A predictive model for creep deformation following vertebral compression fractures

A predictive model for creep deformation following vertebral compression fractures

Jin Luo PhD[1], Patricia Dolan PhD[2], Michael A. Adams PhD[2],

Deborah J. Annesley-Williams FRCR[3], Yue Wang MD, PhD[4]

[1]School of Biomedical Sciences, University of West London, London W5 5RF, U.K.

[2]Centre for Applied Anatomy, University of Bristol, Bristol BS2 8EJ, U.K.

[3]Royal Derby Hospital, Derby DE22 3NE, U.K.

[4]Spine Lab, Department of Orthopaedic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

Correspondence to:

Dr Jin Luo, School of Biomedical Sciences, University of West London, St Mary's Rd, Ealing, London W5 5RF, U.K. Tel: 44 20 8231 2468, Email: jin.luo@uwl.ac.uk OR Dr Yue Wang, Spine Lab, Department of Orthopaedic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, Tel: 86 571 87236128, China. Email: wangyuespine@zju.edu.cn.

Declarations of interest: none

Abstract

Many vertebral compression fractures continue to collapse over time, resulting in spinal deformity and chronic back pain. Currently, there is no adequate screening strategy to identify patients at risk of progressive vertebral collapse. This study developed a mathematical model to describe the quantitative relationship between initial bone damage and progressive ("creep") deformation in human vertebrae. The model uses creep rate before damage, and the degree of vertebral bone damage, to predict creep rate of a fractured vertebra following bone damage. Mechanical testing data were obtained from 27 vertebral trabeculae samples, and 38 motion segments, from 26 human spines. These were analysed to evaluate bone damage intensity, and creep rates before and after damage, in order to estimate the model parameter, p, which represents how bone damage affects the change of creep rate after damage. Results of the model showed that p was 1.38 (R^2 = 0.72, p < 0.001) for vertebral trabeculae, and 1.48 for motion segments (R^2 = 0.22, p = 0.003). These values were not significantly different from each other (P > 0.05). Further analyses revealed that p was not significantly influenced by cortical bone damage, endplate damage, disc degeneration, vertebral size, or vertebral areal bone mineral density (aBMD) (P > 0.05). The key determinant of creep deformation following vertebral compression fracture was the degree of trabecular bone damage. The proposed model could be used to identify the measures of bone damage on routine MR images that are associated with creep deformation so that a screening tool can be developed to predict progressive vertebral collapse following compression fracture.

Key words: vertebral compression fractures; creep; deformity; mathematical model

1 Introduction

Vertebral compression fractures are common in the elderly, particularly in women. Approximately 10-20% of women who are 65 years or older have at least one fractured vertebra [1]. Typically, vertebral compression fractures lead to significant back pain that requires bed rest and/or clinical intervention. Healthcare and social costs related to vertebral fractures constitute a heavy burden in an ageing society [2]. Currently, fewer than one third of vertebral fractures are diagnosed, meaning that many patients miss the opportunity to receive appropriate treatment [3].

Although most patients with vertebral compression fractures respond favourably to clinical treatment, 7-37% of patients develop progressive vertebral collapse over time [4], resulting in spinal deformity, chronic back pain, disability, and possibly neurological complications [5,6]. Such long-term complications substantially impair the patients' quality of life, and often require complicated surgical intervention. Hence, it is clinically important to identify this subgroup of patients as early as possible so that appropriate clinical treatments can be applied in time to alleviate or prevent progressive vertebral collapse.

Currently, dual-energy X-ray absorptiometry (DXA) is most commonly used to conduct vertebral fracture assessment (VFA) [7]. However, VFA has limitations in determining the acuity of vertebral fracture. On the other hand, magnetic resonance (MR) imaging is very sensitive in the detection of acute bone lesion [8], making it the imaging modality of choice in the evaluation of vertebral fracture. A number of methods have been developed to predict the occurrence of progressive vertebral collapse. Most use qualitative measurements acquired from MR images or radiographs [6,9,10]. In particular, a number of recent studies have investigated

whether MR imaging, due to its ability to provide valuable information on damage and healing within bone tissue, can potentially be used for this purpose [10-12]. However, there is currently no reliable and practical screening tool to identify patients who are at high risk of progressive vertebral collapse [9]. This is due, in a large part, to a limited understanding of the determinants of progressive vertebral collapse following fracture.

