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Review Article

Masticatory muscle function affects the pathological conditions of dentofacial deformities

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SUMMARY

The causes of dentofacial deformities include various known syndromes, genetics, environmental and neuromuscular factors, trauma, and tumors. Above all, the functional effects of muscles are important, and deformation of the mandible is often associated with a mechanical imbalance of the masticatory muscles.

With the vertical position of the face, weakness of the sling of the masseter muscle and medial pterygoid muscle causes dilatation of the mandibular angle. In patients with a deep bite, excessive function of the masticatory muscles is reported.

Myosin heavy chain (MyHC) properties also affect jawbone morphology. In short-face patients, the proportion of type II fibers, which are fast muscles, is high. The proportions of muscle fiber types are genetically determined but can be altered by postnatal environmental factors. Orthognathic surgery may results in the transition of MyHC to type II (fast) fibers, but excessive stretching enhances the release of inflammatory mediators and causes a shift toward a greater proportion of slow muscle fibers. This feature can be related to postoperative relapse.

Bones and muscles are in close crosstalk, and it may be possible to use biochemical approaches as well as biomechanical considerations for the treatment of jaw deformities.

1. Introduction

Correction of dentofacial deformities has generally become widespread and safe. Dentofacial deformities are noted in approximately 5 % of the population in Western countries [1]. The causes of dentofacial deformities can be classified into the following categories - 1) known syndromes; 2) hereditary causes; 3) environmental and neuromuscular causes; 4) trauma; and 5) tumors. However, apparent causes are typically not recognized in most non-syndromic patients.

Many congenital anomalies/syndromes related to jaw deformities have been reported, such as Treacher Collins syndrome, van der Woude syndrome, Stickler syndrome, achondroplasia, craniosynostosis (Crouzon, Apert, and Pfeiffer syndromes), and cleft lip and palate, among others.

On the other hand, the involvement of genetic predisposition is relatively high in jaw deformities [2,3], especially mandibular prognathism [4]. Some dentofacial deformities, such as Class III deformities, are more common in certain races [5–8]. Recently some reports have examined the genotype of jaw deformity patients [9]; for example, single nucleotide polymorphisms (SNPs) in myosin 1H (MYO1H) encoding a part of myosin, which is an important component of muscle, are associated with mandibular prognathism [10–12]. In addition, the association of mandibular prognathism with fibroblast growth factor/receptor (FGF/FGFR) or growth hormone receptor (GHR) expression has also been suggested [11,13]. With regard to mandibular retrognathia and facial asymmetry, although the number of reports is small, it has been suggested that some of the responsible genes are different from those responsible for mandibular prognathism [14,15].

However, in identical twins, the morphological characteristics of the maxillofacial bones are occasionally different (Fig. 1). This finding suggests that genetic factors and environmental factors are responsible for jaw deformities, as noted for cleft palate, hypertension, and diabetes. Thus, it can be considered a multifactorial disease.

As an environmental factor, neuromotor effects during growth are involved in bone morphology, and muscle properties are largely

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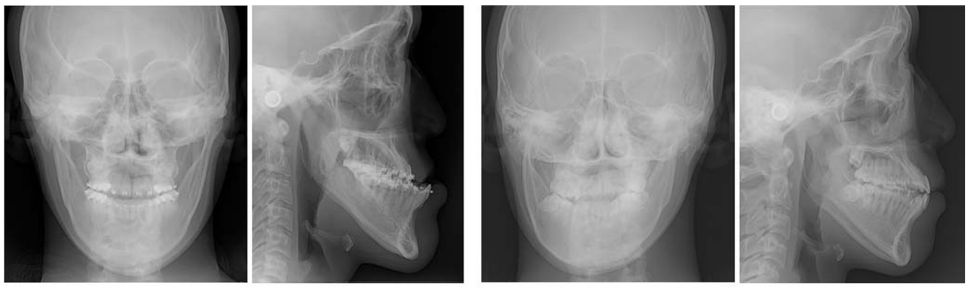

Fig. 1. Different jaw deformity patterns in identical twins.
A. Cephalogram of the older brother; symmetrical mandibular prognathism.
B. Cephalogram of the younger brother; mandibular asymmetry.

related to not only genetic factors but also to environmental factors such as habits and diet.

