

ORIGINAL ARTICLE

# Association between Modic changes and endplate sclerosis: Evidence from a clinical radiology study and a rabbit model

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## KEYWORDS

Computed tomography;  
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**Abstract Purpose:** To analyse the presence of endplate sclerosis in patients with various types of Modic changes (MCs) and to confirm the results using a rabbit model.

**Methods:** Participants in the clinical study included 1023 consecutive inpatients with lumbar degenerative disease who attended the Department of Orthopaedics between August 2011 and August 2015. All patients underwent computed tomography (CT) and magnetic resonance imaging of the lumbar spine. In those patients with MCs, endplate sclerosis was evaluated from sagittally reconstructed CT images. In addition to the clinical study, MCs type I, II and III were initiated using a previously developed rabbit model of MCs. Specimens of MCs type I, II and III and normal endplates were harvested, bone mineral density and bone volume/tissue volume of "treated" vertebrae were evaluated using  $\mu$ CT and osteogenic protein expressions of runt-related transcription factor 2 and osteocalcin were assessed using immunohistochemical staining. Measurements were compared between vertebrae with normal endplates and those with different types of MCs.

**Results:** Of 1023 patients, 214 (20.9%) had MCs in one or more endplates; these changes affected 1044 (10.2%) of 10230 endplates. Type I, II and III MCs were seen in 164 (1.6%), 838 (8.2%) and 40 (0.4%) endplates, respectively. Of 1044 endplates with MCs, 274 (26.2%) showed evidence of sclerosis on CT images including: 26/164 endplates (15.8%) with type I MCs, 208/838 (24.8%) with type II and 40/40 (100%) with type III. HU (CT value) ratios for sclerotic and nonsclerotic endplates with MCs were  $2.0 \pm 0.3$  and  $1.1 \pm 0.1$ , respectively. In the animal study, the bone mineral density, bone volume/tissue volume and expression of runt-

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related transcription factor 2 and osteocalcin of endplates with type I and II MCs were higher than those of normal endplates and lower than those of endplates with type III MCs.

*Conclusion:* Sclerosis can occur in endplates with any type of MCs. However, the clinical and animal study suggests that sclerosis is greatest in endplates showing type III MCs.

*The translational potential of this article:* The study showed that sclerosis can occur in endplates with MCs type I, II and III. In patients with endplate sclerosis on plain radiographs or CT scans, the endplate can still represent an inflammatory process associated with chronic lower back pain.

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## Introduction

Signal intensity changes [Modic changes (MCs)] in the vertebral body bone marrow adjacent to the endplates are commonly seen on magnetic resonance imaging (MRI) scans, and several studies have shown a correlation between MCs and chronic lower back pain (LBP) [1–3]. Initially, Modic et al. [4,5] classified these changes into three types: type I lesions involve low T1 and high T2 signals and indicate an ongoing active degenerative process with vascularised fibrous tissue within the bone marrow; type II lesions involve high T1 and T2 signals, which are more stable during a 3-year follow-up and reflect fatty replacement of the bone marrow; and type III lesions develop later and involve low T1 and T2 signals and are thought to be associated with endplate sclerosis [5]. The presence of different types of MC within the endplate was later regarded as mixed MCs, such as mixed type I-II and type II-III [6].

Many studies of MCs have focused on the lumbar vertebral endplate and its pathology [7–14]. Several have reported no definite correlation between type I and type II changes and the presence of sclerosis on radiographs, others suggest that endplate sclerosis exists only in association with type III MCs [4,5,15]. However, in our clinical practice, endplate sclerosis is very often seen on plain film radiographs and computed tomography (CT) even when MRI scans show evidence of type I or II MCs in the endplates (Figures 1A–C).

The purpose of this study was to evaluate the presence of endplate sclerosis in patients with different types of MC and to determine whether findings in patients could be confirmed in a rabbit model of MCs (developed in a previous study; Figure 2) [16,17]. We hypothesise that endplate sclerosis co-exists in patients with type I and II MCs.