Progressive vertebral collapse may involve disturbed healing of fractured trabecular bone following excessive biomechanical loading [6]. It is well established that an interfragmentary strain range of 6%-20% enhances trabecular bone healing via endochondral ossification, while strains over 20% hinder the bridging between bone fragments and may lead to a large amount of fibrous cartilage [13]. Bone biopsies obtained from fractured human vertebrae showed that trabecular bone in the late stage of healing was often accompanied by newly fractured bone, suggesting that the orderly repair of vertebral trabeculae could be hindered by ongoing injury [14]. The initial unrecoverable strains within fractured vertebral trabeculae, defined as the permanent deformation of the specimen divided by its initial height, are relatively small (<4%) [15], but can be substantially elevated by time-dependent deformation under constant load, a process called 'creep' [16,17]. Creep damage is often accompanied by cycle-dependent fatigue damage in living bone. Both creep and fatigue contribute to damage accumulation in bone [18]. Due to its limited magnitude, creep deformation of undamaged trabecular bone is usually insignificant [16]. However, our previous mechanical experiments demonstrated that sufficient damage to trabecular bone can boost creep deformation to such an extent that it may interfere with bone healing [19], suggesting that the degree of bone damage was a major

determinant of progressive vertebral deformation and collapse. Further work is needed to translate this experimental finding into clinical use.

The aim of the current study is to develop a mathematical model to characterize the quantitative relationship between initial bone damage and consequent creep deformation in human vertebrae.

2 Materials and Methods

2.1 Model

Based on Kachanov's creep damage theory [20,21], a mathematical model was proposed to predict the effect of bone damage on creep rate in human vertebrae. The assumptions of the model are: 1) the human vertebral body is treated as a continuum of trabecular bone; 2) a constant compressive load is applied; 3) creep deformation is measured in the sagittal plane. The model can be expressed as:

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

where $\dot{\varepsilon}_c$ is the creep rate with bone damage, $\dot{\varepsilon}_0$ the creep rate with no damage, ω the damage intensity ($0 \leq \omega < 1$; $\omega = 0$ at no damage; $\omega = 1$ at failure), and p is the model parameter. The model parameter p was estimated from previous experimental data [17,19,22] which measured creep rate with and without bone damage ($\dot{\varepsilon}_c$ and $\dot{\varepsilon}_0$) and damage intensity (ω).

2.2 Experimental data

Two sets of previously-acquired mechanical testing data were used in the current study. Experimental details have been published elsewhere [17,19,22].

The first dataset concerns 27 trabecular bone samples which were cored from human thoracic or lumbar vertebrae (3 males and 2 females, mean age 57 years, range 36-73 years, spinal level T8-L5) and made into cylindrical specimens (axial diameter 6.3 mm, height 19.3–28.4 mm) [19]. Trabecular samples first underwent a creep test (static compressive stress of 0.4 MPa, which is equivalent to the average compressive stress on vertebral trabeculae when a spinal motion segment was subjected to 1000 N creep load) for 30 minutes, and then were compressed to a specified strain level (1.0%

for 8 samples; 1.5% for 7 samples; 2.5% for 5 samples; or 4% for 7 samples) to induce different degrees of bone damage. 1.0% represents yield strain; 1.5% goes beyond yield strain; and 2.5% and 4% represent post-ultimate strains. Samples were then creep loaded (0.4 MPa) again for 30 minutes. Creep strain curves showed that the primary creep phase occurred within the first 10 min, and demonstrated a high and variable creep rate. The secondary creep phase showed a low but steady creep rate that lasted beyond the 20^{th} min. Creep rate of bone samples was measured from graphs of creep strain *vs* time, between the 10^{th} and 20^{th} minutes, within the secondary creep phase, using a linear regression model [23]. Elastic modulus of each sample was measured from stress-strain graphs obtained during compressive loading before and after bone damage. Bone damage intensity (ω) was calculated as percentage reduction of the elastic modulus [19].

A second dataset concerns 38 spinal motion segments (with intact ligaments and intervertebral discs) from 21 human cadaveric spines (15 males and 6 females, mean age 78 years, range 51-92 years, spinal level T8-L4)[17,22]. As these motion segments were from two different studies conducted previously in our lab, there were slight differences in their experimental details. Ten of the 38 motion segments comprised 2 vertebrae and 28 had 3 vertebrae. Each motion segment underwent the following experimental protocol: firstly, a creep test which involved a static compressive load of 1000 N (30 minutes for 2-vertebra motion segments and 60 minutes for 3-vertebra motion segments), followed by compressive loading to induce bone damage in one of the vertebrae in the motion segment. Motion segments were then creep loaded at 1000N, again for 30 or 60 minutes. Vertical deformation of the anterior, middle, and posterior regions of each vertebral body was monitored in the sagittal plane using an optical technique that tracks reflective markers attached to pins

