Orthop Res 1992;10:134-144.

2 Quinn J, Joyner C, Triffitt JT, Athanasou NA. Polymethylmethacrylate-induced inflammatory macrophages resorb bone. J Bone Jt Surg 1992;74-B:652–658.

3 Sabokbar A, Fujikawa Y, Brett J, Murray DW, Athanasou NA. Increased osteoclastic differentiation by PMMA particle-associated macrophages – inhibitory effect by interleukin 4 and leukemia inhibitory factor. Acta Orthop Scand 1996;67:593–598.

4 Kadoya Y, Revell PA, Kobayashi A, Al Saffar N, Scott G, Freeman MAR. Wear particulate species and bone loss in failed total joint arthroplasties. Clin Orthop Rel Res 1997;340:118–129.

5 Malchau H, Herberts P. Prognosis of total hip replacement and revision rate in THR: A revision risk study of 148,359 primary operations. New Orleans: 65th Ann Meet Am Acad Ortho Surg; 1998. (obtainable from www.jru.orthop.gu.se)

6 Crowe JF, Sculco TP, Kahn B. Revision Total Hip Arthroplasty: Hospital Cost and Reimbursement Analysis. Clin Orthop Rel Res. 2003;413:175-182.

7 ASTM F2118-03 (2003) Standard Test Method for Constant Amplitude of Force Controlled Fatigue Testing of Acrylic Bone Cement Materials, American Society for the Testing of Materials.

8 Harper EJ, Bonfield W. Tensile Characteristics of Ten Commercial Acrylic Bone Cements. J Biomed Mater Res 2000;53-A:605-616. Errata 200*;5*-A:216.

9 Johnson JA, Provan JW, Krygier JJ, Chan KH, Miller J. Fatigue of acrylic bone cement – effect of frequency and environment. J Biomed Mater Res 1989;23:819-831.

10 Dunne NJ, Orr JF, Mushipe MT, Everleigh RJ. The relationship between porosity and fatigue characteristics of bone cement. Biomaterials 2003;24:239-245.

11 Graham J, Pruitt L, Reis M, Gundaih N. Fracture and fatigue properties of acrylic bone cement. J Arthoplasty 2000;15:1028-1035.

12 Jeffers JRT, Browne M, Taylor M. Damage accumulation, fatigue and creep behaviour of vacuum mixed bone cement. Biomaterials 2005;26:5532-5541.

13 Murphy BP, Prendergast PJ. On the magnitude and variability of the fatigue strength of acrylic bone cement. International Journal of Fatigue 2000;22: 855–864.

14 Wang JS, Franzén H, Jonsson E, Lidgren L. Porosity of Bone-Cement reduced by mixing and collecting under vacuum. Acta Orthop Scand 1993;64:143-146.

15 Lewis G. Relative roles of cement molecular weight and mixing method on the fatigue performance of acrylic bone cement: Simplex®P versus Osteopal®. J Biomed Mater Res (Applied Biomater) 2000;53:119-130.

16 Lewis G, van Hooy-Corstjens CJS, Bhattaram A, Koole LH. Influence of the radiopacifier in an acrylic bone cement on its mechanical, thermal and physical properties: barium sulfate-containing cement versus iodine-containing cement. J Biomed Mats Res 2005;73-B:77-87.

17 Murphy BP, Prendergast PJ. Multiaxial fatigue failure of orthopaedic bone cement – experiments with

tubular specimens. J Mater Sci Mater Med 2003;14:857-861.

18 Lewis G, Janna S. Effect of test specimen cross-sectional shape on the *in vitro* fatigue life of acrylic bone cement. Biomaterials 2003;24:4315- 4321.

19 Dall GF, Simpson PMS, Breusch SJ. *In vitro* comparison of Refobacin-Palacos R with Refobacin® bone cement and Palacos R+G. Acta Orthop 2007;78:404-411.

20 Dall GF, Simpson PMS, Mackenzie SP, Breusch SJ. Inter- and intra-batch variability in the handling characterisatics and viscosity of commonly used antibiotic loaded bone cements. Acta Orthop 2007;78:412-420.

21 Lewis G, Austin GE. Mechanical properties of vacuum mixed bone cement. J App Biomater 1994;5:307-314.

22 Cristofolini L, Minari C, Viceconti, M. A methodology and criterion for acrylic bone cement fatigue tests. Fatigue Fract Engng Mater Struct 2000;23:953-957.

23 Hendriks JGE, van Horn JR, van der Mei HC, Busscher HJ. Backgrounds of antibiotic-loaded bone cement and prosthesis-related infection. Biomaterials 2004;25:545-556.

24 Neut D, van de Belt H, van Horn JR, van den Mei HC, Busscher HJ. The effect of mixing on gentamicin release from polymethylmethacrylate bone cements. Acta Orthop Scand 2003;74:670-676.

25 Baleani M, Cristofolini L, Minari C, Toni A. Fatigue strength of PMMA bone cement mixed with gentamicin and barium sulphate vs. pure PMMA. Proc I Mech E Part H: J Eng Med, 2003;217H:9-12.

26 Kjellson F, Wang JS, Almén T, Mattson A, Klaveness J, Tanner KE, Lidgren L. Tensile Mechanical Properties of a Bone Cement containing Non-Ionic Contrast Media. J Mater Sci: Mater Med 2001;12:889-894.

27 Verdonschot N, Huiskes R. Creep Behavior of Hand-Mixed Simplex P Bone Cement under Cyclic Tensile Loading. J. App. Biomater 1994;5:235-243.

28 Suwanprateeb J, Tanner KE, Turner S, Bonfield W. Creep in Polytheylene and Hydroxyapatite Reinforced Polyethylene. J Mater Sci: Mater Med 1995;6: 804-807.