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Research Paper
TMJ Disorders

Cartilage changes link retrognathic mandibular growth to TMJ disc displacement in a rabbit model

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Abstract. Recent experimental research demonstrated that non-reducing temporomandibular joint (TMJ) disc displacement in growing rabbits impaired mandibular growth. TMJ disc displacement is also shown to induce histological changes of the condylar cartilage. The authors hypothesized that the severity of these changes would correlate to the magnitude of mandibular growth. Bilateral non-reducing TMJ disc displacement was surgically created in 10 growing New Zealand White rabbits. Ten additional rabbits constituted a sham operated control group. Aided by tantalum implants, growth was cephalometrically determined for each mandibular side during a period equivalent to childhood and adolescence in man. At the end of the growth period, histologically classified cartilage features were correlated with the assessed ipsilateral mandibular growth. Non-reducing displacement of the TMJ disc during the growth period induced histological reactions of the condylar cartilage in the rabbit model. The severity of cartilage changes was inversely correlated to the magnitude and the direction of mandibular growth, which resulted in a retrognathic growth pattern.

Keywords: adaptive modelling; adolescence; biomechanical function; mandibular retrognathia; temporomandibular joint.

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The mandibular condyles represent important growth sites within the facial skeleton. Condylar growth does not set the pace of mandibular growth, but it provides regional adaptive growth of considerable clinical significance because the upward and backward directed condylar growth displaces the mandible anteriorly and inferiorly as a whole[7].

It has repeatedly been demonstrated in animal models that temporomandibular joint (TMJ) disc displacement induces condylar cartilage changes[1,15,16], with a positive correlation between the severity of disc displacement and the severity of cartilage reaction[3]. The condylar cartilage is a biologically unique articular cartilage with an exceptional capacity for adaptive modelling in response to external stimuli[24]. The cellular activity of the cartilage is regulated by various local growth factors[22] and changes in the cartilage's biophysical environment, such as altered articulating function, triggers or impairs their endogenous expression, leading to increased or decreased condylar growth[6,24].

Several clinical studies of facial asymmetry and mandibular retrognathia, have reported an association with coexisting non-reducing TMJ disc displacement in adults as well as in children and adolescents[8,10,20,21,23,25]. Whether the adverse craniofacial growth predisposed for displacement of the TMJ disc or *vice versa* was clinically unclear, but cause and effect has been established in longitudinal