inserted into the cortex of each vertebral body [16]. Creep stain curves showed typical primary and secondary creep phase as in vertebral trabecular bone samples. Using a linear regression model, creep rate in the anterior cortex was obtained from graphs of creep strain *vs* time between the 10th min and 20th minute within the secondary creep phase [23]. Compressive stiffness of each motion segment was measured from load-deformation graphs obtained during compressive loading before and after damage. As the compressive stiffness of each vertebral body could not be measured independently, vertebral bone damage intensity (ω) was calculated as the percentage reduction of compressive stiffness of the whole motion segment (ω_{MS}), which was then adjusted by the following equations (details presented in the Appendix).

For 2-vertebra motion segments:

$$\omega = \frac{2\omega_{MS}}{1+\omega_{MS}} \qquad (2)$$

For 3-vertebra motion segments:

$$\omega = \frac{3\omega_{MS}}{1+2\omega_{MS}} \qquad (3)$$

where ω_{MS} is the vertebral bone damage intensity calculated as the percentage reduction of motion segment compressive stiffness, and ω is the adjusted vertebral bone damage intensity of the vertebral body. It was assumed that only one vertebra was damaged in both equations.

Using dual-energy X-ray absorptiometry (DXA), the areal bone mineral density (aBMD) of each vertebral body was measured in the sagittal plane before mechanical tests. Endplate damage and cortical bone damage of the fractured vertebra were confirmed on radiographs and anatomical dissection. The intervertebral disc adjacent to the fractured vertebra was evaluated for disc degeneration, with a scale of 1 (non-

degenerated) to 4 (severely degenerated)[24]. Dimensions of the vertebral body, including maximal anterior-posterior and mediolateral diameters, were measured at the superior endplate. Vertebral cross-sectional area was calculated using a method for calculating the area of an ellipse:

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

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

2.3 Estimation of the model parameter (p)

To transform to a linear equation, equation 1 can be rewritten as:

$$\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0 = p[-\ln(1-\omega)] \qquad (5)$$

Using experimental data, the model parameter (p) can then be estimated as the regression coefficient in a linear regression model of $(\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0)$ and $-\ln(1-\omega)$. Estimation of p was initially conducted separately on data from trabecular bone samples (p_T) and vertebral bodies (p_{VB}).

Mechanical testing data of the 27 vertebral trabecular bone samples were used to estimate p_T. The difference in the natural logarithm of creep rate before and after fracture $(\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0)$ and the natural logarithm of bone damage intensity $\ln(1-\omega)$ were calculated. As bone damage in these samples was induced only in trabecular bone, p_T reflects the contribution of trabecular bone damage. Similarly, testing data of the 38 motion segments were used in regression analysis to estimate p_{VB} for the vertebral body, with p_{VB} representing the contributions of trabeculae, endplate and cortical bone damage, and structural parameters of the vertebral body.

2.4 Moderation analysis

Vertebral bodies differ from trabeculae samples in size, aBMD, inclusion of endplate and cortical bone, and loading through the intervertebral discs. The influence of these factors on p_{VB} was examined using regression-based moderation analysis [25,26], using the following regression model:

$$\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0 = p_{VB}[-\ln(1-\omega)] + b_M M + b_I M\,[-\ln(1-\omega)] + constant \quad (6)$$

where variable *M* is one of the moderation factors that may influence p_{VB}, including endplate damage (1=no, 2=yes), cortical bone damage (1=no, 2=yes), disc degeneration grade (1 to 4), vertebral cross-sectional area, and vertebral aBMD; b_M is the regression coefficient for variable *M*; variable $M[-\ln(1-\omega)]$ is constructed as the product of *M* and $-\ln(1-\omega)$ to represent the interaction; and b_I is the regression coefficient for $M[-\ln(1-\omega)]$. By examining the statistical significance of b_I, one can assess whether a moderation factor has significant influence on p_{VB}.

2.5 Statistical analysis

The slopes (i.e. p_T or p_{VB}) and constants of the linear regression models for vertebral trabeculae and vertebral bodies were compared using a Z-test. If not statistically different, the two datasets were pooled for regression analysis to estimate a combined model parameter p_{COMB}.

Statistical analyses were performed with SPSS 22.0 (IBM, Armonk, NY, USA) with the PROCESS command tool for moderation analysis [25,26]. For all analyses, $P<0.05$ were considered as significant.