## Methods

### Patients

Participants in the clinical study included 1023 consecutive inpatients with lumbar degenerative disease (e.g., disc herniation, canal stenosis, scoliosis, spondylosis, degenerative spondylolisthesis, etc.) who attended the Department of Orthopaedics at the author's hospital between August 2011 and August 2015. All patients (452 women and 571

men; mean age, 60.4 years; age range, 36–86 years) underwent CT and MRI examinations that were evaluated retrospectively. The presence, location and type of MCs were assessed from the MRI scans, and in those patients with MCs, endplate sclerosis was evaluated from sagittally reconstructed CT images.

Patients were excluded if they had an acute vertebral fracture, known or suspected spondylodiscitis, a recent spinal surgery (<4 months) or a history of malignant tumours.

The ethical approval was obtained from the medical ethics committee of the hospital (study approval number is SRRSH2011061901). Additionally, all patients gave written informed consent for their information to be stored in the hospital's database and used for research.

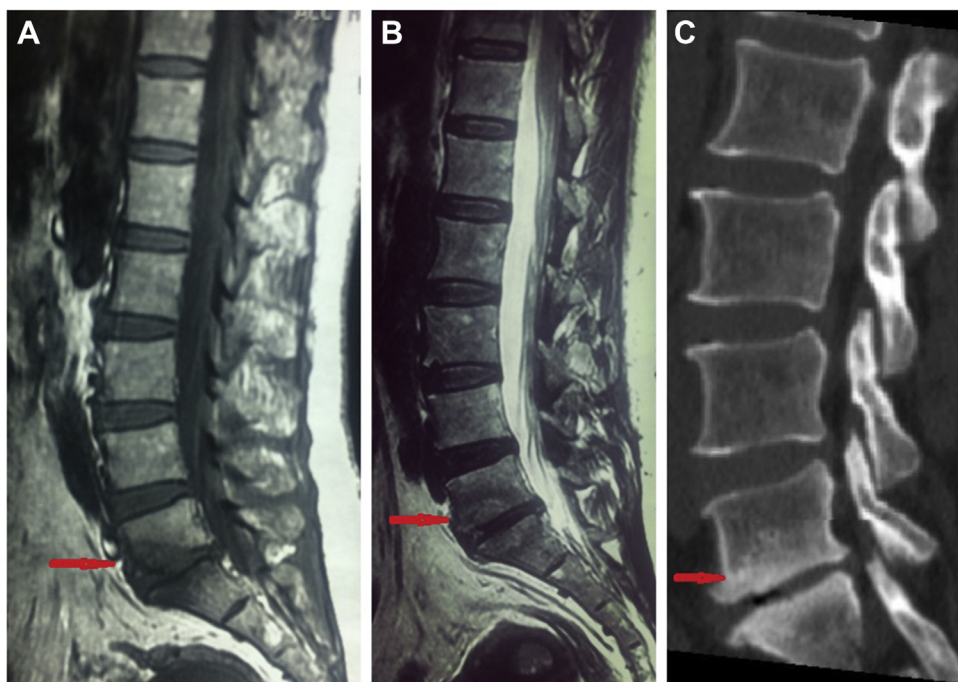
### Computed tomography and magnetic resonance imaging

The CT of the lumbar spine was performed using a 16-slice CT scanner (GE LightSpeed Pro 16; GE Healthcare) with a detector configuration of  $16 \times 1.25$  mm. A standard lumbar spine protocol with a tube voltage of 120 kV, tube current of 100–650 mA and rotation time of 0.8 s was used. Automatic tube current modulation based on the patient's size and X-ray attenuation was used. The slice thickness and reconstruction interval were 1.25 mm and 0.625 mm, respectively.