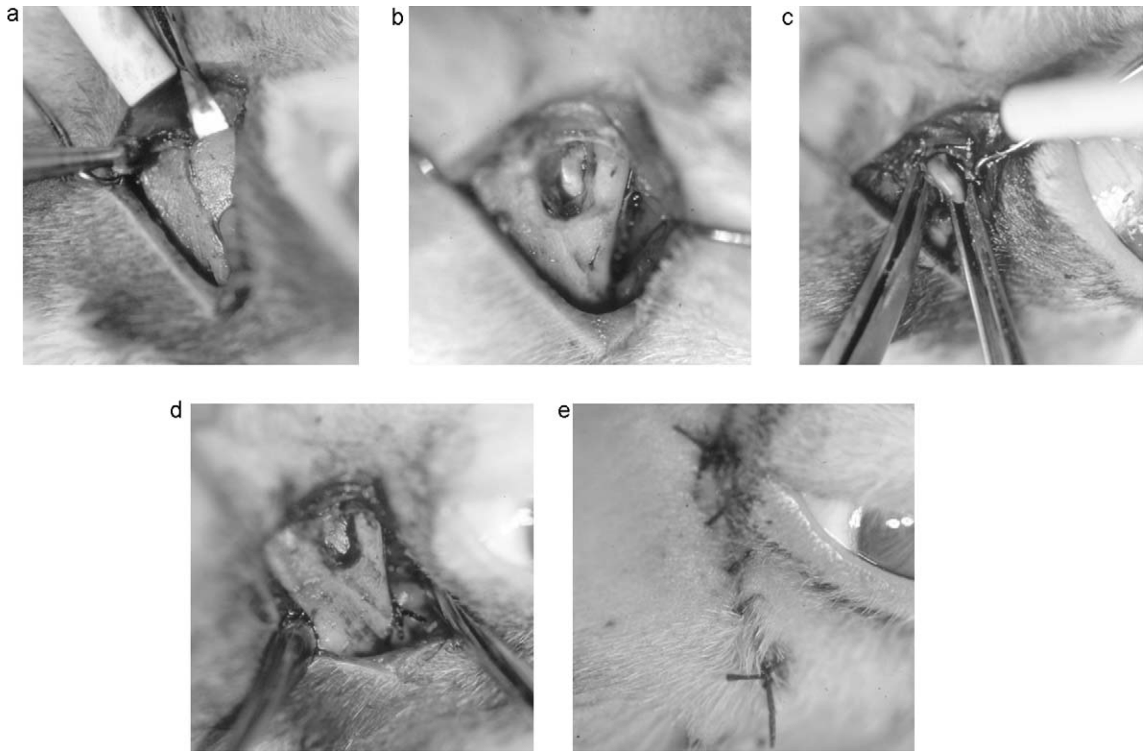

Fig. 1. Procedure for surgically created bilateral TMJ disc displacement. (a) Approach to the TMJ via a skin incision posterior to the orbit with blunt dissection to disclose the joint area. (b) Removal of a part of the zygomatic arch with a dental bur to achieve adequate view of the disc. (c) The medial, anterior, and lateral disc attachments detached. (d) A ligature through the disc via a hole drilled in the zygomatic arch anchored the displaced disc anteriorly. (e) The wound was closed in layers.

experimental studies verifying that surgically induced non-reducing TMJ disc displacement with onset during the growth period in a rabbit model, caused subsequent ipsilateral impairment of mandibular growth[13,14], and that with bilateral joint affliction, the extent of growth impairment corresponded to the development of mandibular retrognathia in man[4].

A non-deranged TMJ articulation seems necessary for maintenance of an optimal biophysical environment for the condylar cartilage, so the authors hypothesized that the severity of cartilage reactions following TMJ disc displacement would correlate with the magnitude of mandibular growth. The aim of this study was to perform a histological evaluation of the condylar cartilage response to non-reducing TMJ disc displacement during the growth period in a rabbit model and to correlate histologically classified cartilage features with ipsilateral mandibular growth.

Materials and methods

Twenty New Zealand White rabbits (*Oryctolagus cuniculus*) were randomized into two groups: an experimental group ($n = 10$) in which bilateral non-reducing TMJ disc displacement was surgically created; and a sham operated control group ($n = 10$) in which the same surgical procedure was performed but without manipulation of the TMJ disc.

The animals were 10 weeks old at the beginning of the study and were allowed to grow for a mean of 96 days (range 93–98 days). The rabbit's growth period[18] approximated childhood and adolescence in man[17]. A non-operated third control group was not considered ethically justified because the sham operation, as performed in this study, has previously been proven not to influence facial growth[13,14]. The animals were given free access to a regular diet of pellets throughout the study. One animal in the experimental group initially had problems consuming normal food after the surgery and was given soft food for the first week postoperatively. This animal was capable of eating normally during the rest of the study period. No animal was lost during the study.

The study was approved by the Ethics committee on animal experiments, Umeå University, Sweden (Registration No. A 128-00).

TMJ surgery

Bilateral TMJ disc displacement was surgically created in each experimental animal[2,4]. The approach to the TMJ was made via a skin incision posterior to the orbit. Blunt dissection of the soft tissue covering the joint was performed, and the joint area was disclosed (Fig. 1a). A small part of the zygomatic arch was removed with a dental bur, providing an adequate view of the surgical area. The continuity of the zygomatic arch was maintained (Fig. 1b). The capsule was incised. The disc and its attachments were identified and a ligature was sutured through the anterior part of the disc. The medial, anterior, and lateral disc attachments were detached (Fig. 1c) and the disc was pulled anteriorly, placing the intact posterior disc attachment above the condyle. A ligature through a hole drilled in the zygomatic arch anchored the displaced disc anteriorly (Fig. 1d). Maintenance of the incorrect disc position was checked, and the wound was closed in layers (Fig. 1e).

The sham operation followed the same procedure until the disc was exposed. The wound was closed without any disc manipulation.