3 Results

Experimental data for vertebral trabecular bone samples and for vertebral bodies (**Figure 1)** demonstrated a linear relationship between $\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$ on the y-axis and $-\ln(1-\omega)$ on the x-axis. Regression analysis confirmed a significant fit of the model to experimental data (**Table 1**). The fit of the model was better for trabeculae samples, where the model explained more than 70% of variance in the experimental data. The model explained less variance in experimental data of vertebral bodies (R^2 = 0.22, P = 0.003, n=38). Separate regression analysis showed that the fit of the model was significant if only 2-vertebra motion segments were analysed (R^2=0.59, P=0.009, n=10), but was not significant if only 3-vertebra motion segments were analysed (R^2=0.07, P=0.166, n=28). For both vertebral trabecular bone samples and vertebral bodies, the constants in the regression models were not significantly different from zero (P>0.05).

There was no significant difference in the estimated model parameter (p_T and p_{VB}) (Z=0.2, P>0.05) or constant (Z=0.6, P>0.05) between vertebral trabeculae and vertebral bodies. The two datasets were then combined to estimate a combined model parameter p_{COMB} (**Table 1**).

Of the 38 vertebral bodies 23 had endplate fracture, and 24 had cortical bone damage. Disc degeneration was assessed as grade 2 in 11 specimens, grade 3 in 20, and grade 4 in 7 specimens. The average vertebral cross-sectional area and aBMD were 1858 mm^2 (range 834 - 3080) and 0.58 g/cm^2 (range 0.24 -1.26), respectively. Multiple moderation analyses revealed that the model parameter (p_{VB}) was not influenced by endplate damage, cortical bone damage, disc degeneration, vertebral cross-sectional area, and vertebral aBMD (**Table 2**).

The highest bone damage intensity in the experimental data was 91% for vertebral trabeculae and 89% for vertebral bodies. Using the combined model parameter ($p_{COMB} = 1.45$), the analytical model showed that the creep rate of a damaged vertebra could be nearly 30 times greater, if its bone damage intensity reached approximately 90% (**Figure 2**).

4 Discussion

4.1 Summary of findings

An analytical model based on Kachanov's creep damage model was established to delineate the association between the degree of vertebral damage and consequent creep deformation. The model was based on *in vitro* mechanical experiments, one on vertebral trabecular bone samples and another on spinal motion segments. The model demonstrates that the degree of trabecular bone damage is the key determinant of creep deformation following vertebral compression fracture. Other factors such as the presence of endplate and cortical bone damage, the degree of disc degeneration, and vertebral characteristics, do not play a substantial role in creep deformation of vertebrae. The proposed model could potentially be used in a clinical setting to predict creep deformation of fractured vertebral bodies, if measures of vertebral damage on routine MR images can be reliably assessed.

4.2 Strengths and weaknesses of the study

To our knowledge, this is the first model for the prediction of creep deformation of damaged human vertebrae. A model that can be used to predict the risk of progressive vertebral collapse is clinically important but currently unavailable. An important feature of our model is that its variables can be readily measured on clinical MR images so that the model can be validated for use in a clinical context. Bone damage intensity (ω in **Equation 1**) may be determined from the area of a lesion within a fractured vertebra [11]. Because a fractured vertebra has a loading history similar to the adjacent undamaged vertebrae, the pre-damage creep rate in a fractured vertebra ($\dot{\varepsilon}_0$ in **Equation 1**) could be estimated from morphological changes in adjacent vertebrae by measuring their change in vertebral height between initial assessment

and follow-up and dividing this by the relevant time period [27]. Similarly, post-damage creep rate of a fractured vertebra ($\dot{\varepsilon}_c$ in **Equation 1**) could be measured directly from height loss occurring between initial and follow-up MR images. This means that the loading history of a fractured vertebra is not required for the validation of the model on clinical images, which is a major advantage as loading history for a patient changes over time and is difficult to quantify. Another strength is that estimation of the model parameter (p) is based on experiments on elderly human vertebral bone under physiological loading, which enhances the external validity of the model.

There are, however, some limitations in our study. A number of assumptions and simplifications were used in the model. For example, the vertebral body was assumed to be a continuum of trabecular bone, while adjacent structures such as the vertebral cortical shell, vertebral endplates, and intervertebral discs were not included in the model. However, multiple moderation analyses revealed that these structures did not have a significant influence on the model parameter (p), which justified simplifications in the model. Nevertheless, future work using time-dependent finite element analysis is needed to understand how these structures influence vertebral creep and whether the simplification of the model is optimal. The model assumed a constant compressive load on the vertebra, but human vertebrae may also experience cyclic loading *in vivo*. This may limit the model's predictive capability because cyclic loading also contributes to damage accumulation in bone [18]. However, creep rate can be used to predict damage accumulation resulting from cyclic load as they are highly correlated [28]. The experimental conditions used in the study may also have effects on the model. The height of the vertebral trabecular samples is relatively high in comparison to their diameter. This may have caused heterogeneous distribution of

