Condylar lesions in relation to mandibular growth in untreated and intra-articular corticosteroid-treated experimental temporomandibular joint arthritis

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Abstract

Objective

To evaluate condylar lesions in relation to mandibular growth in experimental temporomandibular joint (TMJ) arthritis and to assess the outcome of treating this condition with repeated intra-articular corticosteroid injections (IACIs).

Methods

Forty-two 10-week-old rabbits were randomly divided into four groups. Seven animals served as controls. Experimental TMJ arthritis was induced in five animals which received intra-articular TMJ saline injections. Fifteen animals had TMJ arthritis induced and were left untreated and 15 animals had TMJ arthritis induced and were treated with IACIs one week after each TMJ antigen-challenge procedure.

Inter-group growth differences were evaluated from head computerised tomography scans taken at the time of arthritis induction and 12 weeks later. The variables assessed were: progression of condylar lesions (erosions/flattening/osteophytes), mandibular bone volume changes, condylar and sagittal ramus growth.

Results

No inter-group differences in the progression of condylar lesions were observed despite reduced mandibular growth in all three experimental groups. The most pronounced unfavourable mandibular growth alterations were observed in the corticosteroid-treated arthritis animals.

Conclusion

No evidence was found in support of a relation between reduced mandibular growth and condylar lesions. We propose that: 1) condylar lesions are not the only causative factor of reduced mandibular growth in experimental TMJ arthritis, and 2) repeated IACIs have a very unfavourable impact on mandibular growth in experimental TMJ arthritis – treatment is more detrimental to mandibular growth than the TMJ arthritis itself.

Key words

Mandibular condyle, growth, intra-articular injections, steroids, experimental arthritis, temporomandibular joint, bone resorption

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Introduction

Temporomandibular joint (TMJ) arthritis is known to alter the mandibular development in children diagnosed with juvenile idiopathic arthritis (JIA) (1-5). It affects the condylar cartilage that forms the basis for the endochondral ossification process partly responsible for the mandibular growth (6). The location of this growth zone within the TMJ is an unique characteristic of this joint. Resultant abnormalities include condylar lesions, an unfavourable posterior mandibular rotation pattern, micrognathia, malocclusion with an anterior open bite, altered joint and muscular function occasionally associated with pain (2, 7-9). Condylar lesions (erosions/flattening/osteophytes) have been regarded as the primary contributory cause to the mandibular growth deviations in JIA patients with TMJ arthritis. Today, determination of the presence of TMJ inflammation as well as the long-term prognosis of mandibular growth when TMJ arthritis has been diagnosed are therefore based on the presence of condylar lesions. The extent of these lesions is believed to play a significant role in the mandibular and facial morphological deviations seen in JIA patients with TMJ arthritis (2). Naturally, this perception may be changed as new imaging methods, such as MRIs, gain a foothold in the diagnosis of early TMJ arthritis in JIA.

In JIA patients with TMJ arthritis, treatment mainly comprises orthopaedic procedures and corrective orthognatic surgery when condylar lesions are present and mandibular growth disturbances have occurred (10, 11). Obvious advantages would therefore be gained if growth abnormalities and condylar lesions could be minimised or totally avoided through early aggressive intervention targeting the inflammatory changes in the joint. Intra-articular TMJ corticosteroid injections (IACI) have shown good results in terms of symptomatic relief and functional improvements in JIA patients (12-15). However, recommending IACI directly into the TMJs of growing JIA patients should await a deeper understanding of how the mandible and the lower face develop under the influence of TMJ arthritis. Besides their anti-inflammatory and immunosuppressive effect, corticosteroids are also known to suppress endochondral bone formation (16) which could have a most unfavourable long-term impact on mandibular growth because of the superficial position of the mandibular growth plate. This aspect, yet to be resolved, has not been addressed in previous studies investigating IACIs in JIA patients with TMJ arthritis. The aim of the present experimental study was therefore to evaluate the following parameters in growing rabbits with untreated and IACI-treated antigen-induced TMJ arthritis: 1) The progression of condylar lesions as a reflection of the relationship between condylar lesions and mandibular growth. 2) The mandibular bone volume changes during the growth period observed. 3) The mandibular growth in specific mandibular areas of interest as assessed from 3-dimensional superimpositions.

