

Journal of the Hellenic Veterinary Medical Society

Vol 70, No 3 (2019)



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doi: [10.12681/jhvms.21782](https://doi.org/10.12681/jhvms.21782)

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To cite this article:

TSOLAKIS, I., VERIKOKOS, C., PERREA, D., BITSANIS, E., & TSOLAKIS, A. (2019). Effects of diet consistency on mandibular growth. A review. *Journal of the Hellenic Veterinary Medical Society*, 70(3), 1603–1610.
<https://doi.org/10.12681/jhvms.21782>

Effects of diet consistency on mandibular growth. A review

I.A. Tsolakis¹, C. Verikokos², D. Perrea¹, E. Bitsanis, A.I. Tsolakis³

¹*Laboratory for Experimental Surgery and Surgical Research, School of Medicine, National and Kapodistrian University, Athens, Greece*

²*Second Surgery Clinic, School of Medicine, National and Kapodistrian University, Athens, Greece*

³*Orthodontic Department, School of Dentistry, National and Kapodistrian University, Athens, Greece*

ABSTRACT. This article is a review that focuses on the diet consistency and how this affects mandibular morphology. Various published studies focused on the relationship between mastication and growth of the mandible because it is considered that mandibular growth is dependent on the loads exerted by the function of the masticatory muscles. Moreover it has been pointed out that the increase of orthodontic anomalies is due to the modern softer diet. Even in rats, soft diet is one of the factors causing malocclusions. All of the studies have been experimental, mainly in rodents, since this research is impossible to be applied on humans in a short period of time. Most experimental studies suggested that occlusal loading affects bone mass, bone amount, bone density, the length and the width of the bone, the degree of mineralization, the genetic expression, the collagen immunoreaction and the chondrocytes action on the cartilage. It is stated that bone volumes and thickness of the mandible of rats fed with soft diet were smaller when compared to animals fed with hard diet. Also the mandibles and condyles were smaller and less dense in the rats of soft diet as compared to controls. Furthermore the length and the width of the condyle in the soft diet group of animals were smaller as compared to the condyle of the hard diet group of animals. Soft diets affect also the degree of mineralization, and the action of the chondrocytes on the cartilage.

Keywords: soft diet, mandible, condyle

Corresponding Author:
Ioannis A. Tsolakis, Tsimiski 45, 41221 Larissa, Greece.
E-mail address: tsolakisoannis@gmail.com

*Date of initial submission: 08-02-2017
Date of revised submission: 04-12-2017
Date of acceptance: 19-09-2018*

ΠΕΡΙΛΗΨΗ. Το παρόν άρθρο είναι μια ανασκόπηση που διαπραγματεύεται την επίδραση της σύστασης της διατροφής στην μορφολογία της κάτω γνάθου. Πολλές δημοσιευμένες εργασίες έχουν επικεντρωθεί στη μελέτη της σχέσης της μαστητικής λειτουργίας και της αύξησης της κάτω γνάθου, εξαιτίας της θεώρησης ότι η αύξηση της κάτω γνάθου εξαρτάται από τις φορτίσεις που ασκούνται από τους μαστητήριους μύες. Επιπρόσθετα ο σύγχρονος τρόπος διατροφής με μαλακές τροφές έχει ενοχοποιηθεί για την αύξηση των ορθοδοντικών ανωμαλιών. Ακόμα και στους επίμυς η διατροφή με μαλακή τροφή θεωρείται ένας από τους παράγοντες που συντελεί σε ανωμαλίες της σύγκλεισης. Όλες οι δημοσιευμένες εργασίες είναι πειραματικές, κυρίως σε τρωκτικά ζώα, επειδή είναι αδύνατον να εφαρμοσθούν ανάλογες μελέτες σε ανθρώπους σε σύντομο χρονικό διάστημα. Οι περισσότερες πειραματικές μελέτες συμπεραίνουν πως οι μαστητικές φορτίσεις επηρεάζουν την οστική μάζα, τη ποσότητα του οστού, τη πυκνότητα του οστού, το μήκος και το πλάτος του οστού, το βαθμό της επιμετάλλωσης, την γενετική έκφραση, και την ανοσοιστοχημική αντίδραση του κολλαγόνου, όπως και τη δράση των χονδροκυττάρων στο χόνδρο του κονδύλου της κάτω γνάθου. Έχει διατυπωθεί πως το βάρος και η πυκνότητα των γνάθων επίμυων που είχαν διατραφεί με μαλακή τροφή ήταν μικρότερα από τα αντίστοιχα των ζώων που είχαν διατραφεί με σκληρή τροφή. Επίσης οι γνάθοι και οι κόνδυλοι επίμυων που έχουν διατραφεί με μαλακή τροφή ήταν μικρότεροι σε μέγεθος και παρουσιάζουν μικρότερη πυκνότητα σε σύγκριση με τις γνάθους και τους κονδύλους των ζώων ελέγχου. Επιπρόσθετα το μήκος και το πλάτος των κονδύλων των ζώων που είχαν διατραφεί με μαλακή τροφή ήταν μικρότερα από τα αντίστοιχα των κονδύλων των ζώων που είχαν διατραφεί με σκληρή τροφή. Η μαλακή διατροφή διαπιστώθηκε ότι επηρεάζει τέλος το βαθμό επιμετάλλωσης όπως και τη δράση των χονδροκυττάρων στο χόνδρο.