MRI images of the lumbar spine were obtained using a General Electric 1.5-T magnet with a T1-weighted sequence (repetition time/echo time, 560 ms/12 ms; field of view,  $320 \times 256$ ; receiver bandwidth, variable; 4.0-mm slice with a gap of 1.0 mm; number of excitations, 3) and a T2-weighted sequence (repetition time/echo time, 3000 ms/100 ms; field of view,  $320 \times 256$ ; receiver bandwidth, variable; 4.0-mm slice with a gap of 1.0 mm; number of excitations, 3).

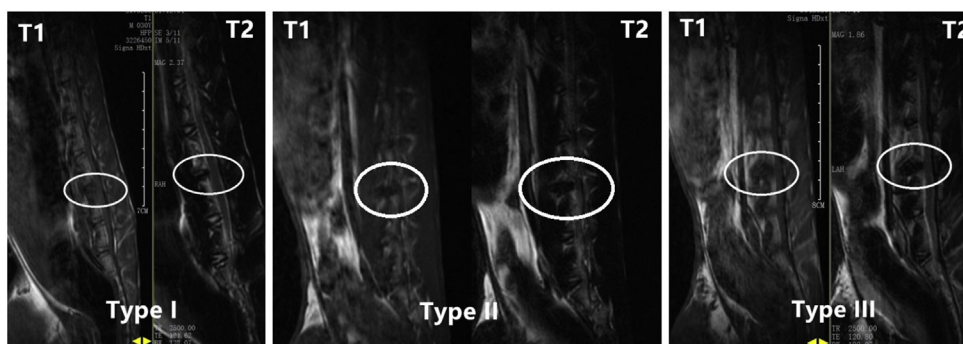
### Imaging evaluation

Classification of MCs and the presence of endplate sclerosis were determined by an experienced radiologist and orthopaedic surgeon who were blinded to the patient information. Endplate sclerosis was evaluated using CT which showed a higher bone density. A consensus was reached in



**Figure 1** (A) T1-weighted MR images of lumbar endplates showing the presence of type I Modic changes (indicated by low signal on T1 and high signal on T2) on L5-S1 level; (B) T2-weighted MR images of lumbar endplates showing the presence of type I Modic changes (indicated by low signal on T1 and high signal on T2) on L5-S1 level; (C) endplate sclerosis can be seen from the sagittally reconstructed CT images.

MR = magnetic resonance; CT = computed tomography.



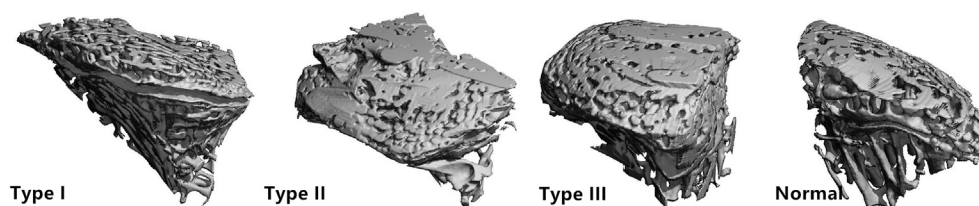
**Figure 2** Rabbit model of Modic changes type I, II, and III (type I involve low T1 and high T2 signals; type II involve high T1 and T2 signals; and type III involve low T1 and T2 signals).

cases where there was initial disagreement. Endplate sclerosis was also evaluated by the HU ratio (HU value for an affected endplate/HU value for a normal endplate, HU value: CT value) from CT scans.