Implant surgery

At study inception, tantalum spheres were inserted on the left side and tantalum pins on the right side of the mandible, to allow

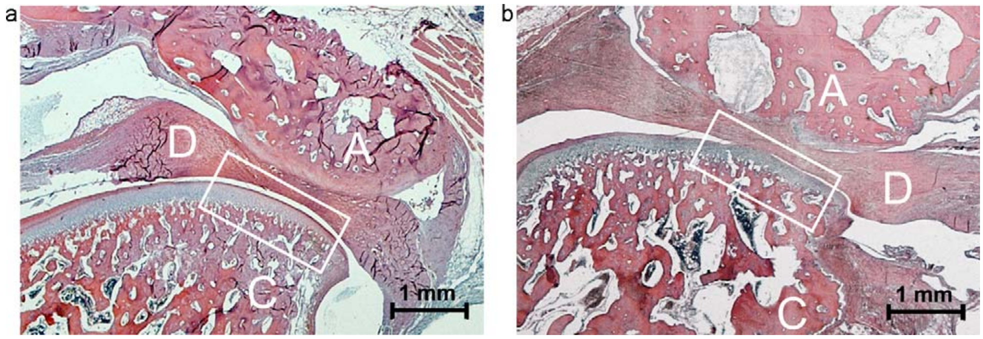

Fig. 2. (a) The anterosuperior part of the condyle (C), opposing the articular tubercle (A), was chosen as the region of interest for cartilage evaluation (white square). Example from one control animal; note posterior thick part of the TMJ disc (D) in normal position between the articulating surfaces. (b) Example from one experimental animal; note posterior thick part of the TMJ disc, displaced anterior to the condyle.

longitudinal cephalometric evaluation of growth of each side. Two titanium alloy screws in the calvarium served the dual purpose of reproducibly positioning the animal's head in a specially designed cephalostat, and providing reference structures for superimposition of serial cephalograms[5]. The tantalum implant interfered with a lower incisor in one control animal and in two experimental animals resulting in biassed growth measurements. These measurements were discarded, as were the ipsilateral joint specimens, resulting in a total number of 37 specimens with matching mandibular growth measurements.

Anaesthesia

TMJ surgery and the insertion of screws and implants was performed under general anaesthesia with 0.4 ml midazolam Dormicum®/kg of body weight, intraperitoneally, and 0.2–0.3 ml of fentanyl, fluanison Hypnorm®/kg of body weight, intramuscularly. Subcutaneous injections of 0.3–0.5 ml felypressin, prilokain Citanest Octapressin® were given prior to incisions in the scalp, the TMJ area, and the alveolar mucosa to achieve local anaesthesia.

Following the surgical procedures, the animal was given 0.1 ml buprenorphine (Temgesic®) subcutaneously/kg of body weight for analgesia, and approximately 15 ml of saline/kg of body weight to prevent dehydration.

After 3 months, the animal was killed with an intravenous injection of approximately 1.2 ml tiopental Pentotal®/kg of body weight.

Radiography and analysis

Lateral cephalograms were exposed at study inception and after 3 months. The cephalograms were digitized and superimpositions and measurements were conducted on a personal computer. Positions of the left and right tantalum implants were plotted digitally in each cephalogram, giving them x- and y-coordinates to the nearest tenth of a millimetre. The position of each tantalum implant in the inceptive cephalogram was defined as the implant's baseline position (origin), and the magnitude and direction of growth after 3 months was determined for the left and right sides, respectively. This experimental cephalometric method had a proven measurement precision of 0.4 mm in longitudinal studies[5]. The technique and the effect of surgically induced bilateral non-reducing TMJ disc displacement on overall mandibular growth in the present material have been presented previously[4]. The present study makes use of the technique's ability to identify growth for right and left mandibular sides, respectively, to correlate the intra-individual cartilage reactions with the subsequent amount of ipsilateral mandibular growth.

Histological analysis

After death, the rabbit was decapitated and the skull skinned. Intermaxillary fixation with a wire maintained the intercuspal position. The skull was kept in 10% buffered formalin (pH 7.0) until block preparation. Each TMJ specimen was removed *en bloc*, approximately $4 \times 2 \times 2$ cm in size. The tissue laterally over the joint was left intact.

The specimen blocks were decalcified for 2 weeks in 22% trisodium citrate buffered formic acid that was exchanged every second day. After decalcification, the specimens were dehydrated in graded alcohol for 3 days followed by incubation in methyl salicylate (HistoLab AB, Sweden) overnight at 37 °C and subsequently in a mixture of 1% celloidin in methyl salicylate at 37 °C for 3 days. The specimens were immersed in three graded methyl salicylate/paraffin mixtures followed by pure paraffin for 2 days. The paraffin embedded specimens were cut sagittally throughout the lateral into the central part of the TMJ using a scroll saw and thereafter cut in 5 μm sections that were stained with haematoxylin and eosin.