Λέξεις ενρετηρίασης: μαλακή διατροφή, κάτω γνάθος, κόνδυλος

It is well accepted that the growth of the craniofacial system is determined both by hereditary and environmental factors (Watt and Williams 1951). Also bone growth and development is closely dependent on the loading forces exerted by muscular function. The mandibulofacial growth is closely associated to the movements of the jaws and loads of the orofacial region. Thus environmental factors including mastication seem to be responsible for a variety of developmental changes in the stomatognathic system. This may be the rationale for explaining the mean increase of malocclusions in industrial societies in the 20th Century (Beecher and Corruccini 1981). During the last century, the modern dietary habits have been pointed out as contributors to the increased frequency of malocclusion, due to their reduced demands on

masticatory muscles (Waugh, 1937;Corruccini and Lee 1984). Also, Soft diet causes malocclusions in rats (Dontas et al 2010). Several experiments on the consistency of diet provided to animals and especially to rodents have been carried out in order to test the interrelationship between function and mandibular growth.

INTERACTION BETWEEN MUSCULAR FUNCTION AND BONE GROWTH

The human masticatory system is a complex musculoskeletal system where activation of the masticatory muscles, movements of the jaw, and loads and deformations in both the temporomandibular joint and jaw are closely interrelated (Berger, 1992; Ciochon et al, 1997, Odman et. al. 2008). If one of these

factors changes by means of intrinsic or extrinsic cause, it will affect all the others. This evidently concerns the activation patterns of the masticatory muscles adapting to a new environment and it occurs as a consequence of, for instance, craniofacial growth and development (Ciochon et al, 1997). Studies in growing rodents have shown that reduced masticatory function causes morphological changes in the mandible. Recent studies reveal that myostatin deficient mice with increased muscle mass, physiological cross-section, and contractile muscle forces exhibit greater bone mineral density than normal mice in the spine and temporomandibular joint (Hamrick et al, 2003; Nicholson et al, 2006; Ravosa et al, 2007). Therefore, the craniofacial mandibular structure and its degree of mineralization can be considered to be closely associated with masticatory muscle behavior. A method used to alter the masticatory function is feeding young animals a soft diet. Altering the consistency of the diet in this way has been shown to cause overall size differences in the ramus region (Watt and Williams, 1951).

