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Abstract [250 words]

Purpose: A damaged vertebral body can exhibit accelerated 'creep' under constant load, leading to progressive vertebral deformity. However, the risk of this happening is not easy to predict in clinical practice. The present cadaveric study aimed to identify morphometric measurements in a damaged vertebral body that can predict a susceptibility to accelerated creep.

Methods: 27 vertebral trabeculae samples cored from five cadaveric spines (3 male, 2 female, aged 36 to 73 (mean 57) yrs) were mechanically tested to establish the relationship between bone damage and residual strain. Compression testing of 28 human spinal motion segments (three vertebrae and intervening soft tissues) dissected from 14 cadaveric spines (10 male, 4 female, aged 67 to 92 (mean 80) yrs) showed how the rate of creep of a damaged vertebral body increases with increasing "damage intensity" in its trabecular bone. Damage intensity was calculated from vertebral body residual strain following initial compressive overload using the relationship established in the compression test of trabecular bone samples.

Results: Calculations from trabecular bone samples showed a strong non-linear relationship between residual strain and trabecular bone damage intensity ($R^2 = 0.78$, $P < 0.001$). In damaged vertebral bodies, damage intensity was then related to vertebral creep rate ($R^2 = 0.39$, $P = 0.001$). This procedure enabled accelerated vertebral body creep to be predicted from morphological changes (residual strains) in the damaged vertebra.

Conclusion: These findings suggest that morphometric measurements obtained from fractured vertebrae can be used to quantify vertebral damage and hence to predict progressive vertebral deformity.

Key words: vertebral morphometry; residual strain; vertebral damage; creep; deformity; clinical imaging

1. Introduction

Human thoracolumbar vertebrae support the upper body and protect the spinal cord. In older people, these vertebrae are often weakened by osteoporosis, making them vulnerable to fracture. With conservative treatment, most vertebral fractures heal within 6-8 weeks. However, in a minority (7-37%) of patients [1], damage progresses over time, leading to vertebral collapse, spinal deformity, and even spinal cord compression [2]. These conditions can cause severe pain and disability, so it is important to identify those fractures which are likely to progress. A key risk factor for progression is the extent of initial vertebral damage [3, 4], but this is not easy to quantify in clinical practice.

Vertebral damage may involve trabecular bone, cortical bone, and vertebral endplates (which comprise perforated cortical bone and hyaline cartilage). The mechanical properties of fractured vertebrae are largely determined by trabecular bone damage [3, 5], which may include fractures of individual trabeculae, or more diffuse damage and microcracks. Trabecular damage can be quantified precisely using imaging techniques such as microscopy, and synchrotron radiation micro-computed tomography (micro-CT) [6, 7]. However, these techniques can be difficult to employ clinically because of large radiation exposure, and because only small regions of tissue are visualised.

Clinically, plain radiographs and dual-energy X-ray absorptiometry (DXA) are the primary imaging modalities for evaluating vertebral fractures [8]. They indicate the extent of vertebral deformity, and can quantify fracture severity, but have limited prognostic usefulness because they do not differentiate between old and recent (unhealed) fractures. CT and Magnetic Resonance Imaging (MRI) can be used for this latter purpose, and assist in the prediction of vertebral collapse [9], although they are less sensitive when quantifying vertebral damage.

What is needed is a clinical method that can quantify vertebral damage and also predict progressive vertebral deformity.

Previous experiments on cadaveric spines related progressive vertebral deformity under load to precise measures of vertebral damage obtained using physiologically-reasonable complex loading [4, 10, 11]. Subsequent research developed a mathematical model to explain the observed relationship between initial damage and progressive deformity [3]. However, it remains to be determined how vertebral damage can be measured clinically. The aim of the present study was to investigate whether morphometric measurements can be used to quantify vertebral damage and improve predictions of progressive deformity in fractured vertebrae.

2. Materials and methods

2.1 Experimental data

This study uses data from two previous experimental studies which quantified how initial damage increased subsequent time-dependent deformity in loaded vertebral bone.

