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Abstract: The high stiffness of bone cements used in vertebroplasty has been hypothesized to contribute to the propensity of adjacent vertebral fractures after treatment. Therefore, new low-modulus cements have been developed; however, there are currently no studies assessing the biomechanical aspects of vertebroplasty with these cements in an ex vivo non-prophylactic model. In this study, we induced wedge fractures through eccentric uniaxial compression to single whole-vertebrae, before and after augmentation with either standard or low-modulus cement. Compressive strength and stiffness of individual vertebrae were measured, on 19 samples from metastatic spines and 20 samples from elderly, osteopenic spines. While both cement types increased the strength of both the metastatic (+34% and +63% for standard and low-modulus cement, respectively) and the elderly vertebrae (+ 303% and +113%, respectively), none of them restored the initial stiffness of metastatic specimens (-51% and -46%, respectively). Furthermore, low-modulus cement gave a lower total stiffness (-13%) of elderly specimens whereas standard cement increased it above initial levels (+17%). Results show that vertebroplasty with low-modulus cement could provide restoration of the initial stiffness while increasing the strength of fractured elderly vertebrae and hence represent a treatment modality which is closer to pre-augmented behaviour. Also, this study indicates that stiffness-modified cement needs to be optimized for patient/pathology specific treatment.

Biomechanics of Low-modulus and Standard Acrylic Bone Cements in Simulated Vertebroplasty: A Human Ex Vivo Study

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Abstract

The high stiffness of bone cements used in vertebroplasty has been hypothesized to contribute to the propensity of adjacent vertebral fractures after treatment. Therefore, new low-modulus cements have been developed; however, there are currently no studies assessing the biomechanical aspects of vertebroplasty with these cements in an ex vivo non-prophylactic model. In this study, we induced wedge fractures through eccentric uniaxial compression to single whole-vertebrae, before and after augmentation with either standard or low-modulus cement. Compressive strength and stiffness of individual vertebrae were measured, on 19 samples from metastatic spines and 20 samples from elderly, osteopenic spines. While both cement types increased the strength of both the metastatic (+34% and +63% for standard and low-modulus cement, respectively) and the elderly vertebrae (+ 303% and +113%, respectively), none of them restored the initial stiffness of metastatic specimens (-51% and -46%, respectively). Furthermore, low-modulus cement gave a lower total stiffness (-13%) of elderly specimens whereas standard cement increased it above initial levels (+17%). Results show that vertebroplasty with low-modulus cement could provide restoration of the initial stiffness while increasing the strength of fractured elderly vertebrae and hence represent a treatment modality which is closer to pre-augmented behaviour. Also, this study indicates that stiffness-modified cement needs to be optimized for patient/pathology specific treatment.

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1. Introduction

With a current lifetime risk of experiencing a vertebral fracture of 30% in women and 20% in men, adequate treatment of these fractures is important for improving the quality of life of the patient, as well as in reducing the global healthcare's economic burden (Kanis and Johnell, 2005). Vertebral bone can deteriorate due to different diseases, including primary or secondary osteoporosis (Freedman et al., 2008) and cancers such as multiple myeloma and osteolytic metastases (Georgy, 2008). As many as 70% of patients with osteolytic lesions will suffer from vertebral compression fractures (VCFs) (Lecouvet et al., 1997). In osteoporotic and metastatic patients suffering from VCFs, percutaneous vertebroplasty with acrylic bone cements has shown good results in terms of reducing further height loss and being of positive benefit to pain management (Klazen et al., 2010; O'Brien et al., 2000).

It is generally accepted that the spinal load transfer mechanism is related to the structural stiffness of the vertebrae (Sun and Liebschner, 2004). Consequently, changes to the vertebral stiffness from cement augmentation should be minimised whilst at the same time attaining maximum strength. However, most acrylic cements used in vertebroplasty exhibit a very high elastic modulus (1700-3700 MPa) and compressive strength (85-114 MPa) (Hernandez et al., 2008; Kurtz et al., 2005) compared to the elastic modulus (10-900 MPa) and compressive strength (0.1-15 MPa) of cancellous bone (Helgason et al., 2008; Morgan et al., 2003; Nazarian et al., 2008). These large differences have raised concerns about the suitability of these cements, since clinical studies have reported 12-20% patients suffering new vertebral fractures following vertebroplasty, with a greater number (41-67%) of subsequent fractures observed adjacent to treated vertebrae (Grados et al., 2000; Trout et al., 2006; Uppin et al., 2003). These so called adjacent vertebral fractures (AVF) have also been

reported to occur earlier within patient cohorts undergoing augmentation (Trout et al., 2006; Uppin et al., 2003). However, the exact mechanism by which premature AVFs occur is subject to competing theories including the natural course of the disease, local changes in the biomechanical environment arising from differences in spinal shape, as a response to increased vertebral body (VB) stiffness or as a combination of the three (Baroud and Bohner, 2006; Liebschner et al., 2001). Other factors may be the limitation of the natural bulging of the endplates (Baroud et al., 2003; Polikeit et al., 2003) secondary to the maximum filling approach in which a large amount of cement forms a rigid bolus within the entire VB (Baroud et al., 2003; Berlemann et al., 2002).

Experimental studies have shown that after augmentation, cement and bone behave as a composite material with mechanical properties that are closer to those of the cement than to those of the bone (Helgason et al., 2012; Race et al., 2007; Williams and Johnson, 1989). This is because the cement represents a majority of the volume fraction of that composite for typical bone volume fractions with BV/TV≤0.20 (Fields et al., 2011; Morgan et al., 2003). This effect becomes more pronounced due to thinning of trabeculae in elderly bone, often affected by osteoporosis, and when soft tumour lesion infiltrates adjacent bone. Therefore, cements with a lower elastic modulus may be more suitable particularly in relatively low volume fraction bone associated with these two pathologies.

However, the adequacy of low-modulus cements in terms of restoring the mechanical properties of a previously fractured vertebral body is yet to be investigated in vertebrae of relevant pathologies. To the authors' knowledge, only two studies have focused on the biomechanics of low-modulus cements in a human ex vivo model (Boger et al., 2007; Kinzl et al., 2012a). Both studies used a prophylactic approach, i.e. the specimens were not fractured prior to augmentation, even though vertebroplasty is most commonly used for treating vertebral compression fractures (Boger et al., 2007; Kinzl et al., 2012a).

Therefore, the main aim of the present study was to assess the effectiveness of vertebroplasty with low-modulus cement by comparing the mechanical properties of vertebrae before and after augmentation with standard and low-modulus cement. This was accomplished within two groups of vertebral samples, the first group from elderly donors with bone prone to degradation, and the second cohort comprised metastatic donors. Within this study standard cement refers to the unmodified cement, whereas low-modulus describes modified cement with approximately 25% of the stiffness of standard cement.

2. Methods

2.1 Specimen Preparation and Handling

The experimental design is schematized in Figure 1. Twenty-four thoracolumbar vertebrae (T6-L5) from two donors with metastatic infiltration to the spine and twenty-four thoracic vertebrae (T7-T11) from five elderly donors were used (Table 1), acquired from two non-transplant tissue banks (Science Care®, USA, and GIFT, Leeds General Infirmary, UK) following ethics committee approval. From collection to 12 hours before dissection, the samples were stored frozen at -80ºC. The vertebrae were thawed overnight at 5°C and allowed to reach room temperature before testing. The vertebrae were dissected free of soft tissue and disarticulated at the intervertebral disc. The posterior and transverse processes were detached whilst keeping the neural arch intact per the protocol used previously (Furtado et al., 2007). Between experimental stages, the vertebrae were wrapped in tissue soaked with purified water, placed in sealed plastic bags, and kept frozen at -20°C until 24 hours prior to the next stage. As before the vertebrae were thawed for 12 hours at 5ºC and allowed to reach room temperature before testing.

2.2 Micro Computed Tomography (microCT)

The morphological properties of the vertebrae were measured after each experimental stage by scanning in purified water (Figure 1) using a microCT100 (Scanco Medical AG,

Brüttisellen, Switzerland) at an isotropic resolution of 70.8µm with 500 projections. Initial scans were used to estimate the vertebral body volume (V_{VB}), the bone mineral density (vBMD), and bone volume fraction (BV/TV). vBMD and BV/TV were estimated from a cylindrical volume of interest (∅= 60% of the anterior-posterior length; h= 80% of the height) within the trabecular bone in each VB (Furtado et al., 2007), with BV/TV calculated using a single value threshold based on an iterative user-independent selection method (Ridler and Calvard, 1978).

Benchmarking of the samples was done based on the Latin rectangle design (Bailey, 1996). In each of the pathological groups, the VBs were assigned to two groups, each of which contained the same distribution of specimens in terms of predicted strength from all donors. The theoretical strength was obtained from analysis of the initial scans with a beam-theory based fracture prediction model (Whealan et al., 2000), adopted and validated for eccentrically loaded single vertebrae. This permitted starting the augmentation phase before initial fracture of all specimens was completed. Appropriateness of the distribution was confirmed against initial fracture data.

2.3 Uniaxial Compression Testing

Intact vertebrae were first eccentrically loaded to failure to induce a wedge fracture and the same protocol (Figure 2) was used after augmentation to refracture the vertebrae.

