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Specimen-Specific Nonlinear Finite Element Modeling to Predict Vertebrae Fracture Loads after Vertebroplasty

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Abstract

Study Design—Vertebral fracture load and stiffness from a metastatic vertebral defect model were predicted using nonlinear finite element models (FEM) and validated experimentally.

Objective—The study objective was to develop and validate an FEM-based tool for predicting polymer-augmented lytic vertebral fracture load and stiffness and the influence of metastatic filling materials.

Summary of Background Data—Percutaneous vertebroplasty has the potential to reduce vertebral fracture risk affected with lytic metastases by providing mechanical stabilization. However, it has been shown that the mismatch in mechanical properties between poly(methyl-methacrylate) (PMMA) and bone induces secondary fractures and intervertebral disc degeneration. A biodegradable co-polymer, poly(propylene fumarate-co-caprolactone) [P(PF-co-CL)], has been shown to possess the appropriate mechanical properties for bone defect repair.

Methods—Simulated metastatic lytic defects were created in 40 cadaveric vertebral bodies, which were randomized into four groups: intact vertebral body (*Intact*), simulated defect without treatment (*Negative*), defect treated with P(PF-co-CL) (*Co-polymer*), and defect treated with PMMA (*PMMA*). Spines were imaged with quantitative computerized tomography (QCT), and QCT/FEM-subject-specific, non-linear models were created. Predicted fracture loads and stiffness were identified and compared to experimentally measured values using Pearson's correlation analysis and paired t-test.

Results—There was no significant difference between the measured and predicted fracture loads and stiffness for each group. Predicted fracture loads were larger for PMMA-augmentation (3960 N (1371 N)) compared to that of the co-polymer, negative and intact groups (3484 N (1497 N), 3237 N (1744 N) and 1747 N (702 N)). A similar trend was observed in the predicted stiffness.

Moreover, predicted and experimental fracture loads were strongly correlated ($R^2 = 0.78$), while stiffness showed moderate correlation ($R^2 = 0.39$).

Conclusion—QCT/FEM was successful for predicting fracture loads of metastatic, polymer-augmented vertebral bodies. Overall, we have demonstrated that QCT/FEM may be a useful tool for predicting in situ vertebral fracture load resulting from vertebroplasty.

Keywords

Spine; Fracture Prediction; Finite Element Analysis; Vertebroplasty; Polymer; Prevention; Vertebral Fracture Load; Nonlinear; Augmentation; Fracture Risk

Introduction

More than 1.5 million new cancer cases were projected to occur in the United States in 2013¹, with up to one-third of cancer patients developing spinal metastasis.² Vertebrae affected with lytic metastases are structurally weakened, and the risk of fracture is elevated.^{3, 4} Percutaneous vertebroplasty, first advocated for the treatment of metastatic lesions in 1987⁵, is a minimally invasive, imaging-guided intervention in which poly(methyl-methacrylate) (PMMA) bone cement is injected into structurally-weakened vertebrae to provide pain relief and mechanical stabilization. Over the past 20 years the technique has been applied for the treatment of an increasing population of metastatic patients.^{6, 7} However, because PMMA has a higher modulus than trabecular bone, it can lead to stress shielding with consequential bone resorption and disc degeneration adjacent to the reconstruction. This can be especially problematic for osteoporotic patients since the vertebrae above and below the augmented vertebra may develop an increased risk of fracture.^{8–10}

Previous biomechanical cadaver studies have experimentally demonstrated the strength and stiffness of vertebrae after vertebroplasty using PMMA^{11–20}, calcium phosphate^{21–24}, hydroxyapatite²⁵, and poly(propylene fumarate) (PPF)²⁶. These studies demonstrated that the fracture loads of augmented vertebrae could be better conserved using materials with moduli less than that of PMMA cement. Pursuing this strategy, an injectable, biocompatible, biodegradable co-polymer, poly(propylene fumarate-co-caprolactone) [P(PF-co-PL); a 50/50 ratio of PPF and poly(caprolactone) (PCL)], has been synthesized with mechanical properties resembling those of trabecular bone.^{27–29} While new injectable biomaterials may be effective in limiting unfavorable bone remodeling, the support and protection against failure that they impart to the impaired structure needs to be evaluated preoperatively.

