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Long-term mechanical properties of a novel low-modulus bone cement for the treatment of osteoporotic vertebral compression fractures

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ABSTRACT

In spite of the success of vertebroplasty (VP) and balloon kyphoplasty (BKP), which are widely used for stabilizing painful vertebral compression fractures, concerns have been raised about use of poly(methyl methacrylate) (PMMA) bone cements for these procedures since the high compressive modulus of elasticity (E) of the cement is thought to be one of the causes of the higher number of adjacent-level vertebral fractures. Therefore, bone cements with E comparable to that of cancellous bone have been proposed. While the quasi-static compressive properties of these so-called "low-modulus" cements have been widely studied, their fatigue performance remains underassessed. The purpose of the present study was to critically compare a commercial bone cement (control cement) and its low-modulus counterpart on the basis of quasi-static compressive strength (CS), E, fatigue limit under compression-compression loading, and release of methyl methacrylate (MMA). At 24 h, mean CS and E of the low-modulus material were 72% and 77% lower than those of the control cement, whereas, at 4 weeks, mean CS and E were 60% and 54% lower, respectively. The fatigue limit of the control cement was estimated to be 43–45 MPa compared to 3–5 MPa for the low-modulus cement. The low-modulus cement showed an initial burst release of MMA after 24 h followed by a plateau, similar to many other commercially available cements, whereas the control cement showed a much lower, stable release from day 1 and up to 1 week. The low-modulus cement may be a promising alternative to currently available PMMA bone cements, with the potential for reducing the incidence of adjacent fractures following VP/BKP.

1. Introduction

Vertebroplasty (VP) and balloon kyphoplasty (BKP) are widely used treatments for patients who suffer persistent pain due to osteoporotic vertebral compression fractures (Filippiadis et al., 2017; Huang et al., 2020). These techniques involve the injection of a bone cement, usually based on poly(methyl methacrylate) (PMMA), into the fractured vertebra which relieves the pain, and in some cases may restore its height. However, it is believed that the change in load distribution in the spinal segment, attributed to the high stiffness of the cement compared to that of the osteoporotic vertebral bone, results in new fractures in the vicinity of the treated vertebrae (Sun et al., 2011; Li et al., 2012; Uppin et al., 2003). The risk of these fractures has been reported to be significant (12–20%) (Uppin et al., 2003; Trout et al., 2006; Polikeit et al., 2003; Luo et al., 2017), with a large number of them occurring at a level adjacent to the treated vertebra (36–67%) (Sun et al., 2011; Li et al., 2012; Uppin et al., 2003; Trout et al., 2006; Muijs et al., 2009; Ko et al., 2019; Yang et al., 2018). It might be possible to reduce the occurrence of adjacent-level fractures by using cements that a have a lower compressive modulus of elasticity (E) (Holub et al., 2015; López et al., 2014; Robo et al., 2021; Telera et al., 2018; Bornemann et al., 2016; Mauri et al., 2018), in the range of that of the cancellous bone in the vertebral body (10–900 MPa) (Morgan et al., 2003; Nazarian et al., 2008; Helgason et al., 2008; Crawford et al., 2003). Schulte et al. (2013) comparatively assessed the performance of a low-modulus silicon-based bone cement (VK100) and standard PMMA bone cement in a human *ex vivo* vertebral augmentation model, and concluded that the stiffness of the augmentation material had a significant effect on the stiffness of the augmented vertebrae. Similar results have been attained for PMMA bone cements modified with linoleic acid (LA), which are another promising low-modulus alternative whose functional properties have been thoroughly investigated (Holub et al., 2015; López et al., 2014; Robo et al., 2018a, 2021).

After injection into a fractured vertebral body, the bone cement will experience dynamic cyclical loading, mainly in compression (Wilke et al., 1999; Kazarian and Graves, 1977; Callaghan and McGill, 1995)

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and therefore, such loading condition is most relevant to replicate in an *in vitro* setting. Fatigue properties of standard bone cements alone have already been reported (Robo et al., 2018b; Ajaxon and Persson, 2014; Sheafi and Tanner, 2017, 2019; Schönning et al., 2020; Panpisut et al., 2019), as well as studies that evaluated cements in an *in vitro* or *ex vivo* augmented models (Lewis et al., 2008; Aghyarian et al., 2015, 2017a, 2017b). Moreover, unreacted monomer release is a recognized unavoidable effect after implantation of PMMA-based bone cements, which is rarely reported but is believed to have an effect on the initial mechanical properties of the material (López et al., 2014; Vallo et al., 1998).