The first experiment used 27 trabecular bone samples cored from human thoracolumbar vertebrae (3 male, 2 female, aged 36 to 73 (mean 57) yrs, spinal levels T8-L5) and made into cylindrical specimens with axial diameter 6.3 mm, and height 19.3–28.4 mm (Table 1). Two cores were first extracted from the middle region of the left and right halves of each vertebral body with a third core being extracted from the centre of the vertebral body, along the sagittal mid-line, if the specimen was large enough. Samples were then press-fit into two custom-made stainless steel endcaps, which were aligned with the longitudinal axis of the cylindrical sample so that only uniaxial loading occurred during mechanical testing. A Mach-1™ material testing device (Biomomentum, Canada), with a 100N load cell and a resolution of 0.001 mm displacement and 0.005 N load, was used to compress the sample which was placed in a test chamber filled with phosphate buffered saline (PBS) solution at room

temperature. Samples were subjected to a 'creep' test (constant compressive stress of 0.4 MPa for 30 mins), and then were compressed at a constant strain rate of 0.04% per second to various strain levels to induce different degrees of bone damage (1.0% strain for 8 samples; 1.5% for 7 samples; 2.5% for 5 samples; or 4% for 7 samples). After this 'overload' cycle, bone samples were immediately reloaded to the previous strain level (Figure 1). This is the 'reload cycle'. Samples were then subjected to a second creep test (0.4 MPa for a further 30 mins) [4]. Trabecular bone 'damage intensity' was quantified as the % reduction of elastic modulus between the overload and reload cycles [4]. In the present study, 'residual strain' was calculated as the difference in strain measured at 0.2 MPa between the overload and reload cycles (Figure 1). This enabled the relationship between residual strain and damage intensity to be determined. However, the shape of the stress-strain curve showed that residual strain was dependent upon the applied stress so additional analyses were also performed at 0.1 MPa and 0.3 MPa to check the sensitivity of the model predictions to variations in the loading conditions under which measurements were made.

The second experiment used 28 'motion segments' comprising three vertebrae and the intervening disc and ligaments from 10 male and 4 female cadavers (aged 67 to 92 (mean 80) yrs, spinal levels T8-L4) (Table 2) [10]. Specimens were secured in cups of dental plaster and loaded on a hydraulic materials testing machine (Dartec-Zwick-Roell, Leominster, UK) fitted with a 10 kN load cell (Figure 2). Mechanical tests were conducted at room temperature and humidity, with specimens wrapped in cling film to prevent water loss. Each motion segment underwent a static creep test (1000 N compression, for 60 min) while positioned in 0° of flexion, after which compression was applied at 3mm/s in 'flexed' posture to induce damage in one of the vertebrae. Specimens were then subjected to a linear ramp loading/unloading cycle lasting 10 seconds where the compressive force, applied in 0° of flexion, was increased from 50 N up to a maximum of 1.0 kN and then reduced to 50 N

(Figure 3) to simulate muscle force acting on the spine during light manual handling [12]. The creep test was then repeated, as before. During these tests, vertical deformation of the anterior, middle, and posterior regions of each vertebral body was monitored in the sagittal plane using an optical measurement system (MacReflex, Qualisys Ltd., Goteborg, Sweden) that tracks reflective markers attached to pins inserted into the cortex of each vertebral body. Measurements were made at 50 Hz with an in-plane accuracy of 10 μm [10]. In creep tests performed before and after damage, vertebral creep rate, which represents the progressive deformation of vertebral bodies, was calculated in the anterior cortex of the fractured vertebra between the 10^{th} and 20^{th} minutes of the secondary creep phase [13]. In the present study, vertebral deformations in the anterior region of the fractured vertebral body were also assessed during the ramp loading/unloading cycle. Maximal compressive strain was measured at the peak load of 1kN and residual strain was calculated as the average strain over 3 seconds at the end of the loading cycle once the compressive load had returned to 50N (Figure 3). These measurements indicate morphometric changes in vertebral bodies under normal physiological loading [10, 12, 14].

