Effect of mechanical loading on the metabolic activity of cells in the temporomandibular joint: a systematic review

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Abstract

Objectives The purpose of this systematic review was to elucidate how different modalities and intensities of mechanical loading affect the metabolic activity of cells within the fibrocartilage of the temporomandibular joint (TMJ).

Materials and methods A systematic review was conducted according to PRISMA guidelines using PubMed, Embase, and Web of Science databases. The articles were selected following a priori formulated inclusion criteria (viz., in vivo and in vitro studies, mechanical loading experiments on TMJ, and the response of the TMJ).

A total of 254 records were identified. After removal of duplicates, 234 records were screened by assessing eligibility criteria for inclusion. Forty-nine articles were selected for full-text assessment. Of those, 23 were excluded because they presented high risk of bias or were reviews. Twenty-six experimental studies were included in this systematic review: 15 in vivo studies and 11 in vitro ones.

Conclusion The studies showed that dynamic mechanical loading is an important stimulus for mandibular growth and for the homeostasis of TMJ cartilage. When this loading is applied at a low intensity, it prevents breakdown of inflamed cartilage. Yet, frequent overloading at excessive levels induces accelerated cell death and an increased cartilage degradation.

Clinical Significance Knowledge about the way temporomandibular joint (TMJ) fibrocartilage responds to different types and intensities of mechanical loading is important to
improve existing treatment protocols of degenerative joint disease of the TMJ, and also to better understand the regenerative pathway of this particular type of cartilage.

**Keywords** Mechanical loading · Fibrocartilage · Temporomandibular joint · Cartilage degradation

**Introduction**

The temporomandibular joint (TMJ) is covered by fibrocartilage, and its turnover depends on a balance between synthesis and degradation of the extracellular matrix (ECM). Synthesis of the ECM involves the production of collagen fibers, proteoglycans, and aggrecans, and its degradation is caused by the action of enzymes such as aggrecanases and matrix metalloproteinases (MMPs). An important mechanism responsible for the regulation of ECM turnover in the TMJ is mechanical loading [1, 2].

Two categories of mechanical loading can be discerned in the TMJ. The first is static loading, which occurs during teeth clenching, jaw bracing, and activities like swallowing. The second is dynamic loading, which occurs during tooth grinding, jaw thrusting, talking, and chewing. Bone and cartilage are responsible for transmitting and absorbing this mechanical loading [3, 4].

As cartilage is avascular, it needs to receive nutrients from the synovial fluid. This occurs by diffusion due to the movement of the fluid in and out of the cartilage matrix. This movement is caused by the cyclic mechanical loading of the joints (pumping). Pumping may also influence the diffusion of some solutes, such as growth factors, hormones, enzymes and their inhibitors, and cytokines towards the cells. In addition, cyclic mechanical loading helps the drainage of acidic waste materials, such as lactate and CO₂ [5]. Future in vitro or finite element studies could elucidate the mechanism of activation of chondrocytes (i.e., direct transduction of mechanical signals to the chondrocytes vs. activation of chondrocytes by facilitated diffusion) in response to TMJ cartilage loading.

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**Fig. 1** PRISMA flow chart: The flow describes the information through the different phases of a systematic review. It maps out the number of records identified, those included and excluded, and the reasons for exclusions.
Thus, stimuli induced by mechanical loading can be highly beneficial for the maintenance and integrity of articular cartilage, as well as the development of the mandibular condyle [6].

While moderate dynamic loading is known to maintain the integrity of articular tissue during turnover and growth (anabolic effect), overloading can induce cartilage degradation (catabolic effect) [7]. It is not clear yet how these different loading intensities affect the TMJ cartilage, because in contrast with most synovial joints, which are covered by hyaline cartilage, the TMJ is covered by fibrocartilage. The collagen fibers contained in this TMJ fibrocartilage may provide some additional resistance against mechanical loading.

Knowledge about the way TMJ fibrocartilage responds to different types and intensities of mechanical loading is important to improve existing treatment protocols of degenerative joint disease (DJD) of the TMJ [8], and also to better understand the regenerative pathway of this particular type of cartilage. Therefore, we conducted this systematic review to find out how the TMJ fibrocartilage is affected by different modes of mechanical loading.