To the authors' knowledge, there are only five literature reports available on the fatigue performance of low-modulus bone cements (Robo et al., 2018b; Boger et al., 2008a, 2008b; Harper et al., 1995; Kolb et al., 2013). Kolb et al. (2013) investigated the fatigue fracture force (FFF) (defined as the force, during cyclical loading, at which the deformation experienced a sudden increase) of a commercial VP cement, Vertecem™ V+ (E = 1937 MPa) and its low-modulus counterpart, Vertecem™ V+, which contained 8 mL of fetal bovine serum (E = 955 MPa). The standard and low-modulus cements were injected into multi-segmental cadaveric fractured osteoporotic lumbar vertebrae and subjected to cyclic loading (4 Hz), inducing coupled flexion-compression forces. Both groups of cements stabilized and restored the fractured vertebrae to a level at least as high as that of the intact spine, with comparable FFF (($FFF_{unmodified\ cement} = 1760 \pm 251$ N; $FFF_{modified} = 1583 \pm 407$ N); FFF of native vertebrae ($FFF_{native} = 1440 \pm 590$ N)). Harper et al. (1995) investigated the fatigue properties of bone cement based on n-butyl methacrylate monomer (PEMA-nBMA) whose E was 700 MPa. Fatigue tests were performed by subjecting the specimens to uniaxial cyclic tension-tension loads (2 Hz), where the upper stress level corresponded to 30–70% of the tensile strength of each bone cement composition. The fatigue limit of this cement was determined to be 12 MPa at 10^5-10^6 cycles to failure. Boger et al., 2008a, 2008b carried out dynamic compression tests (4.5 MPa, 14 400 cycles at 4 Hz) in demineralized water at room temperature on augmented biopsy specimens of an experimental VP cement, porous hyaluronic acid-modified Vertecem (E = 480 MPa). None of the specimens failed. Robo et al. (2018b) determined the fatigue limit of the commercial low-modulus cement Resilience®, under compressive-compressive loading. Resilience® did not exhibit lower E until 2 weeks after immersion in an aqueous solution and had a fatigue strength in air of 31 MPa at 5 million cycles (2 Hz, tests started after at least 2 weeks of storage in PBS at 37 °C).

There are three shortcomings of the literature on the characterization of low-modulus cements are: First, in most studies, the quasi-static compressive properties were not determined after ageing in a biosimulating medium even though it has been reported that test conditions (in particular, temperature) have a significant influence on the mechanical properties of PMMA bone cements (Nottrott et al., 2007; Baleani et al., 2001); Second, there are no studies in which the fatigue properties were determined, in such medium, under relevant loading scenarios (namely, compression-compression (2 MPa–5 MPa, at a frequency of 2 Hz); Third, there are no studies in which the aforementioned conditions have been applied to low-modulus cement compared to its higher modulus counterpart.

The purpose of the present study was to compare a novel experimental low-modulus PMMA bone cement (whose properties are attained by modification with small amounts of linoleic acid) intended for use in VP/BKP with its higher modulus counterpart, through (i) determination of its CS after ageing in PBS at 37 °C for times between 1 day and 4 weeks; (ii) estimation of its fatigue limit from compression-compression tests performed in PBS at 37 °C; and (iii) determination of the monomer released up to 7 days from both formulations in comparison with a commercial low-modulus cement.

2. Materials & methods

2.1. Materials

A commercial VP bone cement, V-Steady™ (G21 S.r.l., San Possidonio, Italy) hereby referred to as VS, was used as control to be modified with the additive, linoleic acid (LA). The modified (low-modulus) cement is referred to as VS-LA. For both cements, the powder is comprised of pre-polymerized PMMA beads, benzoyl peroxide, and zirconium dioxide (ZrO_2) and the liquid is comprised of methyl methacrylate monomer, N,N-di-methyl-*p*-toluidine, and hydroquinone. The only difference in composition between the two cements is that, for the low-modulus cement, 12 vol% of LA was pre-blended with the liquid. The concentration of LA was based on preliminary studies in which it was found that concentration gave a cement with an E that was in the range of that of vertebral cancellous bone (10–900 MPa) (Morgan et al., 2003; Nazarian et al., 2008; Helgason et al., 2008; Crawford et al., 2003). A summary of the materials and tests is presented in Table 1.