The histological sections were evaluated under light microscope and classified by two observers in consensus. The anterosuperior part of the condyle, opposing the articular tubercle, was chosen as the region of interest (Fig. 2). The histological feature of each condylar cartilage was graded based on the degree of divergence from normative cartilage configuration and classified as no, minor, moderate, severe or destructive changes (Fig. 3). For detailed classification criteria see Fig. 3 legend.

Statistics

Mann–Whitney's non-parametric test was used to test for differences in histological cartilage changes between experimental and control condyles. Independent-samples t-test for equality of means was used to test whether cartilage changes in the mandibular condyles were associated with altered magnitude and direction of mandibular growth. Spearman's non-parametric correlation test was used for intra-individual correlation between the histologically classified features of the condylar cartilage and ipsilateral mandibular growth. p-Values <0.05 were considered statistically significant.

Results

All but one control condyle and five experimental condyles had an even, convex contour (as in Fig. 2a). The remaining 13 experimental condyles displayed modelling with loss of convexity and a flattened enlargement of the articulating surface (as in Fig. 2b). All control con-

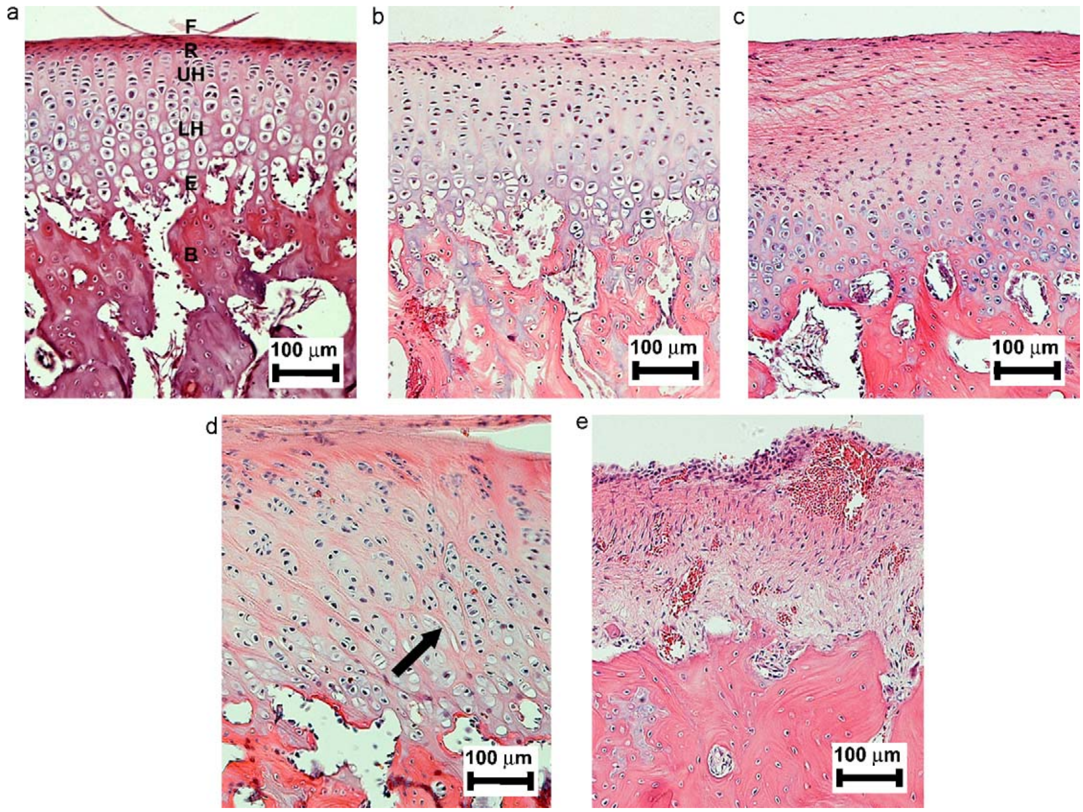

Fig. 3. Classification of condylar cartilage. (a) No changes ($n = 14$): normal condylar cartilage with five well organized basic layers: fibrous layer (F), reserve cell layer (R), upper hypertrophic layer (UH), lower hypertrophic layer (LH), and the erosive zone (E) with endochondral ossification towards the subchondral bone (B). (b) Minor changes ($n = 5$): intact layers but with slightly altered thickness of separate layers, indication of cellular atrophy. (c) Moderate changes ($n = 5$): absence of specific layers, moderate cartilage hypo- or hyperplasia, modest cellular atrophy, indication of vertical fibrous bundles between the fibrous layer and the subchondral bone. (d) Severe changes ($n = 12$): loss of layer organization, pronounced cartilage hypo- or hyperplasia, severe cellular atrophy, apparent vertical fibrous bundles between the fibrous layer and the subchondral bone (arrow). (e) Destructive changes ($n = 1$): splitting or absence of condylar cartilage – osteoarthrosis. Note how the bone surface is covered with synovial tissue in the example.

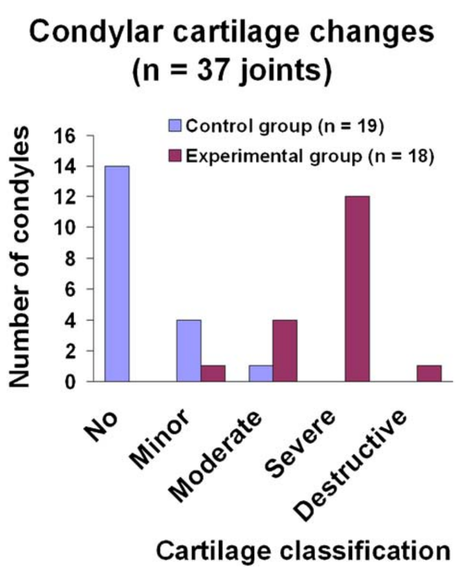