Each vertebra was tested in an eccentric custom-built compression-rig mounted onto an Instron 3366 materials testing machine (10 kN load-cell, Instron, Norwood, MA, USA) to simulate quasi-static compression (Dall'Ara et al., 2010; Furtado et al., 2007) according to the protocol shown in Figure 2. Minor preload at a constant force (typically <5% of fracture load) helped to reduce slipping in the toe-region of the load-displacement curve. The relaxation period at the end of the test aimed to assess any restoration properties of the cement. The latter was however not analyzed in the framework of this study.

Since the whole bone load-displacement response tends to be highly non-linear a robust method of stiffness estimation was needed. Here, the vertebral stiffness [kN/mm] was defined as the maximum slope of the load-displacement curve over a 1% strain window prior to the zero-slope yield load (Buckley et al., 2009), which was proven to be more reliable than the traditional best-fit line. The vertebral strength [kN] was evaluated using the proof-load approach and defined as load at intersection of the stiffness line offset by 1% strain. In both cases the 1% strain was defined from total compression displacement normalised to the total height of the sample.

2.4 Bone Cement Preparation

Osteopal®V (Heraeus Medical GmbH, Hanau, Germany) radiopaque bone cement for vertebroplasty was used as the standard cement and as the base for the low-modulus cement. The latter was prepared by dissolving 9-cis,12-cis-linoleic acid (5.9 % v/v) (≥99%, Sigma-Aldrich, St. Louis, MO, USA) in the monomer phase of Osteopal®V before mixing the two phases as described elsewhere (López et al., 2014; Persson et al., 2015). The elastic modulus and ultimate strength measured under uniaxial quasi-static compression after storage in PBS at 37°C for 24h of the standard cement was 1500(±140 SD) MPa and 103(±3 SD) MPa, respectively, whereas that of the low-modulus cement was 374(±30 SD) MPa and 15(±1 SD) MPa, respectively. Specimens of 6mm diameter and 12mm high were tested at 20mm/min, in accordance with the ISO5833 standard (ISO, 2002).

2.5 Needle Placement and Simulated Vertebroplasty

Prior to augmentation all vertebrae were submerged in phosphate buffered saline (PBS, 0.03 % w/w sodium azide) solution and preheated to 37°C for 1 hour. Stainless steel needles (11 G, 5 cm; Tizaro, Wilmington, DE, USA) were transpedicularly inserted by a spinal surgeon (VB) through both pedicles under fluoroscopic guidance using an X-ray image BV 25 unit (Philips, Amsterdam, The Netherlands). Bi-pedicular augmentation was performed using 5

mL luer lock polypropylene syringes. The maximum total volume of injected cement was set to 30% of the vertebral body volume (V_{VB}), of which half was injected through each pedicle. Augmentation was stopped when either the targeted volume had been injected, extensive extravasation to the spinal canal occurred, or when it was no longer possible to inject more cement by hand. Immediately after augmentation, each sample was again submerged in PBS solution and kept at 37°C for 24 hours to simulate physiological conditions for the curing. The vertebrae were then stored for scanning and subsequent fracturing, followed by refracture per the same scenario used for the initial fracture.

2.6 Statistical Analysis

Statistical analysis was carried out using IBM SPSS Statistics v21 (IBM, Chicago, IL, USA) at a significance level of α=0.05. A General Linear Model (GLM) for repeated measures was used to investigate the between-subjects effects of (i) pathology (metastatic or elderly) and (ii) cement type (standard or low-modulus) as well as the within-subjects effect of before and after fracture and augmentation, on the stiffness and strength of the individual vertebrae. A t-test was used to confirm appropriateness of distribution of vertebrae into the two cement groups.

3. Results

Examples of the morphological differences in the two groups are illustrated in the μCT images shown in Figure 3 whereas vBMD and BV/TV values are presented in Table 1. The degree of osteoporotic pathology of the elderly spines was established based only on the microCT-based vBMD assessment. Lack of standardization of acquiring data from this modality, however, prevented direct comparison with other studies. Here, samples were compared to available qCT-based vBMD classification (ACR, Revised 2013 (Resolution 32)) whilst considering the hard-coded beam hardening correction used in this study (1200mgHA/cm^3), and the size of the samples together with their low density, which is

known to increase the predicted density (Fajardo et al., 2009). **A**ll elderly spines except for one (which was deemed highly osteoporotic) could be classified as affected by mild osteoporosis (osteopenia) (Table 1). The only spine classified as highly osteoporotic was excluded from further analysis due to the low number of samples for this pathological classification. Highly mineralized areas were more common among the metastatic specimens but only 3 out of the 24 vertebrae exhibited focalised lytic lesions. Simulated vertebroplasty failed to deliver the targeted cement volume to five metastatic vertebrae, probably due to very high BV/TV preventing injection of the target of 30% VB fill. These samples were injected with volumes <15% VB volume fill, whereas all other samples were injected with confirmed volumes between 28 and 31%. Hence these samples were excluded from analysis. The vertebrae were distributed between cement groups without significant differences in strength ($p=0.343$ and 0.983, for metastatic and elderly specimens, respectively) or stiffness ($p=0.539$ and 0.649, for metastatic and elderly specimens, respectively), which allowed comparison of the results within each pathological group.

Figure 4 shows representative images of vertebrae after each experimental stage, demonstrating the induced wedge fracture as indicated by the eccentric (anterior) compression of the vertebral body, as well as the endplate to endplate augmentation with bone cement. Vertebroplasty did not fully restore the height of the vertebrae, with 14.5 ± 5.8 % lower and 17.0 ± 5.1 % lower height after fracture and augmentation than the initial anterior height, for metastatic and elderly vertebrae, respectively.

Representative load-displacement curves are shown in Figure 5. Non-augmented vertebrae featured an initial linear increase in the compressive load up to the fracture load (vertebral body strength [kN]), followed by a drop and finally slight increase in the load until the end of the test is reached. Augmented vertebrae featured a continuous non-linear increase in the

compressive load until reaching the endpoint (ε). The elderly vertebrae augmented with standard cement reached particularly high fracture loads.

While the within-subjects effect of before and after fracture and augmentation was statistically significant and independent of the between-factor effects for the strength (direct effect $p<0.001$, interactive effects $p>0.05$, Table 3), the stiffness change before and after fracture and augmentation depended on the between-subject factors, i.e. pathology and cement type (interactive factors were statistically significant, Table 3), which is further illustrated in Figures 6 A and B.

Prior to augmentation, metastatic vertebrae were on average 80 ± 48 % stronger than elderly vertebrae (Figure 6 A) and 59 ± 42 % stiffer (Figure 6 B) than elderly vertebrae.

After augmentation, metastatic vertebrae had similar average strength regardless of the type of cement they were augmented with (Figure 6 A). Elderly vertebrae augmented with standard cement were however 73 ± 34 % stronger than those augmented with low-modulus cement (Figure 6 A). In terms of stiffness after augmentation, metastatic specimens again had a similar average stiffness regardless of the cement type, while elderly vertebrae augmented with standard cement were 45 ± 28 % stiffer than those augmented with low-modulus cement (Figure 6 B).

The changes in mechanical properties before and after fracture and augmentation, normalized for each individual vertebra's initial properties, and hence taking into account the natural variation, are shown in Figures 6 C and D. Standard cement increased the strength of both metastatic and elderly vertebrae, with a much stronger effect on the elderly vertebrae (Figure 6 C, a positive net change in strength of +34% for metastatic and +303% for elderly specimens). Low-modulus cement also gave an increase in strength after fracture and augmentation of both metastatic and elderly vertebrae (Figure 6 C, 63% and 113%, respectively).

None of the cements restored the initial stiffness of the metastatic vertebrae (Figure 6 D, changes of -51% and -46% for standard and low-modulus cements). However, the standard cement increased the stiffness of the elderly, osteopenic vertebrae (Figure 6 D, a net change of +17%) and the low-modulus cement decreased the stiffness of elderly, osteopenic vertebrae (Figure 6 D, a net change of -13%).

4. Discussion

In developing vertebral augmentation procedures, preclinical studies have an important role to play. A number of biomechanical studies have already addressed some of these issues utilising both experimental investigations (Boger et al., 2007; Furtado et al., 2007) and computational modelling (Chevalier et al., 2008; Kinzl et al., 2012b; Wijayathunga et al., 2008). The volume (Belkoff et al., 2001; Liebschner et al., 2001; Molloy et al., 2003), efficiency of PMMA against ceramic cements (Tomita et al., 2003) as well as the cement delivery method (Liebschner et al., 2001; Molloy et al., 2005; Tohmeh et al., 1999) have been common subjects of investigation within osteoporotic models. In terms of injected volumes, clinically between 1-6mL (~10-30%) (Diamond et al., 2003) is being injected or the endpoint of injection is limited only in order to avoid possible extravasation (Barragan-Campos et al., 2006; Kaufmann et al., 2006). The stiffness and strength have been found to be only weakly correlated with the volume fill (Dean et al., 2000; Liebschner et al., 2001; Reidy et al., 2003), suggesting that even relatively small amounts of high-stiffness PMMA cements provide a large increase in stiffness. An excessive increase in stiffness may have negative effects on the normal stress distribution profile (McMillan et al., 1996). In fact, rigid bone cements have been reported to alter the natural inward bulging of the endplate and increase the pressure on the adjacent discs (Kinzl et al., 2012a). Low-modulus bone cements have therefore been proposed to minimize the risk for AVFs (Boger et al., 2008; Boger et al., 2009). In a previous study, we saw that low-modulus linoleic acid-modified bone cements

can reduce the stiffness and increase the contribution of the bone fraction to the overall strength and stiffness of a bovine bone/cement composite (López et al., 2014). In the present study, this was confirmed in human whole-vertebra specimens, where the effect of morphology, and BV/TV specifically, on mechanical properties, both before and after fracture and augmentation, was evident. The average vBMD was similar in both the metastatic and the elderly group, since the measurements were taken at a distance from both the lesions and the highly mineralized areas. On the other hand, the average BV/TV was 47 ± 35 % higher in metastatic than in elderly vertebrae. The resulting difference between the metastatic and the elderly vertebrae upon augmentation with either cement, confirms that cement contribution to strength and stiffness increases with a decrease in the bone volume fraction (Table 1, Figure 6), which is also in agreement with previous studies (Heini et al., 2001; Luo et al., 2007; Sun and Liebschner, 2004). Therefore, the influence of the type of cement on the strength and stiffness of the vertebral body depends on the initial morphological characteristics of the trabecular bone and the contribution of the cement to the properties was more evident in elderly vertebrae.