#### Rabbit model of Modic changes

All animal experiments comply with the ARRIVE guidelines and were carried out in accordance with the UK Animals (Scientific Procedures) Act, 1986 and associated guidelines. A rabbit model of MCs type I, II and III was generated according to a previous study (Figure 2) [16,17]. Ninety-six clean grade male New Zealand white rabbits with a mean age of  $6.14 \pm 0.91$  months (range, 5–7 months) and a mean body weight of  $2.83 \pm 0.59$  kg (range, 2.12–3.38 kg) were used in this study. Specimens of MCs type I, II, III and normal

endplates (10 samples each) from L4–5 or L5–6 were harvested. CT scans of the endplate and underlying trabecular bone (to a depth of 3 mm) were obtained (Figure 3) using a  $\mu$ CT scanner ( $\mu$ CT80, Scanco Medical) at a resolution of 37  $\mu$ m/voxel. Settings for the voltage, current and integration time were 70 kVp, 114 mA and 300 ms, respectively. The bone mineral density (BMD) and bone volume/tissue volume (BV/TV) were estimated from the  $\mu$ CT images using image analysis software, and the resulting data were compared between endplates with MCs type I, II and III and normal endplates to evaluate endplate sclerosis. In order to assess the endplate sclerosis, the osteogenic protein expressions of runt-related transcription factor 2 (Runx2) and osteocalcin (OCN) in endplate chondrocytes were evaluated using immunohistochemical staining (IHC). Five stained



**Figure 3**  $\mu$ CT scans of rabbit vertebral bodies showing the endplate and underlying trabecular bone (to a depth of 3 mm). Images are shown for endplates with type I, II and III Modic changes and for a normal endplate. CT = computed tomography.

sections of each group were counted for the quantification analysis of IHC. The average numbers of cells positively stained with Runx2 and OCN were counted from 10 random views under microscope, and expressive percentage of IHC were automatically calculated by Image Pro Plus 6.0.

### Statistical analysis

All patient and image interpretation data were collected in an Excel database (Microsoft Corp.) and analysed statistically using SPSS 18.0 software (PASW Statistics, IBM Corp.). Kolmogorov–Smirnov test was used for normal distribution, and all the data were normally distributed. In the clinical study, HU ratios in patients showing sclerotic and non-sclerotic endplates were compared using an unpaired *t* test. The association between occurring rate of MCs and endplate sclerosis with gender and age were analysed using Chi-square test. In the animal study, differences in BMD, BV/TV and expressive percentage of IHC between normal rabbit endplates and those showing MCs type I, II and III were also compared using one-way analysis of variance and least significant difference. A *p* value < 0.05 was considered statistically significant.

## Results

### Patient study

#### Evaluation of Modic changes

Of 1023 patients, 214 (20.9%) had MCs at one or more endplate levels, and these changes affected 1044 (10.2%) of 10230 endplates. Type I, II and III changes were seen in 164 (1.6%), 838 (8.2%) and 40 (0.4%) endplates, respectively, mostly occurring at the L5-S1 level (450/2046, 22.0%) and L4/5 level (348/2046, 17.0%).

#### Evaluation of endplate sclerosis

Of 1044 endplates with MCs, 274 (26.2%) had sclerosis on CT images. Type I, II and III changes with sclerosis were seen in

26 endplates (26/164, 15.8%), 208 endplates (208/838, 24.8%) and 40 endplates (40/40, 100%), respectively. HU ratios for sclerotic and nonsclerotic endplates with MCs were  $2.0 \pm 0.3$  and  $1.1 \pm 0.1$  ( $P = 0.041$ ), respectively.

#### Influence of age and gender

The patients were classified as young group (<60 y) and aged group ( $\geq 60$ y) based on age, and occurring rate of MCs and endplate sclerosis were compared; we found that the occurring rate of MCs and endplate sclerosis in aged group was higher than that of the young group ( $p = 0.038$ ;  $p = 0.042$ ). Besides, we also found there is no association between occurring rate of MCs and endplate sclerosis with gender ( $p = 0.058$ ;  $p = 0.063$ ).

#### Rabbit model of Modic changes

The BMD and BV/TV of endplates with type I and II changes were higher than those of normal endplates ( $p = 0.031$ ) and lower than those of endplates with type III changes ( $p = 0.018$ ). There were no significant differences in these parameters between endplates with type I and type II changes ( $p = 0.124$ ), as shown in Table 1.