Fig. 4. Distribution of normative condylar cartilage and different grades of cartilage changes ($n = 37$). Cartilage changes were significantly more frequent and more severe in the experimental condyles than in the control condyles ($p < 0.001$). The majority of the experimental condyles displayed severe cartilage changes. A minority of the control condyles had minor or moderate cartilage changes opposing iatrogenic postoperative defects in the temporal bone.

dyles and all but one experimental condyle were covered with an intact layer of fibrous tissue (Fig. 4).

Cartilage features differed significantly between experimental and control condyles ($p < 0.001$). All 18 experimental condyles displayed cartilage changes of different grades, the majority of them (72%) classified as severe or destructive (Fig. 4) and consistently appearing in areas exposed to articular loading. The majority of the control condyles (74%) had normative cartilage (Fig. 4). The remaining control condyles displayed minor or moderate cartilage changes, which opposed small iatrogenic irregularities on the temporal joint component, caused by the sham surgery.

When condylar cartilage changes were present, mandibular growth on the same side was significantly reduced compared with growth when condylar cartilage was unaffected ($p = 0.025$) and the horizontal growth vector was significantly shorter ($p = 0.001$) (Table 1). There was

Table 1. Growth in mm of each mandibular side in relation to five grades of histologically classified cartilage features in the ipsilateral condyle.

	Mandibular growth		Horizontal vector		Vertical vector	
Cartilage classification	Mean	SD	Mean	SD	Mean	SD
No changes ($n = 14$)	9.5	0.96	8.7	0.80	3.7	1.25
Minor changes ($n = 5$)	9.4	0.36	8.4	0.24	4.1	0.75
Moderate changes ($n = 5$)	9.2	0.72	7.8	1.44	4.7	1.09
Severe changes ($n = 12$)	8.4	1.16	7.0	1.16	4.0	2.47
Destructive changes ($n = 1$)	6.6	–	5.2	–	4.1	–
No cartilage changes ($n = 14$)	9.5*	0.96	8.7***	0.80	3.7 ns	1.25
Cartilage changes ($n = 23$)	8.7*	1.10	7.4***	1.27	4.2 ns	1.86
T-test Sig. (2-tailed)	0.025		0.001		0.345	

Independent-samples t-test for equality of means was used to test whether cartilage changes in the mandibular condyles were associated with altered magnitude and direction of mandibular growth. When cartilage changes were present in mandibular condyles, mandibular growth on the same side was significantly reduced ($n = 23$) (mean = 8.7 mm, SD = 1.10) compared with mandibular growth when condylar cartilage was unaffected ($n = 14$) (mean = 9.5 mm, SD = 0.96). The horizontal growth vector was significantly shorter in the presence of cartilage changes (mean = 7.4 mm, SD = 1.27) compared with mandibular growth when condylar cartilage was unaffected (mean = 8.7 mm, SD = 0.80).