In a clinical setting, it is vertebrae that undergo an in vivo fracture that in some cases are treated with vertebroplasty. Using specimens without confirmed in vivo fractures may hence bias the mechanical properties towards higher values due to a higher bone quality compared to specimens that undergo an in vivo fracture. Future studies should hence focus on specimens classified as osteoporotic. For the same reasons, another limitation of the study is the presence of highly mineralized areas in the majority of metastatic specimens. However, these limitations emphasize the effectiveness of low-modulus cements under quasi-static compression. Ultimately it would be necessary to assess to what extent low-modulus cements could prevent adjacent vertebral fractures. To this end, cyclic loading of functional spinal segments with augmented caudal vertebrae would be of interest.

To improve the clinical relevance with respect to previous studies with low-modulus cements (Boger et al., 2007; Kinzl et al., 2012a) we induced wedge fractures to account for a typical non-prophylactic augmentation. The results showed that in all pathological groups, vertebroplasty with low-modulus cement increased the vertebral strength with respect to the initial values although significantly less than that found when augmenting with standard cement. In a previous study (Kinzl et al., 2012a) it was shown that when vertebrae without endplates were filled endplate-to-endplate, the specimens with standard cement were on average 47% stronger than a non-augmented control group (in our study elderly specimens were 303% stronger after fracture and augmentation), and 33% stiffer (in our study 17% stiffer). Furthermore, with low-modulus cement, their specimens were on average 30% stronger (in our study elderly specimens were 113% stronger after fracture and augmentation), and 27% stiffer (in our study 13% less stiff). Hence their results gave a difference in stiffness of specimens augmented with standard and low-modulus cements of only 6%, whereas in our study that difference was of 30%. The absence of endplates should have intensified the effect of the different cement properties with respect to our study. However, the results of Kinzl et al. represent a scenario without previous fracture, and different specimens were used for comparison of strength between non-augmented and augmented specimens. Therefore the absence of a pre-induced fracture together with the large natural variation between specimens could have masked any resulting treatment differences. The only other available ex vivo study on low-modulus cement for vertebroplasty was made on FSU's, not single vertebrae (Boger et al., 2007). No differences in strength were found between non-augmented control and specimens augmented with standard or low-modulus cement. However, no pre-induced fracture was present here either and specimen heterogeneity was cited as an issue.

Results here presented show an increase in stiffness of 17% (N=9) when standard cement was used whereas a decrease in stiffness of 13% (N=10) was found in elderly, osteopenic samples when low-modulus cement was used. Although the exact mechanism leading to premature AVFs is yet to be clarified (Baroud and Bohner, 2006), it is believed that such an increase in stiffness could occur at an early stage of development of excessively misbalanced biomechanics. Previous numerical predictions showed that the pillar-effect of a rigid cement bolus was linked to increased bulging of the end-plates and increased pressure onto the adjacent disc, and the authors hypothesized that as little as 17% of pressure increase may be behind the increased occurrence of the AVF. This has also been shown in an in vitro experiment (Kinzl et al., 2012a) in which authors reported notably higher endplate pressure in vertebrae augmented with standard (high-stiffness) cement. Whether such load shift would be minimized with decreasing the vertebral stiffness similar to that observed in our study is yet to be confirmed.

Although this study does not directly simulate AVFs, it demonstrates that using low-modulus cement could be effective in terms of restoring the initial properties of a fractured vertebral body, and may give a closer restoration of strength and stiffness to those prior to vertebral fracture, in comparison to standard cement. It should be noted that the low-modulus cement used in this study, i.e. PMMA modified with linoleic acid, can be tailored in terms of elastic modulus, and hence provide a targeted structural reinforcement depending on the treated pathology, i.e. a higher stiffness and strength cement could for example be used for augmentation of osteopenic samples.

Vertebroplasty with low-modulus cement could become particularly important in highly osteoporotic bone to avoid unnecessary strengthening and stiffening of the augmented vertebral body, and to prevent high stress concentrations on the adjacent endplates.

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Conflict of Interests

One of the materials evaluated in this study has been described in patent application nr PCT/SE2014/050429, where co-authors Cecilia Persson and Alejandro López are co-inventors. Co-authors Ondrej Holub, Vishal Borse, Håkan Engqvist, Nik Kapur, and Richard M. Hall, have no conflict of interests.

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Figure Legends

Figure 1. Experimental design of the 4 arm study utilising both the standard and low-modulus cements for metastatic and elderly vertebrae.

Figure 2. A) General stepwise protocol used to record load-displacement data consisting of displacement controlled (dashed line) and load control region (solid line), more specifically: (1) Displacement control, 1 mm/min up to 50 N; (2) Load control, 50 N for 5 min; (3) Displacement control, 1 mm/min to 75% of initial averaged vertebral height (ε); (4) Displacement control, 1 mm/min to 50 N; (5) Load control, 50 N for 10 min; B) Schematic diagram of the compression setup. A lubricated metal plate was placed on top of the acrylic endcap and a ball-joint was used to transfer the load to the specimen and allow rotation of the metal plate.

Figure 3. Segmented images of the transverse area of metastatic (left) versus elderly (osteopenic) (right) T8 vertebrae showing typical pathological features.

Figure 4. Representative 3D volume renderings of an elderly, osteopenic T9 in its sagittal plane after each experimental stage.

Figure 5. Representative load versus displacement curves: A) Metastatic T9 (vBMD=120.8; BV/TV=0.25) augmented with standard cement; B) Metastatic T6 (vBMD=130.6; BV/TV=0.20) augmented with low-modulus cement; C) Elderly T8 (vBMD=141.3; BV/TV=0.17) augmented with standard cement; D) Elderly T9 (vBMD=133.2; BV/TV=0.17) augmented with low-modulus cement.

Figure 6. Average strength (A) and stiffness (B) values for each group, in terms of within- (pre- and post- fracture and augmentation) and between- (pathology and cement type) subject factors. Note that percentage changes in strength (C) and stiffness (D) for each vertebra is averaged after normalization of each sample for its own initial properties which takes into account natural variability. The error bars represent standard deviations.

Figure 1

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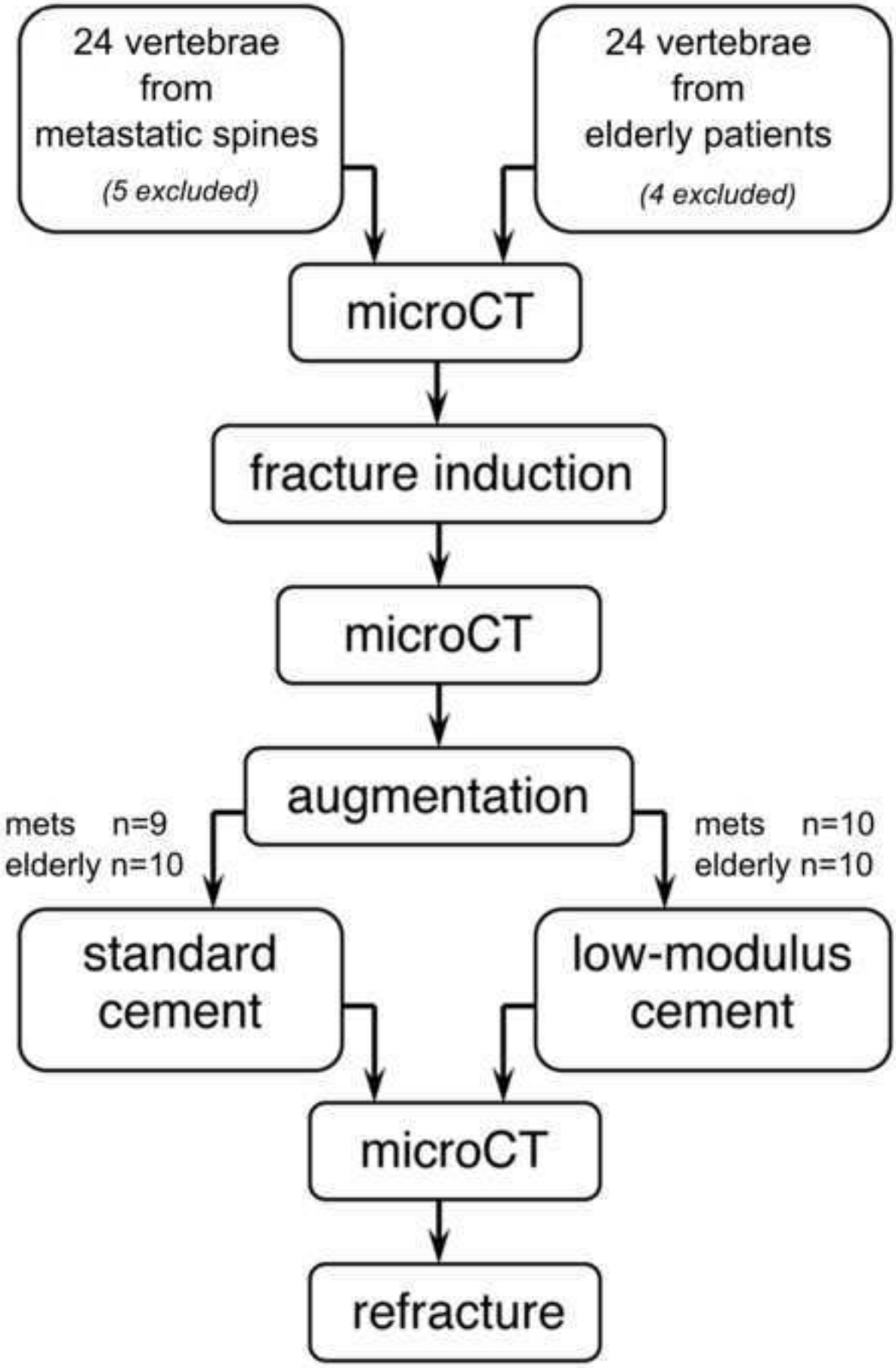