Subject-specific finite element modeling (FEM) is a valuable tool for fracture load assessment.³⁰ Because FEM can take into account bone geometry, architecture, and heterogeneous mechanical properties of bone, models based on quantitative computed tomography (QCT) data may predict fracture load accurately. CT-based FE models can provide accurate predictions of fracture loads and stiffness of vertebra.^{30–35} The purpose of this study was to develop and validate a QCT-based, specimen-specific FEM (QCT/FEM) of vertebral bodies with metastatic lytic lesions capable of predicting vertebral fracture load

and stiffness after vertebroplasty using PMMA bone cement and a lower modulus, biomimetic co-polymer P(PF-co-CL).

Material and Methods

Cadaveric Studies

Forty thoracic and lumbar vertebral bodies (T2-T8 and L3-L5) from four fresh-frozen cadavers (age range 53–83 years; median age 70 years) were obtained from our institutions anatomical bequest program. Four of the vertebral bodies harvested could not be included due to deformity. The vertebrae were randomly divided into four groups: intact vertebral body (*Intact*, $n=4$), simulated defect without treatment (*Negative*, $n=10$), defect treated with P(PF-co-CL) (*Co-polymer*, $n=15$), and defect treated with poly(methyl-methacrylate) (*PMMA*, $n=7$). Specimen demographics and group characteristics are described in Table 1. Simulated metastatic lytic defects were made by removing a central core of the trabecular bone in each vertebral body with an approximate volume of 25% through an access hole in the side of the vertebrae, as previously described.³⁶ Defects were then filled by injecting either P(PF-co-CL) or PMMA (DePuy Spine, LeLocle, Switzerland) *in-situ* cross-linkable formulations using a vertebroplasty instrument (Kyphon, Inc, Sunnyvale, CA, USA). P(PF-co-CL) (50:50 PPF to PCL ratio) was synthesized using methods previously described.²⁸ The spines were placed on top of a calibration phantom (Midways Inc., San Francisco, CA, USA) containing five rods of reference materials and imaged with QCT using a Siemens Somatom Definition scanner (Siemens, Malvern, PA, USA, 120 kVp, 210 mA, slice thickness 0.4 mm, pixel width 0.3 mm). Post imaging, single vertebral body segments were harvested and cleaned of soft tissue using a scalpel in preparation for mechanical testing. Vertebral bodies were potted in 3-mm deep caps of PMMA cement at each end to ensure uniform loading. Specimens were then compressed using a multipurpose servohydraulic test system (MTS 858 MiniBionix II, Eden Prairie, MN, USA) at a rate of 5 mm/min either to failure, signaled by a sudden drop in the force-displacement curve, or to 25% reduction in body height, whichever occurred first. Fracture load was defined as the first peak on the force-displacement curve and stiffness was calculated from the slope of the initial linear region of this curve.

Model Development

Nonlinear Finite Element Approach—QCT data were imported into the FEM software package (Mechanical Finder, Research Center for Computational Mechanics, Tokyo, Japan) and subject-specific three-dimensional models were created. A nonlinear QCT/FEM analysis was used. The elements were assumed to be bilinear elastoplastic with an isotropic hardening modulus set to 0.05.³² Vertebrae (*Intact*, *Negative*, *Co-polymer* and *PMMA*) were segmented and meshed using linear tetrahedral elements with a 1.2-mm global edge length. The outer surface of the cortical bone was modeled using 1.2-mm triangular shell elements with virtual thickness set to 0.2 mm (Figure 1). The PMMA cement caps on the vertebrae ends were modeled and meshed with linear tetrahedral elements with a 3.6-mm global edge length. The mean number (SD) of nodes, solid elements, and shell elements were 60524 (40062), 333587 (229177), and 12670 (6416), respectively.