Bone is a dynamic tissue, which continuously undergoes adaptive remodelling, i.e. resorption and apposition, to meet the requirements of its functional environment. The remodelling rate is a major determinant of the degree of mineralization of bone (DMB) (Boivin and Meunier, 2002). A higher remodelling rate decreases the time available for secondary mineralization, which results in bone with a lower DMB (Boivin et al, 2009). The remodelling rate of bone is related to the magnitude of intermittent mechanical loading and the resulting dynamic strains in the tissue (Turner, 1998). In general, more heavily loaded bone has a higher remodelling rate and is therefore less mineralized and less stiff than lower loaded bone (Cullen et al, 2001). This regionally heterogeneous organization of bone mineral has been attributed to regional differences in the magnitude and mode of strain brought about by mechanical loading (Skedros et al, 1994). Under physiological conditions, intermittent mechanical loading of bone is caused predominantly by muscular contractions.

The muscles thus provide an important mechanical stimulus for bone remodelling by inducing strains in the skeletal system (Turner, 2000). The significance of muscle-generated bone loading is illustrated by the effect on the skeleton under conditions of increased or decreased muscle activity. For example, the loss of normal physiologic loading after spinal cord injury

causes rapid severe bone loss in the paralyzed extremities of affected individuals, which can be counteracted by long-term electrical stimulation of muscles (Dudley-Javoroski and Shields, 2008).

In 1996, Kiliaridis et al. (1996) demonstrated that masticatory hypofunction caused the reduction of "radiographic" bone mass in the dental alveolar process, the condylar costa, the condylar process, and the lower anterior border of the ramus in the mandible of growing rats. However, it is not clear whether the reduction in radiographic bone mass was due to changes in the amount/thickness of bone and/or to changes in the density of the cortical and trabecular bone, and whether these changes would have a different regional pattern. Three years later Bresin et al. (1999) reported that the amount of bone amount and bone density may be two possible mechanisms used to adjust local mechanical properties within the mandibular functional units. They found that bone mass was larger in the hard diet group in all areas except lateral to incisors. Bone density was higher for the hard diet group only medial to cortical bone on the dentoalveolar process of the first molar and the pterygoid fossa. Thickness of the cortical bone was higher in the hard diet group in the cortical bone below the incisor, adjacent to the mental foramen and through the first molar, the lateral cortical bone on the dentoalveolar process, ramus region above condylar costa, pterygoid fossa and the lateral cortical plate of the pterygoid ridge in the ramus.

DIET AND MANDIBULAR GROWTH

Watt and Williams (1951) compared the mandibles of soft and hard diet rats and they concluded that the weight volume and thickness of the mandibles of the soft group was smaller than the hard diet group. This was explained by the change in density of bone structure. Beecher and Corruccini confirmed these findings in 1981. They also compared the morphology of the mandible in growing rats fed hard and soft diet. In conclusion, they found that the soft diet animals were slightly smaller in body mass, they had smaller mandibles and condyles and they were radiographically more dense. Furthermore, soft diet rats had less width of the maxillary dental arch and they had smaller masseter and temporal muscles. Finally, they found that the soft diet group had skulls consistently smaller in mass and in linear dimensions, although with no significant differences in shape. In 2008 Odman et al, found that a period of 7 months with low masticatory demands in the hypofunctional group during ad-

lescence and early adulthood had a significant effect on the lateral shape of the rat mandible as compared to controls. The area of the mandible was smaller in the hypofunctional compared to the normal group. Interestingly, the alveolar process was shorter in the normal group. Morphometric analysis revealed significant differences such as the area of the angular process and the inclination of the condylar process. The rehabilitation group was only marginally different compared to the hypofunctional group, although a general tendency to approach (catch-up) the normal group was observed, and one morphometric variable (condylar base inclination) was indeed significantly different. Morphometric analysis revealed only marginal changes of the adult rat mandibular morphology during a 6-week period of masticatory function rehabilitation. However, the observed catch-up tendency might suggest that a longer rehabilitation period may have significant effect on mandibular morphology. In 2007 Tanaka et al. studied the effect of food consistency on the degree of mineralization in the rat mandible. They found that the degree of mineralization was significantly lower in the trabecular than in the cortical bone and in the anterior area the mandibular body showed a significantly higher degree of mineralization than the posterior area. In both areas the soft diet group had a significantly higher degree of mineralization than the hard diet group. The trabecular bone in the condyle of the hard diet group showed a significantly higher degree of mineralization than in the soft diet group. Their results indicated the importance of proper masticatory muscle function for craniofacial growth and development. Four years after Grunheid et al. (2011) had the same hypothesis, using rabbits as experimental animals, but their result suggested that a moderate reduction in masticatory functional load does not significantly affect the remodelling rate and the degree of mineralization in areas of the mandible that are loaded during mastication but might induce a more heterogeneous mineral distribution. More specifically, the degree of mineralization of bone did not differ significantly between the experimental and control animals at any of the sites assessed. However, in the rabbits that had been fed soft pellets, both cortical bone at the attachment sites of the temporalis and digastric muscles and cortical bone in the alveolar process had a significantly higher degree of mineralization than cortical bone at the attachment site of the masseter muscle, while there were no significant differences among these sites in the control animals.