Figure 2

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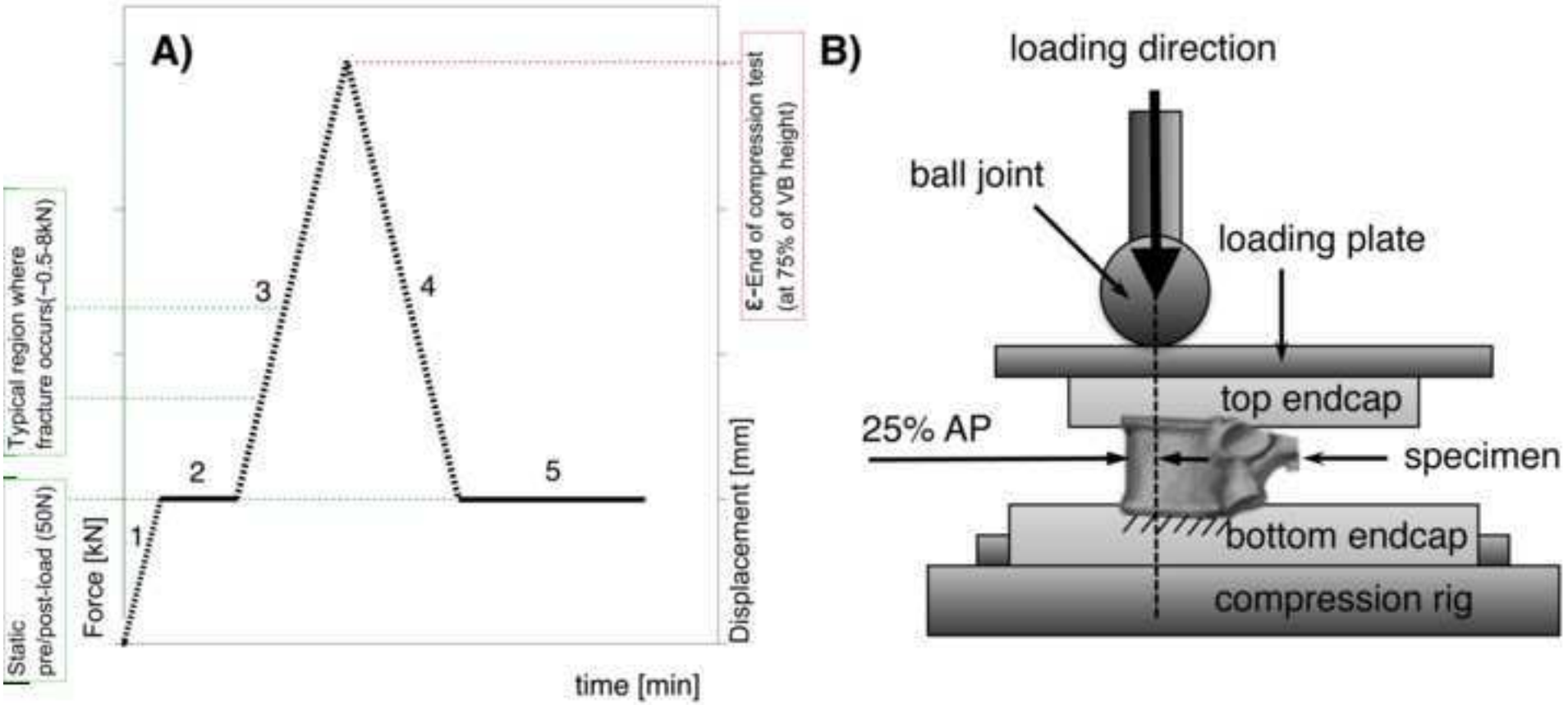

Figure 3

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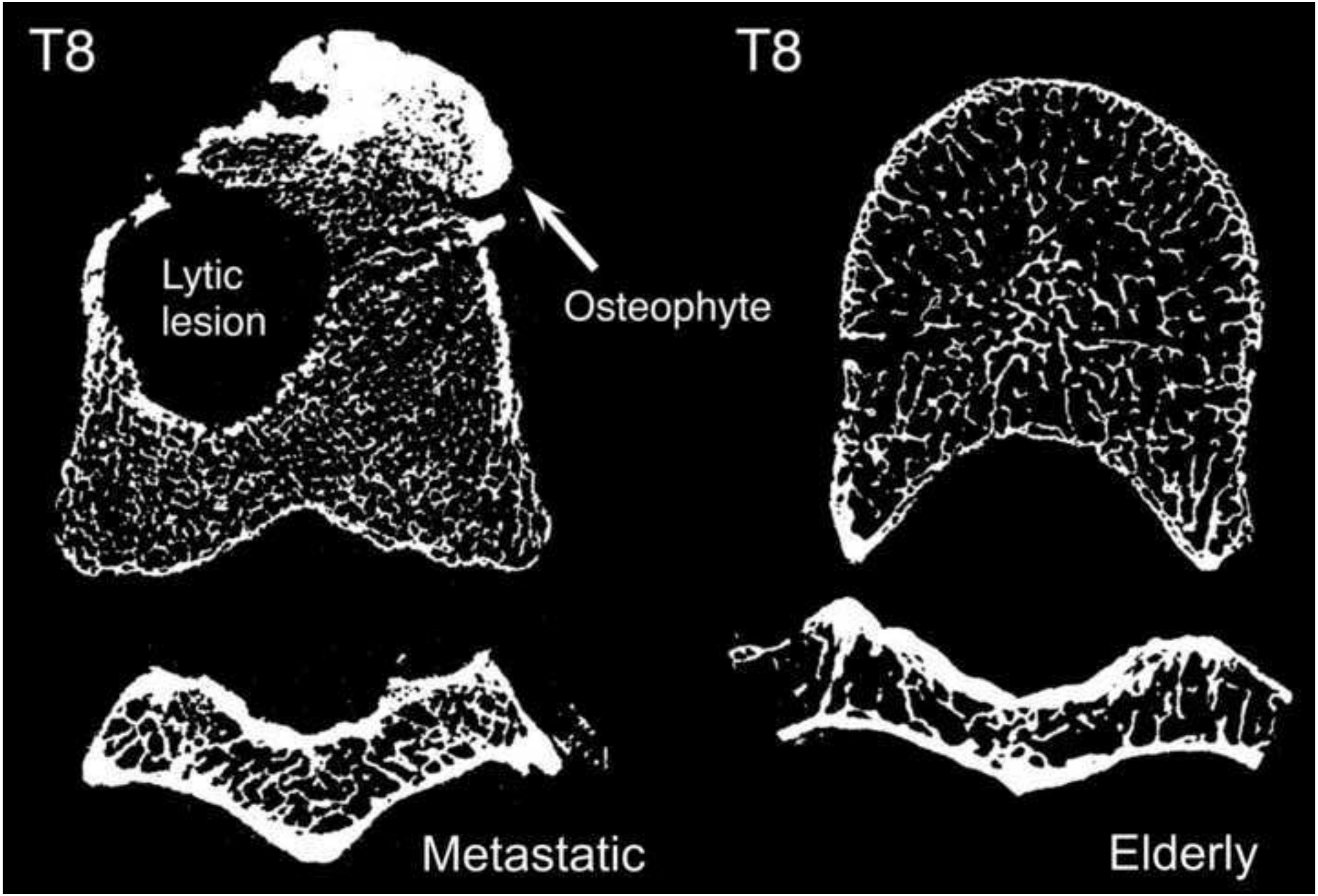