Material and methods

Animals, arthritis induction and interventions

All animal procedures were performed in accordance with a protocol approved by the Danish ethical committee for animal welfare. The material comprised 10-week old female New Zealand white rabbits (n=42) (*Oryctolagus cuniculus*) housed at the animal facilities, Aarhus University, Denmark, with free access to food and water. Animal welfare was monitored by daily evaluation of food and water intake. Prior to arrival, all animals were randomly assigned to four groups by block randomisation (Fig. 1); control group (n=7), placebo group (n=5), an untreated arthritis group (n=15) and a corticosteroid-treated arthritis group (n=15). All animals in the untreated arthritis group and in the corticosteroid-treated arthritis group had TMJ arthritis induced according to method described by Kapila *et al*. (17) and illustrated in Fig. 1. From age 10 weeks to age 14 weeks all animals in the three experimental groups were subcutaneously pre-sensitised towards the antigen ovalbumin (Sigma Chemicals) together with Freunds incomplete/complete adjuvant (IFA, Sigma Chemicals). At

age 14, 17, 20 and 23 weeks, all animals in the untreated arthritis group and the corticosteroid-treated arthritis group were injected with 0.1 ml 10 mg/ml ovalbumin in each TMJ to induce the experimental TMJ arthritis. In the same weeks the animals in the placebo group were injected with 0.1 ml saline in each TMJ. One week after each of the antigen-challenge procedures, the animals in the corticosteroid-treated arthritis group received 0.1 ml of 20 mg/ml Triamcinolone Hexacetonide (Lederspan®) in each TMJ (at age 15, 18, 21, 24 weeks). A total of ten rabbits were lost during the antigen challenge procedures due to anaphylactic shock. The lost animals were from the untreated arthritis group (7 animals) and from the corticosteroid-treated arthritis group (3 animals). No animal was lost during the i.a. TMJ injections of corticosteroid or saline (Fig. 1). At T2, the weights of all animals were obtained.

Two sets of full-head computerised tomographic scans (CT scan) (Philips/Mx8000 IDT 16) were carried out at the time of arthritis induction when the animals reached the age of 14 weeks (T1) and the age of 26 weeks (T2) which gave a 12-week observation period. Prior to the first CT scan session at T1, all animals had two 1.0 x 0.33 mm tantalum implants inserted into the right side of the mandible. The CT-scans were used for the evaluation of; 1) progression of condylar lesions; 2) mandibular bone volume changes; 3) evaluation of condylar and sagittal growth on 3-dimensional superimpositions.

Condylar lesions

Condylar lesions were scored in a blinded fashion in accordance with a semi-quantitative modified Rohlin and Petersson scale on regular 2-dimensional cuts together with 3-dimensional reconstructions of the mandibles (18). A condylar lesion score was assessed for each TMJ at T1 and T2. Each condyle was assessed with a lesion score from 0-5 as defined in Table I. A total condylar lesion progression score per TMJ was assessed (score at T2 minus score at T1 for each condyle), and for each animal a total score of the right and left joint was calculated to evaluate the total TMJ lesion progression score per animal. The total TMJ lesion progression score per animal was used in the statistical analysis of the test results to meet the requirements of independence in the statistical tests used. As an exception to this, only the right side progression score values were used in the evaluation of the correlation between the right side condylar growth and the condylar lesion progression scores, so that a direct correlation from the same side was obtained.

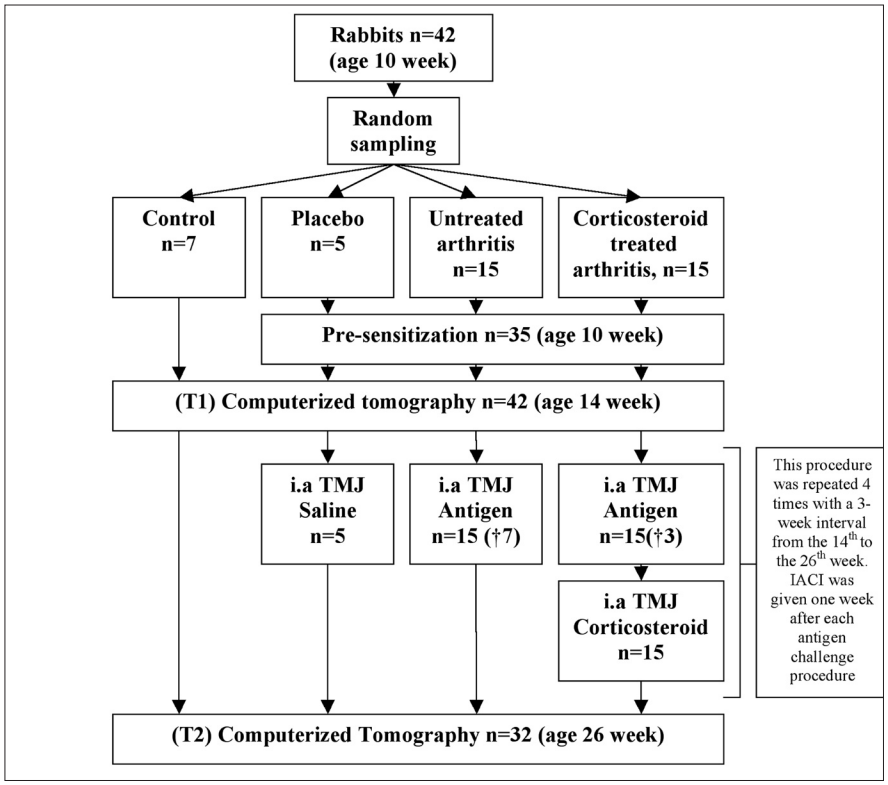

Fig. 1. New Zealand White Rabbits (n=42) age 10 weeks, were randomly divided into four groups. †number of animals lost before the second computed tomographic scan session; thus data from 32 animals were available for the final growth analysis at T2.