Materials and methods

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (www.prisma-statement.org). Embase.com, PubMed, and ISI/Web of Science were searched (by BFB and JCFK) from inception up to September 20th 2016 (see Supplementary information/Search strategy).

The following terms were used (including synonyms and closely related words) as index terms or free-text words: “bite force” or “shear stress” or “mechanical loading” and “cartilage” and “temporomandibular joint.” The full search strategies for all the databases can be found in the Supplementary Information. Duplicate articles were excluded. Articles written in English were accepted.

The articles were selected by two independent authors (BFB and VE), following a priori formulated inclusion criteria (viz., in vivo and in vitro studies, mechanical loading experiments on TMJ, and the response of the TMJ). After a subsequent analysis of confounding factors and quality of the research design, papers with sufficient quality were finally selected for this review.

Results

Literature identification

With the above-described literature search strategy, 254 records were identified. The complete inclusion process is shown in Fig. 1. No additional records were identified through other sources. After removal of duplicates, 234 records were screened by assessing eligibility criteria for inclusion.

Forty-nine articles were selected after the eligibility inclusion and exclusion criteria for a full-text assessment. Of those, 23 articles were excluded for the following reasons: reviews of experimental studies or abstracts (n = 12), a finite element study (n = 1), or presence of risk of bias (n = 10) (Tables 1 and 2).

Twenty-six experimental studies were included in this systematic review: 15 were in vivo studies, of which 5 were dealing with changes in the hardness of diet and 10 were focusing on forced movement, and 11 were in vitro studies, of which 4 were dealing with compressive loading on the chondrocytes, 6 with tensile loading, and 1 with shear loading.

Main findings

A wide variation of studies was included in this review. To enable sensible comparison of the results, several groups of studies were distinguished.

In the in vivo studies, different food consistencies, forced jaw movements (by the application of intraoral devices to restrict the jaw position or motion), or surgical intervention (e.g., osteotomies) were used to cause an alteration of the habitual mechanical loading, resulting in a change of the amplitude and/or direction of the TMJ loading. The effect of the

Table 1 Risk of bias (exclusion criteria)

| Study                | Reason for exclusion                        |
|----------------------|---------------------------------------------|
| Pirttiniemi et al.   | Lack of proper controls<sup>a</sup>           |
| (1996)               |                                              |
| Herring et al.       | Possible local differences in loading were not analyzed. The study can only be used to indicate the site of proliferation but does not show the effect of loading on proliferation. |
| (2002)               |                                              |
| Wattanachai et al.   | Lack of proper controls<sup>b</sup>          |
| (2009)               |                                              |
| Fujimura et al.      | Lack of proper controls<sup>b</sup>          |
| (2005)               |                                              |
| Pirttiniemi et al.   | Lack of proper controls<sup>a</sup>          |
| (2004)               |                                              |
| Tuominen et al.      | Lack of proper controls<sup>a</sup>          |
| (1996)               |                                              |
| Magara et al.        | Lack of proper controls<sup>b</sup>          |
| (2012)               |                                              |
| Wen et al.           | Lack of proper controls<sup>d</sup>          |
| (2016)               |                                              |
| Henderson et al.     | Lack of proper controls<sup>c</sup>          |
| (2015)               |                                              |
| Lin, H et al.        | Lack of proper controls<sup>b</sup>          |
| (2009)               |                                              |

<sup>a</sup> The intervention should have been applied to both diet groups: soft and hard diet

<sup>b</sup> A sham-operated group should have been added as control

<sup>c</sup> Unilateral splint could affect the non-loaded joint; a control without splint should have been added

<sup>d</sup> Lack of a control group with an injection of salubrinal but without loading

