

Mechano-regulation model of metastatic lesions in vertebrae of multiple myeloma patients suggests cancer-induced remineralisation post-treatment.

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INTRODUCTION: Vertebral metastatic lesions are a common complication of multiple myeloma (MM), a cancer of the plasma cells, white blood cells that make antibodies as part of the immune defence system. Abnormal plasma cells proliferate in the bone marrow of vertebrae, forming osteolytic bone lesions. MM represents around 2% of new cancers in the UK and the number of cases and deaths has more than doubled worldwide in the last 30 years [1]. Patients with MM are most affected by spinal involvement (80-90%) [2] with 34-36% of patients suffering from spinal fracture [3]. Anti-myeloma treatments have significantly improved over the last 30 years, increasing the 5-year survival rate for patients with MM by 12-50% and 11-44% in men and women, respectively [4], [5].

This growing population of MM survivors require treatment to stabilise the spine, with the standard of care being invasive surgical intervention to prevent vertebral collapse and spinal cord damage. However, due to the age of most patients at diagnosis (>70 years), the surgery is associated with increased morbidity and high infection risk [6]. It is proposed that by adopting a non-surgical strategy for appropriate MM patients, provided the spine is externally braced [7], [8], then significant bone growth and remodelling will internally stabilise the spine. Bone growth has been observed both within the tumour bed and as thickened cortical shells around vertebrae. However, whether this increases vertebral strength, and is mechanobiologically driven or due to some other mechanism remains unknown.

METHODS: A mechano-regulation model was developed using control data (n=10 non-cancer volunteers, 2 QCT scans each, where baseline and follow-up were 12 months apart) to predict the changes in compressive strain within the vertebrae. 3D finite element (FE) models of the vertebra were reconstructed from the quantitative computed tomography (QCT) scans performed at baseline and 12 months. Bone was modelled as heterogenous, isotropic, and elastic-plastic, with material properties based on the patient-specific densitometry calibration and phenomenological relationships. FE analysis simulated physiological loading by uniaxial compression (0.15% strain, ANSYS).

The mechano-regulation algorithm was developed by parametrically thresholding using the ratio of strain energy density to density (U/ρ) of each element, increasing, or decreasing the density accordingly using Equation 1. The thresholds, K_{min} and K_{max} , were determined by altering incrementally from an initial value from the literature [9] ($K_{min}=0.0036$ and $K_{max}=0.0044$) until the mechano-regulation model correctly predicted the change in compressive strain in the whole vertebra at the 12 month follow-up. The rates of change (R_{min} and R_{max}) were calculated from the average decrease and increase in density.

To investigate a novel cohort of MM patients (n=3) that were treated with bracing, we then explored whether this algorithm could predict the changes in material properties (normalised stiffness, MPa) over time between two scans.

$$\frac{\partial \rho}{\partial t} = \left\{ \begin{array}{lll} B \left(\frac{U}{\rho} + R_{min} \right) & \text{if } \frac{U}{\rho} < K_{min} & \text{Bone loss} \\ 0 & \text{if } K_{min} \leq \frac{U}{\rho} \leq K_{max} & \text{Lazy zone} \\ B \left(\frac{U}{\rho} + R_{max} \right) & \text{if } \frac{U}{\rho} > K_{max} & \text{Bone formation} \end{array} \right\} \quad \text{Equation 1}$$

$R_{min} = -0.05$, $R_{max} = 0.04$, $K_{min} = \text{lower threshold}$, $K_{max} = \text{upper thresholds}$, $\rho = \text{density (g/cm}^3\text{)}$

RESULTS SECTION: All three MM patients experienced an increase in normalised stiffness (normalised stiffness: average per month 4.7% \pm 2.5%). The mechano-regulation model, however, predicted a decrease in bone stiffness in all patients over time (Figure 1). This can also be seen by the strain distribution in the transverse cross section view in Figure 2 where there is a slightly higher proportion of high strains (red) in the predicted strain compared to the follow-up. Qualitatively, the predicted change in strain distribution from baseline follows the pattern seen in the follow-up scan (as seen by the red arrows in the bottom right corners of the sagittal cross section of the vertebra in Figure 2), indicating that the mechano-regulation model is correctly capturing structural changes in response to mechanical loading.

DISCUSSION: This study observed an increase in the material properties following bracing, confirming the hypothesis that bracing alone is sufficient to increase vertebral strength in these patients. However, the mechano-regulation model, which was trained to predict changes in control data, failed to predict this increase in material properties. This suggests the mechanisms behind the remineralisation are not regulated by mechanics alone and may instead be induced by crosstalk with cancer cells, or the absence thereof. The inclusion of biological regulation, such as the number of osteoclasts and osteoblasts, could improve the predictability of the model but will require a multi-scale approach and the adaptation of Equation 1.