Runx2 and OCN were detected by immunohistochemistry (Figures 4 and 5). The expressive percentage of IHC in type I and II changes were higher than those of normal endplates ( $p = 0.032$ ) and lower than those of endplates with type III changes ( $p = 0.043$ ). There were no significant differences between endplates with type I and type II changes ( $p = 0.242$ ), as shown in Figure 6.

## Discussion

MCs are pathological changes of the vertebral endplate and bone marrow that are visible on MRI scans, and they are considered clinically relevant because of their association with chronic LBP, especially type I MCs [9,18–21]. The prevalence of MCs varies from 18% to 62% in patients with LBP, with different ratios for each type of MC [18,22–24].

**Table 1** BMD and BV/TV for “normal” endplates and those with type I, II or III Modic changes.

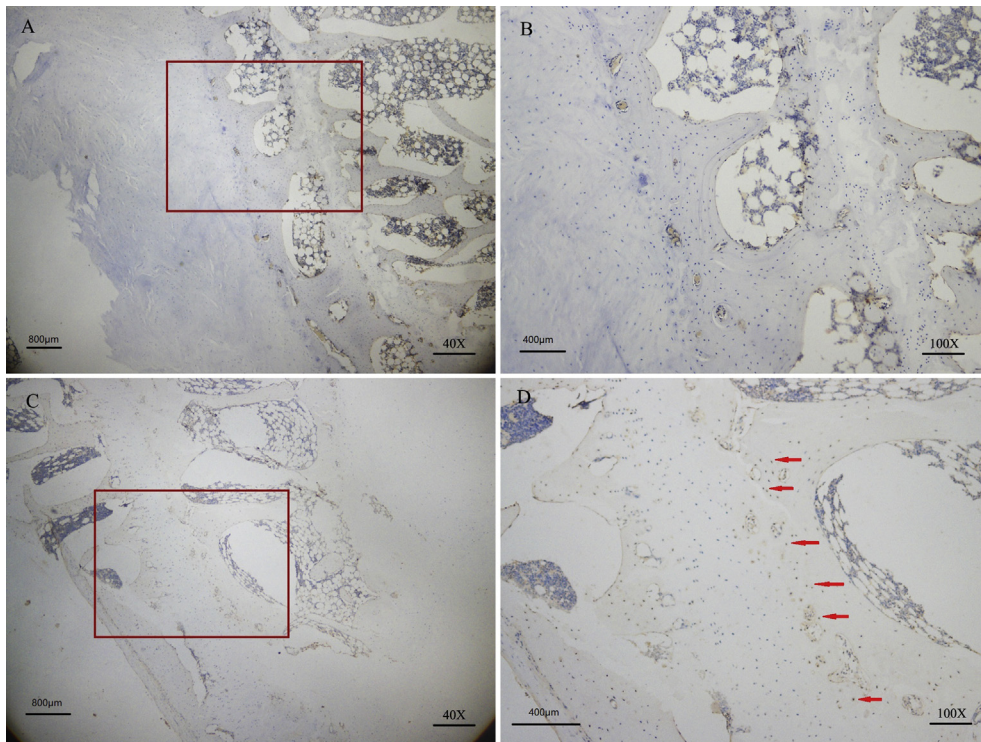
$\mu$ CT parameter/group	Type I	Type II	Type III	Normal
BMD (mg HA/ccm)	$358 \pm 38^{*, **}$	$371 \pm 45^{*, **}$	$402 \pm 61^*$	$294 \pm 29$
BV/TV	$0.399 \pm 0.091^{*, **}$	$0.412 \pm 0.102^{*, **}$	$0.542 \pm 0.137^*$	$0.304 \pm 0.083$