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| Study                                      | Study design  | Sample                          | How loading was applied                                      | Where the effects were looked for                                                                 | Main findings                                                                 | Conclusions                                                                 |
|-------------------------------------------|---------------|---------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| J.C. Nickel et al. 2004 [9]               | In vitro      | 50 TMJ discs from mixed-breed pigs | Static compressive loading: EG1 (10 N, 10 s) EG2 (10 N, 60 s) | Disc mechanical properties: Maximum tractional force, maximum compressive stress, peak stress     | EG1: max tractional force EG2: max compressive stress                         | The magnitudes of forces and compressive stresses produced on the surface of the disc depended on duration of pre-loading. |
| G.D. Nicodemus et al. 2007 [10]           | In vitro      | 5 bovine heads, TMJ cell isolation | Dynamic compressive loading: CG (unloaded) EG (15% strain) EG1 (24 h) EG2 (48 h) | Cellular response: Collagen type I, collagen type II and aggrecan gene expression                 | Gene expression of Coll I, II, and aggrecan: CG = EG1 > EG2                  | Dynamic compressive strains resulted in inhibition of gene expression, cell proliferation, and proteoglycan synthesis. |
| M.J. Ravosa et al. 2006 [11]              | In vivo       | 20 rabbits                      | Functional loading: CG (soft diet) EG (hard diet)            | Condylar structure: Collagen type II, apoptotic chondrocytes                                      | EG: increase of Col II and number of apoptotic chondrocytes                   | Compensatory mechanism to cartilage degradation serves to maintain the overall functional integrity of each joint. |
| K. Fujimura et al. 2005 [12]              | In vivo       | 30 rabbits                      | Functional loading: CG (unloaded) EG (100 g force applied by a coil spring) EG1 (1 week) EG2 (2 weeks) EG3 (4 weeks) EG4 (8 weeks) | Condylar structure: Collagen type II and histological synovitis score                            | Synovitis began 1–2 weeks after loading started                              | Mild, continuous mechanical loading of the glenoid fossa induces synovitis of the articular capsule and induces organic changes of the articular cartilage but not the degradation of these tissues. |
| T. Soube et al. 2011 [13]                 | In vivo       | 48 mice                         | Functional loading: CG (unloaded) EG (1 h continuous forced month opening/day) EG1 (25 N) EG2 (50 N) | Cellular response: Gene expression (collagen type I and II, PTHrp and sox9)                     | EG1: no significant changes EG2: increase gene expression and increase of the trabecular spacing in the subchondral bone | Forced mouth opening causes increased expression of mandibular chondrocyte maturation markers and decrease in the subchondral bone volume. |
| N. Hichijo et al. 2014 [4]                | In vivo       | 14 rats                         | Functional loading: CG (normal diet) EG (soft diet)           | Cellular response and condylar structure: Cartilage thickness, IGF-1r expression                | EG: reduction of the cartilage thickness, and reduction of IGF-1r immune positive cells | A decrease in masticatory demand during the growth period leads to insufficient mandibular development, decreasing the IGF-1r expression and cartilage thickness. |
| W. Chen et al. 2013 [2]                   | In vitro      | Rats Isolated mandibular cartilage cells | Dynamic compressive loading: CG (unloaded) EG (2000, 4000, 6000 μ strain for 6,12 and 24 h) EG1–9 | Cellular response: Collagen and proteoglycans synthesis plasminogen activator (PA) activity      | EG 2000 and 4000: increase of Collagen and proteoglycans synthesis, and low PA activity EG 6000: decrease of proteoglycans and collagen synthesis and increase of PA activity | Mechanical overload upregulated PA activity, providing a proteolytic environment of extracellular matrix components and contributing to cartilage degradation in TMJ osteoarthritis. |