DIET AND TEMPOROMANDIBULAR GROWTH

Approximately 10% of the population over the age of 18 has pain in the temporomandibular joint (TMJ) region and about 15% of the people who have TMJ pain have degenerative diseases of the TMJ (TMD). (LeResche, 1997; Grünheid et al, 2011). The exact etiology for TMD is unknown; however, most dentists and physicians have been inclined to believe that the single most important etiological factor is mechanical loading that surpasses the adaptive capacity of the joint. (Emshoff et al, 2003; Milam, 2005). In dentofacial orthopaedics an effort is made to influence mandibular growth. The main target in this effort is the condylar cartilage of the mandible. There has been a great deal of controversy over the years concerning the true effects of this treatment rationale. Animal experiments and condylar cartilage tissue examination revealed that the condylar cartilage responded favorably in functional mandibular advancement and extra growth of the cartilage tissue was evident (Zarb and Carlsson, 1999). For the aforementioned reasons recent studies focused more on the TMJ response to the mechanical forces.

The TMJ is formed by the mandibular condyle and the mandibular fossa of the temporal bone. Separating these two bones from direct contact is the articular disc. Unlike other joints, which are composed of hyaline cartilage, the articular portion of the mandibular condyle and disc is comprised of fibrocartilage. The mandibular condylar cartilage can be organized into four zones. The most superficial layer is called the articular zone and cells in this zone are characterized by their expression of Proteoglycan 4 (Prg4) (McNamara and Carlson, 1979). The second zone is the polymorphic zone, which contains the precursor cells for the flattened and hypertrophic zones. The third zone is the flattened zone. The cartilage cells in this layer are characterized by the expression of Collagen type II (Ohno et al, 2006). The fourth and deepest zone is the hypertrophic zone. In this zone, the chondrocytes are characterized by the expression of Collagen type X (Chen J. et al, 2009).

In 1999 Kiliaridis et al supported that low masticatory function leads to decreased growth of the condyle and changes in the thickness of the cartilage. They found that the rats fed a soft diet showed a thinner condylar cartilage in the anterior part of all portions. In contrast, the cartilage was thicker in the soft group in the posterior part of the condyle. The length and the width of the condyle in the group who fed soft diet