Table I. Condylar lesion progression score scale used for the semi-quantitative evaluation.

Grade 0	*Normal joint* Bony joint surface of the condyle with a convex and well defined outline
Grade 1	*Slightly abdormal joint* Single, minor changes interpreted as uncertain
Grade 2	*Definitive early abnormality sign* Definitive minor surface-changes such as erosions
Grade 3	*Moderate destructive abnormality* Erosions and local condylar changes such as a V-shaped tubercle
Grade 4	*Severe destructive abnormality* Extensive mediolateraly erosions of the condyle extending through a minimum of 1/3 of the total sagittal condylar dimension
Grade 5	*Mutilating abnormality* Total resorption of the condylar head with disappearance of the articular surface

Mandibular segmentations

On all CT-images the mandibles were manually separated from the base of the cranium using the software program Mimics (Mimics 10.1, Materialise, Leuven, Belgium). The segmentations were assessed in a blinded fashion before group assignment was revealed. Additionally, evaluation of the intra-observer variance in relation to the creation of the manual segmentation procedures was performed by ten randomly chosen duplicate segmentations.

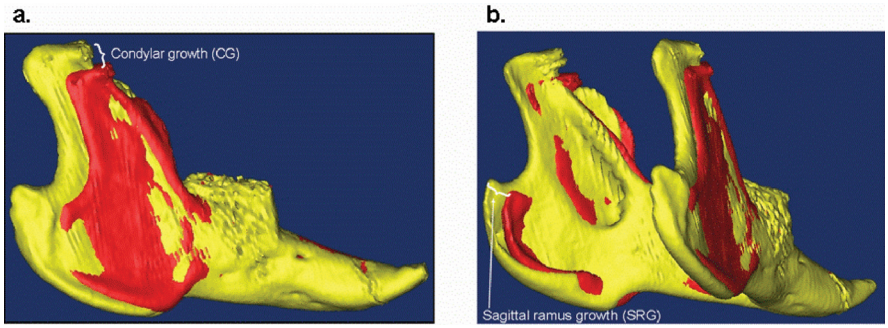

Fig. 2. Superimposition of a control group animal. The red parts represent the mandible at age 14 weeks (T1) and the yellow parts represent the mandible at age 26 weeks (T2). Mandibular scans from each animal at T1 and T2 were superimposed on implants and stable anatomical landmarks. The condylar growth distance is illustrated together with the sagittal ramus growth distance. Both of these variables were measured on all superimpositions.