This narrative review aimed at highlighting the characteristics of the muscles and discuss their relationship with the jaw deformities.

2. Jawbone morphology and masticatory muscle function

As described by Posnick [1], there are various etiology of jaw deformities. But there are few pathogenetic factors that can be identified. Therefore, it is surmised that environmental and neuromuscular factors are the most clinically common. It is clear that malocclusion is accompanied by functional abnormalities, and the goal of orthognathic surgery is to improve function [16,17]. The masticatory function is produced by muscles, and the relationship between the shape of the facial bones and the size and contractile force of the masticatory muscles has long been known. And deformation of the mandible can be evoked by a mechanical imbalance of the masticatory muscles [18–20]. Changes in muscle traction cause local distortions in the bone tissue of the mandible. Avis proved that muscular imbalance causes both mandibular deformation and mandibular asymmetry via unilateral masseter muscle removal in animal experiments [21].

With the vertical position of the face, the muscle sling formed by the masseter and medial pterygoid muscle plays important roles [22,23]. Progressive open bite occurs when a disease causes muscle dysfunction, such as muscular dystrophy, and develops in the growing phase [24,25]. The gonial angle tends to be large in congenital myopathy patients [26], and functional muscle deficiency is associated with open bite even without systemic myopathic disease [27–29].

Conversely, in deep-bite patients, excessive function of the masticatory muscles is affected [30,31]. The thickness and cross-sectional area of the masseter muscle correlates with the length of the mandible [32], and the masseter muscle volume has a negative correlation with the gonial angle [33]. The masseter muscle force (occlusal pressure) itself is larger in patients with a deep bite than in patients with an open bite [34,35], and muscle weakness in the masticatory muscles causes dilatation of the mandibular angle [36–39]. Similar trends have been reported by electromyographic analysis [40,41] and for fatigability [42].

For these reasons, the importance of active muscle training has been suggested to improve jawbone morphology [43]. In fact, muscle functional training may be applied in the prevention of jaw deformities [44].

3. Genetic and environmental effects on skeletal muscle

Mechanical stress is important for bone remodeling, and bone adapts to surrounding stress and changes its shape and strength [45]. The largest source of mechanical stress for bone is muscle tissue [46], and bone volume decreases locally when muscle paralysis occurs. During growth, muscles and bones show related increases (biomechanical interaction theory) [47,48], and decrease as functional units with age and disease [49].

The importance of surrounding muscle to bone function and morphology is revealed by mechanical stress and endocrine crosstalk [50]. Humoral factors produced by muscle cells, such as interleukin (IL)-6 and IL-15, which are secreted during exercise and involved in bone hypertrophy [51,52]; irisin, which promotes osteoblast differentiation [53,54]; and myostatin (growth differentiation factor-8; GDF-8, etc.), which suppresses myocyte proliferation and skeletal muscle growth [55], negatively regulate bone function [56] and are called myokines, which affect bone tissue through endocrine or paracrine functions. Furthermore, skeletal muscle is considered important for the healing of fractures, and fractures of long bones exhibit delayed healing if they are not covered with muscles [57–59]. This process involves endocrine and skeletal muscle, which is a source of bone progenitor cells [60,61].

Conversely, bone also functions like an endocrine organ, and fibroblast growth factor 23 (FGF23) [62], osteocalcin (bone gamma-carboxyglutamate protein, BGLAP) [63], sclerostin, insulin-like growth factor (IGF), transforming growth factor-β (TGF-β), bone morphogenetic protein (BMP) affect muscle tissue [51].