Figure 4
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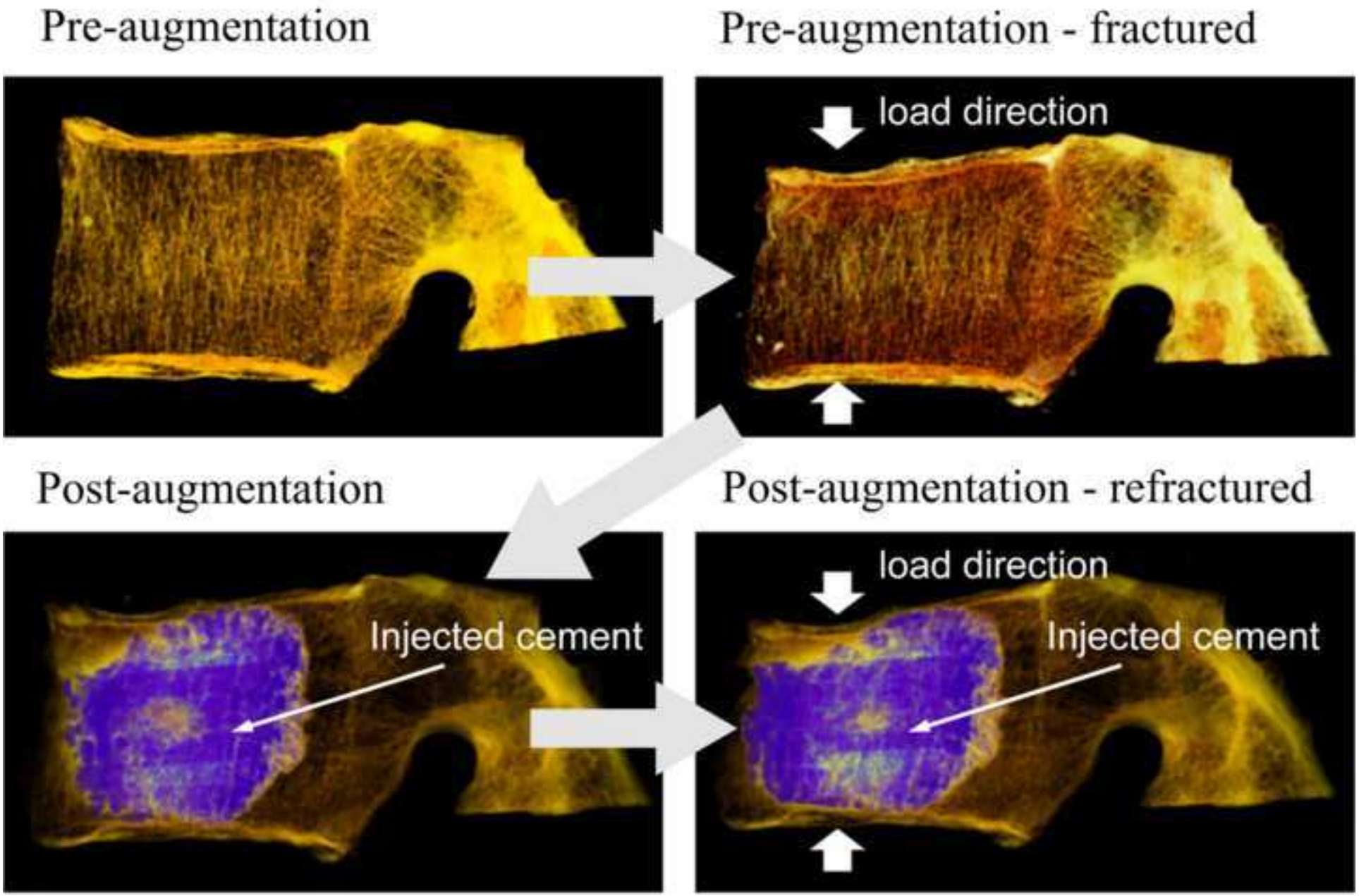

Figure 5

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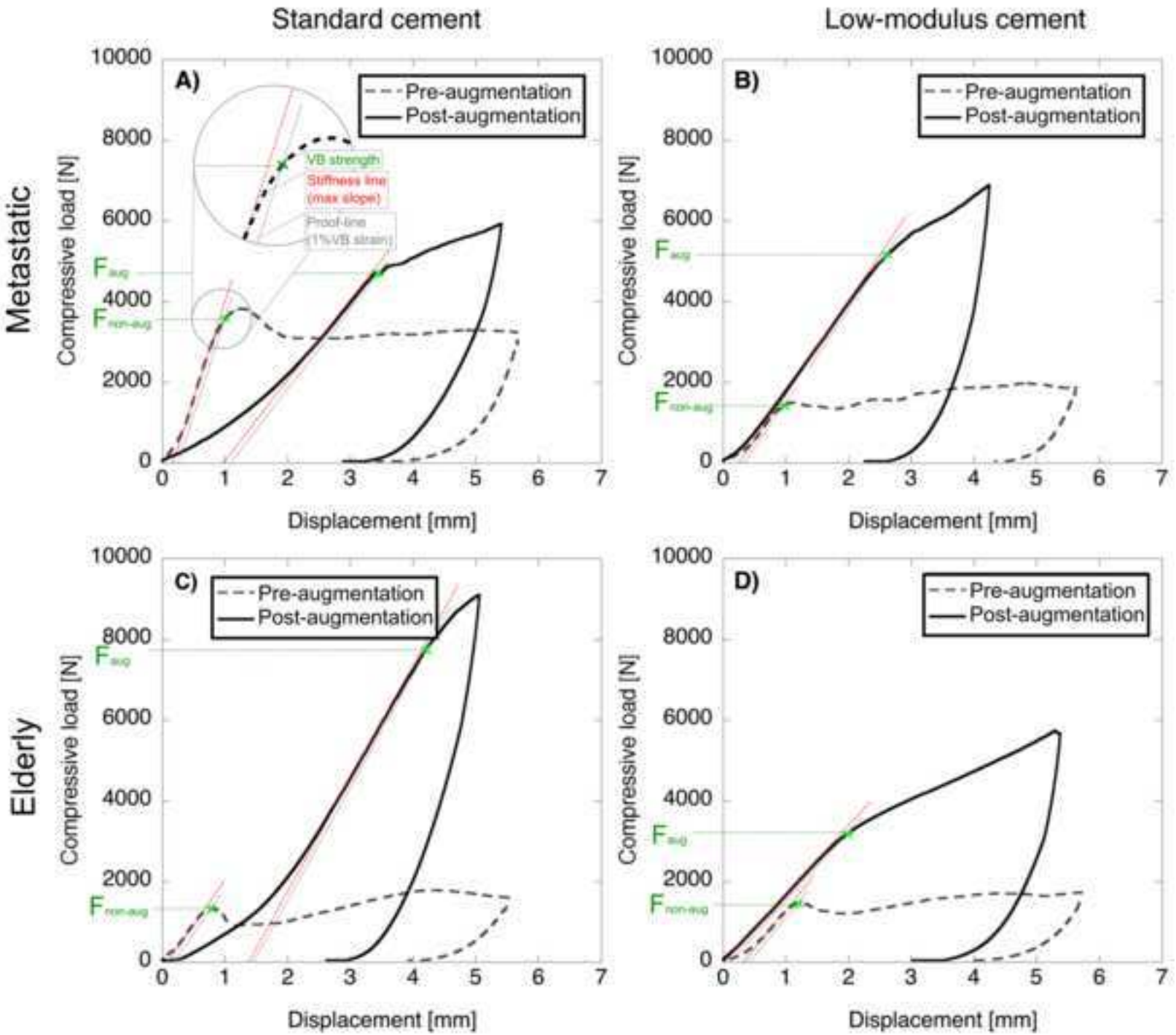