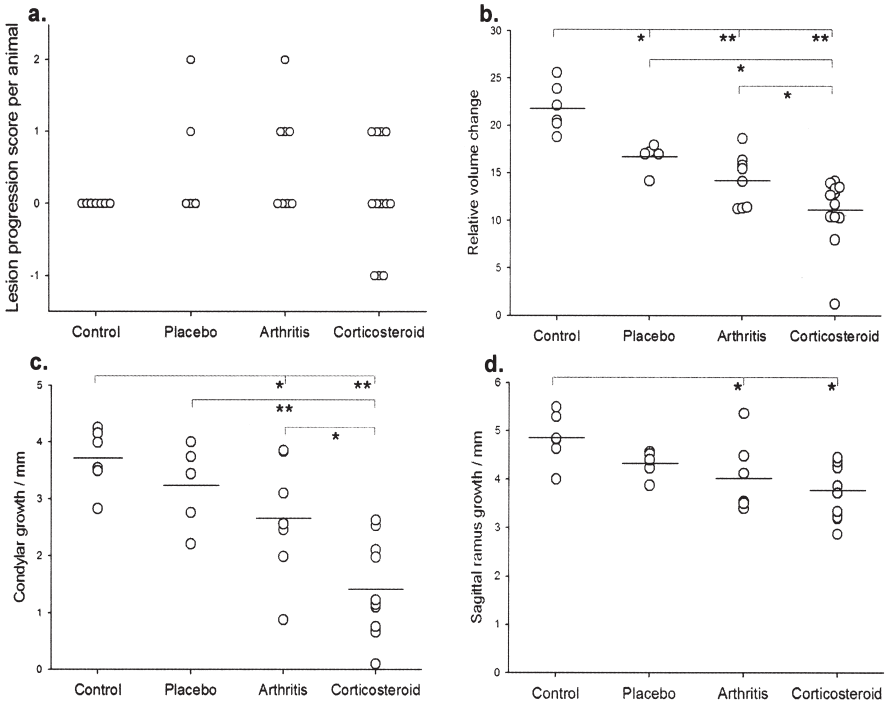

Fig. 3. a) Total lesion progression score per animal between T1 and T2. The lesion score of the right and the left TMJ were added for a total lesion progression score per animal. Probability of inter-group differences p=0.37. Notice that 3 animals obtained a negative condylar lesion progression score indicating improvements in the condylar dysmorphology between T1 and T2. **b)** Mean relative bone-volume changes (%) in each group during the 12 weeks of growth observed. The mean value is depicted with a straight line. **c)** Inter-group differences in absolute condylar growth; mean value is depicted with a straight line. **d)** Inter-group differences in absolute sagittal ramus growth; mean value is depicted with a straight line.* indicates a significance level of p<0.05 and ** indicates a significance level of p<0.001.

Mandibular superimpositions

Each 3-dimensional mandibular T1 image was superimposed on the T2 image of the same animal. Superimpositions were created on the inserted implants and stable anatomical landmarks. Two anatomical variables were measured on the superimpositions for a quantitative evaluation of inter-group changes in mandibular development; condylar growth (CG) and sagittal ramus growth (SRG) (Figures 2a and 2b).

The animals were sacrificed at the age 26 weeks after the second CT scan session (T2). Implant operations, TMJ injections and euthanisation were carried out under general anaesthesia. All intra-articular TMJ injections and surgical procedures were carried out by trained specialists in a blinded fashion. The animals that did not complete the full length of the study were excluded from the final analysis. Thus, data from 32 animals were available for the final analysis. Only statistical analyses pre-specified in the trial protocol were performed, except for the two variables CG and SRG measured on the superimpositions.

Statistics, condylar lesions

The reproducibility of the condylar lesion progression score per TMJ, expressed in Kappa values, was evaluated by duplicate assessments two months apart in a blinded fashion by the same observer (PS). A Wilcoxon matched-paired rank-test was used for the evaluation of *intra*-group differences between T1 and T2. A non-parametric Kruskall-Wallis test was used for the evaluation of *inter*-group differences in the TMJ lesion progression score per animal at T2.

Statistics, mandibular segmentations

Intra-observer variance in the mandibular segmentation process was evaluated according to the guidelines for duplicate measurements described by Bland and Altmann (19). Absolute mandibular *inter*-group growth differences at baseline (T1) were evaluated by an ANOVA one-way analysis. Evaluation of absolute mandibular *intra*-group growth between T1 and T2 was carried out by paired Student's *t*-test. *Inter*-group differences in relation to relative mandibular bone volume changes between the T1 and T2 were evaluated by a one-way ANOVA analysis with two-paired *t*-tests serving as post-ANOVA tests.

Statistics, mandibular superimpositions

Inter-group differences in condylar growth and sagittal ramus growth were evaluated by one-way-ANOVA tests with two-paired *t*-tests serving as post-ANOVA tests. The need for Bonferroni corrections to avoid mass significance in the post-ANOVA *inter*-group *t*-tests was evaluated. However, to avoid type-1 error due to the correlation between the variables evaluated in each animal, this correction was considered too strong and therefore was not implemented in the statistical analysis. A p-value of <0.05 was considered significant.

Results

No *inter*-group differences in the animals' weights were observed at T2 (ANOVA, probability of *inter*-group differences p=0.29).

Condylar lesions

Kappa statistics from duplicate assessments at T2 showed an acceptable reproducibility of 78% per TMJ. No *inter*-group differences at T1 were observed. The condylar lesion progression scores for all animals in each of the groups are illustrated in Fig. 3a. No *intra*-group differences between T1 and T2 were observed. Additionally, no inter-group differences in the progression of the condylar lesions were observed.

Mandibular segmentations

All variables were evaluated for normal distribution. Duplicate manual mandibular segmentations showed an intra-individual variation coefficient of 0.99 in relation to the bone volume variable. This variation was found acceptable after graphical evaluation (19). At T1, we observed no significant *inter*-group differences in bone volume changes. Significant mandibular *intra*-group bone volume changes were seen between T1 and T2 in all four groups. Table II depicts T1 and T2 bone volume properties (mean ± SD) for each of the groups. At T2, significantly reduced relative mandibular bone volume enlargements were observed in the placebo group (16.7%, 95-CI: 14.9–18.4), the arthritis group (14.2%, 95-CI: 11.9–16.6) and the corticosteroid group (11.1%, 95-CI: 8.8–13.3) compared with the control group (21.8%, 95-CI: 19.2–25) (Fig. 3b). During the 12 weeks of observation, the significantly smallest relative bone volume changes were observed in the corticosteroid-treated animals.