* Statistically significant difference at the 0.05 level.

*** Statistically significant difference at the 0.001-level. ns, no significant difference.

a significant inverse correlation between the histologically classified features of the condylar cartilage and the magnitude of ipsilateral mandibular growth ($r_s = -0.444$) ($p = 0.006$). A strong negative correlation was seen between the cartilage features and the length of the horizontal growth vector ($r_s = -0.624$) ($p < 0.001$). Negative correlations were also present between the degree of cartilage changes and the magnitude of ipsilateral mandibular growth ($r_s = -0.482$) ($p = 0.020$) and between the degree of cartilage changes and the length of the horizontal growth vector ($r_s = -0.557$) ($p = 0.006$) (Table 2). The assessed growth of individual mandibular sides is accounted for in Table 1 and Fig. 5.

Discussion

The mandibular condylar cartilage is frequently ascribed a unique capability of adaptive modelling in response to altered functional biomechanics, an assumption that forms the fundamental rationale for orthodontic functional therapy[24]. Another unique feature of TMJ condylar cartilage has been suggested to reside in the capability of the articulating fibrous layer to drop collagen anchors into the subchondral bone during overloading conditions to prevent bone–cartilage interface splitting[3]. This conclusion is supported by the authors' observations of collagenous anchorage into the subchondral bone in experimental animals displaying the largest impairment of ipsilateral mandibular growth.

Altered articulating biomechanics triggers a cascade of molecular events involved in the modelling of the articular tissues in response to changed functional demands. If the functional demands exceed the tissues' adaptive capacity, the same biochemical pathways could lead to tissue degeneration and joint disease[19]. This was demonstrated in fully grown animals with experimentally created partial rotational disc displacement. Increasingly displaced and faulty functioning TMJ disks correlated with gradient adaptive cartilage changes. Osteoarthrotic changes occurred solely in the most advanced cases of disc displacement[3]. Furthermore, the longer time a non-reducing TMJ disc remained displaced, the more severe the cartilage changes[1,16]. Besides the progressive status of disc displacement, age apparently plays a significant role in the severity of cartilage changes. Two previous experimental studies utilized the same surgical technique for creation of non-reducing TMJ disc displacement, which consistently induced gross morphological modelling of the mandibular condyles[1,15]. The only difference between the experimental models was age. Whilst the fully grown animals developed destructive changes with erosion and loss of articulating cartilage after 2 weeks, the articulating surfaces remained intact throughout a 3-month period in the growing animals; the same as observed in the present study. Given the same alteration of articulating biomechanics, the higher plasticity and regenerative capacity in adolescents could explain the difference in cartilage response between age groups. The experimental finding of gross adaptive morphological changes with flattening of the condyle although the articulating cartilage mostly remains intact in growing animals, could suggest a clinical risk of false-positive radiographic findings of TMJ osteoarthrosis in children and adolescents in particular. This assumption is supported by radiographic and histologic research on human TMJs, verifying that osseous changes, to date classified as osteoarthrosis at radiographic hard tissue evaluation, were normal bone

Table 2. Correlations between cartilage classification and mandibular growth, horizontal and vertical vectors.

Cartilage classification	Mandibular growth	Horizontal vector	Vertical vector
Cartilage features (5 grades)			
n	37	37	37
Correlation coefficient (r_s)	−0.444**	−0.624***	0.065
Sig. (2-tailed)	0.006	0.000	0.704
Cartilage changes (4 grades)			
n	23	23	23
Correlation coefficient (r_s)	−0.482*	−0.557**	0.082
Sig. (2-tailed)	0.020	0.006	0.710
Nonparametric correlations, Spearman's rho			

Non-parametric correlation test revealed a significant inverse correlation between the histologically classified features of the condylar cartilage ($n = 37$) and the magnitude of ipsilateral mandibular growth ($r_s = -0.444$). A strong negative correlation was seen between the histologically classified cartilage features and the length of the horizontal growth vector ($r_s = -0.624$). Negative correlations were also present between the different degrees of cartilage changes ($n = 23$) and the magnitude of ipsilateral mandibular growth ($r_s = -0.482$), and between the different degrees of cartilage changes and the length of the horizontal growth vector ($r_s = -0.557$). Correlation coefficient (r_s) and p-value for mandibular growth and its horizontal and vertical growth vectors.

