Unbalanced cartilage calcification during development contributes to the formation of irregular articular surfaces as revealed by micro-CT images

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Introduction: The histological features of irregular mandibular condylar surfaces revealed on CT images remain unknown.
Aim: In order to seek clarification, the aim of the study was to describe the histological features of irregular mandibular condylar surfaces detected on micro-CT images.
Materials and methods: Due to different modelling requirements, thirty rats were exposed to five experimental occlusal disturbance models at 6- or 8-weeks of age. Another six age-matched rats were used as controls. After 10 or 12 weeks of modelling, the mandibular condyles were sampled for micro-CT scanning and histology, immunohistochemistry and immunofluorescence assessment. The condyles with irregular surface signs were chosen for analysis.
Results: Based on the micro-CT images, 10 out of the 30 condyles were diagnosed as having irregular articular surfaces which typically appeared as lacunae on histological sections. The lacunae were filled with degraded cartilage, a fibrous mass, or calcified islets. Type II collagen-, type X collagen- and osterix-positive cells were observed at the side walls of the lacunae. Cleaved caspase-3-positive cells, CD90-positive cells and fibronectin-positive areas were observed inside the lacunae. However, in the subchondral bone at the lower margin of the lacunae, TRAP-positive cells were seldom observed.
Conclusions: Irregular mandibular condylar surfaces revealed by micro-CT images during development appeared to be a result of unbalanced cartilage calcification.
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Introduction

An irregular condylar surface, diagnosed through computed tomography (CT) imaging, is often taken as a sign of condylar resorption during orthodontic and orthognathic surgery treatments.[1] The histological assessment of the patients' TMJs is usually not practical in clinical settings, and so, animal studies are indicted.

The temporomandibular joint (TMJ) has a close biomechanical relationship with the dental occlusion and often responds to occlusal alterations by remodelling. Recently, five animal occlusal disturbance models have been reported, four written in English, and termed gradually-induced disordered occlusion (GIDO),[2–4] unilateral anterior crossbite (UAC),[5–9] bilateral anterior elevation (BAE)[10–12]

and bilateral anterior crossbite (BAC),[13] and one in Chinese, termed mandible deviation occlusion (MDO). Histological degenerative and regenerative responses of the TMJ condyles were elicited in those models.[4,6,9,10,13] Irregular condylar surfaces on micro-CT images were often noted. Clearly, these animal models present an attractive opportunity to describe the corresponding histological features underlying the irregular condylar surfaces and to investigate the potential cellular mechanisms.

In the present study, micro-CT methods were used, followed by histomorphologic assay, to assess the articular surfaces of the TMJ condyles. Immunohistochemistry was also performed by staining for type II collagen (Col-II), a marker of cartilage matrix; type X collagen (Col-X), a marker of chondrocytes terminal differentiation; osterix (OSX), a marker of osteoblast differentiation; fibronectin (FN), a marker of fibrosis; cleaved caspase-3 (CCP3), a marker of cell death; and CD90, a marker of chondro-progenitors.[14] The purpose was to identify the histological features of an irregular mandibular condylar surface revealed by micro-CT and further, to identify the potential cellular mechanisms which could indicate the development of future therapeutic strategies.

Materials and methods

Animals and samples

Thirty 6-week-old (140–160 g) and six 8-week-old (180–200 g) female Sprague-Dawley (SD) rats were acquired and provided by the Animal Centre of the University. All animal procedures were approved by the Administration Committee of Experimental Animals and performed according to the National Institutes of Health guidelines for the care and use of laboratory animals. The six-week-old rats were randomly divided into four anterior occlusal disturbance groups and one control (CON) group, and the eight-week-old rats, whose posterior teeth had fully developed, were used for the one posterior occlusal disturbance group (n = 6).

All operations were completed within 5 min for each rat. The rats were anaesthetised using 1% pentobarbital (0.4 mL/100 g weight) before operation. The appearances of the created occlusal disturbance models are presented in Figure 1.