creep strain within the trabecular samples which means that strain in some regions may differ from the reported level. The different durations of creep loading in motion segments may have some influence on measured creep rate, although our previous studies showed that creep measured during 2 h is not much greater than that measured during 30 min [16]. While creep tests were performed at room temperature, it is likely that the creep rate of a vertebral body will be greater at body temperature [29]. In addition, creep rate was measured in a 10-minute interval whereas creep *in vivo* may occur over a much longer period, even though it decreases over time [16]. It is also possible that some minor damage might have been induced in trabecular bone samples during the coring process, although samples were visually assessed for any presence of mechanical damage. However, experimental conditions are similar before and after bone damage so their effects on creep rate may have been cancelled out in the model. Nevertheless, further studies are still needed to validate the model using clinical imaging data in order to assess its potential application in patients. Finally, although a relatively large sample of vertebral bones were studied, the fit of the model to experimental data was weaker for vertebral bodies than for vertebral trabecular bone samples. One main reason may be that vertebral bone damage intensity had to be calculated from motion segment stiffness using equations 2 and 3, because vertebral body stiffness was not measured in our experiment. The calculation method assumes that a motion segment comprises only vertebral bodies so the calculated value is an approximation which does not include other structures such as intervertebral discs that can also contribute significantly to the elastic deformation and stiffness of a motion segment [30]. The extent of approximation is likely to be greater in 3-vertebra motion segments than 2-vertebra motion segments because the former has two intervertebral

discs. This may explain why the model fits the experimental data better in 2-vertebra motion segments than in 3-vertebra motion segments.

4.3 Relationship to previous work

Previously, mathematical models have been developed to describe bone creep behaviour. For undamaged trabecular samples, the creep rate depends on the structure and material properties of bone tissue such as bone mineral density, bone volume fraction, and trabecular bone architecture [31-33], and varies nonlinearly with the stress applied [34,35]. Mathematically, findings can be described as a power law relationship between steady-state creep rate and normalised stress (i.e. applied stress divided by elastic modulus of bone) [34-36]. Mathematical models have also been developed to predict damage accumulation and secondary creep rate during bone creep [18,28], and some incorporated damage variables to simulate non-linear time dependent behaviour in bone creep [37]. These models, however, used applied stress and elastic modulus as predictive variables, which are difficult to measure in clinics.

Previous studies revealed that trabecular bone, as well as endplates, cortical shell, and the intervertebral discs, may play significant roles in creep deformation in intact vertebral bodies [16,38,39]. The current study, however, found that the effect of bone damage on creep behaviour was similar for vertebral trabecular samples and for whole vertebral bodies, and that the relationship was not significantly influenced by endplate and cortical bone damage, disc degeneration, vertebral cross-sectional area and aBMD. This could be explained by previous findings that although trabecular bone, cortical shell, and endplate play significant roles of load sharing in an undamaged vertebral body [40], the mechanical behaviour of a damaged vertebral body is dominated by the

trabecular bone [15]. Findings suggest that the extent of trabecular damage is the major determinant of creep behaviour for a damaged vertebral body.

4.4 Clinical significance

The proposed model explains a mechanism underlying progressive vertebral collapse. As shown in Figure 2, the steady-state creep rate increases dramatically with bone damage intensity, and can be 30 times greater than pre-damage levels. This can induce excessive bone strain within a vertebral body, which in turn may disrupt and delay fracture healing, leading to progressive vertebral collapse. Furthermore, the model also suggests that increased creep rate after vertebral fracture can be predicted by estimating vertebral trabeculae damage (ω in Equation 1). Because model variables can be readily measured on clinical images, our future work will aim to translate this model into a clinical tool for the identification of patients who are at risk of developing progressive vertebral collapse.

4.5 Unanswered questions and future research

The model developed in the current study is based on in vitro mechanical tests on human vertebral specimens. The degree of vertebral trabecular damage was measured using mechanical indices (i.e. modulus reduction). It is yet to be determined how vertebral trabecular damage can be measured clinically, for example using MR imaging. However, the model provides a way to answer this critical question as it establishes a mechanistic relationship between vertebral bone damage and creep deformation. This relationship can help identify the measures of bone damage on MR images that are associated with creep deformation. Our future research will use the model to analyse initial and follow-up MR images to obtain measures of vertebral trabecular damage for the prediction of vertebral collapse.