2.2. Cement specimen preparation

The VS was prepared according to the manufacturer's instructions for use by mixing the powder and the liquid manually in a glass mortar with a spatula for 30–45 s at room temperature. The VS-LA was prepared by adding 12 vol% linoleic acid in the liquid and mixing it until dissolved in a centrifuge tube and then mixing the powder and the modified liquid manually in glass mortar with a spatula for 30–45 s at room temperature. The cement dough was transferred into metal moulds (6 mm and 12 mm in diameter and height, respectively) in agreement with ISO 5833 (2002). The specimens were allowed to set in air at 37 °C for 1 h before being stored in PBS at 37 °C.

2.3. Quasi-static compression testing

Quasi-static compressive properties of the cements were determined

Table 1
Summary of the experimental design and number of specimens tested.

Material	Number of specimens tested (n), pre-conditioning, and test conditions		
	Pre-conditioned in PBS, at 37 °C, for 24 h, 2 weeks, or 4 weeks	Pre-conditioned in PBS at 37 °C for a minimum of 14 days prior to testing	Monomer release in water at 37 °C
	Quasi-static compression testing in air at RT[a]	Fatigue testing in PBS at 37 °C	
VS Commercial, higher-modulus bone cement (V-Steady™)	6[b]	23	12
VS-LA Experimental low-modulus bone cement	6	25	12
Resilience® low-modulus bone cement previously available in the market	n/a[c]	n/a[c]	12

[a] One supplementary test was carried out in PBS at 37 °C after specimens had been pre-conditioned in PBS, at 37 °C for 2 weeks.
[b] Number of specimens tested.
[c] Material was discontinued at the time of preparation of this manuscript, which resulted in these experiments not being possible to complete.

in air at room temperature, after storage in PBS at 37 °C, for 24 h, 2 weeks, and 4 weeks. One supplementary test was carried out in a biobath with PBS at 37 °C on specimens stored in PBS at 37 °C for 2 weeks. All tests were performed using a universal testing machines (AGS-X; Shimadzu, Kyoto, Japan or MTS Mini Bionix; MTS Systems Corp., Eden Prairie, MN, USA) at a crosshead speed of 20 mm/min, as stipulated in ISO 5833 (2002). E and compressive strength (CS) of the cements were determined from the load versus-displacement curves, following the protocol detailed in ISO 5833 (2002).

2.4. Fatigue testing

Specimens having surface flaws (>~0.25 mm in diameter) and/or internal defects (>~1 mm in diameter) were rejected ASTM F2118 (2009). Accepted specimens were stored in PBS at 37 °C for a minimum of 14 days, as stipulated in ASTM F2118 (2009). Tests were performed in a universal testing machine (MTS Mini Bionix), using the up-and-down method (Cristofolini et al., 2000; Baleani et al., 2007), as previously described (Callaghan and McGill, 1995), due to this being an efficient method; however, with the exception that the present tests were carried out on specimens immersed in a circulating biobath containing PBS at 37 °C. A compressive preload of 20 N was applied to a specimen, followed by a constant-amplitude cyclical compression-compression load at a frequency of 2 Hz. A test was stopped when either the specimen failed (loss of 15% of its original height (Cristofolini et al., 2000)) or upon completion of 2 million cycles, herein defined as run-out. The applied loads corresponded to maximum stress of between 40 and 80 MPa for the unmodified cement specimens and between 2 and 25 MPa for the modified cement specimens. The first specimen was tested at a stress level of two-thirds of the quasi-static compression strength after 2 weeks, and, thereafter, steps (up or down) depending on whether the specimen survived to run-out or not of 2.5 MPa were used. A minimum of three specimens had to survive at a particular stress level for it to be defined as the fatigue limit. Additional testing was performed at additional stress levels (40 MPa for VS and 3.75 MPa for VS-LA) to determine the fatigue limit from an Olgive-type fit (Krause et al., 1988). A Wölher diagram, or S-N_f curve (S = stress amplitude in MPa; N_f = number of cycles to failure) was plotted, as suggested in previous studies (Krause et al., 1988; Lewis, 2003) and the Olgive equation was fitted to the results (Equation 1) in order to confirm the up-and-down test:

$$S = A + \frac{B - A}{1 + \left(\frac{\log N_f}{C}\right)^D}$$

where A, B, C, and D are cement constants, S is the applied stress amplitude (MPa), and N_f being the number of cycles to failure. The lower and upper asymptotes of the S-N_f curve correspond to A and B, respectively. C is the number of cycles at the inflection point of the curve while D is correlated to the slope at the inflection point (Krause et al., 1988). The Levenberg-Marquardt non-linear regression method (Levenberg, 1944; Marquardt, 1963) (Curve Fitting Toolbox™ in MATLAB® versionR2012a; The MathWorks® Inc., Natick, MA, USA) was used to obtain estimates of the cement constants.