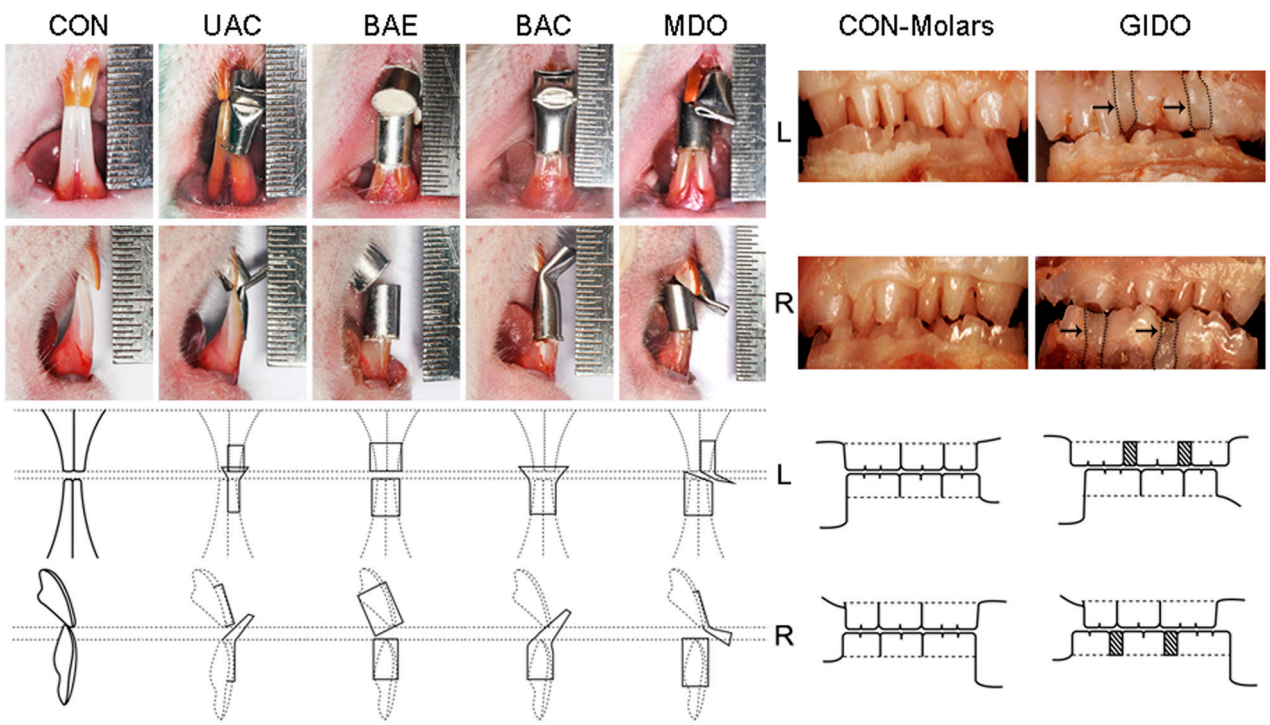

Figure 1. Representative frontal and lateral views, and a sketch map of the incisors' occlusal relationship in experimental group rats. BAE, bilateral anterior elevation; BAC, bilateral anterior crossbite; CON, blank control; GIDO, gradually induced disordered occlusion; MDO, mandibular deviated occlusion.

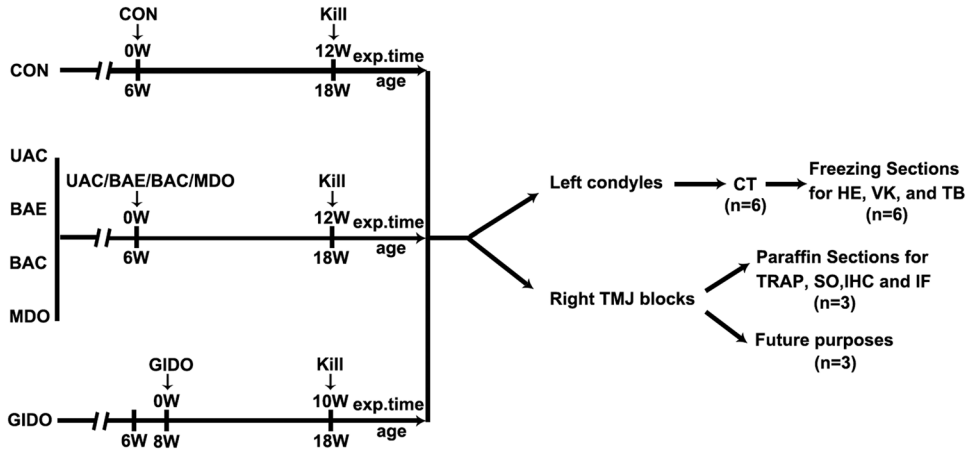

Figure 2. The timeline of the entire experiment.