* Statistically significant correlation at the 0.05-level.

** Statistically significant correlation at the 0.01-level.

*** Statistically significant correlation at the 0.001-level.

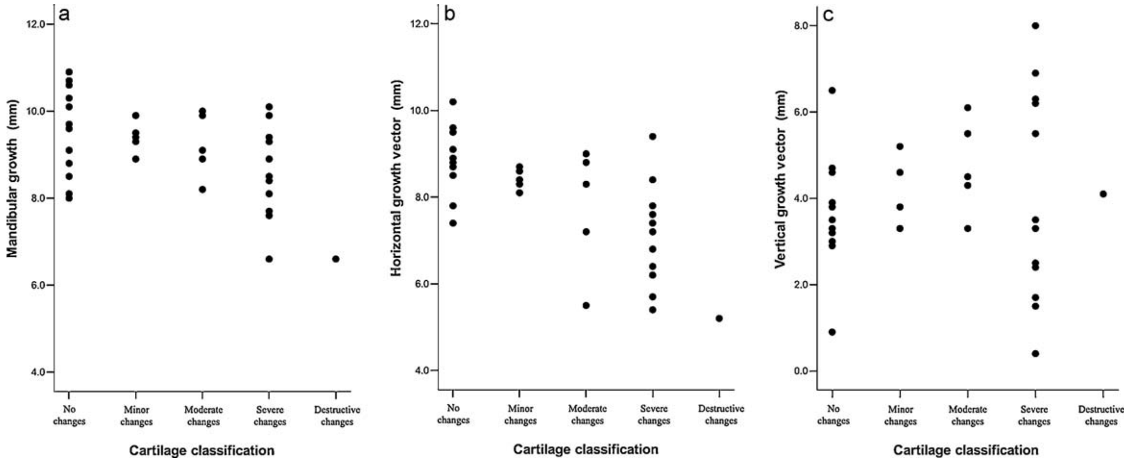

Fig. 5. Scatter plots for visual presentation of the material showing growth in mm for each mandibular side in relation to five grades of histologically classified cartilage features of the ipsilateral condyle ($n = 37$). Graphs show each individual measurement of mandibular growth (a) as well as its horizontal (b) and vertical (c) growth vectors. Mean and SD are presented in Table 1.

remodelling beneath intact articular soft tissue[11].

Delineation of the viscoelastic properties of the TMJ disc clearly pointed to the crucial importance of the disc functioning between the bony joint components to prevent damage to the cartilage and subchondral bone in areas susceptible to load concentrations[12]. In non-deranged TMJs the articular load remains evenly applied between the congruous articulating surfaces of the disc and osseous joint components. With non-reducing disc displacement, the lack of an interposed disc between the bony joint components results in sites of excessive load due to pointed contact between incongruous articulating surfaces. The authors therefore chose the area where the condyle opposes the temporal bone as the region of interest for evaluation of the condylar cartilage in the present study.

At non-reducing disc displacement the retrodiscal tissues (posterior disc attachment and capsular tissue, both outlined by synovial membrane) become interposed and compressed between the articulating surfaces. Compression of synovial cells was recently shown to enhance osteoclast formation, and continuous compressive force may induce osteoclastic bone resorption in the TMJ[9]. Whether the cartilage changes observed in the present experimental study constitute a primary adaptive response to altered biomechanics with a direct influence on mandibular growth, or developed as a secondary adaptive compensation to a growth inhibiting subchondral osteoclastic bone resorption, or both, will require improved methodology to substantiate.

The present experimental study has revealed that protective cartilage reactions following surgically induced non-reducing TMJ disc displacement are associated with reduction of mandibular growth in the rabbit model. Non-reducing TMJ disc displacement during the animal's growth period caused histological changes of the condylar cartilage, which were strongly associated with ipsilateral mandibular growth. Severe cartilage reactions were linked to ipsilateral impairment and retrognathic direction of mandibular growth. By verifying how histological condylar cartilage reactions and subsequent ipsilateral retrognathic mandibular growth are linked sequals to surgically created non-reducing TMJ disc displacement during growth in the rabbit model; the present experimental study might contribute to the understanding of the reported clinical association between facial as ymmetry and non-reducing TMJ disk displacement in humans[8,10,20,21,23,25]

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Competing interest

None declared.

Ethical approval

The study was approved by the Ethics committee on animal experiments, Umeå University, Sweden (Registration No. A 128-00).

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