Mandibular superimpositions

Figures 3c and 3d depict *inter*-group differences in absolute condylar growth and sagittal ramus growth. The condylar growth was significantly reduced in the corticosteroid-treated animals (1.4 mm 95-CI: 0.9–1.9) compared with the control group (3.7 mm, 95-CI: 3.2–4.3), the placebo group (3.2 mm, 95-CI: 2.3–4.1) and the arthritis group (2.7 mm, 95-CI: 1.8–3.5). When examining the sagittal ramus growth (SRG), this variable was significantly reduced in the arthritis animals (4.0 mm, 95-CI: 3.5–4.6) and in the corticosteroid-treated animals (3.8 mm, 95-CI: 3.4–4.1) compared with the control group animals (4.9 mm, 95-CI: 4.3–5.4).

Table II. Age 14 weeks (T1) and age 26 weeks (T2) data with reference to mandibular bone-volume, condylar growth and sagittal ramus growth between T1 and T2.

Group	Mean bone-volume changes (T2-T1) (mm^3) ± (SD)	Mean condylar growth (mm) + (SD)	Mean sagittal ramus growth (mm) ± (SD)
Control group	1957 ± (202)	3.71 ± (0.5)	4.85 ± (0.21)
Placebo group	1479 ± (128)	3.23 ± (0.32)	4.32 ± (0.13)
Arthritis group	1241 ± (246)	2.66 ± (0.22)	4.01 ± (0.24)
Corticosteroid group	1008 ± (359)	1.41 ± (0.239	3.77 ± (0.16)

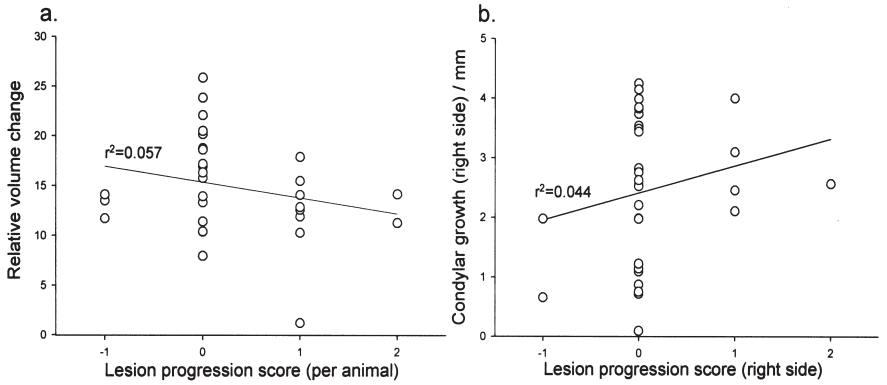

Fig. 4. a) Lesion progression score (per animal) in relation to mandibular relative bone volume changes. **b)** Right side lesion progression score in relation to the right side condylar growth. Notice, that only the right side lesion progression scores were used in this evaluation, so that a direct correlation between condylar growth and the lesion progression score from the same side was evaluated. A visual inspection of the two graphs as well as their regression lines (correlation r^2-values) indicate no relationship between the severity of the condylar lesion progression scores and the reductions in mandibular growth observed in this experimental temporomandibular joint arthritis model.

Progression of condylar lesions in relation to mandibular growth

A direct comparison between the condylar progression scores and the growth variables relative volume changes and condylar growth are illustrated in Fig. 4.

Discussion

The primary objective of this study was to evaluate the relation between condylar lesions and mandibular growth in untreated and IACI-treated experimental TMJ arthritis. The findings of this study were the following. Firstly, the mandibular growth was reduced in all three experimental groups compared with controls in terms of relative bone volume changes (Fig. 3b). Secondly, reduced mandibular growth was observed in the untreated arthritis group compared with the control group which supports the perception that arthritis activity *per se* reduces mandibular growth. Thirdly, the most pronounced unfavorable mandibular growth alterations were observed in the corticosteroid-treated arthritis animals. Fourthly, *inter*-group differences in mandibular growth occurred without any *inter*-group differences in the progression of condylar lesion scores. No relationship between the severity of the condylar lesion progression scores and the reductions in the mandibular growth variables was found. Fifthly, experimental TMJ arthritis has an extra-articular consequence such as reduced sagittal ramus growth which is seen in the untreated arthritis group and the corticosteroid-treated arthritis group.

Extant research has been debating the effect of condylar lesions on mandibular growth for decades (2, 20, 21). In

the clinical evaluation of the presence and severity of TMJ arthritis in JIA children, many pediatric rheumatologists believe that condylar lesions are the primary factor causing mandibular alterations and growth reduction (7, 22). The present findings allow us to question this claim. A contrast-enhanced MRI study by Küseler *et al*. (1998) documented the existence of inflammatory changes in the TMJ in JIA patients before they could be revealed by conventional radiographics and clinical symptoms (8, 23). Recent cohort studies from Twilt *et al*. have demonstrated mandibular retrognathia and posterior rotations in JIA patients without detectable condylar alterations on orthopantomograms. Twilt *et al*. also observed improvement and even regeneration of these TMJ alterations over time (5, 24). Argyropoulou *et al*. found that an abnormal condyle and articular eminence was correlated with a long inflammatory activity duration (25). In accordance with these findings, our results allow us to hypothesise that condylar alterations are the product of manifest and long-term inflammatory TMJ changes rather than an initial occurring condition in early TMJ arthritis. Our results also invite us to suggest that TMJ inflammation may critically affect the endochondral condylar ossification even in the absence of condylar lesions. Future clarification of this is essential and of utmost importance for the diagnostic and therapeutic understanding of mandibular growth alterations in JIA children.