Briefly, following past reported methods, a gradually-induced disordered occlusion (GIDO) was produced by moving the left-side maxillary first molar and right-side mandibular first molar mesially, and by moving the left-side maxillary third molar and right-side mandibular third molar distally, to produce an unmatched occlusal contact of the moved molars.[3] A unilateral anterior crossbite (UAC) was created by placing a pair of aberrant prostheses on the left side of the maxillary and mandibular incisors. The pair of prosthetic left incisors was created in a crossbite relationship, while the right natural incisors were maintained in a normal overjet and overbite.[2,15] A bilateral anterior elevation (BAE) occlusion was created by attaching metal tubes onto the two maxillary incisors and the two mandibular incisors, which produced an edge-to-edge relationship of the tubed incisors.[10,11] A bilateral anterior crossbite (BAC) model was produced by placing a metal tube (diameter = 5.5 mm) with a plate leaning to the labial side of the mandibular incisors to create a cross-bite relationship between the bilateral natural maxillary incisors and the tubed mandibular incisors. A mandibular deviation occlusion (MDO) model was produced by attaching a metal tube (diameter = 3 mm) with a deflective plate to cover the left-side maxillary incisors, and another metal tube (diameter = 5.5 mm) with an oblique aspect to cover the two mandibular incisors. The tubed incisors occluded in a relationship that caused the lower jaw to deviate to the right side.

The animals were sacrificed when 18-week old. The rats were grouped and sampled as shown in Figure 2. All of the left-side TMJ condyles and all of the right TMJ tissue blocks were removed and post-fixed in 40 g/L paraformaldehyde for 24 hours.

Gross morphology observation and micro-CT scanning

Immediately after sampling, the articular surfaces of the left-side TMJ condyles were imaged using a dissecting microscope (M250FA; Leica, Wetzlar, Germany). Each condyle was then post-fixed before being scanned using a micro-CT system (GE explore Locus SP, Woonsocket, USA). Scanning was performed at 80 kV and 80 μA. The X-ray beam was collimated to irradiate the TMJs and was used for reconstruction at an isotropic voxel size of 8 μm. Three-dimensional images acquired from the micro-tomographic slices were used for observation.

Histomorphology and immunohistochemistry

After micro-CT scanning, the left condyles were prepared for sagittal serial sections (5-μm-thick) using a freezing microtome (HM525NX, Thermo Scientific, Waltham, MA, USA). The serial freezing sections were selected for haematoxylin-eosin (HE), von Kossa (VK), and toluidine blue (TB) staining.[11] The histological images were acquired using a light microscope (DM2500, Leica, Wetzlar, Germany), and were analysed under a Leica DFC490 system (Leica, Wetzlar, Germany).

The right TMJ blocks were prepared for paraffin sections in the sagittal plane using a rotary microtome (RM2135, Leica, Wetzlar, Germany). Three samples in each group were used while the