Figure 6 - revision2

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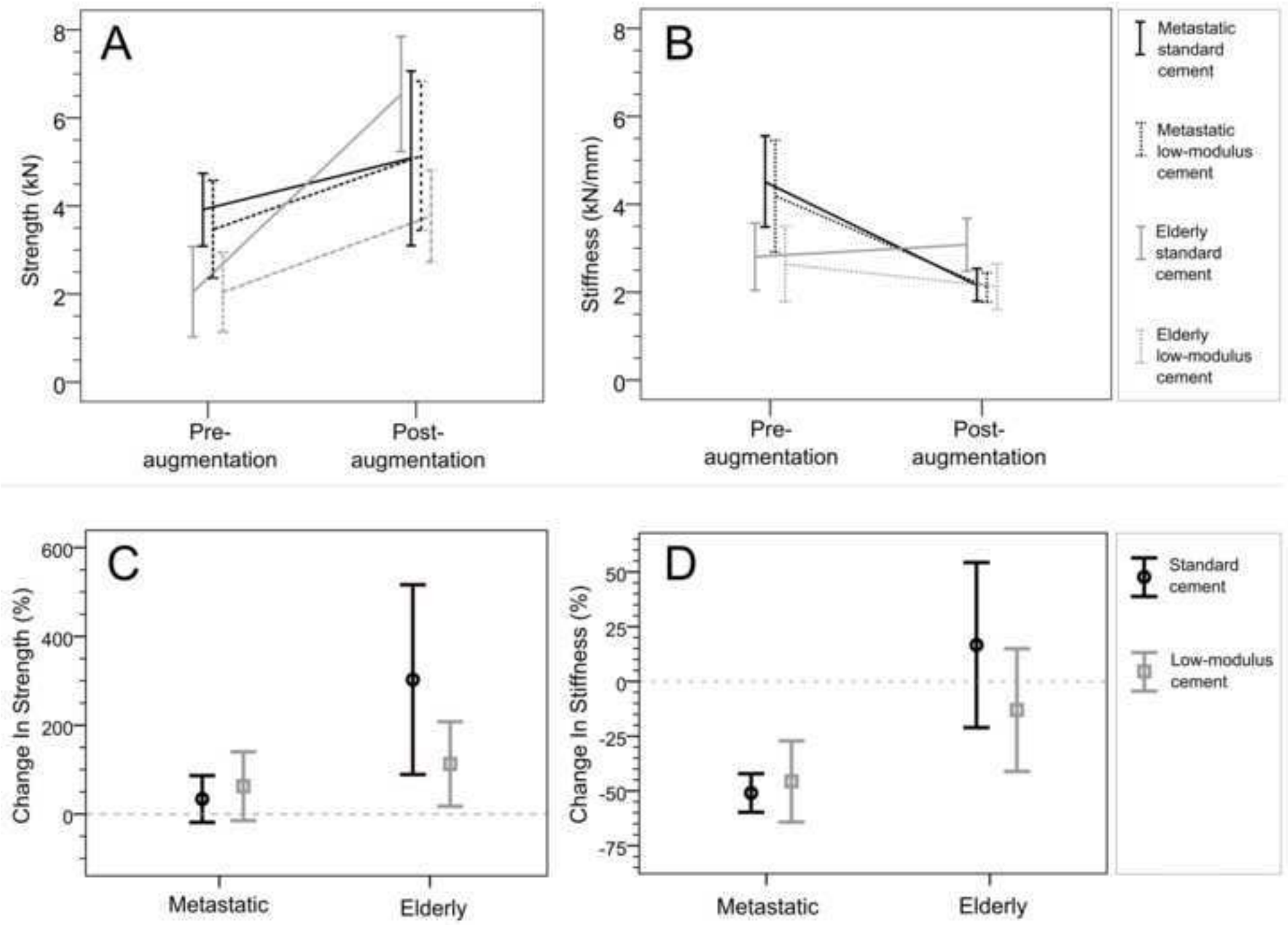

Table

Table 1. Summary of donor demographics, vBMD and BV/TV (± standard deviation) for each of the spines used, including averaged pre-augmentation biomechanical assessment (± standard deviation).

Sample population demographics						Pre-augmentation biomechanical assessment			
Spine type	**Age**	**Gender**	**Levels tested**	**Levels excluded**	**Indication of pathology**	**vBMD [mg HA/cm^3]**	**BV/TV [1]**	**Strength [kN]**	**Stiffness [kN/mm]**
Metastatic	41	F	T6-L5	T6-T10	Inflammatory breast CA+mets	174.82 (±30.84)	0.32 (±0.02)	3.83 (±0.42)	4.42 (±1.06)
Metastatic	85	M	T6-L5	-	Lung CA+mets	122.51 (±14.2)	0.23 (±0.03)	3.59 (±1.21)	4.3 (±1.24)
				Average metastatic		**148.66 (±35.57)**	**0.28 (±0.05)**	**3.68 (±0.99)**	**4.34 (±1.15)**
Elderly	66	F	T7-T11	-	Osteopenia/ mild osteoporosis	122.89 (±11.17)	0.15 (±0.02)	1.27 (±0.38)	2.28 (±0.77)
Elderly	93	F	T7-T11	-	Osteopenia/ mild osteoporosis	124.32 (±11.48)	0.2 (±0.01)	3.07 (±0.53)	3.31 (±0.61)
Elderly	102	F	T7-T11	-	OP not confirmed	194.6 (±7.86)	0.22 (±0)	2.49 (±0.92)	3.18 (±0.77)
Elderly	74	F	T7-T11	-	Osteopenia/ mild osteoporosis	137.31 (±5.72)	0.17 (±0.01)	1.35 (±0.13)	2.12 (±0.25)
				Average elderly non-metastatic		**144.78 (±39.95)**	**0.19 (±0.03)**	**2.05 (±0.94)**	**2.72 (±0.8)**
Elderly *	77	F	T7-T8, T11	T10**	Highly osteoporotic	66.08 (±13.81)	0.13 (±0.04)	0.50 (±0.05)	1.07 (±0.32)

* Spine was excluded due to **the low number of samples for this pathological classification.**

**T10 was excluded due to excessive leakage and a pre-existing fracture.

Table 2. Summary of group allocation and vBMD (± standard deviation) for each of tested groups.

	Cement used	Sample population	vBMD [mgHA/cm^3]
Elderly	**Standard**	10	148.93 (±33.16)
	Low-modulus	10	140.63 (±30.44)
Metastatic	**Standard**	9	135.86 (±29.59)
	Low-modulus	10	135.21 (±16.82)

Table 3. Results from repeated measures GLM analysis. (§): Statistically significant parameter coefficient at a significance level of α=0.05

Within-Subjects Effects		**p-value**
Strength		
Direct	Before / After fracture and augmentation	<0.001§
Interactive	Before / After fracture and augmentation*Pathology	0.314
Interactive	Before / After fracture and augmentation*Cement Type	0.063
Interactive	Before / After fracture and augmentation*Pathology*Cement Type	0.060
Stiffness		
Direct	Before / After fracture and augmentation	0.002§
Interactive	Before / After fracture and augmentation*Pathology	<0.001§
Interactive	Before / After fracture and augmentation*Cement Type	0.045§
Interactive	Before / After fracture and augmentation*Pathology*Cement Type	0.002§
Between-Subjects Effects		**p-value**
Direct	Pathology	0.007§
Direct	Cement Type	0.020§
Interactive	Pathology*Cement Type	0.112

Word count Introduction – Acknowledgements: 3752; max 4000

1. Introduction

With a current lifetime risk of experiencing a vertebral fracture of 30% in women and 20% in men, adequate treatment of these fractures is important for improving **the** quality of life **of the patient**, as well as in reducing the global healthcare's economic burden (Kanis and Johnell, 2005). Vertebral bone can deteriorate due to different diseases, including primary or secondary osteoporosis (Freedman et al., 2008) and cancers such as multiple myeloma and osteolytic metastases (Georgy, 2008). As many as 70% of patients with osteolytic lesions will **suffer from** vertebral **compression** fractures **(VCFs)** (Lecouvet et al., 1997). In osteoporotic and metastatic patients suffering from **VCF**s, percutaneous vertebroplasty with acrylic bone cements has shown good results in terms of reducing further height loss and **being of positive benefit** to pain **management** (Klazen et al., 2010; O'Brien et al., 2000).

It is generally accepted that the spinal load transfer mechanism is related to the structural stiffness of the vertebrae (Sun and Liebschner, 2004). Consequently, changes to the vertebral stiffness from cement augmentation should be minimised whilst at the same time attaining maximum strength. However, most acrylic cements used in vertebroplasty exhibit a very high elastic modulus (1700-3700 MPa) and compressive strength (85-114 MPa) (Hernandez et al., 2008; Kurtz et al., 2005) compared to the elastic modulus (10-900 MPa) and compressive strength (0.1-15 MPa) of cancellous bone (Helgason et al., 2008; Morgan et al., 2003; Nazarian et al., 2008). These large differences have raised concerns about the suitability of these cements, since clinical studies have reported 12-20% patients suffering new vertebral fractures following vertebroplasty, with a greater number (41-67%) of subsequent fractures observed adjacent to treated vertebrae (Grados et al., 2000; Trout et al., 2006; Uppin et al., 2003). These so called adjacent vertebral fractures (AVF) have also been

reported to occur earlier within patient cohorts undergoing augmentation (Trout et al., 2006; Uppin et al., 2003). However, the exact mechanism by which premature AVFs occur is subject to competing theories including the natural course of the disease, local changes in the biomechanical environment arising from differences in spinal shape, as a response to increased vertebral body (VB) stiffness or as a combination of the three (Baroud and Bohner, 2006; Liebschner et al., 2001). Other factors may be the limitation of the natural bulging of the endplates (Baroud et al., 2003; Polikeit et al., 2003) secondary to the maximum filling approach in which a large amount of cement forms a rigid bolus within the entire VB (Baroud et al., 2003; Berlemann et al., 2002).

Experimental studies have shown that after augmentation, cement and bone behave as a composite material with mechanical properties that are closer to those of the cement than to those of the bone (Helgason et al., 2012; Race et al., 2007; Williams and Johnson, 1989). This is because the cement represents a majority of the volume fraction of that composite for typical bone volume fractions **with** BV/TV≤0.20 (Fields et al., 2011; Morgan et al., 2003). This effect becomes more pronounced due to thinning of trabeculae in elderly bone, often affected by osteoporosis, and when soft tumour lesion infiltrates adjacent bone. Therefore, cements with a lower elastic modulus may be more suitable particularly in relatively low volume fraction bone associated with these two pathologies.