| D. Yu et al. 2007 [1]                     | In vivo       | 100 rats                        | Functional loading: CG 1–5 (soft diet during 6,12,24 and 48 h and 9 days) | Cellular response: Immunohistochemical (IHC) analysis and western blot (WB)                   | EG (only on IHC, no difference was found on WB) aggrecanase-1 was higher at 12 and 24 h, after 48 h, there was no difference. | Temporary increases in aggrecanases-1 and TIMP-3 occurred in the hard diet group, showing the complex cartilage response during altered dietary loading. |
| Study                          | Study design     | Sample       | How loading was applied                                                                 | Where the effects were looked for                  | Main findings                                                                                     | Conclusions                                                                                     |
|-------------------------------|------------------|--------------|---------------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Y.-D. Liu et al. 2014 [14]    | In vivo          | 40 rats      | EG 1–5 (hard diet during 6, 12, 24 and 48 h and 9 days)                                | aggrecanase-1 and TIMP-3                          | TIMP-3 was lower at 6 h                                                                           | Lower level of functional loading by providing small-size diet could reduce TMJ degradation induced by biomechanical stimulation from abnormal occlusion. |
| A. Poikela et al. 2000 [15]   | In vivo          | 86 rabbits   | Functional loading: CG1 (small size diet) CG2 (large size diet)                        | Cellular response and condyle structure:          | CG1 and CG2: no difference on thickness and TRAP( osteoclast) EG1 and EG2: decrease the cartilage thickness, but 2 more than 1. EG1 and EG2: Increase osteoclast activity but 2, more than 1. EG1 and EG2: Col II and Aggrecan gene expression decrease in both groups | The mechanical properties of the articular cartilage after a period of unilateral mastication was impaired, and it is possible that this makes the joint cartilage more susceptible to pathological events. |
| T. Fujiwara et al. 2003 [16]  | In vivo          | 9 rabbits    | Functional under loading: CG1 = no grinding 25 days CG2 = no grinding 35 days EG1 = unilateral grinding molars right side, twice a week, 25 days EG2 = unilateral grinding molars right side, twice a week, 35 days | Cellular response: Histological analyses (Safranin O staining) Contents and distribution of proteoglycans in the condyle cartilage | 25 days rabbits: Proteoglycans amount Right condyle EG1<CG1 Left condyle EG1 = CG1 35 days Rabbits: Proteoglycans amount Right and Left Condyles EG2<CG1 | Repetitive, forced-jaw-opening can induce OA-like lesions. |
| M. Orajävi et al. 2012 [11]   | In vivo          | 36 rats      | Functional under loading + hormonal: CG1 = non-ovarectomized + normal diet CG2 = non-ovarectomized + soft diet EG1 = ovarectomized + normal diet EG2 = ovarectomized + soft diet | Cell response and histomorphometric: Cartilage thickness: EG1<CG1 Number of cells: EG2<CG2 | Histomorphometric: Cartilage thickness: EG1<CG1 Number of cells: EG2<CG2 Col II: EG1 /2 > CG1/2 MMP-3: EG1/2 > CG1/2 | Condylar cartilage is sensitive to both estrogen level and mechanical loading, i.e., estrogen reduced MMP-3 expression and a soft diet enhanced the area covered by collagen type II and X. |
| M. Zhang et al. 2016 [17]     | In vivo          | 160 rats     | Functional over loading: CG (unloading) EG (anterior cross bite for 2, 4, 6, 8, 12, and 20 weeks) | Tissue response: Calcified cartilage thickness, | EG(2 Weeks): ↑ collagen fibers and hypertrophic chondrocytes EG(2, 8 Weeks): ↓ Chondrogenic markers: Col-2, X and aggrecan | Light forces provide benefits for TMJ remodeling while heavy force induce degenerative process on the TMJ. |
Table 2 (continued)