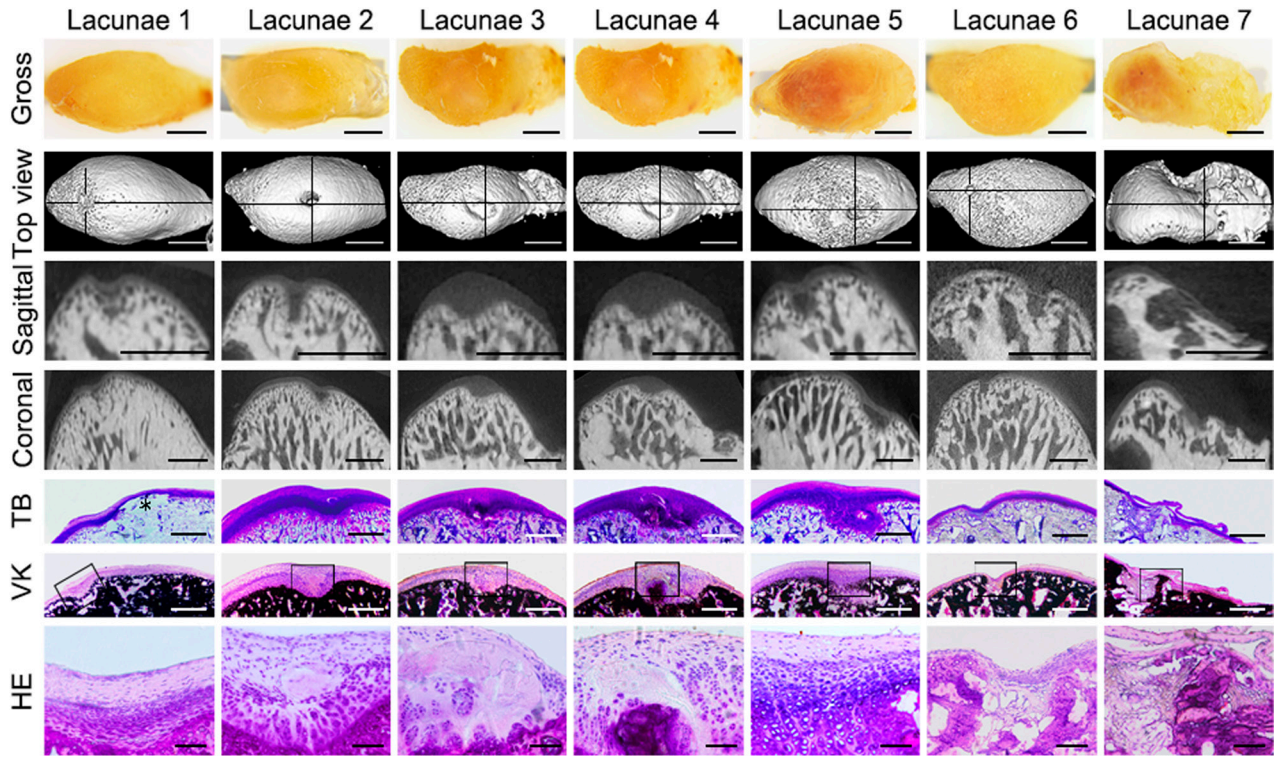

Figure 3. Morphology of the lacunae revealed by gross observation, micro-CT images, and toluidine blue (TB) and von Kossa (VK) staining. For Gross morphology, micro-CT images, TB and VK staining images, bars = 500 μm; for HE staining images, bars = 100 μm.

other three were reserved for future purposes. Those showing similar histological features to those observed in the samples that had irregular articular surface signs on micro-CT images were selected. TRAP staining and Safranin O (SO) staining were performed, along with immunohistochemical (IHC) staining for the expression of Col-II (sc-52658, Santa Cruz), Col-X (ab58632, Abcam), OSX (sc-393325, Santa Cruz), and FN (15613-1-AP, Proteintech), and immunofluorescent (IF) staining for the expression of CD90 (ab225, Abcam) and CCP3 (AF7022, Affinity) using previously reported methods.[11]

Results

Gross morphology and micro-CT images

The condyle from the control group was spindle-shaped, while deformation was obvious in the samples from the UAC, BAC, MDO and GIDO groups, but not from the BAE group. The superficial fibrous cover of all the condyles was intact. Fibril-like excrescences, dark in colour, were frequently observed on the surface of the deformed condyles (Figure 3). Ten out of 30 left-side condyles from the CON (1/6), UAC (1/6), BAC (3/6), MDO (3/6), and GIDO (2/6) groups showed irregular articular surfaces of the TMJ condyles as revealed by micro-CT images, while none in BAE group showed such signs.