Areal bone mineral density (aBMD) of each vertebral body was measured using DXA. Endplate damage and cortical bone damage of the fractured vertebra were confirmed on radiographs and by anatomical dissection. The intervertebral disc adjacent to the fractured vertebra was evaluated for disc degeneration, on a scale of 1 (non-degenerated) to 4 (severely degenerated) [15]. Dimensions of the vertebral body, including maximal anterior-posterior and medio-lateral diameters, were measured at the superior endplate. This enabled the cross-sectional area of the vertebral body to be calculated using the formula for the area of an ellipse:

$$A = \pi ab/4 \qquad (1)$$

where A is the cross-sectional area, a is the maximal medio-lateral diameter, and b is the maximal anterior-posterior diameter.

2.2 Data analysis

Data from *trabecular bone samples* provided a direct measure of damage intensity based on the reduction in elastic modulus, and this was used to determine the relationship between residual strain and trabecular bone damage, using non-linear regression analysis. This relationship was then applied to experimental data from *motion segments* in order to estimate vertebral bone damage from residual strain measured in the fractured vertebra during ramp loading/unloading. The derived vertebral damage values, together with vertebral creep rate before and after damage, were then used to estimate the model parameter of a predictive model that was developed in a previous study [3]. The model relates the degree of vertebral damage to subsequent creep deformation, as follows:

$$\dot{\varepsilon}_c = \frac{\dot{\varepsilon}_0}{(1-\omega)^p} \qquad (2)$$

where $\dot{\varepsilon}_c$ is the vertebral creep rate following bone damage, $\dot{\varepsilon}_0$ is the vertebral creep rate before damage, ω is the vertebral damage intensity (ranging from 0 at no damage, to 1 at ultimate compressive failure), and p is the model parameter.

The model can be transformed to a linear format to enable the use of linear regression analysis:

$$\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0 = p[-\ln(1-\omega)] \qquad (3)$$

where $(\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0)$ is the difference in the natural logarithm of vertebral creep rate before and after damage, $\ln(1-\omega)$ is the natural logarithm of vertebral damage, and p is the model parameter as in equation 2.

Having established the above model, multiple linear regression using a stepwise method was employed to examine how factors such as endplate damage (1=no, 2=yes), cortical bone

damage (1=no, 2=yes), spinal level, disc degeneration grade (1 to 4), vertebral cross-sectional area, and vertebral aBMD affect the relation between $\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$ (outcome variable) and $[-\ln(1-\omega)]$ (predictor variable). The estimated value of parameter *p* in the linear regression model was compared with the value obtained previously [3] using a Z-test.

Finally, the relation between maximal and residual strain in motion segments during the ramp loading/unloading cycle was examined using linear regression.

Statistical analyses were performed with SPSS 25.0 (IBM, Armonk, NY, USA). For all analyses, $P<0.05$ was considered significant.

3. Results

Data from *trabecular bone samples* revealed a strong non-linear relationship between residual strain measured at 0.2MPa and trabecular bone damage (Fig. 4) represented by the following equation ($R^2 = 0.78$, n = 27):

$$\omega = 100 - \frac{51.4}{(\varepsilon_{res}+0.518)} \qquad (4)$$

where ω is the damage intensity (%), and ε_{res} is the residual strain (%).

M*otion segment* data was based on 25 fractured vertebrae because reflective markers could not be tracked reliably in 3/28 specimens. 8/25 vertebrae had endplate fracture, 8 had cortical bone damage, and 9 had endplate plus cortical bone damage. Disc degeneration was assessed as grade 2 in nine specimens, grade 3 in twelve specimens, and grade 4 in four specimens. Average vertebral cross-sectional area and aBMD were 1793 mm^2 (range 1033 - 2854) and 0.56 g/cm^2 (range 0.24 -1.10), respectively.