However, the adequacy of low-modulus cements in terms of restoring the mechanical properties of a previously fractured vertebral body is yet to be investigated in vertebrae of relevant pathologies. To the authors' knowledge, only two studies have focused on the biomechanics of low-modulus cements in a human ex vivo model (Boger et al., 2007; Kinzl et al., 2012a). Both studies used a prophylactic approach, i.e. the specimens were not fractured prior to augmentation, even though vertebroplasty is most commonly used for treating vertebral compression fractures (Boger et al., 2007; Kinzl et al., 2012a).

Therefore, the main aim of the present study was to assess the effectiveness of vertebroplasty with low-modulus cement by comparing the mechanical properties of vertebrae before and after augmentation with standard and low-modulus cement. This was accomplished within two groups of vertebral samples, the first group from elderly donors with bone prone to degradation, and the second cohort comprised metastatic donors. Within this study standard cement refers to the unmodified cement, whereas low-modulus describes modified cement with approximately 25% of the stiffness of standard cement.

2. Methods

2.1 Specimen Preparation and Handling

The experimental design is schematized in Figure 1. Twenty-four thoracolumbar vertebrae (T6-L5) from two donors with metastatic infiltration to the spine and twenty-four thoracic vertebrae (T7-T11) from five elderly donors were used (Table 1), acquired from two non-transplant tissue banks (Science Care®, USA, and GIFT, Leeds General Infirmary, UK) following ethics committee approval. From collection to 12 hours before dissection, the samples were stored frozen at -80ºC. The vertebrae were thawed overnight at 5°C and allowed to reach room temperature before testing. The vertebrae were dissected free of soft tissue and disarticulated at the intervertebral disc. The posterior and transverse processes were detached whilst keeping the neural arch intact per the protocol used previously (Furtado et al., 2007). Between experimental stages, the vertebrae were wrapped in tissue soaked with purified water, placed in sealed plastic bags, and kept frozen at -20°C until 24 hours prior to the next stage. As before the vertebrae were thawed for 12 hours at 5ºC and allowed to reach room temperature before testing.

2.2 Micro Computed Tomography (microCT)

The morphological properties of the vertebrae were measured after each experimental stage by scanning in purified water (Figure 1) using a microCT100 (Scanco Medical AG,

Brüttisellen, Switzerland) at an isotropic resolution of 70.8µm with 500 projections. Initial scans were used to estimate the vertebral body volume (V_{VB}), the bone mineral density (vBMD), and bone volume fraction (BV/TV). vBMD and BV/TV were estimated from a cylindrical volume of interest (∅= 60% of the anterior-posterior length; h= 80% of the height) within the trabecular bone in each VB (Furtado et al., 2007), with BV/TV calculated using a single value threshold based on an iterative user-independent selection method (Ridler and Calvard, 1978).

Benchmarking of the samples was done based on the Latin rectangle design (Bailey, 1996). In each of the pathological groups, the VBs were assigned to two groups, each of which contained the same **distribution of** specimens **in terms of predicted strength** from all donors. The theoretical strength was obtained from analysis of the initial scans with a beam-theory based fracture prediction model (Whealan et al., 2000), adopted and validated for eccentrically loaded single vertebrae. This permitted starting the augmentation phase before initial fracture of all specimens was completed. Appropriateness of the distribution was confirmed against initial fracture data.

2.3 Uniaxial Compression Testing

Intact vertebrae were first eccentrically loaded to failure to induce a wedge fracture and the same protocol (Figure 2) was used after augmentation to refracture the vertebrae.

Each vertebra was tested in an eccentric custom-built compression-rig mounted onto an Instron 3366 materials testing machine (10 kN load-cell, Instron, Norwood, MA, USA) to simulate quasi-static compression (Dall'Ara et al., 2010; Furtado et al., 2007) according to the protocol shown in Figure 2. Minor preload at a constant force (typically <5% of fracture load) helped to reduce slipping in the toe-region of the load-displacement curve. The relaxation period at the end of the test aimed to assess any restoration properties of the cement. The latter was however not analyzed in the framework of this study.

Since the whole bone load-displacement response tends to be highly non-linear a robust method of stiffness estimation was needed. Here, the vertebral stiffness [kN/mm] was defined as the maximum slope of the load-displacement curve over a 1% strain window prior to the zero-slope yield load (Buckley et al., 2009), which was proven to be more reliable than the traditional best-fit line. The vertebral strength [kN] was evaluated using the proof-load approach and defined as load at intersection of the stiffness line offset by 1% strain. In both cases the 1% strain was defined from total compression displacement normalised to the total height of the sample.

2.4 Bone Cement Preparation

Osteopal®V (Heraeus Medical GmbH, Hanau, Germany) radiopaque bone cement for vertebroplasty was used as the standard cement and as the base for the low-modulus cement. The latter was prepared by dissolving 9-cis,12-cis-linoleic acid (5.9 % v/v) (≥99%, Sigma-Aldrich, St. Louis, MO, USA) in the monomer phase of Osteopal®V before mixing the two phases as described elsewhere (López et al., 2014; **Persson et al., 2015)**. The elastic modulus and ultimate strength measured under uniaxial quasi-static compression after storage in PBS at 37°C for 24h of the standard cement was 1500(±140 SD) MPa and 103(±3 SD) MPa, respectively, whereas that of the low-modulus cement was 374(±30 SD) MPa and 15(±1 SD) MPa, respectively. Specimens of 6mm diameter and 12mm high were tested at 20mm/min, in accordance with the ISO5833 standard (ISO, 2002).

2.5 Needle Placement and Simulated Vertebroplasty

Prior to augmentation all vertebrae were submerged in phosphate buffered saline (PBS, 0.03 % w/w sodium azide) solution and preheated to 37°C for 1 hour. Stainless steel needles (11 G, 5 cm; Tizaro, Wilmington, DE, USA) were transpedicularly inserted by a spinal surgeon (VB) through both pedicles under fluoroscopic guidance using an X-ray image BV 25 unit (Philips, Amsterdam, The Netherlands). Bi-pedicular augmentation was performed using 5

mL luer lock polypropylene syringes. The maximum total volume of injected cement was set to 30% of the vertebral body volume (V_{VB}), of which half was injected through each pedicle. Augmentation was stopped when either the targeted volume had been injected, extensive extravasation to the spinal canal occurred, or when it was no longer possible to inject more cement by hand. Immediately after augmentation, each sample was again submerged in PBS solution and kept at 37°C for 24 hours to simulate physiological conditions for the curing. The vertebrae were then stored for scanning and subsequent fracturing, followed by refracture per the same scenario used for the initial fracture.

2.6 Statistical Analysis

Statistical analysis was carried out using IBM SPSS Statistics v21 (IBM, Chicago, IL, USA) at a significance level of α=0.05. A General Linear Model (GLM) for repeated measures was used to investigate the between-subjects effects of (i) pathology (metastatic or elderly) and (ii) cement type (standard or low-modulus) as well as the within-subjects effect of before and after fracture and augmentation, on the stiffness and strength of the individual vertebrae. **A t-test was used to confirm appropriateness of distribution of vertebrae into the two cement groups.**

3. Results

Examples of the morphological differences in the two groups are illustrated in the μCT images shown in Figure 3 whereas vBMD and BV/TV values are presented in Table 1. The degree of osteoporotic pathology of the elderly spines was established based only on the microCT-based vBMD assessment. Lack of standardization of acquiring data from this modality, however, prevented direct comparison with other studies. Here, samples were compared to available qCT-based vBMD classification (ACR, Revised 2013 (Resolution 32)) whilst considering the hard-coded beam hardening correction used in this study (1200mgHA/cm^3), and the size of the samples together with their low density, which is

known to increase the predicted density (Fajardo et al., 2009). **A**ll elderly spines except for one (which was deemed highly osteoporotic) could be classified as affected by mild osteoporosis (osteopenia) (Table 1). The only spine classified as highly osteoporotic was excluded from further analysis due to the low number of samples for this pathological classification. Highly mineralized areas were more common among the metastatic specimens but only 3 out of the 24 vertebrae exhibited focalised lytic lesions. Simulated vertebroplasty failed to deliver the targeted cement volume to five metastatic vertebrae, probably due to very high BV/TV preventing injection of the target of 30% VB fill. These samples were injected with volumes <15% VB volume fill, whereas all other samples were injected with confirmed volumes between 28 and 31%. Hence these samples were excluded from analysis. The vertebrae were distributed between cement groups without significant differences in strength (p=**0.343 and 0.983, for metastatic and elderly specimens, respectively**) or stiffness (p=**0.539 and 0.649, for metastatic and elderly specimens, respectively**), which allowed comparison of the results within each pathological group.

Figure 4 shows representative images of vertebrae after each experimental stage, demonstrating the induced wedge fracture as indicated by the eccentric (anterior) compression of the vertebral body, as well as the endplate to endplate augmentation with bone cement. Vertebroplasty did not fully restore the height of the vertebrae, with 14.5 ± 5.8 % lower and 17.0 ± 5.1 % lower height after fracture and augmentation than the initial anterior height, for metastatic and elderly vertebrae, respectively.

Representative load-displacement curves are shown in Figure 5. Non-augmented vertebrae featured an initial linear increase in the compressive load up to the fracture load (vertebral body strength [kN]), followed by a drop and finally slight increase in the load until the end of the test is reached. Augmented vertebrae featured a continuous non-linear increase in the

compressive load until reaching the endpoint (ε). The elderly vertebrae augmented with standard cement reached particularly high fracture loads.