The cell unit that constitutes a muscle is the muscle cell (myocyte; myofiber), in which a large number of myofibrils are present. Myofibrils are composed of two types of filaments, myosin and actin. Myosin consists of two heavy chains and four light chains. Myosin heavy chain (MyHC) has several isoforms: type I fibers or so-called slow muscle fibers: and type II fibers, known as fast muscle fibers [64]. Type II fibers are further classified as IIx and IIa. The contraction rate increases in the order of IIx, IIa, and I, and endurance exhibits the reverse order. The proportions of these components are determined by the site and type of muscles and genetics [65,66], but some changes may occur due to environmental factors [67,68].

Genetic factors strongly influence the size, strength, and height of muscles [65,66], and 40–80% of skeletal phenotypes are genetically determined. The same can be said for muscles [69,70].

Myofibers are known to undergo a progressive transition due to changes in muscle activity, and when muscles are loaded by stress in training, they usually change from type IIx to type IIa to type I [67]. Conversely, MyHC isoforms shift in the direction of I → IIa → IIx due to the reduction of mechanical stimuli, such as during hindlimb suspension and space flight, and the cross-sectional area of muscle also decreases significantly [68]. Pharmacological treatment with the β 2-adrenergic receptor agonist clenbuterol can induce a shift to fast muscles [71,72].

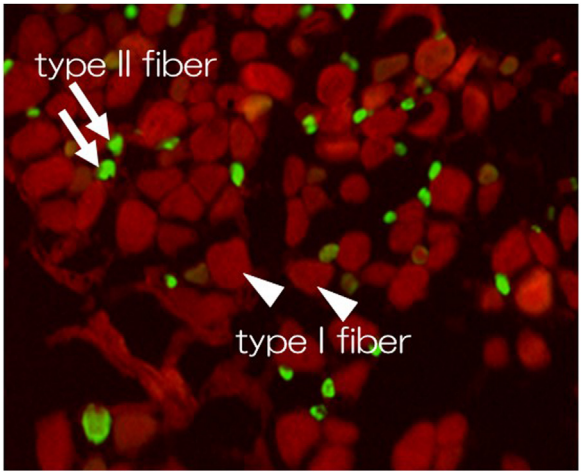

Fig. 2. Immunohistochemical staining for MyHC in the masseter muscle of a mandibular prognathism patient.
Relatively thin type II fibers are recognized among the dominant type I fibers.

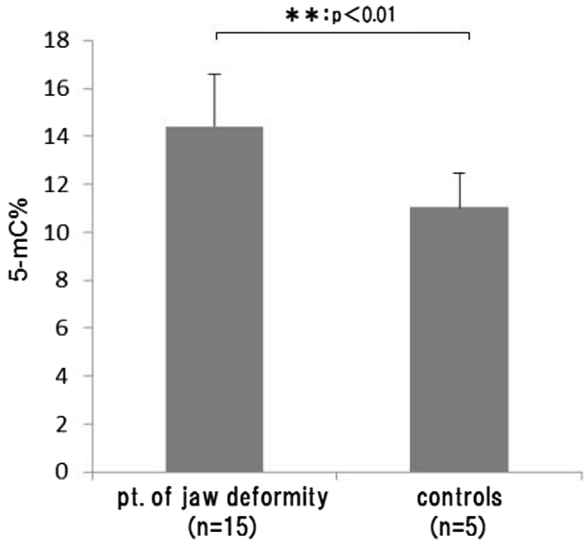

Fig. 3. Methylation of the masseter muscle in jaw deformity patients and controls.
Methylation is enhanced in the masseter muscle of jaw deformity patients.

4. Molecular characteristics of masticatory muscles

The MyHC of the masseter muscle is characterized by a proportion of 90% or more of type II fibers in rodents, such as rats and carnivores [73–75], while type I fibers predominate in omnivores [76]. More than 70% of the human masseter muscle consists of type I fibers, but there are large individual differences [77] (Fig. 2; MyHc staining of human masseter muscle). Herbivores with long, slow chewing movements have more type I fibers [78].