Histology

Histologically, the irregular osseous surfaces shown on the micro-CT images appeared typically as lacunae which had different widths and depths (Figure 3). The only lacuna in the control group was shallow in shape and filled with normally arranged zonal cartilage that transitioned well to the neighbouring cartilage. The neighbouring cartilage was slightly thinner than that observed at the lacuna site (Lacuna #1 in Figure 3). However, the lacunae in the experimental groups (Lacunae #2 - 7 in Figure 3) were larger in width and depth, and were filled with disordered or decayed cartilage that frequently contained cell-free areas (Lacunae #2 in Figure 3), clustered chondrocytes (Lacuna #3 in Figure 3), calcified islets (Lacuna #4 in Figure 3), a mineralised bridge (Lacuna #5 in Figure 3), or a fibrous mass (Lacunae #6 and #7 in Figure 3), as revealed by the VK staining results. The lacunae could be separated from the underlying

bone marrow by calcified tissues (Lacunae #2 - 4 in Figure 3), passed through by the bridge-like calcified tissue from the lateral wall (Lacuna #5 in Figure 3), or extended to the bone marrow (Lacunae # 6 and #7 in Figure 3). In some condyles in the BAC group (Lacuna #7 in Figure 3), there were multiple lacunae on one condylar surface as revealed by the micro-CT images. The enhancement of the calcified cartilage was impressive as revealed on the VK staining slices.

IHC and IF staining

Based on the observation on the paraffin sections, the Col II-, Col X-, and OSX-positive cells were more abundant at the side wall of the lacunae but were absent inside or at the bottom of some lacunae (Figure 4). The CD90-positive cells were predominantly located in the upper part of the lacunae, while the CCP3-positive cells were predominant in the deep layer of the lacunae. A few areas in the lacunae lacked cells. The expression of FN in the lacunae was positive at the site where cells were missing. There was no apparent increase in TRAP-positive cells in the subchondral bone at the margins of the lacunae (Figure 5).

Discussion

In TMJ condylar cartilage, chondrocytes display depth-dependent phenotypes. Cells in the superficial proliferation zone differentiate into Col-II-expressing pre-hypertrophic and Col-X-expressing hypertrophic chondrocytes, and then into osterix-expressing osteoblasts and osteocytes.[16–19] In this way, the condyle grows in height (Figure 6A).

The TMJs have a close biomechanical relationship with the dental occlusion. During the masticatory process, the TMJs function as axes that support mandibular movements and, at the same time, resist the loading derived from the contraction of the jaw muscles. When the occlusion functions inefficiently upon mastication, the joints may suffer unbalanced loading because the masticatory muscles have to contract in an alternative pattern modulated by periodontal feedback.[20] In this situation, occlusal disturbance leads to condylar morphological changes via aberrant joint remodelling activity.[2] Cells in the superficial zone have not only a greater capacity for proliferation compared with the deep zone cells but also a greater resistance to atypical loadings and cell death.[5,21–25] Cells in the deep zone cartilage