Bone heterogeneity was modeled by defining mechanical properties of each element based on corresponding Hounsfield unit (HU) values at their location. Each element represented the average ash density of the voxels within the element (Figure 2). Bone was modeled as an elastic-plastic material, with Young's modulus (Equation 1) and yield stress (Equation 2) assumed to be directionally isotropic and based on the following equations³⁷:

$$\text{Young's Modulus: } \rho=0, E=0.001; 0<\rho, E=1890\rho^{1.92} \quad [1]$$

$$\text{Yield stress: } \rho \leq 0.2, \sigma_y = 1 \times 10^{20}; 0.2 < \rho, \sigma_y = 284\rho^{2.27} \quad [2]$$

The Young's modulus used for each shell element was assigned based on the same equation with an input HU of either the value of its adjacent tetrahedral element or a value of 1000, whichever was greater. Poisson's ratio for each element was set to 0.3, as used in previous reports.³⁸ Young's modulus for elements of the filled lytic metastases were assigned to model either P(PF-co-CL) or PMMA (70 MPa or 2.5 GPa, respectively), and Poisson's ratio was set to 0.3 for both materials. The voids of the untreated defect vertebrae were modeled to contain no elements. The interface between the P(PF-co-CL) or PMMA and bone was based on manual thresholding and segmentation, and the nodes between these surfaces were tied. A compressive displacement was applied to the PMMA cement cap at the cranial end of the vertebrae at ramped displacement increments of 0.01 mm (Figure 2). PMMA cement cap elements at the bottom end of the vertebrae were encastred. Yielding of elements was defined to occur when their Drucker–Prager equivalent stress reached the element yield stress (Equation 2).³⁹ Predicted vertebral fracture loads were identified by a rapid decrease in the slope of the force/displacement curve due to yielding elements, and stiffness values were calculated from the slope of the initial linear portion of the force-displacement curve.

Statistical Analysis

A paired t-test was performed to compare experimentally measured and QCT/FE-predicted data for each group. Pearson correlation analysis was carried out to determine the quality of the predictions compared to measured data for both the individual groups and for the pooled data, generating best fit line parameters and a coefficient of determination (R^2). P -values less than 0.05 were considered to be significant.

Results

There was no significant difference between the measured and predicted fracture loads when comparing individual groups (Table 2). The strongest correlation was found between the measured and predicted fracture load results for the PMMA group ($R^2 = 0.90$) follow by the co-polymer, negative and intact groups (0.81, 0.76 and 0.48, respectively). Similarly, when pooling all the data together a strong correlation was found for the fracture load ($R^2 = 0.78$). Individual groups showed no significant difference in stiffness when comparing experimental and predicted values. The strongest correlation was found for the intact group ($R^2 = 0.80$) followed by the PMMA, co-polymer and negative groups ($R^2 = 0.70, 0.61$ and

0.50, respectively). Pooled data for stiffness showed a moderate correlation ($R^2 = 0.39$) (Figure 3).

Predicted fracture load values for the PMMA group (3960 N (1371 N)) were higher than the co-polymer, negative and intact groups (3484 N (1497 N), 3237 N (1744 N) and 1747 N (702 N), respectively). Predicted stiffness showed a similar trend with the PMMA exhibiting larger values (4097 N/mm (2076 N/mm)) compared to the co-polymer, negative and intact groups (3347 N/mm (1413 N/mm), 3037 N/mm (1677 N/mm) and 1755 N/mm (837 N/mm), respectively).

Discussion

In this study, we have developed and validated a QCT/FEM model for predicting polymer-augmented lytic vertebral fracture loads and stiffness and the influence of metastatic filling materials in vertebral behavior. The unique characteristics of the QCT/FEMs used in the present study consist of (1) the use of tetrahedral elements to model an accurate surface form for the entire vertebral body and augmented material and (2) the use of Drucker–Prager equivalent stress as an element yield criterion.