2.5. Determination of monomer release

Extracts were prepared as recommended by ASTM F451 (2008), for monomer analysis of cured bone cement. Commercial low-modulus cement Resilience® was also tested, in addition to VS and VS-LA, for comparison. Rectangular specimens (thickness = 3 ± 0.1 mm, width = 5 ± 0.1 mm, length = 15 ± 0.1 mm) of standard and low-modulus cements were prepared as described in subsection 2.2 and were allowed to cure at 30 ± 1 min in air at room temperature. After that, the specimens were placed in 5 mL of Type II reagent water at 37 °C for 1 h, 24 h and 7 days. Afterwards, 2 mL aliquots from each solution were introduced in a headspace vial and closed hermetically. The vials were incubated at 80 °C for 30 min. Monomer analysis was performed by headspace gas chromatography-mass spectrometry (HS-GC/MS), by injecting 0.1 mL of the vapor phase through a special syringe kept at 85 °C. A Trace GC gas chromatograph with Triplus headspace autosampler coupled to a DSQII mass spectrometer (ThermoFisher Scientific, Waltham, MA) was used. A TRB-624 column (60 m × 0.32 mm × 1.8 μm) with a helium flow of 1.8 mL/min was used for separation. The oven temperature program consisted of a 2 min hold at 60 °C, followed by an 8 °C/min ramp to 220 °C and a 5 °C/min hold at 220 °C. The temperatures of the injector, interface, and ionization source were set at 220, 260, and 200 °C, respectively. The concentration of monomer released in the extracts was determined from integration of the corresponding peak area in the headspace chromatogram.

2.6. Statistical analysis

IBM SPSS Statistics v.22 (IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. The Shapiro-Wilk test was used in combination with normality plots to assess normality of the data. Thereafter, the Levene test was used to test for homogeneity of variances. Since the latter was significant in some cases, Welch's robust ANOVA was thereafter applied, in conjunction with the *post hoc* Tamhane test to evaluate statistical differences between groups for E, CS and released monomer. A difference was considered significant if $p < 0.05$.

3. Results and discussion

The compressive properties of the cements are presented in Table 2. VS showed a non-statistically significant decrease in E ($p > 0.999$) and CS ($p > 0.96$) when stored over time at physiological conditions up to 4 weeks. On the other hand, VS-LA showed a statistically significant increase in E ($p < 0.001$) when stored over time at physiological conditions up to 4 weeks. However, there was no statistically significant difference for CS between 24h vs 2 weeks ($p > 0.999$) and 24 h vs 4 weeks ($p = 0.26$), although a statistically significant difference was found between 2 and 4 weeks ($p < 0.001$). At 24 h, the E and CS of VS-LA were 77% and 72% lower than those of VS and these differences were statistically significant ($p < 0.001$). Whereas, at 4 weeks, the E and CS of VS-LA were 54% and 60% lower than those of VS and these differences were statistically significant ($p \leq 0.01$). The compressive properties of VS-LA, at 4 weeks, were in the upper range of healthy vertebral cancellous bone (Crawford et al., 2003; Banse et al., 2002). Furthermore, the complementary test, which consisted in testing the 2-weeks group in PBS at 37 °C indicated that CS was 12% lower ($p < 0.04$) and E was 89% higher ($p < 0.001$) for VS, and that CS was 32% lower ($p < 0.001$) and E was 19% higher ($p < 0.001$) for VS-LA, with respect to the same cements when tested in air at room temperature. These differences, depending on the testing conditions, have previously been reported

Table 2
Quasi-static compressive properties of V-steady™ (VS) and V-steady™ modified with linoleic acid (VS-LA) after 24 h, 2 weeks and 4 weeks. All specimens were conditioned in PBS at 37 °C up until they were tested. All compressive tests were carried out in air at room temperature except for one supplementary test which was done in PBS at 37 °C of the 2 weeks groups. Six specimens per group and time point were tested in compression.