For each motion segment, damage intensity (ω) was calculated by substituting the measured values of residual strain into equation (4). Values of ω were then used to determine the relationship between vertebral damage intensity and creep deformation using equation (3). A

significant linear relationship existed between $\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$ and $-\ln(1-\omega)$ (R^2 = 0.39, P = 0.001, n = 25) (Fig. 5). Multiple regression indicated that fracture type (endplate or cortical bone), disc degeneration, spinal level, cross-sectional area, and aBMD made no significant contribution to the model predictions of creep deformation (P > 0.05). The estimated model parameter *p* had a mean (S.E.) value of 1.01 (0.26) and was not significantly different from the mean value reported previously (1.48, S.E. 0.47, Z= 0.87, P > 0.05) [3].

Following compressive overload, a strong correlation was observed between maximal and residual strain during the ramp loading/unloading cycle (R^2 = 0.92, P < 0.001, n = 25) (Fig. 6). The regression model indicates that maximal compressive strain at 1kN is around 2.4 times greater than residual strain at 50N.

Additional analyses based on residual strains measured at 0.1 and 0.3 MPa in the trabecular bone samples produced regression curves similar to those shown at 0.2 MPa with values of the model parameter, p, varying from 0.95 at 0.1 MPa to 1.12 at 0.3 MPa (Appendix 1). Based on these model parameters, estimates of damage intensity were up to 5.6% lower at 0.1 MPa and up to 5.2% greater at 0.3 MPa compared to those made at 0.2 MPa indicating that model predictions were not greatly influenced by small changes in the loading conditions.

4. Discussion

4.1 Summary of findings

Residual strain in a damaged vertebra, measured under physiological loading conditions, can be used to determine vertebral damage intensity and predict future vertebral deformity under load. Maximal compressive strain can function in a similar way because it is strongly correlated with residual strain. Factors such as disc degeneration, spinal level, BMD, cross-sectional area and fracture type, had no significant influence on the model predictions. In principle, therefore, morphometric measurements obtained following initial vertebral damage

could be used to predict progressive vertebral deformity. However, these findings are based on in-vitro experiments and need to be confirmed in the clinical setting.

4.2 Strengths and weaknesses

Experimental data were obtained using cadaver spines from donors mostly aged over 50 years, so results are applicable to the clinical problem of osteoporotic vertebral fractures.

The relationship between residual strain and damage was obtained from trabecular bone samples where damage could be more directly quantified, and this relationship was applied to fractured vertebrae to derive vertebral damage intensity. This approach is justified based on previous findings that trabecular bone damage is the key determinant of mechanical behaviour of a damaged vertebral body [3, 5].

In trabecular bone samples, residual strain was influenced by the applied stress so it was necessary to standardise the stress at which measurements were made. A value of 0.2 MPa was chosen to be comparable with test conditions in the motion segments. In the latter case, stress in the vertebral body could not be measured directly and was difficult to estimate from measures of vertebral cross-sectional area because a variable proportion of the applied load would be borne by the neural arch [16]. To overcome this problem, residual strain was measured under 50N load when stress within the vertebral body would be low and inter-specimen differences in stress would be minimised. Under these conditions, residual strains in 19 of the 25 fractured vertebrae were below 3.3% (Figure 6). This strain level represented the upper limit of the data obtained in the trabecular bone samples where the regression curve relating residual strain to damage intensity started to plateau (Figure 4). These findings suggest that damage intensity could be estimated with reasonable accuracy in fractured vertebrae, even where residual strains exceeded 3.3%. Additional analyses where residual strains in trabecular bone were evaluated at 0.1 and 0.3 MPa showed that predictions of

damage intensity deviated by no more than 5.6% from those obtained at 0.2MPa suggesting they were fairly robust to small variations in the loading conditions.

The motion segment experiments enabled vertebral strain to be measured in the sagittal plane using an optical system which can track reflective markers attached to vertebral bodies with in-plane errors less than 10 μm [17]. Such measurements are clinically relevant because sagittal images of the spine are often used for vertebral fracture assessment [8].