In previous experimental studies, we have shown that IACIs reduce the inflammatory response in growing rabbits challenged with antigen-induced TMJ arthritis (26, 27). Arabshahi *et al*. (2005) obtained good clinical results by treating TMJ arthritis in JIA with a single IACI which induced significant pain resolution, improved joint function and induced resolution of joint effusion detected by MRI (12). Ringold *et al*. (2008) have published data demonstrating improved TMJ function following the initial IACI, but a minimal response to subsequent injections (15). These studies support symptomatic effect of IACIs against TMJ arthritis in JIA. However, these studies have generally seen neglected the important issue of a potential negative effect of the injected corticosteroids on the condylar cartilage and mandibular growth described in experimental studies (28-30): the potential long-term side-effects on mandibular growth may outweigh the beneficial short-term functional improvements of IACIs against TMJ inflammation. Unlike other joints, the condylar cartilage is an intra-articular active site for endochondral bone formation of utmost importance to mandibular development (6). The mandibular growth plate is situated just beneath the fibrocartilage of the condylar head, and this study supports the perception that this position makes it vulnerable to inflammation within the TMJ and that the disease activity itself interferes with mandibular growth. Our results suggest that this localisation makes the condylar cartilage even more vulnerable to TMJ arthritis treated with repeated IACIs – even more than if the TMJ arthritis was left untreated. Of particular importance is that mandibular growth was most reduced in the corticosteroid-treated arthritis animals, which indicates that corticosteroid-induced mandibular growth is hampered despite the beneficial effect of IACIs on TMJ inflammation described by Kristensen *et al*. (27).

A number of limitations in this study need further considerations. The corticosteroid-treated arthritis animals received more intra-articular injections per animal than any of the other group. However, we have previously shown that intra-articular TMJ saline injections *per se* do not result in any inflammatory or destructive structural changes in the joint (27). We therefore do not attach particular importance to the fact that the corticosteroid-treated animals received a higher number of actual TMJ injections per joint than the animals that received no corticosteroids.

Significantly reduced relative mandibular bone volume changes were observed at T2 in the placebo group compared with the control group. We ascribe this finding to the fact that the placebo animals were systemically pre-sensitised from age 10 to age 14 weeks, which is at the end of the rabbit growth spurt that terminates around age 16 weeks (31). In contrary to the three experimental groups, the control animals were not pre-sensitised. We hypothesise that the bone volume difference between the placebo and the control animals at T2 are due to the rather harsh systemic ovalbumin presensitisation given to the experimental groups. This procedure may have created a general inflammatory condition influencing the well-being of the placebo animals causing reduced mandibular bone volume changes in this group. Ideally, the control group should have been subjected to the same systemic ovalbumin presensitisation procedures as the three experimental groups. However, it is important to emphasise that in relation to the important variable, condylar growth, no differences between the control animals and the placebo treated animals were observed at T2. Based on the context of the present study the condylar growth variable is a more descriptive variable than the mandibular bone volume because it directly describes the product of the single regional growth centre situated within the TMJs on the condylar head. In contrast, the final mandibular bone volume is the product of several regional mandibular growth areas, all potentially influenced by extra-articular occurrences such as systemic pre-sensitisation, resulting in reduced mandibular bone volume.

A substantial limitation to this study is the great loss of animals (n=7) from the untreated arthritis group before the final analysis. Together with the lost corticosteroid treated animals (n=3), these were lost due to an anaphylactic reaction a few minutes after the ovalbumin was injected into the TMJs. If these animals were lost because they were most severely affected by the experimental arthritis, it could be anticipated that they would also have the most pronounced mandibular growth deviations. Yet, the study design does not allow us to conclude on this.

When a study consists of a reduced amount of animals it is always a limitation when further loss of animals occur and great intra-group result deviations are seen. In this study, great deviations

were seen within the condylar growth variable. However, these deviation very much reflect the great histological intra-group deviations seen in this study presented by Kristensen *et al*. (27).

In this study the arthritis was introduced at age 14 weeks in conformity with the Danish regulations on animal welfare. For the evaluation of an early treatment intervention against inflammatory changes in the TMJs in young subjects, it would have been preferable to initiate the trial in even younger animals in which case we would expect even greater inter-group differences in mandibular disturbances. Evaluation of mandibular catch-up growth after expiry of the effect of the corticosteroid on the condylar endochondral ossification is not possible due to the design of the study. In rabbits, approximately 90% of the overall mature sagittal and transversal mandibular growth is achieved within the sixteenth week and has ceased at age 26 weeks (31) so it is questionable if growth could be expected after the 26th week.