Time Point	VS cement		VS-LA cement	
	CS (±SD)	E (±SD)	CS (±SD)	E (±SD)
24 h (tested in air)	100.7 (±3.1)	2140.4 (±128.8)	28.3 (±5.1)	494.7 (±51.8)
2 weeks (tested in air)	96.3 (±5.2)	2075.2 (±114.3)	30.5 (±0.8)	803.3 (±65.8)
2 weeks (tested in PBS at 37 °C)	84.4 (±3.5)	3918.6 (±215.5)	20.9 (±0.5)	951.8 (±39.4)
4 weeks (tested in air)	91.5 (±16.5)	2070.0 (±103.1)	36.5 (±0.6)	947.8 (±64.4)

(Nottrott et al., 2007, 2008; Baleani et al., 2001) and were expected.

A different development of CS and E over time between VS and VS-LA can be pointed out; the compressive properties of VS remained stable with a slight non statistically significant tendency to decrease, whereas those of VS-LA tended to increase. As briefly described by Nottrott et al. (2008), two mechanisms controlling the compressive properties of a bone cement may take place, competing with one another, from the start of the conditioning of the bone cement in physiological-like conditions: i) continuous polymerization and ii) plasticizing effects. Since monomer conversion in acrylic bone cements is limited by vitrification (Vallo et al., 1998), residual monomer will continue to slowly diffuse, and to react with remaining free radicals, which in turn increases the overall molecular weight contributing towards higher CS and E. On the other hand, PBS at 37 °C, residual monomer, and residual linoleic acid may all act as plasticizers and contribute to lower CS and E. Nottrott et al. (2007) reported an increase in CS and E after 1 week followed by a decrease of both properties onwards over a period of 1 year, for Palacos® R cement, which contains 67% less ZrO_2 radio-opacifier than VS. This was attributed to water uptake (Nottrott et al., 2007). In the case of VS, since no 1-week time point was available, only a slight decrease in CS and E was observed over the entire period, which can be attributed to the plasticizing effect of the PBS, at 37 °C, absorbed by the material during conditioning (Nottrott et al., 2007, 2008; Kühn et al., 2005). In contrast, VS-LA exhibited an increase in CS and E over time which can be explained by the continuing delayed polymerization, which due to presence of the linoleic acid that reduces glass transition temperature, results in an earlier vitrification and hence a larger amount of residual monomer than in VS (López et al., 2014; Vallo et al., 1998). This residual monomer will continue to polymerize and leach out and contributes to the higher CS and E after 4 weeks. The effect and mechanism of action of linoleic acid which explains the low-modulus of VS-LA with respect to VS has already been addressed elsewhere (López et al., 2014; Persson et al., 2015; Guo and Schork, 2008; Adeodato Vieira et al., 2011).

Three VS cement samples (out of 3) survived a dynamic compressive stress amplitude of 42.5 MPa until runout and 2 specimens (out of 4) survived a compressive stress amplitude of 45.0 MPa (Fig. 1); hence the fatigue limit was estimated to be between 42.5 and 45.0 MPa. The VS-LA cement specimens survived compressive stress amplitudes between 2.5 and 5 MPa until runout (Fig. 1), particularly 1 specimen (out of 4) survived a stress amplitude of 5.0 MPa and 3 specimens (out of 3) a stress amplitude of 2.5 MPa. An additional three samples were tested at 3.75 MPa, which all survived to run-out. Hence, the fatigue limit of VS-LA was estimated to be between 3.75 and 5.0 MPa.

The $S\text{-}N_f$ results obtained and fit of the Olgive equation to them are presented in Fig. 2, with the estimated values of the Olgive equation parameters being given in Table 3.

The parameter B is an estimate of CS of the cement, with the results being within the range obtained in the quasi-static tests. The parameter A is an estimate of the fatigue limit of the cement, with the result for VS-LA cement being within the range obtained using the up-and-down fatigue test method. The fit of the Olgive equation to the results obtained using VS specimens (Fig. 2) was poorer ($R^2 = 0.92$; SSE = 358.33; RMSE = 3.95) than that obtained using VS-LA ($R^2 = 0.94$; SSE = 78.29; RMSE = 1.74). This and the more unusual shape of the best-fit curve to the VS data may be explained in terms of the free volume which is less in VS compared to other standard cements, and especially compared to VS-LA due to e.g. the presence of the relatively large linoleic acid molecules. Considering that free volume can help dissipate internal heating, less free volume will result in lower fatigue strength at high stress amplitudes rather than showing a plateau. Nonetheless, the estimated fatigue limit of VS cement is on the order of 40–50 MPa, which is consistent with the estimate obtained using the up-and-down fatigue test method.