The ramp loading/unloading cycles used to assess maximal and residual strains following vertebral damage were chosen to mimic physiological loading in life [10, 12]. The initial load (50 N) simulates spinal loading in lying where low levels of trunk muscle activity act to stabilise and protect the spine [18, 19], while the maximal load (1.0 kN) simulates moderate muscle forces in standing posture [14]. In theory, similar morphometric measurements could be made clinically although the resolution of current imaging techniques may limit the ability to measure small residual strains. However, residual strains in fractured vertebrae are highly correlated with maximal strains which are considerably larger (Figure 6) and may be more readily assessed in vivo. Height changes measured on lateral radiographs taken concurrently in lying and then standing can provide a measure of maximal strain, comparable to that measured in vitro. From these measurements, residual strain could be estimated and used to determine vertebral damage intensity so that progressive creep deformation of the fractured vertebra could be predicted using the mathematical model developed in this study (Equation 2). Current image analysis techniques can measure vertebral height on plain radiographs with less than 3% precision error [20], suggesting that residual strains as small as 1% could potentially be estimated from maximal strain data.

Limitations of the study include the small number of donors from whom samples were obtained for the trabecular bone experiments. However, donors spanned a wide age range

(36-73 yrs) and samples were taken across numerous spinal levels (T8-L5) in order to improve the generalisability of the results. Consequently, the estimated parameter values in this study (equation 4), are similar to those obtained in a previous study that used samples from a much larger number of donors [5]. Another limitation is that experiments were conducted at room temperature. There is no reliable evidence that death *per se* affects the spine's mechanical properties [21], but normal body temperature (37^{o}C) would be expected to increase the rate of creep in living bone [22], at least until some equilibrium was approached. This possibility should be explored in future studies.

There are also some foreseeable problems with the clinical application of this study's findings. Measurements obtained from clinical radiographs may be influenced by the obliquity of the beam or superimposition of other structures so further clinical investigations are needed to evaluate how such factors may influence the model's predictions. It is also likely that maximal and residual strains following fracture may decrease over time, as vertebral deformation progresses, so application of this model may be most suitable at an early stage, providing an opportunity for timely intervention to prevent spinal deformity.

4.3 Relationship to previous work

The current study uses the relationship between vertebral damage and creep deformation established previously [3]. As in the previous study, we found that trabecular bone damage was the key determinant of creep deformation following vertebral compression fracture. However, the methods to obtain vertebral damage were different. In the previous study, vertebral damage was derived from the reduction of vertebral stiffness following damage, whereas in the current study vertebral damage was derived from residual strain measured post-damage. Despite these differences, the value of the estimated model parameter p in the present study did not differ significantly from that reported previously [3]. Vertebral damage

estimated from residual strain (present paper) actually fits the model better than estimated based on vertebral stiffness ($R^2 = 0.39$ vs. $R^2 = 0.22$). This may be because residual strain was measured directly in the fractured vertebra, while in the previous study vertebral stiffness was approximated from motion segment stiffness. It should also be noted that although percentage *reduction* of vertebral stiffness is an established method to calculate vertebral damage [5], it is difficult to employ this method in a clinical setting because vertebral stiffness before fracture cannot normally be obtained. As morphometric measurements are widely used in routine clinical imaging to assess vertebral fracture [8], the findings of the current study represent significant progress regarding the clinical application of the predictive model [3].

4.4 Clinical significance

Our results provide a biomechanical rationale for previous clinical findings that vertebral deformity often increases slowly over time [23], and that some vertebral fractures are 'mobile' in the sense that their shape changes between standing and supine postures [20, 24]. Mobile fractures have previously been linked with increased back pain [24-26], and our findings suggest that they are also associated with vertebral damage and progressive vertebral deformity.

Findings from the current study may lead to improved diagnosis and evaluation of vertebral fractures using routine clinical imaging. Currently, morphometric measurements of the vertebral body are used to assign fractures into different categories based on the nature and severity of post-fracture deformity [8]. The current study indicates that vertebral morphometry can also be used to identify symptomatic 'mobile' fractures and to predict future, progressive vertebral deformity.