We found no significant difference between the mean measured and predicted fracture loads and stiffness in each group. In addition, we observed a strong correlation between the measured and predicted fracture loads. Although the correlations between the measured and predicted stiffness values were moderate, these were nonetheless lower than the measured fracture load correlations. Even though the predicted fracture loads do not depend strongly on the material density-elastic property relations, the stiffness values are highly affected by the material of choice.³³ In addition, predicted stiffness values were obtained by applying previously published empirical equations which might have increased our estimated error. The FEA model results for fracture loads and stiffness tended to under-predict the experimental outcomes with some groups showing a low coefficient of determination. Factors contributing to differences between physical and predicted results could include material constitutive model selection, failure criterion, and differences in vertebral geometry between the models and the physical specimens - especially at the micro-architectural level where computed tomography at clinical resolutions is unable to fully capture trabecular structure and cortical thickness. Despite these potential effects, fracture loads and stiffness for different augmentation materials could be correlated to experimental outcomes and predicted using a validated metastatic FEA model. Since the ultimate goal of the method is to prevent vertebral fracture and increase fracture risk prediction, we believe that accurate prediction of fracture load is more important than predicting vertebral stiffness.

Zeinali et al. showed good results in QCT/FEM evaluation of vertebrae compressive strength using 1-mm isotropic voxel elements.³⁴ Similarly, Mirzaei et al. developed a vertebroplasty model using the same method.³⁸ However, the vertebral body and augmented material geometry are more complex, and it is difficult to simulate behavior accurately using a voxel element based model. On the other hand, good and repeatable results have been demonstrated with QCT/FEMs of vertebrae using tetrahedral element based models.^{30, 32} A study by Imai et al. looked into fracture risk of osteoporotic vertebrae in vivo using this

automated tetrahedral mesh method.^{40, 41} Although their method showed promising results for non-surgical treatment, it is less ideal for application to augmented vertebral bodies, as the applied 2 mm mesh size is too large.

Currently, due to the low spatial resolution of clinical computed tomography, the density of the cortical bone edge tends to be underestimated. Because the material property of the shell element is dependent on its Hounsfield unit value, the strength of this element tends to be weaker. In previous studies of vertebral bone, the thickness and Young's modulus of the cortex was set to 0.35–0.60 mm and 0.475–10 GPa, respectively.^{32, 35, 42} In our study, preliminary analysis led to a selection of the shell element thickness of 0.3 mm, as setting this parameter to 0.2 and 0.4 mm resulted in an approximate 15% decrease and increase in fracture load, respectively, compared to the measured outcome. Similarly, the Young's modulus was set to be generally dependent on the adjacent tetrahedral element. A material sensitivity analysis was executed using previously published empirical equations. Using Keyak's material equation⁴³, the predicted fracture loads and stiffness were about 50% and 220% the experimental measured values Carter and Hayes's equation^{44–46} led to a 20% and 35% difference while Kopperdahl's showed a 60% and 140% difference.