Funding: This work was supported by research grants from Sir Halley Stewart Trust and Action Medical Research, UK [Grant numbers 0994, 1083, and 1161].

References

[1] Cauley J.A., L. Palermo, M. Vogt, K.E. Ensrud, S. Ewing, M. Hochberg, M.C. Nevitt, D.M. Black, Prevalent vertebral fractures in black women and white women, J. Bone Miner. Res. 23 (2008) 1458-67.

[2] Svedbom A., E. Hernlund, M. Ivergard, J. Compston, C. Cooper, J. Stenmark, E.V. McCloskey, B. Jonsson, J.A. Kanis, EU Review Panel of IOF, Osteoporosis in the european union: A compendium of country-specific reports, Arch. Osteoporos. 8 (2013) 137,0. Epub 2013 Oct 11.

[3] Fink H.A., D.L. Milavetz, L. Palermo, M.C. Nevitt, J.A. Cauley, H.K. Genant, D.M. Black, K.E. Ensrud, What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa?. 20 (2005) 1216-22.

[4] Lee S.H., E.S. Kim, W. Eoh, Cement augmented anterior reconstruction with short posterior instrumentation: A less invasive surgical option for kummell's disease with cord compression, J. Clin. Neurosci. 18 (2011) 509-14.

[5] Baba H., Y. Maezawa, K. Kamitani, N. Furusawa, S. Imura, K. Tomita, Osteoporotic vertebral collapse with late neurological complications, Paraplegia. 33 (1995) 281-9.

[6] Ito Y., Y. Hasegawa, K. Toda, S. Nakahara, Pathogenesis and diagnosis of delayed vertebral collapse resulting from osteoporotic spinal fracture, Spine J. 2 (2002) 101-6.

[7] Zeytinoglu M., R.K. Jain, T.J. Vokes, Vertebral fracture assessment: Enhancing the diagnosis, prevention, and treatment of osteoporosis, Bone. 104 (2017) 54-65.

[8] Ryu K.N., W. Jin, Y.T. Ko, Y. Yoon, J.H. Oh, Y.K. Park, K.S. Kim, Bone bruises: MR characteristics and histological correlation in the young pig, Clin. Imaging. 24 (2000) 371-80.

[9] Goldstein S., Y. Smorgick, Y. Mirovsky, Y. Anekstein, R. Blecher, S. Tal, Clinical and radiological factors affecting progressive collapse of acute osteoporotic compression spinal fractures, J. Clin. Neurosci. 31 (2016) 122-6.

[10] Takahashi S., M. Hoshino, K. Takayama, K. Iseki, R. Sasaoka, T. Tsujio, H. Yasuda, T. Sasaki, F. Kanematsu, H. Kono, H. Toyoda, H. Nakamura, Predicting delayed union in osteoporotic vertebral fractures with consecutive magnetic resonance imaging in the acute phase: A multicenter cohort study, Osteoporos. Int. 27 (2016) 3567-75.

[11] Lee J.M., Y.S. Lee, Y.B. Kim, S.W. Park, D.H. Kang, S.H. Lee, What effects does necrotic area of contrast-enhanced MRI in osteoporotic vertebral fracture have on further compression and clinical outcome?, J. Korean Neurosurg. Soc. 60 (2017) 181-8.

[12] Fujiwara T., K. Akeda, J. Yamada, T. Kondo, A. Sudo, Endplate and intervertebral disc injuries in acute and single level osteoporotic vertebral fractures: Is there any association with the process of bone healing?, BMC Musculoskelet. Disord. 20 (2019) 336-5.

[13] Claes L., M. Reusch, M. Gockelmann, M. Ohnmacht, T. Wehner, M. Amling, F.T. Beil, A. Ignatius, Metaphyseal fracture healing follows similar biomechanical rules as diaphyseal healing, J. Orthop. Res. 29 (2011) 425-32.

[14] Diamond T.H., W.A. Clark, S.V. Kumar, Histomorphometric analysis of fracture healing cascade in acute osteoporotic vertebral body fractures, Bone. 40 (2007) 775-80.

[15] Kopperdahl D.L., J.L. Pearlman, T.M. Keaveny, Biomechanical consequences of an isolated overload on the human vertebral body, J. Orthop. Res. 18 (2000) 685-90.

[16] Pollintine P., J. Luo, B. Offa-Jones, P. Dolan, M.A. Adams, Bone creep can cause progressive vertebral deformity, Bone. 45 (2009) 466-72.