Applying findings obtained in experimental studies to man requires careful consideration. Even so, in terms of altered mandibular growth caused by TMJ arthritis, this experimental study does allow us to propose two interesting statements essential for future clinical investigations: 1) TMJ inflammation interferes with condylar growth and mandibular development and growth may be reduced even in the absence of condylar alterations; 2) Although treatment with IACI for TMJ arthritis has shown clinical improvement (12, 15) none of the human studies, so far, have described the long-term effect of IACI on mandibular growth in children. It is still unknown whether the use of repeated IACIs for TMJ arthritis in children may reduce mandibular growth even more than if the arthritis is left untreated, as we have observed in this experimental study.

To avoid potential mandibular growth reductions caused by TMJ inflammation other pharmalogical approaches could be considered. Recently, we have shown that intervention with systemic etanercept monotherapy equivalent to the recommended human dose (0.8 mg/kg weekly) has an anti-inflammatory effect on the synovial tissues in the TMJ and furthers mandibular growth towards an original morphology in experimental TMJ arthritis in rabbits (32, 33).

We believe that our results are of importance for clinicians treating children with TMJ arthritis as repeated IACIs against TMJ arthritis may have an unexpected negative effect on mandibular growth. We therefore recommend a careful follow-up of patients with TMJ injections in clinical studies to evaluate the potential negative influence of IACIs on the mandibular growth in humans.

Reference

1. BILLIAU AD, HU Y, VERDONCK A, CARELS C, WOUTERS C: Temporomandibular joint arthritis in juvenile idiopathic arthritis: prevalence, clinical and radiological signs, and relation to dentofacial morphology. *J Rheumatol* 2007; 34: 1925-33.
2. KJELLBERG H: Juvenile chronic arthritis. Dentofacial morphology, growth, mandibular function and orthodontic treatment. *Swed Dent J Suppl* 1995; 109: 1-56.
3. MERICLE PM, WILSON VK, MOORE TL *et al*.: Effects of polyarticular and pauciarticular onset juvenile rheumatoid arthritis on facial and mandibular growth. *J Rheumatol* 1996; 23: 159-65.
4. SIDIROPOULOU-CHATZIGIANNI S, PAPADOPOULOS MA, KOLOKITHAS G: Dentoskeletal morphology in children with juvenile idiopathic arthritis compared with healthy children. *J Orthod* 2001; 28: 53-8.
5. TWILT M, SCHULTEN AJ, NICOLAAS P, DULGER A, SUIJLEKOM-SMIT LW: Facioskeletal changes in children with juvenile idiopathic arthritis. *Ann Rheum Dis* 2006; 65: 823-5.
6. ENLOW DH, HANS MG, EDITORS: Growth of the mandible. Essential of facial growth. Philadelphia, Saunders, 1996: 57-78.
7. PEDERSEN TK, JENSEN JJ, MELSEN B, HERLIN T: Resorption of the temporomandibular condylar bone according to subtypes of juvenile chronic arthritis. *J Rheumatol* 2001; 28: 2109-15.
8. PEDERSEN TK, KUSELER A, GELINECK J, HERLIN T: A prospective study of magnetic resonance and radiographic imaging in relation to symptoms and clinical findings of the temporomandibular joint in children with juvenile idiopathic arthritis. *J Rheumatol* 2008; 35: 1668-75.
9. STABRUN AE: Impaired mandibular growth and micrognathic development in children with juvenile rheumatoid arthritis. A longitudinal study of lateral cephalographs. *Eur J Orthod* 1991; 13: 423-34.
10. PEDERSEN TK, GRONHOJ J, MELSEN B, HERLIN T: Condylar condition and mandibular growth during early functional treatment of children with juvenile chronic arthritis. *Eur J Ortho* 1995; 17: 385-94.
11. PEDERSEN TK: Clinical aspects of orthodontic treatment for children with juvenile chronic arthritis. *Acta Odontol Scand* 1998; 56: 366-8.
13. ARABSHAHI B, DEWITT EM, CAHILL AM *et al*.: Utility of corticosteroid injections for temporomandibular arthritis in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 3563-9.
14. BEUKELMAN T, GUEVARA JP, ALBERT DA, SHERRY DD, BURNHAM JM: Usage of intra-articular corticosteroid injections for the treatment of juvenile idiopathic arthritis: a survey of pediatric rheumatologists in the United States and Canada. *Clin Exp Rheumatol* 2008; 26: 700-3.
15. WEISS PF, ARABSHAHI B, JOHNSON A *et al*.:High prevalence of temporomandibular joint arthritis at disease onset in children with juvenile idiopathic arthritis, as detected by magnetic resonance imaging but not by ultrasound. *Arthritis Rheum* 2008; 58: 1189-96.
15. RINGOLD S, TORGERSON TR, EGBERT MA, WALLACE CA: Intraarticular corticosteroid injections of the temporomandibular joint in juvenile idiopathic arthritis. *J Rheumatol* 2008; 35: 1157-64.
16. MACRAE VE, FARQUHARSON C, AHMED SF: The pathophysiology of the growth plate in juvenile idiopathic arthritis. *Rheumatology* (Oxford) 2006; 45: 11-9.
17. KAPILA S, LEE C, TAVAKKOLI JOU MR, MILLER AJ, RICHARDS DW: Development and histologic characterizations of an animal model of antigen-induced arthritis of the juvenile rabbit temporomandibular joint. *J Dent Res* 1995; 74: 1870-9.
18. HU YS, SCHNEIDERMAN ED: The temporomandibular joint in juvenile rheumatoid arthritis: 1. Computed tomographic findings. *Pediatr Dent* 1995; 17: 46-53.
19. BLAND JM, ALTMAN DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-10.
20. LARHEIM TA, HAANAES HR, RUUD AF: Mandibular growth, temporomandibular joint changes and dental occlusion in juvenile rheumatoid arthritis. A 17-year follow-up study. *Scand J Rheumatol* 1981; 10: 225-33.
21. STABRUN AE, LARHEIM TA, HOYERAAL HM, ROSLER M: Reduced mandibular dimensions and asymmetry in juvenile rheumatoid arthritis. Pathogenetic factors. *Arthritis Rheum* 1988; 31: 602-11.
22. TWILT M, VAN DER GE, MOBERS SM, TEN CATE R, SUIJLEKOM-SMIT LW: Abrupt condylar destruction of the mandibula in juvenile idiopathic arthritis. *Ann Rheum Dis* 2003; 62: 366-7.
23. KUSELER A, PEDERSEN TK, HERLIN T, GELINECK J: Contrast enhanced magnetic resonance imaging as a method to diagnose early inflammatory changes in the temporomandibular joint in children with juvenile chronic arthritis. *J Rheumatol* 1998; 25: 1406-12.
24. TWILT M, SCHULTEN AJ, VERSCHURE F, WISSE L, PRAHL-ANDERSEN B, SUIJLEKOM-SMIT LW: Long-term followup of temporomandibular joint involvement in juvenile idiopathic arthritis. *Arthritis Rheum* 2008; 59: 546-52.
25. ARGYROPOULOU MI, MARGARITI PN,