While the within-subjects effect of before and after fracture and augmentation was statistically significant and independent of the between-factor effects for the strength (direct effect $p<0.001$, interactive effects $p>0.05$, Table 3), the stiffness change before and after fracture and augmentation depended on the between-subject factors, i.e. pathology and cement type (interactive factors were statistically significant, Table 3), which is further illustrated in **Figures 6 A and B**.

Prior to augmentation, metastatic vertebrae were on average 80 ± 48 % stronger than elderly vertebrae (**Figure 6 A**) and 59 ± 42 % stiffer (**Figure 6 B**) than elderly vertebrae.

After augmentation, metastatic vertebrae had similar average strength regardless of the type of cement they were augmented with (**Figure 6 A**). Elderly vertebrae augmented with standard cement were however 73 ± 34 % stronger than those augmented with low-modulus cement (**Figure 6 A**). In terms of stiffness after augmentation, metastatic specimens again had a similar average stiffness regardless of the cement type, while elderly vertebrae augmented with standard cement were 45 ± 28 % stiffer than those augmented with low-modulus cement (**Figure 6 B**).

The changes in mechanical properties before and after fracture and augmentation, **normalized for each individual vertebra's initial properties, and hence taking into account the natural variation,** are shown in **Figures 6 C and D**. Standard cement increased the strength of both metastatic and elderly vertebrae, with a much stronger effect on the elderly vertebrae (**Figure 6 C**, a positive net change in strength of +34% for metastatic and +303% for elderly specimens). Low-modulus cement also gave an increase in strength after fracture and augmentation of both metastatic and elderly vertebrae (**Figure 6 C,** 63% and 113%, respectively).

None of the cements restored the initial stiffness of the metastatic vertebrae (**Figure 6 D**, changes of -51% and -46% for standard and low-modulus cements). However, the standard cement increased the stiffness of the elderly, osteopenic vertebrae (**Figure 6 D**, a net change of +17%) and the low-modulus cement decreased the stiffness of elderly, osteopenic vertebrae (**Figure 6 D**, a net change of -13%).

4. Discussion

In developing vertebral augmentation procedures, preclinical studies have an important role to play. A number of biomechanical studies have already addressed some of these issues utilising both experimental investigations (Boger et al., 2007; Furtado et al., 2007) and computational modelling (Chevalier et al., 2008; Kinzl et al., 2012b; Wijayathunga et al., 2008). The volume (Belkoff et al., 2001; Liebschner et al., 2001; Molloy et al., 2003), efficiency of PMMA against ceramic cements (Tomita et al., 2003) as well as the cement delivery method (Liebschner et al., 2001; Molloy et al., 2005; Tohmeh et al., 1999) have been common subjects of investigation within osteoporotic models. In terms of injected volumes, clinically between 1-6mL (~10-30%) (Diamond et al., 2003) is being injected or the endpoint of injection is limited only in order to avoid possible extravasation (Barragan-Campos et al., 2006; Kaufmann et al., 2006). The stiffness and strength have been found to be only weakly correlated with the volume fill (Dean et al., 2000; Liebschner et al., 2001; Reidy et al., 2003), suggesting that even relatively small amounts of high-stiffness PMMA cements provide a large increase in stiffness. An excessive increase in stiffness may have negative effects on the normal stress distribution profile (McMillan et al., 1996). In fact, rigid bone cements have been reported to alter the natural inward bulging of the endplate and increase the pressure on the adjacent discs (Kinzl et al., 2012a). Low-modulus bone cements have therefore been proposed to minimize the risk for AVFs (Boger et al., 2008; Boger et al., 2009). In a previous study, we saw that low-modulus linoleic acid-modified bone cements

can reduce the stiffness and increase the contribution of the bone fraction to the overall strength and stiffness of a bovine bone/cement composite (López et al., 2014). In the present study, this was confirmed in human whole-vertebra specimens, where the effect of morphology, and BV/TV specifically, on mechanical properties, both before and after fracture and augmentation, was evident. The average vBMD was similar in both the metastatic and the elderly group, since the measurements were taken at a distance from both the lesions and the highly mineralized areas. On the other hand, the average BV/TV was 47 ± 35 % higher in metastatic than in elderly vertebrae. The resulting difference between the metastatic and the elderly vertebrae upon augmentation with either cement, confirms that cement contribution to strength and stiffness increases with a decrease in the bone volume fraction (Table 1, Figure 6), which is also in agreement with previous studies (Heini et al., 2001; Luo et al., 2007; Sun and Liebschner, 2004). Therefore, the influence of the type of cement on the strength and stiffness of the vertebral body depends on the initial morphological characteristics of the trabecular bone and the contribution of the cement to the properties was more evident in elderly vertebrae.

In a clinical setting, it is vertebrae that undergo an in vivo fracture that in some cases are treated with vertebroplasty. Using specimens without confirmed in vivo fractures may hence bias the mechanical properties towards higher values due to a higher bone quality compared to specimens that undergo an in vivo fracture. Future studies should hence focus on specimens classified as osteoporotic. For the same reasons, another limitation of the study is the presence of highly mineralized areas in the majority of metastatic specimens. However, these limitations emphasize the effectiveness of low-modulus cements under quasi-static compression. Ultimately it would be necessary to assess to what extent low-modulus cements could prevent adjacent vertebral fractures. To this end, cyclic loading of functional spinal segments with augmented caudal vertebrae would be of interest.

To improve the clinical relevance with respect to previous studies with low-modulus cements (Boger et al., 2007; Kinzl et al., 2012a) we induced wedge fractures to account for a typical non-prophylactic augmentation. The results showed that in all pathological groups, vertebroplasty with low-modulus cement increased the vertebral strength with respect to the initial values although significantly less than that found when augmenting with standard cement. In a previous study (Kinzl et al., 2012a) it was shown that when vertebrae without endplates were filled endplate-to-endplate, the specimens with standard cement were on average 47% stronger than a non-augmented control group (in our study elderly specimens were 303% stronger after fracture and augmentation), and 33% stiffer (in our study 17% stiffer). Furthermore, with low-modulus cement, their specimens were on average 30% stronger (in our study elderly specimens were 113% stronger after fracture and augmentation), and 27% stiffer (in our study 13% less stiff). Hence their results gave a difference in stiffness of specimens augmented with standard and low-modulus cements of only 6%, whereas in our study that difference was of 30%. The absence of endplates should have intensified the effect of the different cement properties with respect to our study. However, the results of Kinzl et al. represent a scenario without previous fracture, and different specimens were used for comparison of strength between non-augmented and augmented specimens. Therefore the absence of a pre-induced fracture together with the large natural variation between specimens could have masked any resulting treatment differences. The only other available ex vivo study on low-modulus cement for vertebroplasty was made on FSU's, not single vertebrae (Boger et al., 2007). No differences in strength were found between non-augmented control and specimens augmented with standard or low-modulus cement. However, no pre-induced fracture was present here either and specimen heterogeneity was cited as an issue.

Results here presented show an increase in stiffness of 17% (N=9) when standard cement was used whereas a decrease in stiffness of 13% (N=10) was found in elderly, osteopenic samples when low-modulus cement was used. Although the exact mechanism leading to premature AVFs is yet to be clarified (Baroud and Bohner, 2006), it is believed that such an increase in stiffness could occur at an early stage of development of excessively misbalanced biomechanics. Previous numerical predictions showed that the pillar-effect of a rigid cement bolus was linked to increased bulging of the end-plates and increased pressure onto the adjacent disc, and the authors hypothesized that as little as 17% of pressure increase may be behind the increased occurrence of the AVF. This has also been shown in an in vitro experiment (Kinzl et al., 2012a) in which authors reported notably higher endplate pressure in vertebrae augmented with standard (high-stiffness) cement. Whether such load shift would be minimized with decreasing the vertebral stiffness similar to that observed in our study is yet to be confirmed.

Although this study does not directly simulate AVFs, it demonstrates that using low-modulus cement could be effective in terms of restoring the initial properties of a fractured vertebral body, and may give a closer restoration of strength and stiffness to those prior to vertebral fracture, in comparison to standard cement. It should be noted that the low-modulus cement used in this study, i.e. PMMA modified with linoleic acid, can be tailored in terms of elastic modulus, and hence provide a targeted structural reinforcement depending on the treated pathology, i.e. a higher stiffness and strength cement could for example be used for augmentation of osteopenic samples.

Vertebroplasty with low-modulus cement could become particularly important in highly osteoporotic bone to avoid unnecessary strengthening and stiffening of the augmented vertebral body, and to prevent high stress concentrations on the adjacent endplates.

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Conflict of Interests

One of the materials evaluated in this study has been described in patent application nr PCT/SE2014/050429, where co-authors Cecilia Persson and Alejandro López are co-inventors. Co-authors Ondrej Holub, Vishal Borse, Håkan Engqvist, Nik Kapur, and Richard M. Hall, have no conflict of interests.

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Conflict of interest statement

To whom it may concern,

We hereby declare that one of the materials evaluated in this study has been described in patent application nr PCT/SE2014/050429, where co-authors Cecilia Persson and Alejandro López are co-inventors. Co-authors Ondrej Holub, Vishal Borse, Håkan Engqvist, Nik Kapur, and Richard M. Hall, have no conflict of interests.

On behalf of all authors,
Cecilia Persson