As expected, VS-LA cement exhibited a significantly lower fatigue limit (4.7 MPa) in PBS at 37 °C than its higher modulus counterpart, VS under compression-compression; however, this is still three times higher than the intradiscal pressures during normal daily activities (Wilke et al., 1999; Nachemson, 1981). It is worth pointing out that at the time of the submission of the present work, there is no commercially available low-modulus PMMA-based bone cement. Resilience®, which is referred to in this and previous work as a predicate device, has been removed from the market due to a need for re-certification following the transition to a new regulatory framework for medical devices used in the European Union (https://eumdr.com/). The fatigue limit of Resilience®, in air and at room temperature has been measured to be 31.0 MPa under compression-compression (Robo et al., 2018b). However, the properties of this cement are not attained immediately but within 30 days as a result of a leaching process of one of its components, poly(amino acid), which would result in this cement exhibiting higher properties in the initial time points. Since the majority of adjacent vertebral fractures occur within 1–4 months after vertebral augmentation (Uppin et al., 2003; Nieuwenhuijse et al., 2013; Takahara et al., 2016; Bae et al., 2017), a cement displaying a lower modulus immediately could be beneficial. However, this remains to be demonstrated in the clinical application.

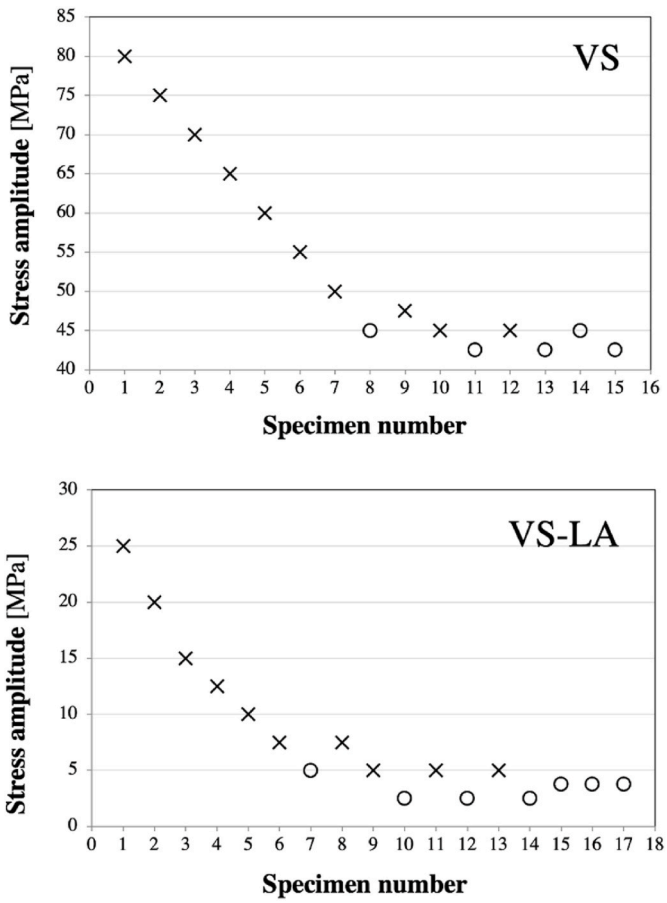

Fig. 1. Data from the "up-and-down method" for VS and VS-LA where [×] represents failed specimens and [O] represents surviving specimens at 2 million cycles.