SIGNIFICANCE/CLINICAL RELEVANCE: We have found that the bone fragility through bracing of multiple myeloma patients increases the strength of the affected vertebra, although a simple mechano-regulation model trained from control vertebrae could not capture this increase. The mechanisms behind this post-treatment bone growth are currently unknown, and predicting these patient-specific changes will provide guidance to clinicians in prescribing bracing as a treatment.

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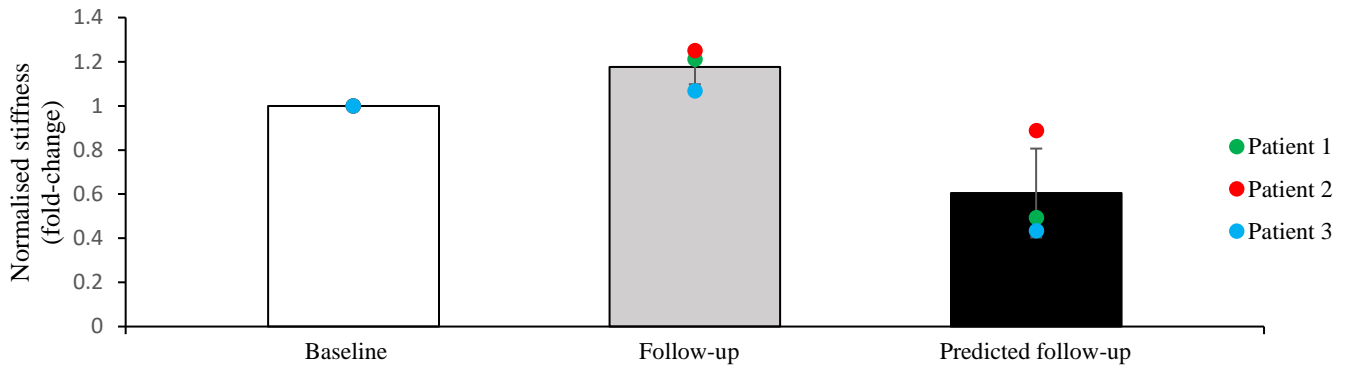


Figure 1. Bar chart showing the averaged normalised stiffness fold-change, in relation to baseline, for baseline, follow-up and predicted follow-up (error bars showing standard deviation).

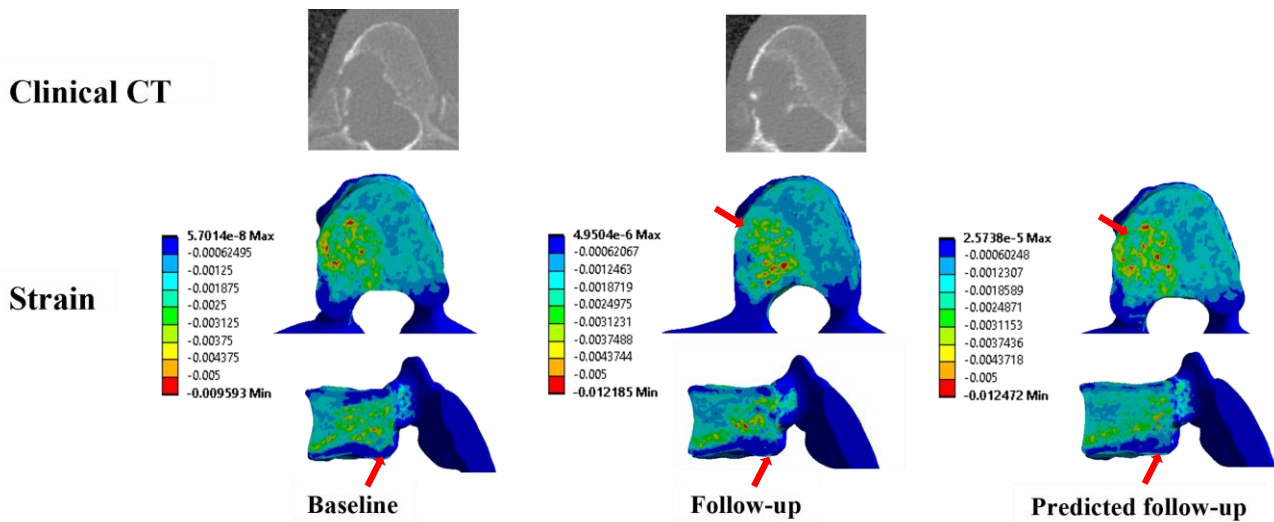


Figure 2. Compressive strain distribution in vertebra at baseline and follow-up scans, compared with the mechano-regulation model follow-up prediction based on the baseline.