BMD = bone mineral density; BV/TV = bone volume/tissue volume

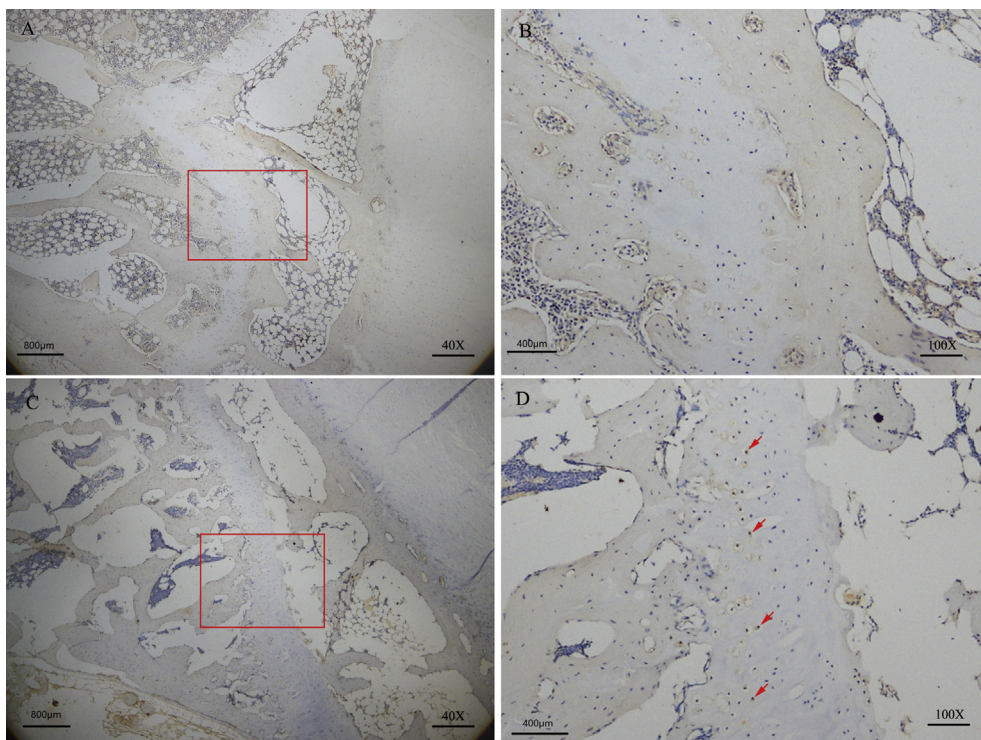
\*Significant differences ( $p < 0.05$ ) from normal are indicated.

\*\*Significant differences ( $p < 0.05$ ) from type III are indicated.

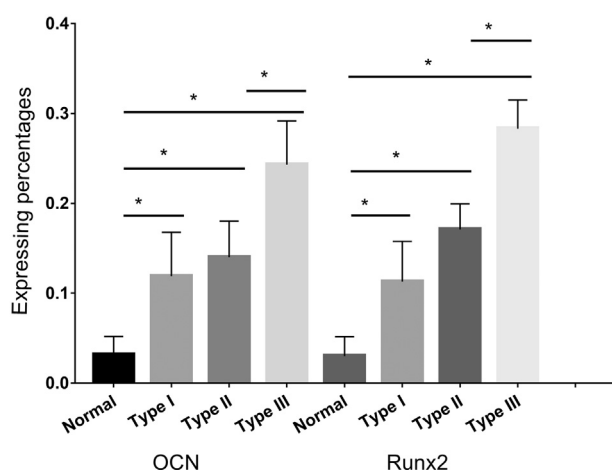




**Figure 4** OCN is detected by immunohistochemistry. (A–B) The protein expression of OCN in normal endplates; (C–D) the protein expression of OCN in endplates with Modic changes type III. There is more positive OCN expression in Modic changes endplates. Arrows: positive expression. OCN = osteocalcin.