[17] Luo J., P. Pollintine, E. Gomm, P. Dolan, M.A. Adams, Vertebral deformity arising from an accelerated "creep" mechanism, Eur. Spine J. 21 (2012) 1684-91.

[18] Carter D.R., W.E. Caler, A cumulative damage model for bone fracture, J. Orthop. Res. 3 (1985) 84-90.

[19] O'Callaghan P., M. Szarko, Y. Wang, J. Luo, Effects of bone damage on creep behaviours of human vertebral trabeculae, Bone. 106 (2018) 204-10.

[20] L.M. Kachanov, Introduction to continuum damage mechanics, Martinus Nijhoff Publishers, Dordrecht, 1986.

[21] R.K. Penny, D.L. Marriott, Design for creep, 2nd ed., Chapman & Hall, London, 1995.

[22] Luo J., D.J. Annesley-Williams, M.A. Adams, P. Dolan, How are adjacent spinal levels affected by vertebral fracture and by vertebroplasty? A biomechanical study on cadaveric spines, Spine J. 17 (2017) 863-74.

[23] Yamamoto E., R. Paul Crawford, D.D. Chan, T.M. Keaveny, Development of residual strains in human vertebral trabecular bone after prolonged static and cyclic loading at low load levels, J. Biomech. 39 (2006) 1812-8.

[24] Adams M.A., P. Dolan, W.C. Hutton, The stages of disc degeneration as revealed by discograms, J. Bone Joint Surg. Br. 68 (1986) 36-41.

[25] A. Field, Moderation, mediation, and more regression, in: A. Field (Ed.), Discovering statistics using IBM SPSS statistics, SAGE Publications Ltd, London, 2013, pp. 392.

[26] A. Hayes, Introduction to mediation, moderation, and conditional process analysis: A regression-based approach, The Guilford Press, New York, 2013.

[27] Lu X., J. Yang, Z. Zhu, X. Lv, J. Wu, J. Huang, L. Yu, Z. Wen, J. Luo, Y. Wang, Changes of the adjacent discs and vertebrae in patients with osteoporotic vertebral compression fractures treated with or without bone cement augmentation, Spine J. 20 (2020) 1048-55.

[28] Cotton J.R., K. Winwood, P. Zioupos, M. Taylor, Damage rate is a predictor of fatigue life and creep strain rate in tensile fatigue of human cortical bone samples, J. Biomech. Eng. 127 (2005) 213-9.

[29] Rimnac C.M., A.A. Petko, T.J. Santner, T.M. Wright, The effect of temperature, stress and microstructure on the creep of compact bovine bone, J. Biomech. 26 (1993) 219-28.

[30] Pollintine P., M.S. van Tunen, J. Luo, M. Brown, P. Dolan, M.A. Adams, Time-dependent compressive deformation of the ageing spine: Relevance to spinal stenosis. 35 (2010) 386-94.

[31] Kim D.G., D. Shertok, B. Ching Tee, Y.N. Yeni, Variability of tissue mineral density can determine physiological creep of human vertebral cancellous bone, J. Biomech. (2011).

[32] Manda K., S. Xie, R.J. Wallace, F. Levrero-Florencio, P. Pankaj, Linear viscoelasticity - bone volume fraction relationships of bovine trabecular bone, Biomech. Model. Mechanobiol. 15 (2016) 1631-40.

[33] Novitskaya E., C. Zin, N. Chang, E. Cory, P. Chen, D. D'Lima, R.L. Sah, J. McKittrick, Creep of trabecular bone from the human proximal tibia, Mater. Sci. Eng. C. Mater. Biol. Appl. 40 (2014) 219-27.

[34] Manda K., R.J. Wallace, S. Xie, F. Levrero-Florencio, P. Pankaj, Nonlinear viscoelastic characterization of bovine trabecular bone, Biomech. Model. Mechanobiol. 16 (2017) 173-89.

[35] Xie S., K. Manda, R.J. Wallace, F. Levrero-Florencio, Simpson, A H R W, P. Pankaj, Time dependent behaviour of trabecular bone at multiple load levels, Ann. Biomed. Eng. 45 (2017) 1219-26.

[36] Bowman S.M., T.M. Keaveny, L.J. Gibson, W.C. Hayes, T.A. McMahon, Compressive creep behavior of bovine trabecular bone, J. Biomech. 27 (1994) 301-10.

[37] Fondrk M.T., E.H. Bahniuk, D.T. Davy, A damage model for nonlinear tensile behavior of cortical bone, J. Biomech. Eng. 121 (1999) 533-41.