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Figure Legends

Fig. 1 Stress-strain graphs for a trabecular bone sample subjected to compressive 'overload' and 'reload' cycles. Residual strain was calculated as strain difference measured at 0.2 MPa

Fig. 2 Each motion segment was secured in two cups of dental plaster and compressed via two low-friction rollers, the height of which could be altered to simulate different postures. Creep tests and ramp loading/unloading cycles were performed in 0° of flexion (left), and compressive overload tests were performed in a flexed posture (right). Black circles represent reflective markers attached to the vertebral bodies in order to assess vertebral deformations.

Fig. 3 Force-time and strain-time graphs for a motion segment during a ramp loading/unloading cycle performed after compressive overload. The compressive force was increased from an initial 50N up to a maximum of 1.0 kN, and back down to 50N. 'Residual strain' in the anterior region of the fractured vertebra was measured at the end of the loading cycle

Fig. 4 Data from 27 trabecular bone samples showing the relationship between trabecular bone damage and residual strain assessed at 0.2 MPa.

Fig. 5 The relationship between increased vertebral creep rate ($\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$) and vertebral damage [$-\ln(1-\omega)$]. Mechanical test data were from 25 vertebral bodies. $\dot{\varepsilon}_0$ is the vertebral creep rate before damage, $\dot{\varepsilon}_c$ is the vertebral creep rate after damage, and ω is the damage intensity derived from residual strain measured in the ramp loading/unloading cycle performed after compressive overload.

Fig. 6 The relationship between maximal strain and residual strain based on data obtained from 25 vertebral bodies. Measurements were made during the ramp loading/unloading cycle performed after compressive overload.

Appendix 1: Figure Legends

Fig. A1 Data from 27 trabecular bone samples showing the relationship between trabecular bone damage and residual strain assessed at 0.1 MPa.

Fig. A2 The relationship between increased vertebral creep rate ($\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$) and vertebral damage $[-\ln(1-\omega)]$ based on data represented in Figure A1. Mechanical test data were from 25 vertebral bodies. $\dot{\varepsilon}_0$ is the vertebral creep rate before damage, $\dot{\varepsilon}_c$ is the vertebral creep rate after damage, and ω is the damage intensity derived from residual strain measured in the ramp loading/unloading cycle performed after compressive overload.

Fig. A3 Data from 27 trabecular bone samples showing the relationship between trabecular bone damage and residual strain assessed at 0.3 MPa.

Fig. A4 The relationship between increased vertebral creep rate ($\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$) and vertebral damage $[-\ln(1-\omega)]$ based on data represented in Figure A3. Mechanical test data were from 25 vertebral bodies. $\dot{\varepsilon}_0$ is the vertebral creep rate before damage, $\dot{\varepsilon}_c$ is the vertebral creep rate after damage, and ω is the damage intensity derived from residual strain measured in the ramp loading/unloading cycle performed after compressive overload.

Table 1 Details of 27 trabecular bone samples in the first experiment

Donor information		Spinal level (n)
Sex (M/F)	Age (yrs)	
3M/2F	Mean: 57 SD: 14 Min: 36 Max: 73	T8: 2 T10: 2 T11: 2 T12: 4 L1: 3 L2: 8 L3: 1 L4: 3 L5: 2

Table 2 Details of 28 motion segments in the second experiment

Note: *Grade of disc degeneration is the average of the two discs of each three-vertebra specimen; $^{+}$BMD values are those of the fractured vertebra; Fracture types are defined as anterior cortex (AC), endplate (EP), or anterior cortex plus endplate (AC+EP).

Donor information		Spinal level (n)	Disc degeneration grade* (n)	BMD^{+} (g/cm^2)	Fracture type (n)	Cross-sectional area (mm^2)
Sex (M/F)	Age (yrs)					
10M	Mean: 80	T8-T10: 2	Grade 2: 9	Mean: 0.59	AC: 9	Mean: 1808
4F	SD: 8	T9-T11: 1	Grade 3: 15	SD: 0.25	EP: 8	SD: 489
	Min: 67	T10-T12: 5	Grade 4: 4	Min: 0.24	AC+EP: 11	Min: 1033
	Max: 92	T11-L1: 8		Max: 1.10		Max: 2854
		T12-L2: 1				
		L1-L3: 3				
		L2-L4: 8				