**Figure 5** Runx2 is detected by immunohistochemistry. (A–B) The protein expression of Runx2 in normal endplates; (C–D) the protein expression of Runx2 in endplates with Modic changes type III. There is more positive Runx2 expression in Modic changes endplates. Arrows: positive expression. Runx2 = runt-related transcription factor 2.



**Figure 6** Quantitative expressing percentages of Runx2 and OCN were calculated by Image Pro Plus 6.0. The expression percentage of Runx2 and OCN of endplates with type I and II MCs were higher than those of normal endplates and lower than those of endplates with type III MCs. There were no significant differences between endplates with type I or type II changes. OCN = osteocalcin; Runx2 = runt-related transcription factor 2. \*  $p < 0.05$ .

According to previous studies, type I and II are the most common patterns found in the lumbar spine. In a study of asymptomatic individuals, where 590 lumbar vertebral endplates from 59 people were assessed, 11 endplates were found to exhibit type I MCs, whereas 38 showed type II changes [25]. In another study of asymptomatic individuals, Weishaupt et al. [26] reported a distribution of 2% for type I, 7% for type II and 2% for type III. These studies showed that type II is more frequent than type I, as in the present study. Additionally, MCs are most commonly found at the L4-L5 and L5-S1 levels.

It is commonly believed that three types of MC represent different stages of the same pathological process. Type I is considered the earliest and most active stage in the process of MCs evolution, type II reflects fatty replacement of the red bone marrow and type III is considered the last stage (endplate sclerosis). It has been suggested that only type III MCs indicate endplate sclerosis, MCs type I and type II show no definite correlation with sclerosis on radiographs. Interestingly, the results of this study are somewhat different from those published previously. We found that not only type III changes but also other MCs types (type I and type II) showed endplate sclerosis in CT. Thus, endplate sclerosis can co-exist with all types of MC. We also confirmed these results in a rabbit model of MCs. Therefore, in clinical work, MCs observed in conjunction with endplate sclerosis on a CT image should not simply be interpreted to represent MC type III, which is a stable stage in the evolution of endplate changes. Generally, it is the MCs type I (represent an inflammatory process) that is considered to have a correlation with chronic LBP not the MCs type III. Our research showed that sclerosis may still represent an inflammatory process associated with chronic LBP. In other words, endplate sclerosis and LBP can occur simultaneously.

Runx2 is a key transcription factor associated with osteoblast differentiation. It regulates the expression of major bone matrix protein genes. OCN is secreted solely by osteoblasts and thought to play a role in the body's metabolic regulation and is proosteoblastic or bone-building, by nature. Runx2 and OCN are often used as markers for the bone formation process. So Runx2 and OCN were assessed for the endplate sclerosis in this study. We found the expressive percentage of IHC in type I and II changes were higher than those of normal endplates and lower than those of endplates with type III changes. There were no significant differences between endplates with type I and type II changes.

From the histopathologic viewpoint, osteosclerosis can be defined as a qualitative increase in bone volume. The sclerosis seen on plain radiographs and CT scans in conjunction with type III MCs is a reflection of dense mineralised bone within the vertebral body rather than the marrow elements [4]. However, the magnetic resonance signal intensity is more a reflection of the vertebral body marrow elements within these trabeculae. We believe that the sclerosis seen in some endplates showing type I or type II changes may reflect a regenerative process in the marrow with new bone formation. The mechanism of endplate sclerosis in MCs type I and II may be explained by inflammatory factors that play an important role in promoting bone formation, which is the next focus of our research.

Our study has some limitations. First, it was a single-centre, retrospective study. Second, the study focussed on the phenotypic analysis of endplate changes on MRI and CT scans, so no correlative mechanism was studied. Evidently, further study is needed in the future.

Nevertheless, we think that the present study's results have clinical significance. The study showed that sclerosis can occur in endplates with MCs type I, II and III. In patients with endplate sclerosis on plain radiographs or CT scans, the endplate can still represent an inflammatory process associated with chronic LBP.

## Conflicts of interest statement

None declared.

## Funding

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