Characteristically, the masseter muscle often contains so-called hybrid fibers with multiple myosin types [76]. Unlike the other skeletal muscles, fetal or embryo-like isoforms are even included in the adult masseter muscle [79]. This feature may indicate that the developmental control of masticatory muscles may be different from that in other skeletal muscles and that the regenerative ability of masticatory muscles is excellent.

The properties of the skeletal muscle fibers are prenatally preprogrammed but are refined by functional requirements [80]. For example, hormones, such as testosterone, cause phenotypical changes toward fast muscle formation in men. The transition of masticatory muscle fibers occurs in response to other environmental factors, such as soft-diet feeding [81].

5. Molecular characteristics of masticatory muscles and jawbone deformities

As mentioned above, while the size and function of the masticatory muscles play important roles in the vertical position of the face, the molecular properties of muscle fibers, particularly the MyHC isoform, also affect the facial height dimension. The type of muscle fiber can be classified by ATPase staining, utilizing the difference in the ATPase activity of myosin, or by immunohistochemical staining for MyHC proteins. For example, patients with a deep bite and maximal occlusion were shown to have more type II fibers, and patients with an open bite and poor occlusion were shown to have more type I fibers [82]. Hunt et al. [23] also reported a relative increase in type II fibers in short-face patients and a relative decrease in type II fibers in long-face patients.

In addition to MyHC staining, it has been reported that patients with distal occlusion have higher expression levels of type I and type IIx mRNA than patients with mesial occlusion [83]. Distal occlusion appears to be more frequent than mesial occlusion in patients with short faces, and it is expected that the function of both muscle fiber types, including fast and slow fibers, is greater in these patients.

Patients with mandibular asymmetry were shown to have predominantly type I fibers (approximately 60%), but the area of type II fibers was larger on the deviated side than on the nondeviated side (deviated side 18.4%: nondeviated side 10.6%) [84]. In general, the mandibular ramus is shorter on the deviated side than on the nondeviated side. Changes similar to those observed in the short face on the deviated side and in the long face on the nondeviated side may have occurred. However, only the percentage of the area exhibited a difference, and there was no difference in the number of fibers. Thus, environmental factors (such as chewing habits) during the growing phase may be more involved in the onset than genetic factors. In our study, a tendency for slow muscle switching was observed on the deviation side (data not shown); the postnatal functional load may cause muscle hypertrophy with slow muscle and lead to a lateral mandibular imbalance.

There have been some reports regarding RNA expression in masticatory muscle other than that involving MyHC. Epigenesis is a change in gene expression or cell phenotype that is inherited even after cell division without a change in the DNA sequence. Epigenesis includes DNA methylation, chemical histone modification, and nontranslational RNA regulation. Histone acetyltransferase (HAT) and K (lysine) acetyltransferase 6B (KAT6B), which are related to histone modification, are positively correlated with mandibular prognathism and type II MyHC [85]. Histone deacetylase 4 (HDAC4) is also plays an important role to make musculoskeletal complex [86]. Furthermore, a strong association has been noted between malocclusion and MYO1C and KAT6B, suggesting an association between type I fibers and KAT6B. However, the details are unknown. Acquired epigenetic changes may be related to muscle characteristics. Muscle characteristics are also related to the proportion of type II fibers and the expression of runt-related transcription factor 2 (RUNX2) and may reflect muscle-bone crosstalk. In our institution, preliminary data (not published) shows that the masseter muscle tissues of patients diagnosed with jaw deformities are hypermethylated, which is an indicator of epigenetic changes (Fig. 3).

6. Response in masticatory muscle after orthognathic surgery

As described above, masticatory muscles are largely involved in jawbone morphology. Although their characteristics are genetically determined to a certain extent, they can be changed by environmental factors. Preoperative corrective treatment temporarily destabilizes the occlusion in patients with jaw deformities and reduces the occlusal force [87,88]. Most of these changes have been investigated in the masseter muscle samples, but it is speculated that similar changes occur in the temporal and medial pterygoid muscles.