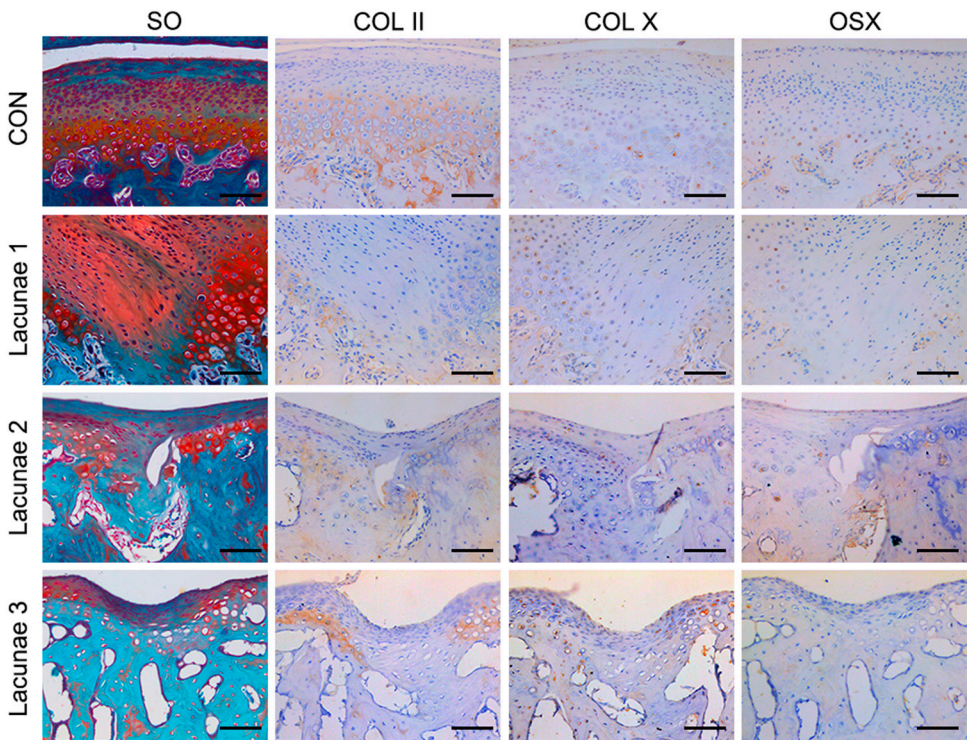

Figure 4. Representative histochemistry, immune-histochemistry (IHC) staining of the condylar lacuna induced by occlusal disturbance. Lacunae were detected by SO staining and IHC staining for Col-II, Col-X, OSX. For SO and IHC staining, bars = 100 μm.

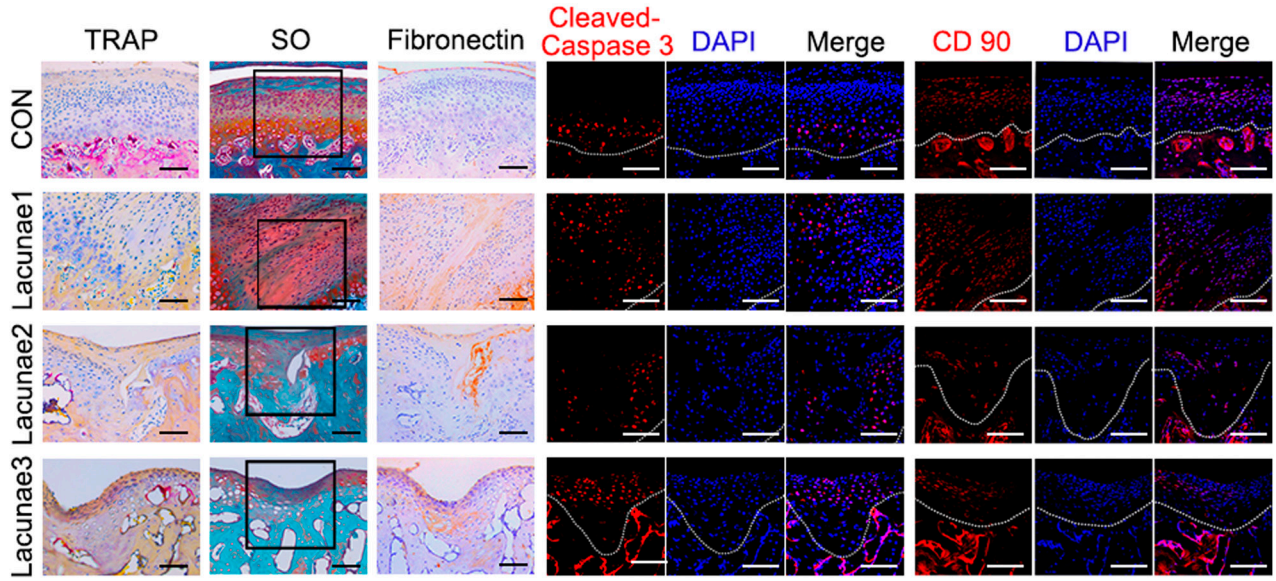

Figure 5. Representative sections with condylar lacunae induced by occlusal disturbance, stained with Tartrate-resistant acid phosphatase (TRAP) and Safranin O (SO), immune-histochemistry (IHC) for FN and immunofluorescence (IF) for cleaved caspase-3 (CCP3) and CD90. The black frames in the SO staining images showed the selected lacunae regions for IF staining. For SO, TRAP and IHC staining, bars = 100 μm. For IF staining, bars = 100 μm.