| Study                  | Study design | Sample          | How loading was applied                                                                 | Where the effects were looked for          | Main findings                                                                 | Conclusions                                                                 |
|------------------------|--------------|-----------------|-----------------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Y. Ikeda et al. 2014   | In vivo      | 40 rats         | Forced mouth opening: EG1 = mouth open, EG2 = liquid diet feeding                       | Tissue response: Cartilage thickness, MMP-13 | EG (12, 20 Weeks): mineral deposits in TMJ cartilage                       | TMJ hypofunction leads to OA-like changes when also exposed to mechanical overloading. |
|                        |              | CG (10)         |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG1 (10)        |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG2 (10)        |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG3 (10)        |                                                                                         |                                            |                                                                                |                                                                               |
| Zhang.C et al. 2015    | In vivo      | 232 rats        | Forced unilateral movements (light and heavy force for 3, 7, 14, and 28 days and rest for 3,7,14 and 28 days) | Tissue response: Cartilage thickness | On the loading side: EG heavy force: cartilage thickness on the anterior part of condyle decrease on the force period and increase during the recovery period; and on the medium and posterior parts the other way around EG light forces: showed the same but was not significant different | Asymmetric heavy force damages the cartilage and light forces provide remodeling responses. |
|                        |              | CG              |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG Light force (1–8) |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG2 heavy force (1–8) |                                                                                         |                                            |                                                                                |                                                                               |
| S. Kartha et al. 2016  | In vivo      | Rats (number of sample not given) | Functional overloading: Forced mouth opening (7 days loading +7 rest days) | Tissue response: Densitometry and IHC Cellular response: MMP-13, HIF-1α and TNF-α | EG1 and EG2: showed OA like lesions EG2: ↑MMP-13, HIF-1α and TNF-α | The upregulation of the cellular markers could predict the maintenance of orofacial pain and TMJ degradation. |
|                        |              | CG1             |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | CG2             |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG1             |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG2             |                                                                                         |                                            |                                                                                |                                                                               |
| H.J. Yang, S.J. Hwang  | In vivo      | Rabbits (15)    | Unilateral osteotomy of the mandible and counter clockwise rotation | Tissue response: Micro CT and histological evaluation | EG1 and EG2: Osteoporotic changes of TMJ condyle (↓bone volume and bone mineral density) ↓cartilage thickness | Changing loading direction can cause a different area of compression/tension/shear of the condyle, leading to degradation. |
| 2014 [21]              |              | CG (03)         |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG1 (06)        |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG2 (06)        |                                                                                         |                                            |                                                                                |                                                                               |
| A. Utreja et al. 2016  | In vivo      | 12 Mice         | Forced mouth opening: CG (no loading) EG (1 loading for 5 days)                          | Cell maturation by fluorescent reporters (DKK3, ColI, ColII, ColX) | EG: DKK increased at superficial zone; ColI and II increased at pre hypertrophic zone; ColX increased at hypertrophic zone | TMJ cartilage responds to static loading by forming thicker cartilage through adaptive remodeling |
|                        |              | CG (06)         |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG (06)         |                                                                                         |                                            |                                                                                |                                                                               |
| S. Fazeli et al. 2016  | In vitro     | 5 pig TMJ discs | Compressive loading after collagenase EG (loading, no treatment)                         | Biomechanical and tissue response: Collagen and GAG content Collagen fiber alignment | EG: Compressive moduli decreases at 50–90% lower collagen and GAG content No differences in GAG amount between ages | Disruption of collagen fibers can lead to mechanical softening of TMJ discs decreasing their mechanical stability under compression |
|                        |              | CG (left disc)  |                                                                                         |                                            |                                                                                |                                                                               |
|                        |              | EG (right disc) |                                                                                         |                                            |                                                                                |                                                                               |
| R.S. Carvalho et al. 1995 | In vitro | 48 rats         | Compressive overloading: EG = No loading EG1 = extensive intermittent compressive loading | Tissue response: Amount of GAG | EG2 increased chondroitin sulfate | Compressive forces in the articular disk may stimulate the development of more cartilaginous-like properties with respect to GAG components |
| Study | Study design | Sample | How loading was applied | Where the effects were looked for | Main findings | Conclusions |
|-------|--------------|--------|-------------------------|-----------------------------------|--------------|-------------|
| C.M. Juran et al. 2013 [24] | In vitro | Porcine fresh TMJ disc cartilage | EG3 (12) EG2 = moderate intermittent compressive loading EG3 = continuous compressive loading Ages of 7 and 9 weeks (24 rats in each group) | EG3: maintain stiffness after compressed and sheared loading EG1 and EG2: decrease the stiffness after compressed and shear loading | The mechanical characteristics of the TMJ disc are highly dependent on the ECM microenvironment and its regional composition. |
| Y.-Y. Lin et al. 2009 [25] | In vitro | Porcine fresh TMJ condyle punch cartilage + bone EG (right condyle) CG (left condyle) | Compressive impact loading: CG = No Loading EG = 200 g mass was dropped from a height of 60 cm onto the top of the holding condylar heads | IL-1β: EG> CG (cartilage and bone) Col II: EG> CG (chondrocytes) IL-1β and IL-1α: EG> CG (subchondral bone) | Impact loading can increase directly IL-1β synthesis in the subchondral region, resulting in a progression of TMJ-OA |
| T. Kamiya et al. 2009 [26] | In vitro | TMJ porcine condyle cartilage cell isolated | Tensile loading: CG (unloaded) EG1 (7%) (12, 24 and 48 h) EG2 (21%) (12, 24, 48 h) | EG1: SZP, IL-1β, TGF-β1 were upregulated after 12, 24 and 48 h EG2: SZP, IL-1β, TGF-β1 were upregulated on 12 h and decreased on 24 and 48 h | SZP is enhanced but optimal mechanical stimuli but inhibited by excessive loading, leading to an cartilage joint degradation by decreasing joint lubrication |
| S. Agarwal et al. 2001 [27] | In vitro | Isolated cartilage cells from rabbit TMJ discs | Tensile loading: CG = No loading + no IL-1β treatment EG1 = Loading 6% strain + no IL-1β treat. EG2 = No loading + IL-1β treatment. EG3 = Loading 6% strain + IL-1β treat. | Proteoglycans Synthesis: 48 h: EG2< (CG, EG1, EG3) 96 h: EG2< (CG, EG1, EG3) | Application of cyclic tensile strain abrogated catabolic effects of IL-1β on TMJ chondrocytes. |
| S.-C. Su et al. 2014 [28] | In vitro | Isolated cells from porcine TMJ condyle cartilage | Tensile loading: CG (unloaded) EG1 (10%) (1,3,6,12,18,24 h) | Cellular response: Cox-2, MMP-3,1 and 9; ADAMTS-5 and PGE2 gene expression | Celecoxib exerts protective effects by decreasing degradation and restoring synthesis of extracellular matrix components. |
different modes of mechanical loading was analyzed using several parameters. The response of the cartilage was assessed by analyzing either the anatomical structure (DJD like lesions) or the changes of the cellular response using microscopy and/or assessment of gene expression by polymerase chain reaction PCR.