After orthognathic surgery, a so-called fast muscle transition occurs, in which the proportion of type I fibers decreases and that of type II fibers increases [89,90]. This phenomenon is thought to occur upon unloading with postoperative intermaxillary fixation, swelling, and temporary dysfunction during the adaptation of neuromuscular function. Furthermore, the upregulation of mRNA (MYH3, 8) related to fetal or embryonic muscle fibers has been reported after surgery [91], and both muscle fiber transition and damaged muscle regeneration have been noted.

Although proper temporal and masseter muscles with biomechanical advantages and increased masticatory efficiency can be achieved through proper orthognathic surgery [92–94], most cases of relapse after orthognathic surgery are caused by inadequate occlusion and inadequate muscle adaptation [95,34,96]. One-third of patients treated with osteotomy experience relapse [97].

When the length of the mandible changes, the moment (force-to-moment ratio; F/M ratio) changes, and muscle adaptation is required [97]. If muscle adaptation is incomplete, relapse occurs. For example, masseteric stretching due to insufficient upper jaw impaction causes the relapse of open bite [91], and suprahyoid muscle stretching via mandibular extension causes the relapse of retrognathia [90].

When muscle is loaded by minimal mechanical tension (stretch), cyclo-oxygenase (COX) and prostaglandin E2 (PGE2) production decreases, and these factors act in an anti-inflammatory fashion. However, when muscle is loaded with longer stretching, the production of these inflammatory mediators increases, and they become proinflammatory [98]. In stretch-induced adaptation of the rat masseter muscle, the mRNA expression of monocyte chemotactic protein 1 (MCIP-1), PPARγ coactivator - 1α (PGC-1a) and COX-1 is upregulated and the calcineurin/nuclear factor of activated T cells (NFAT) pathway that promotes muscle growth and slowing is activated [90]. Muscle adaptation tends to be delayed in Class II patients [97]. Since the downregulation of inflammatory genes is low in Class II patients, this may indicate that the M / F ratio has not been optimized. The expression levels of the stretching-specific genes forkhead box O 3a (FOXO3a), calcineurin, and NFAT1c and the vertical dimension of the face are correlated after surgery in Class II patients [90]. Therefore, Breuel et al. [90] suggested that deep bite should be treated by intrusion of the incisors.

However, when proper muscle adaptation is obtained after orthognathic surgery, various advantages as well as functional improvement in the masticatory system are noted. For example, in patients with jaw deformities, particularly mandibular asymmetry, postural stability is hampered, and lateral scoliosis may also occur [99,100]. This poor posture may be improved after orthognathic surgery [101,102]. Although the mechanism is not clear, the organically curved spine does not improve. However, it is thought that functional or temporary changes induced by some neuromuscular imbalance can be improved by orthognathic surgery in a physiological neuromuscular manner.

Thus, without consideration of the muscles, the postoperative results of orthognathic surgery would be poor. However, proper bone movement and improvements in the masticatory system provide a good masticatory efficiency and facial appearance, as well as neuromuscular balance, yielding positive effects on the entire body, including improvements in attitude.

7. Conclusion

Masticatory muscles, especially the masseter and medial pterygoid slings, play an important role in mandibular morphology, and environmental and neuromuscular factor is one of the etiologies of dentofacial deformities.

The functional association of muscle and bone are emphasized during growth and after injures or surgery.

Biomechanical considerations are important given that muscle overstretching is a major cause of relapse during orthognathic surgery. Proper surgery not only improves masticatory function but can also be expected to have a positive effect on the entire body, such as improvements in posture.

It has gradually become clear that jaw deformities are affected by muscle contraction characteristics and biochemical characteristics. In the future, muscular biomechanical characteristics and biochemical considerations, such as MyHC transitions and myokines, will be necessary for the determination of strategic approaches for treating jaw deformities.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

The authors declare that they have contributed significantly to preparation of the manuscript and that all authors are in agreement with the content of the manuscript.

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None.

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