[38] van der Veen, A. J., M.G. Mullender, I. Kingma, J.H. van, T.H. Smit, Contribution of verftebral bodies, endplates, and intervertebral discs to the compression creep of spinal motion segments, J. Biomech. 41 (2008) 1260-8.

[39] Oravec D., W. Kim, M.J. Flynn, Y.N. Yeni, The relationship of whole human vertebral body creep to geometric, microstructural, and material properties, J. Biomech. 73 (2018) 92-8.

[40] Eswaran S.K., A. Gupta, M.F. Adams, T.M. Keaveny, Cortical and trabecular load sharing in the human vertebral body. 21 (2006) 307-14.

Appendix

Derivation of equations for calculation of vertebral bone damage intensity (ω) as measured by modulus reduction.

A simple model of two or three springs in series was used to represent motion segments consisting of two or three vertebrae, respectively, assuming that all vertebral bodies have the same compressive stiffness, k_1, before damage.

For motion segments comprising two vertebrae, their compressive stiffness before damage, k_{MS2} , can be calculated as

$$\frac{1}{k_{MS2}} = \frac{1}{k_1} + \frac{1}{k_1} \qquad \text{(A1)}$$

therefore

$$k_{MS2} = k_1/2 \qquad \text{(A2)}$$

If one vertebral body is damaged and its stiffness is reduced to k_x after damage, then the compressive stiffness of the motion segment after damage, k_{MS2X}, is calculated as

$$k_{MS2X} = \frac{k_x k_1}{k_x + k_1} \qquad \text{(A3)}$$

Vertebral bone damage intensity may then be calculated as the percentage reduction in compressive stiffness of the motion segment, ω_{MS}, as follows:

$$\omega_{MS} = \frac{k_{MS2} - k_{MS2X}}{k_{MS2}} = \frac{k_1 - k_x}{k_1 + k_x} \qquad \text{(A4)}$$

or as the percentage reduction in compressive stiffness of the vertebral body, ω, given by

$$\omega = \frac{k_1 - k_x}{k_1} \qquad \text{(A5)}$$

Using equation A4, Equation A3 can be transformed as follows:

$$\omega_{MS} = \frac{k_1 - k_x}{k_1 + k_x} = \frac{(k_1 - k_x)/k1}{2 - (k_1 - k_x)/k_1} = \frac{\omega}{2 - \omega} \qquad \text{(A6)}$$

We know from equation A5 that

$$\omega = \frac{2\omega_{MS}}{1 + \omega_{MS}} \qquad \text{(A7)}$$

For motion segments comprising three vertebrae, their compressive stiffness before damage, k_{MS3} can be calculated as

$$k_{MS3} = k_1/3 \qquad \text{(A8)}$$

If one vertebral body is damaged and its stiffness is reduced to k_x after damage, then the compressive stiffness of the motion segment after damage, k_{MS3X}, is calculated as

$$k_{MS3X} = \frac{k_x k_1}{2k_x + k_1} \qquad \text{(A9)}$$

Vertebral bone damage intensity may then be calculated as the percentage reduction in compressive stiffness of the motion segment, ω_{MS}, as follows:

$$\omega_{MS} = \frac{k_{MS3} - k_{MS3X}}{k_{MS3}} = \frac{k_1 - k_x}{k_1 + 2k_x} \qquad \text{(A10)}$$

or as the percentage reduction in compressive stiffness of the vertebral body, ω, given by

$$\omega = \frac{k_1 - k_x}{k_1} \qquad \text{(A11)}$$

Using equation A10, Equation A9 can be transformed as

$$\omega_{MS} = \frac{k_1 - k_x}{k_1 + 2k_x} = \frac{(k_1 - k_x)/k1}{3 - 2(k_1 - k_x)/k_1} = \frac{\omega}{3 - 2\omega} \qquad \text{(A12)}$$

Therefore, we know from equation A11 that

$$\omega = \frac{3\omega_{MS}}{1 + 2\omega_{MS}} \qquad \text{(A13)}$$

Figure 1: The relationship between increased creep rate ($\ln \dot{\varepsilon}_c - \ln \dot{\varepsilon}_0$) and bone damage $[-\ln(1-\omega)]$. Mechanical test data were from 27 samples of vertebral trabeculae and 38 vertebral bodies. $\dot{\varepsilon}_0$ is the creep rate before damage and $\dot{\varepsilon}_c$ is the creep rate after damage, and ω is the damage intensity. MS = motion segment.

Figure 2. A prediction model showing how bone damage intensity increases the creep rate of vertebral bone. The model parameter ($p_{COMB} = 1.45$) was estimated from the combined experimental datasets in **Figure 1** and **Table 1**.