The monomer release results are shown in Fig. 3. The amounts of unreacted MMA released from the VS and VS-LA cements were compared to that released from low-modulus commercial bone cement, Resilience®. The monomer release from VS was the lowest and remained almost constant throughout the 7-day test period, releasing up to 116 mg/L of MMA, with no statistically significant difference between time points ($p > 0.98$). A reason for this could be the lower free volume in this cement compared to other standard cements, as mentioned earlier. VS-LA released higher amounts of monomer than VS, in agreement with previous studies (López et al., 2014; Robo et al., 2018b; Persson et al., 2015); the monomer release from VS-LA consisted of an

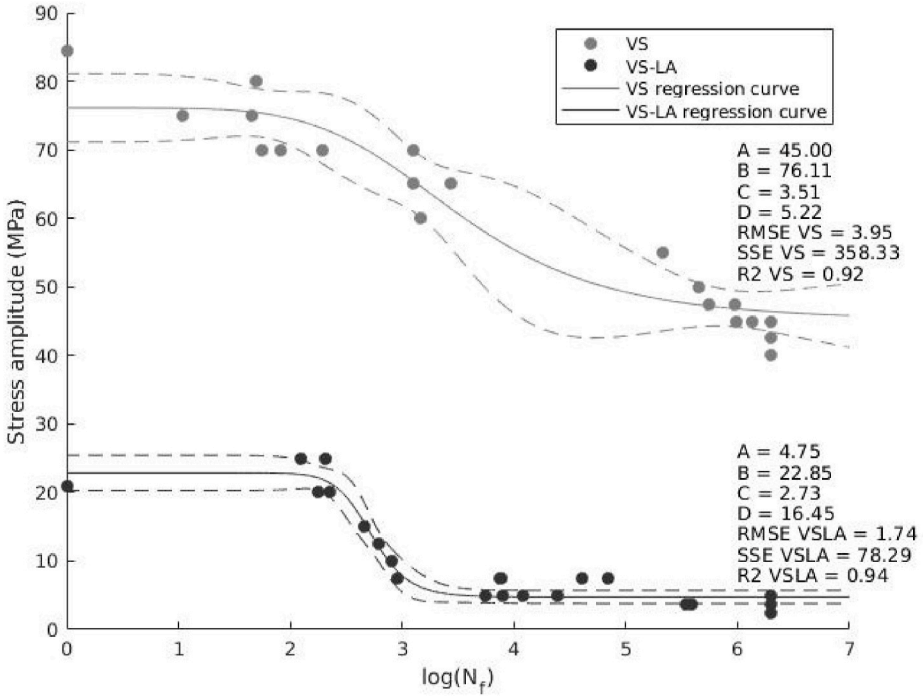

Fig. 2. Fatigue test results (VS and VS-LA) and the Olgive equation fit to these results for VS and VS-LA. N_f is the number of cycles to failure; the dashed curves correspond to the 95% confidence limits.

Table 3
Estimated Olgive equation parameters for VS and VS-LA cements. The 95% confidence intervals are indicated in parentheses.

	A [MPa]	B [MPa]	C	D
VS	45.0	76.1	3.5	5.2
95% confidence interval	(35.6; 54.4)	(71.1; 81.1)	(2.7; 4.3)	(-2.3; 12.8)
VS-LA	4.7	22.8	2.7	16.5
95% confidence interval	(3.8; 5.7)	(20.3; 25.4)	(2.6; 2.8)	(5.2; 27.7)

initial burst release (870 mg/L) that was approximately 780% higher than that of VS (99 mg/L) after 1 day, followed by a more stable but sustained release between day 1 and day 7 for a total release of 1125 mg/L compared to 118 mg/L for VS. There was a statistically significant difference between the amount of monomer released from VS respect to VS-LA at each time point ($p < 0.001$). Resilience® released the highest amount of monomer, behaving similarly to VS-LA; however, the burst release occurred much earlier (5 h) with 778 mg/L followed by a more stable release of up to 1219 mg/L at 7 days. When compared to other cements, VS-LA released less monomer (López et al., 2014; Robo et al., 2018b; Persson et al., 2015). López et al. (2014) reported concentrations of released monomer of approximately 120 mg/L and 750 mg/L at 24 h for regular Osteopal®V cement and its low-modulus counterpart containing 1.5 wt%, (~6 vol%) of LA. Robo et al. (2018a) reported concentrations of released monomer of 1627.8 mg/L and 2418.6 mg/L at 24 h for regular F20® and its low-modulus counterpart containing 2 vol