In the in vitro studies, two types of studies can be identified. In the first type, chondrocytes were isolated from the cartilage and seeded on plates. These cells were then exposed to mechanical forces (compression, tensile, or shear). The response of these cells was determined by analyzing levels of gene expression by PCR. In the second type of studies, fresh pig TMJ discs were exposed to mechanical loading by means of compression, and the outcome measures were quantified as histological changes and alterations of the biomechanics properties of the disc.

Discussion

Strengths and limitations

This article aimed to identify the way in which different frequencies and magnitudes of mechanical loading can affect the fibrocartilage of the TMJ. Clear inclusion and exclusion criteria were used to select articles that would be suited to answer the aim. However, as the selected articles used different experimental designs, it was not possible to compare all the articles with each other. For this reason, the set of articles was split by type of study (in vivo and in vitro) and by how the loading was applied.

Interpretation of the evidence

In vivo experiments

Excessive, repetitive loading can cause soft- and hard-tissue adaptation or degradation. This was shown when continuous static loading, such as forced mouth opening, was applied in vivo. After 1 day of mouth opening, a catabolic effect was noted: cartilage thickness decreased. The cartilage then adapted to this loading and reacted by increasing the synthesis of collagen type II and other elements of the extracellular matrix [16]. After 1 week of forced mouth opening, DJD lesions were nevertheless found [12, 13, 19].

When the same forced mouth opening protocol was applied with different intensities, light forces provided remodeling of the TMJ, while heavy forces induced degeneration and maintained an inflammatory condition [15, 20].

In case of abnormal dynamic and static occlusal relationships, such as unilateral chewing and forced anterior crossbite, the outcomes were always catabolic, with a decrease in the level of proteoglycans and collagen type II, and an
increase in osteoclastic activity in the condyle [11, 14, 17]. It thus seems that functional overloading skews the balance between ECM formation and degradation in the TMJ towards the latter.

When the mechanical loading consisted of differences in diet hardness, a hard diet, leading to sufficient joint loading, induced an increase in the amount of collagen type II and chondrocyte maturation, thus indicating growth. A soft diet, resulting in a reduced joint loading, reduced cartilage thickness as well as the number of IGF-1 receptor positive cells, indicating reduced growth activity. These results support the importance of mechanical loading (such as chewing) as an essential stimulus to increase mandibular growth [4, 18]. TMJ loading through a hard diet was even able to increase collagen and aggrecan production and cartilage thickness when mechanical overloading was induced through forced mouth opening, thereby preventing cartilage degradation.