KARALI A *et al*.: Temporomandibular joint involvement in juvenile idiopathic arthritis: clinical predictors of magnetic resonance imaging signs. *Eur Radiol* 2009; 19: 693-700.

26. KUSELER A, PEDERSEN TK, BARLACH J *et al*.: Contrast-enhanced MRI compared to histological findings in the temporomandibular joint of antigen-induced arthritis in young rabbits. *Clin Exp Rheumatol* 2004; 22: 441-6.
27. KRISTENSEN KD, STOUSTRUP P, KUSELER A *et al*.: Quantitative histological changes of repeated antigen-induced arthritis in the temporomandibular joints of rabbits treated with intra-articular corticosteroid. *J Oral Pathol Med* 2008; 37: 437-44.
28. JUX C, LEIBER K, HUGEL U *et al*.: Dexamethasone impairs growth hormone (GH)-stimulated growth by suppression of local insulin-like growth factor (IGF)-I production and expression of GH- and IGF-I-receptor in cultured rat chondrocytes. *Endocrinology* 1998; 139: 3296-305.
29. SILBERMANN M, MAOR G: Mandibular growth retardation in corticosteroid-treated juvenile mice. *Anat Rec* 1979; 194: 355-67.
30. SILVESTRINI G, BALLANTI P, PATACCHIOLI FR *et al*.: Evaluation of apoptosis and the glucocorticoid receptor in the cartilage growth plate and metaphyseal bone cells of rats after high-dose treatment with corticosterone. *Bone* 2000; 26: 33-42..
31. MASOUD I, SHAPIRO F, MOSES A: Longitudinal roentgencephalometric study of the growth of the New Zealand white rabbit: cumulative and biweekly incremental growth rates for skull and mandible. *J Craniofac Genet Dev Biol* 1986; 6: 259-87.
32. KRISTENSEN KD, STOUSTRUP P, KUSELER A *et al*.: Intra-articular vs. systemic administration of etanercept in antigen-induced arthritis in the temporomandibular point. Part I: histological effects. *Pediatr Rheumatol Online J* 2009; 7: 5.
33. STOUSTRUP P, KRISTENSEN KD, KUSELER A, PEDERSEN TK, GELINECK J, HERLIN T: Intra-articular vs. systemic administration of etanercept in antigen-induced arthritis in the temporomandibular joint. Part II: mandibular growth. *Pediatr Rheumatol Online J* 2009; 7: 6.