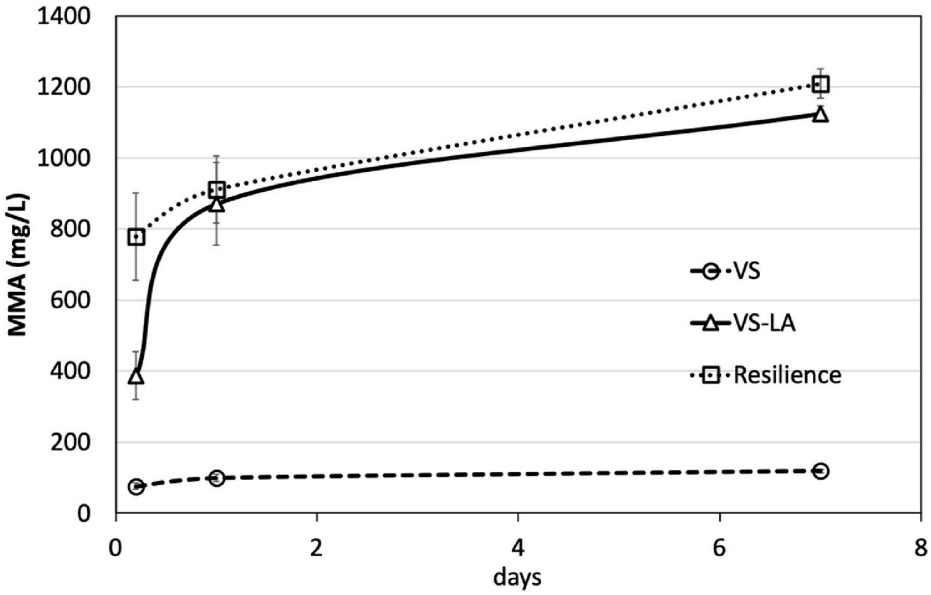

Fig. 3. Concentration of released MMA monomer from VS, VS-LA and Resilience®; n = 12 per time point.

% of LA. It is pointed out that in the present work, extractions were done in water according to specification by ASTM F451-8 (2008). Even though the ions present in PBS might have an influence on the release profile of MMA, the relative results presented are valid for the purpose of comparing between VS, VS-LA and Resilience.

Two limitations of this work are recognized. The first has to do with the number of specimens used in the fatigue test and the monomer release test. In fatigue testing of PMMA bone cement, it is recommended that at least 15 specimens be tested at a given stress amplitude (ASTM F2118, 2009). This was not feasible in the present study. Furthermore, monomer released was determined after only three time points (1 h, 24 h, and 7 d). However, for both cements, the trends of the results are clear. The second study limitation is that the mechanical test specimens did not include supporting bony tissue. This is a limitation because once implanted, bone cement will interdigitate with the surrounding tissue (bone and bone marrow), forming a cement/bone construct, which has been shown to be able to support higher loads than bone cement alone even when low-modulus cement is used (Holub et al., 2015; López et al., 2014). This suggests that cement-only testing models may underestimate the performance of the more relevant cement-bone composite. Therefore, an *ex vivo* fatigue study in an osteoporotic cadaveric spine model, in physiologically relevant conditions, under compression-compression, would be a next appropriate step forward for long-term biomechanical evaluation of VS-LA.

4. Conclusions

In this study, the quasi-static (CS and E) and dynamic (fatigue limit) compressive properties and the monomer release profile of a novel low-modulus PMMA bone cement proposed for use in VP/BKP (LA-modified PMMA bone cement) were determined. After 24 h, the E and CS of the low-modulus material were 77% and 72% lower than those of the control cement (VS), whereas after 4 weeks, the E and CS were 54% and 60% lower, respectively. These quasi-static compressive properties of the low-modulus cement are in the upper range of that of cancellous bone, which could prevent the incidence of subsequent adjacent vertebral fractures. The fatigue limit of the low-modulus cement was 91% lower than that of the control, although still above the stresses experimented in the spine *in vivo*. A more relevant *in vitro* model that utilizes bone/cement constructs in order to consider the effect of cement-bone interdigitation would be recommended for future mechanical testing, to give a better representation of cement performance in a clinical setting. The low-modulus cement exhibited an initial burst release of MMA monomer, which was 780% higher than that of the control after 24 h, yet is comparable to that of another low-modulus cement, and lower than that of many standard cements on the market. The experimental low-modulus cement may be a promising substitute to currently available vertebral augmentation PMMA bone cements with potential for reducing the incidence of adjacent fractures following VP/BKP. While the present *in vitro* results are promising, the long-term performance of the low-modulus cement remains to be evaluated in clinical trials.

Declaration of competing interest

Cecilia Persson is co-owner of Inossia AB, which owns a patent of low-modulus cement. Co-authors Céline Robo and Caroline Öhman have no conflict of interest.

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