were significantly smaller. Chen J. et al (2009) examined the effects of altered functional loading on the expression of other genes found in the various zones of the mandibular condylar cartilage in female mice. They found that altered functional loading for 2-6 weeks caused significant reduction in the thickness of the condylar cartilage whereas, only at 4 weeks was there a significant decrease in the bone volume fraction and trabecular thickness of the subchondral bone. Gene expression analysis showed that altered functional loading for 4 weeks caused a significant reduction in the expression of SRY-box containing gene 9 (Sox9), Collagen type X (Col X), Indian hedgehog (Ihh), Collagen type II (Col II) and Vascular endothelial growth factor (Vegf) and altered loading for 6 weeks caused a significant decrease in the expression of Sox9, Col II, Vegf and Receptor activator of NF- κ B ligand (Rankl) compared to the normal loading group. Altered functional TMJ loading in mice for 2-6 weeks leads to a loss of the condylar cartilage and a transient loss in the density of the mandibular condylar subchondral bone. In 2015 Uekita et al studied the effects of a soft diet on the collagens and chondrocytes in the growing TMJ cartilage. They examined the condylar and glenoid fossa cartilage of rats fed a liquid diet by histology, immunohistochemistry with anti-types I, II, and X collagen antibodies, and transmission electron-microscopy (TEM). The results of this research suggested that the condylar cartilage in the experimental rats showed weak immunoreactions for three types of collagens. The ultrastructure had fewer fine collagen fibrils, the glenoid fossa cartilage showed narrower Alcian blue-positive areas and the immunoreactions for three types of collagen were also weaker compared to those of the controls. The chondrocytes in the experimental rats had extended thin cytoplasmic processes, and had formed gap junctions, as assessed by transmission electron microscopy. Fewer fine collagen fibrils, but thick bands of collagen fibrils were observed in the glenoid fossa of the experimental cartilage. Their results proposed that liquid diet impairs the quality and quantity of collagens and chondrocytes in the TMJ cartilage of growing rats. The same year, another study from Polur et al (2014) looked at the role of Estrogen Receptor (ER) beta in mediating these effects. They used 21-day-old male and female mice. They were exposed to decreased occlusal loading (soft diet administration and incisor trimming) for 4 weeks. At 49 days of age the mice were sacrificed. Proliferation, gene expression, Col 2 immuno-histochemistry and micro-CT analysis were performed on

the mandibular condyles. Their results suggested that decreased occlusal loading induced inhibition of early chondrocyte maturation markers in female mice was attenuated by ER beta deficiency. In 2006 Papachristou et al. examined the involvement of components of the AP-1 transcription factor family such as Fra-1, Fra-2, JunB and JunD in the signalling pathway of mechanical loading of the condylar cartilage, and subsequently the association of mechanical loading to cell differentiation and apoptosis through the involvement of these proteins. They concluded that the JunB, JunD, Fra-1, and Fra-2 members of the AP-1 transcription family in the response of condylar cartilage chondrocytes to functional loading alterations, suggesting that mechanical loading in chondrocytes triggers biochemical responses associated with AP-1 cellular functions such as maturation, differentiation and apoptosis. Downstream, these biological phenomena influence the overall growth of the condylar cartilage.

CONCLUSIONS

They have been various studies looking at the diet consistency and how this affects the mandibular and condylar morphology. The correlation of diet consistency and head growth has high clinical importance since it might give an answer to the evolution of human growth and development. We can understand the human growth and achieve a better treatment for orthodontic anomalies and condylar disorders. Through the aforementioned researches is suggested that occlusal loading affects the bone mass, bone amount and bone density of the mandible, as well as the mandibular length and the width. Also muscular loading affects the degree of mineralization, the genetic expression, the collagen immunoreaction and the chondrocytes action on the cartilage. Never less there are no works studying the long term effects of changes in the diet consistency of the animals and there is a need for new studies focusing on this.

CONFLICT OF INTEREST

None declared.