This study has several limitations. First, the elements were assumed to be directionally isotropic as the software used was unable to create anisotropic material models. As the vertebral body is mostly trabecular bone, we believe load distribution in the microstructure, because of its anisotropic properties, may behave differently than what the model predicts. Second, we did not compare the predicted fracture location with the experimentally observed fracture patterns. Experimental fracture data and QCT scans used for the development and validation of the models were obtained from a previous published study.³⁶ Record of fracture location was not kept and experimental vertebrae were no longer available at the time of model development to retrospectively perform this analysis, preventing a gross examination and comparison of fracture location with the predicted failure patterns from the models. Third, the small number of specimens available in the intact group from a previous study prevented us from obtaining a more representative description of the fracture behavior from that population. This resulted in a lower coefficient of determination for the comparison of measured and predicted values than is representative of the technique. The fracture loads in this group also resulted in lower measured outcomes compared to the negative group specimens. This might also be due to the small size of the intact vertebral bodies which belonged to the upper thoracic spine. However, the small number did not affect the pooled correlations between the measured and predicted values. Future studies should look at vertebrae from lower regions of the spine. Although some individual groups might be under-powered, we were able to generate a metastatic model that truly represents the filling material inside the vertebral bodies and that correlates well with experimental results using different augmentation conditions. Finally, the software allowed for the specimens to be modeled using linear tetrahedral elements. While quadratic elements might seem more appropriate to limit shear-locking issues, we believe that the fine mesh size used in the models compensated for this shortcoming, and bending loading typically associated with this phenomenon is quite limited for the loading applied to this model.

Creating effective treatments and predicting metastatic vertebral fracture loads still remain a challenge in the clinical setting. The results of the present study demonstrated that the QCT/FEMs are able to predict the fracture loads of not only metastatic vertebrae, but also of augmented specimens. In addition, the models were shown to be robust enough to predict differences in failure behavior resulting from different treatments. We were successful in creating a lytic defect model in vertebral bodies which were filled with a lower modulus P(PF-co-CL) co-polymer and the clinically used PMMA. We were able to isolate the filling material from the surrounding trabecular structure and create finite element models of each specimen. Based on the predicted results, successful implementation of these models might predict the fracture load of metastatic vertebrae and virtual augmented vertebrae and be able to determine whether the patient should undergo vertebroplasty treatment. Nevertheless, additional in- vivo studies should be performed to 1) assess the evolution and degradation characteristics of the augmentation polymer material and the effect that these might have on the newly formed vertebral bone, reduction on the incidence of stress-shielding and adjacent disc degeneration; and 2) to evaluate patient vertebrae fracture loads in a clinical setting using routine scanning parameters.

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Figure 1.

Vertebra with defect filled with either PMMA or P(PF-co-CL). The different views show the complexity of the filling material distributed within the trabecular structure of the vertebral body. Vertebra and filling material were meshed using tetrahedral elements.

Figure 2. Bone mineral (material) distribution and boundary conditions. Bottom of the vertebra/PMMA (yellow dots) was constrained in all directions while the top was allowed a uniform downward displacement (red dots and arrow).

Figure 3.

Experimental fracture loads and experimental stiffness for the intact, negative, PMMA and co-polymer groups were predicted by the QCT/FEM models.

Table 1

Summary of specimen characteristics and vertebrae used in each group.

Specimen	Age	Intact	Negative	Co-polymer	PMMA
1	83	T2	T3, T7	T4, T5, T8, L3	T6, L4
2	69	T2	T3, T7, L4	T4, T5, T8, L5	T6, L3
3	71	T2	T3, T7	T4, T5, T8	T6
4	53	T2	T3, T7, L5	T4, T5, T8, L4	T6, L3

Table 2

Summary of experimental and predicted fracture loads and stiffness for each group.

Groups	Fracture Load (N) (mean (SD))			Coefficient of Determination (R ²)	Stiffness (N/mm) (mean (SD))			Coefficient of Determination (R ²)
	Measured	Predicted	P-value		Measured	Predicted	P-value	
<i>Intact</i> (n=4)	2185 (906)	1747 (702)	0.375	0.48	2913 (362)	1755 (837)	0.137	0.80
<i>Negative</i> (n=10)	3278 (2153)	3237 (1744)	0.906	0.76	3509 (1712)	3037 (1677)	0.403	0.50
<i>Co-polymer</i> (n=15)	3220 (1754)	3484 (1497)	0.206	0.81	4121 (2249)	3347 (1413)	0.116	0.61
<i>PMMA</i> (n=7)	4211 (1698)	3960 (1371)	0.296	0.90	5056 (2240)	4097 (2076)	0.180	0.70