undergo apoptosis or terminal differentiation, and the cartilage undergoes an enhanced process of tissue calcification in response to aberrant loadings as those produced by UAC, which leads to deep zone cartilage detectable via micro-CT. [5,25,26]

It was noted that the lacunae in the control group were filled with zonal cartilage, while the lacunae in the experimental malocclusion groups contained degraded or decayed cartilage with or without calcified islets or a fibrous mass. Interestingly, the cells expressing Col-II, Col-X and osterix were more abundant at the side walls of the lacunae, the cells expressing cleaved caspase-3 were more abundant inside the lacunae, and the CD90-positive cells were predominantly in the upper part of the lacunae. It seemed that the stimulated proliferation activity, if present, occurred mainly at the upper region of the lacunae, while apoptosis was enhanced in the rest of the lacunal region especially near the bottom. The enhancement of apoptosis in the deep zone cartilage of the lacunae would impair the process of endochondral bone formation. It seemed that the present lacunae were formed via a process of impaired cartilage calcification rather than subchondral bone resorption. In support of this concept, TRAP-positive cells were seldom observed in the subchondral bone at the lower margin of the lacunae, indicating that there was no enhancement of osteoclast-mediated subchondral bone resorption. The irregular articular surface observed in the CT images, which have been generally identified as bone resorption, could be a result of impaired or unbalanced cartilage calcification (Figure 6B). This is consistent with the report that calcified cartilage was thinner and the interface was often more irregular at mechanically overloaded sites.[27]

Many factors, including inflammation similar to that observed in rheumatoid joints, TMJ trauma and hormone imbalances, contribute to the imaging signs of irregular articular surfaces that are often diagnosed as osseous mandibular condylar resorption.[28] The involved mechanism is relatively well understood. However, other conditions, such as idiopathic condylar resorption (ICR), which is a specific temporomandibular joint (TMJ) pathology that most commonly occurs in teenage females, show a distinct clinical, radiographic, and magnetic resonance imaging (MRI) presentation and the mechanisms are poorly understood.[29] The inability to detect the histological features of the ICR samples in the clinic makes it difficult to describe pathological changes and determine the underlying aetiology. Even though animal models are difficult to interpret and correlate to human disease, the results obtained from animal models are helpful in the exploration of the histological and molecular mechanisms of

diseases. The present animal data indicate that the imaging signs of osseous mandibular condylar lesions at the developmental stage may arise from impaired or unbalanced cartilage calcification.

Condylar resorption often results in the loss of condylar bone mass, a decrease in mandibular ramal height, steep mandibular and occlusal plane angles, a severe occlusal disturbance such as an open bite, facial malformation, and irreversible joint dysfunction.[1,30,31] Although conservative therapy and operative treatments have been proposed,[32–34] it is advised that once condylar resorption is diagnosed, occlusal treatments, such as orthodontics, corrective jaw surgery, or restorative dentistry, be delayed until condylar resorption has become quiescent or has "burnt out". Otherwise, there is an increased risk of persistent TMJ symptom progression and condylar resorption acceleration.[35,36] Unfortunately, there is no objective evidence to support that this delay in treatment is helpful for patients.[37,38] In contrast, the present data indicated that outside the lacunae, endochondral ossification was continuing, while inside the lacunae, the cartilage calcification process was impaired. Because of a lack of reference material in the literature, five different animal models of occlusal disturbance were used to obtain the typical irregular articular surface signs on micro-CT images. The present data indicated that the lacunae in the BAC model seemed most severe, while no lacunae were noted in the BAE model in which cartilage proliferation was promoted. Hence, the formation of lacunae could be an alternative functional remodelling response of the TMJ condyle to biomechanical occlusion. If so, early intervention of the occlusal disturbance is necessary to prevent worsened remodelling of the cartilage, although surgical treatment for ICR at a late stage has demonstrated an improved effect on TMJ pain, headaches, jaw function, diet, and disability.[39–41]