Changes on the direction of the mechanical loading and condyle position after oblique vertical body osteotomy of the mandible and counterclockwise rotation, the same procedure used in Class II orthognathic surgery, induced idiopathic condylar resorption, a kind of DJD. This probably occurred because the trabecular bone patterns reflect the functional loading patterns during the growth period, and this change of condyle position and loading direction exposes an area that is less dense which could decrease the biomechanical properties needed to handle this loading [30].

Apart from loading, hormones may have an effect on the TMJ cartilage. Estrogen seems to inhibit the maturation of the chondrocytes and in cases in which a soft diet loading was applied and was expected to decrease cartilage thickness, such a catabolic effect was partially prevented by the lack of estrogen [25].

**In vitro experiments**

In vitro experiments showed that different types of loading regimes, such as tension, compression, and shear, had different effects on the TMJ cartilage chondrocytes when applied at low, moderate, or high intensity. At high intensity, tension and compression both caused a catabolic effect on the chondrocytes by reducing gene expression of the extracellular matrix components and increasing IL-1β production [26]. Unlike high intensity, low and moderate dynamic compression had an anabolic effect on the chondrocytes, increasing the expression of collagen type I and II and aggrecans [10]. These effects are time-dependent, as Nicodemus et al. [23] showed after application of dynamic compressive overloading. During the first 24 h, the gene expression of collagen type I and II and aggrecan increased, showing an adaptation behavior. After 48 h, the gene expression decreased to a level under the control levels, which demonstrates a catabolic effect of prolonged loading.

The reaction of TMJ disc-derived cells to compression is also time-dependent. When compression was applied for a short period and with longer intervals between cycles, fibrocartilage had more time to recover and return to the initial stage [9, 22]. This capacity to recover is changed when the collagen fiber network is disrupted, i.e., after a collagenase treatment as shown in fresh porcine discs [24]. Such a situation can occur in vivo in cases of intra-articular inflammation where cytokines stimulate degradation of collagen fibers. When shear movements were applied, the different parts of the TMJ disc reacted differently. The posterior zone was more resistant, with better biomechanical properties, and showed less deformation during loading than the anterior and intermediate zones of the disc [27].

In addition to a catabolic effect, cyclic tensile strain can also protect the cartilage from the effects of inflammation, e.g., suppressing the catabolic effect of TNF-α by down-regulating the expression of MMPs by TNF-α-treated chondrocytes [28, 29, 31]. As well as cyclic tensile strain, celecoxib has a protective effect by decreasing degradation and restoring synthesis of ECM in inflamed cartilage [32].

**Recommendations**

More in vivo and in vitro studies in each type of study design are required to clarify how fibrocartilage reacts to different types of mechanical loading. In this regard, we would like to stress the importance of physical measurements of actual loading conditions in the tissues, as these can be quite different from what is assumed. For example, Rafferty et al. demonstrated that during mandibular distraction in minipigs, the increased cartilage thickness on the distraction side was associated with reduced rather than increased loading [33].

In addition, studies are needed to assess how mechanical loading could be incorporated in new protocols for the treatment of DJD, for example by including physiotherapy (e.g., cyclic loading). In vivo studies on the efficacy of orthognathic surgery on the TMJ would be important to predict side effects and to prevent idiopathic condyle resorption in patients.

The mechanical loading described in the included in vivo studies only includes diet and overloading by forced mouth opening and other artificial interventions, but it would be interesting to include other kinds of loading as well, mimicking clenching and grinding, and to assess how the TMJ reacts to these different intensities and frequencies of mechanical loading.

**Conclusion**

Based on the studies included in this review, we could conclude that dynamic mechanical loading is an important stimulus for mandibular growth and for the homeostasis of TMJ.
cartilage. When this loading is applied at a low intensity, it protects inflamed cartilage by effectively antagonizing IL-1β. However, frequent overloading induces accelerated cell death and increased cartilage degradation.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required

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