Author (year)	Aim	Experimental animals	Interventions	Study duration	Outcomes	Methods of outcome assessment	Results	Conclusions
Beecher and Corruccini (1981)	Dietary consistency on craniofacial and occlusal development in the rat.	90 Sprague-Dawley 21 days of age	GrI: Fed pelleted rat chow GrII: Fed a gruel-like porridge consisting of ground chow moistened with water GrIII: Fed soft diet six days with dry pellets provided every seventh day only	4 months	O ₁ : Body mass O ₂ : Mass of the entire masseter O ₃ : Maxillary arch length O ₄ : Maxillary arch breadth O ₅ : Mandibular length O ₆ : Anteroposterior length of condylar articular surface	O ₁ : measurement of Body mass O ₂ : excision of masseter O ₃ : Measurement from incisor to distal edge of last molar O ₄ : Measurement from buccal points of MI O ₅ : Measurement from incisor to MI O ₆ : From the anterior to posterior part of articular surface.	O ₁ : Significantly larger GrI O ₂ : Significantly larger in GrI O ₃ : Increased in GrI O ₄ : Increased in GrI O ₅ : Increased in GrI O ₆ : Increased in GrI	Soft diet animals were smaller in size of entire body, maxilla mandible and condyle.
Kiliaridis Et. al (1996)	The effect of altered masticatory muscle function on bone mass at different sites in the rat mandible	42 growing male rats	GrI: sacrificed at the beginning of the experiment. Used as base line. GroupI: 14 M. GroupI: 14 M (control) Group II: 14 M (control)	28 days	O ₁ : Bone Mass	O ₁ : Lateral radiographs of mandibular halves together with aluminium stepwedge and then image analysis	O ₁ : Significant increased in GrII O ₂ : Increased size of the condyle for GrI	Altered masticatory function influences the amount of bone mass in certain parts of the mandible.
Kiliaridis et.al. (1999)	The influence of functional alterations on the size of the mandibular condyle.	40 male growing rats	GroupI: 20M GroupII: 20M	28 days	O ₁ : Size of the mandibular condyle	O ₁ : Cartilage thinner in the anterior part and thicker in the posterior for GrII. O ₂ : Increase size of the condyle for GrI	O ₁ : Cartilage thinner in the anterior part and thicker in the posterior for GrII. O ₂ : Increase size of the condyle for GrI	Increased condylar cartilage thickness is not necessarily evidence of increased condylar growth
Papachristou et.Al. (2006)	To examine the involvement of the JunD proteins in the mandibular condylar cartilage.	30 female, 14-day-old Wistar rats	GroupI: Fed hard diet GroupII: Fed soft diet	21 days	O ₁ : -GrI:10 rats for histologic analysis -GrII: 10 rats for histologic analysis O ₂ : Size of mandibular condyle	O ₁ : Expression of Fra-1, Fra-2, JunB and JunD proteins O ₂ : -GrI: 10 rats for morphometric terms -GrII: 10 rats for morphometric terms	O ₁ : The condylar cartilage of both groups was immunostained using specific antibodies against Fra-1, Fra-2, JunB and JunD proteins	Mandibular condylar chondrocytes sense functional loading changes and ultimately influence the growth of the condylar cartilage.
Tanaka et.al. (2007)	To analyze the degree of mineralization in the mandible of growing rats fed with a hard or soft diet.	15 Male Wistar Rats	Group I: 6M Group II: 9M	9 weeks	O ₁ : Degree of mineralization of cortical bone O ₂ : Degree of mineralization of trabecular bone	O ₁ : O ₂ ; Cortical and trabecular bone of mandibles were obtained using a microCT system	O ₁ : Group II had a significantly higher degree of mineralization O ₂ : Group I showed a higher degree of mineralization	Muscle function affects the craniofacial growth and development.
Odman et.al. (2008)	The effect of masticatory functional changes on the lateral view morphology of the mandible in adult rats.	60 Male Sprague-Dawley rats (21 day old)	Group I: Fed hard diet for 21 weeks and then divided Group I: 16M Group II: 44M, Group II ₁ : Fed soft diet Group II ₂ : Fed hard diet	27 weeks	O ₁ : morphometric differences between the groups.	O ₁ : cephalometric Xrays and morphometric analysis.	O ₁ : Mandible was smaller in Group II, Group II ₂ had only marginal differences to Group II ₁ , Group II ₂ had a tendency to catch up the development as Group I.	Marginal changes of the adult rat mandibular morphology during a 6-week period of masticatory function rehabilitation..