Mechanical factors that influence cartilage maintenance, degeneration, and regeneration via mechano-transduction of chondrocytes play a critical role in the pathogenesis of joint disorders such as osteoarthritis which is a cartilage degenerative disease. Pressure-induced resorption of the TMJ has been noted in condyles following a sagittal split osteotomy.[28] Understanding disease-associated mechano-transduction mechanisms may herald the development of effective therapeutic strategies for halting progressive cartilage degeneration. The transient receptor potential vanilloid 4 (TRPV4) cation channel, a mechanically-activated ion channel, has been found to affect endochondral ossification.[42] Mechanosensitive Ca^{2+}-permeating channels Piezo1/2

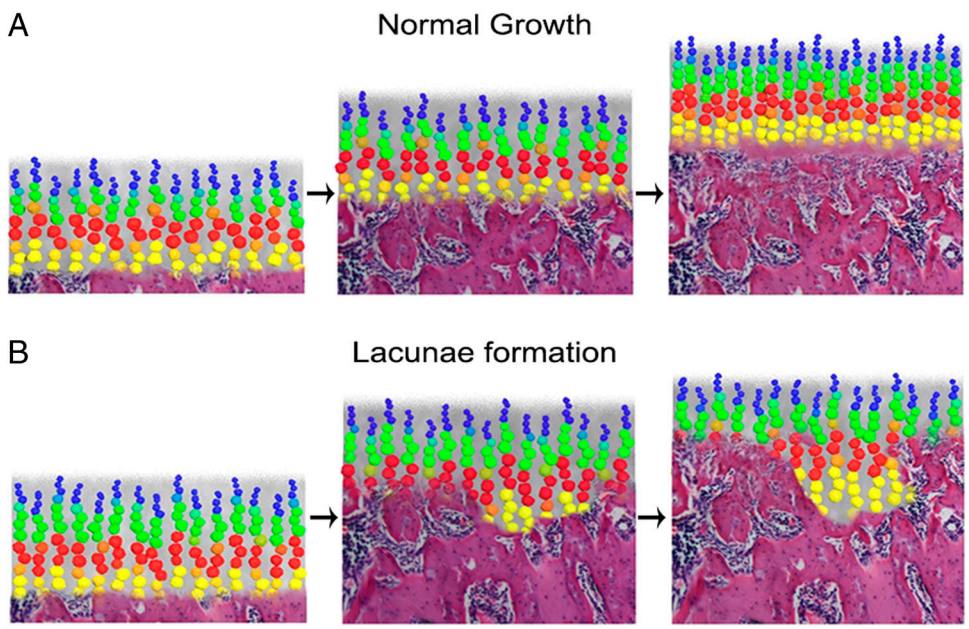

Figure 6. The diagrammatic sketch for normal growth of the condyle (A) and lacunae formation (B).

are also under investigation for their role in triggering force-dependent cartilage remodelling and injury responses.[43] It seems that the pharmacological control of inert cartilage calcification, as was proposed for osseous mandibular condylar resorption,[28] is necessary.

The occlusion is often complex and incorporates three or more dimensional features, involving changes with age. To date, appropriate dental biomechanical or functional assessments are still lacking. Based on the present data, improper management of the occlusion may aggravate the disease process and promote condylar deformation, exposing the orthodontist to potential litigation.[1] The embarrassing possibility of causing a negative outcome might prevent orthodontists from immediately proposing a treatment strategy for patients with condylar resorption signs revealed by CT images. A practical functional assessment of the occlusion is, therefore, imperative, so that considered orthodontic treatment may be provided.

Conclusion

The present animal studies indicate, for the first time, that the "resorption-like" irregular articular surface observed in CT imaging in young subjects could be an outcome of an aberrant occlusion and, seems to be a result of impaired and unbalanced cartilage calcification rather than resorption of the subchondral bone. The present data provide new insight into the interpretation of irregular articular surfaces observed in CT images. Based on the present results, a new therapeutic strategy is proposed, which is to eliminate occlusal disturbances at the initial stage to prevent, or at least attenuate, the degradation of cartilage. The functional assessment and management of the occlusion is an urgent issue that should be prioritised.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

YZ contributed to animal operation, data acquisition and interpretation, draft and manuscript composition. JZ contributed to data explanation and manuscript composition. LX contributes to animal management and sample preparation. M. Wang contributed to the conception, design, data interpretation, and manuscript composition. YZ and JZ these authors contributed equally to this work and should be considered co-first authors.

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