Author (year)	Aim	Experimental animals	Interventions	Study duration	Outcomes	Methods of outcome assessment	Results	Conclusions
Chen et. al. (2009)	To develop a mouse TMJ altered functional loading model.	134 Female mice (21 day old)	Group I: Fed hard pellet diet Group II: Altered functional loading (incisor trimming every other day and soft dough diet)	12 weeks	O ₁ ; mandibular condylar cartilage O ₂ ; subchondral bone volume O ₃ ; genetic expression	O ₁ ; Histology O ₂ ; Microcomputed tomography O ₃ ; real time polymerase chain reaction (PCR) analysis. O ₄ ; Group II caused a significant decrease in the expression of <i>Sox9</i> , <i>Col II</i> , <i>Vegf</i> , and Receptor activator of NF- κ B ligand (<i>Rankl</i>).	O ₁ ; There was a decrease in Safranin O staining in the mandibular condylar cartilage for group II. O ₂ ; Group II had a significant decrease in the width of the condylar cartilage and in the thickness of the mandibular condylar cartilage. O ₃ ; Group II caused a significant decrease in the expression of <i>Sox9</i> , <i>Col II</i> , <i>Vegf</i> , and Receptor activator of NF- κ B ligand (<i>Rankl</i>).	Altered functional TMJ loading in mice for 2–6 weeks leads to a loss of the condylar cartilage and a transient loss in the density of the mandibular condylar subchondral bone.
Donatas et. al. (2010)	The incidence of malocclusion in a longitudinal study of the normal growth and aging of Wistar rats carried out in our laboratory.	40 Wistar rats (20 male, 20 female, 3 wk age)	All animals fed <i>ad libitum</i> a pelleted commercial balanced rat diet consisting of 21% protein, 6.2% fat, 4.5% fiber, 7.5% ash, 1.1% calcium, 0.9% phosphorus, 0.35% sodium	Rats life span	O ₁ ; presence of malocclusion	O ₁ ; Clinical examination	O ₁ ; Malocclusion was found on 60th week of age in a male rat and the 76th week of age in a female rat. Sex did not influence malocclusion: 46% affected rats were female and 54% were male.	Special attention should be given to the potential appearance of malocclusion during long-term rodent studies, because its incidence may adversely affect the animals' health and general wellbeing
Grunheid et. al. (2011)	The effect of a reduction in masticatory functional load on the degree and distribution of mineralization of mandibular bone	16 male juvenile New Zealand White rabbits Group I: 8M Group II: 8M	Group I: Fed soft pellet diet Group II: Fed hard pellet diet	12 weeks	O ₁ ; Degree of bone mineralization (DMB)	O ₁ ; Excision of jaw muscles, condylar head and alveolar process.	O ₁ ; In Group I, both cortical bone at the attachment sites of the temporalis and digastric muscles and cortical bone in the alveolar process had a significantly higher DMB than cortical bone at the attachment site of the masseter muscle, while there were no significant differences among these sites in the Group II.	A moderate reduction in masticatory functional load does not significantly affect the remodelling rate and the DMB in areas of the mandible that are loaded but might induce a more heterogeneous mineral distribution.
Polur et. al. (2015)	To examine the role of Estrogen Receptor (ER) beta in mediating these effects.	49 Mice (21-day-old) Group I: 24 male Group II: 25 female	Fed soft diet administration and incisor trimming was performed	4 weeks	O ₁ ; Gene expression O ₂ ; Condylar cartilage O ₃ ; Bone volume	O ₁ ; PCR O ₂ ; Col 2 immunohistochemistry O ₃ ; Micro-CT	O ₁ ; Both groups had significant decreased Col 10 expression O ₂ ; Decreased subchondral volume O ₃ ; Decreased bone volume.	Decreased occlusal loading induced inhibition of Sox9 and Col 2, did not occur in female ER beta deficient mice.
Uetika et. al. (2015)	To determine the effect of a soft diet on the collagens and chondrocytes in the growing TMJ cartilage.	48 Male Wistar rats Group I: 24M Group II: 24M	Group I: Fed hard diet Group II: Fed soft diet	8 weeks	O ₁ ; Changes on chondrocytes O ₂ ; Changes on collagens	O ₁ ; Electron microscopy O ₂ ; Immunohistology	O ₁ ; Gr II had extended thin cytoplasmic processes, and formed gap junctions O ₂ ; Gr III had weak immunoreactions for 3 types of collagens	Soft diet had deleterious effects on the quality and quantity of collagens and chondrocytes in the TMJ cartilage in growing rats.

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