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Review Article

The usefulness of diagnostic imaging for the assessment of pain symptoms in temporomandibular disorders

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Summary The causes of pain symptoms in the temporomandibular joint (TMJ) and masticatory muscle (MM) regions may not be determined by clinical examination alone. In this review, we document that pain symptoms of the TMJ and MM regions in patients with temporomandibular disorders (TMDs) are associated with computed tomography and magnetic resonance (MR) findings of internal derangement, joint effusion, osteoarthritis, and bone marrow edema. However, it is emphasized that these imaging findings must not be regarded as the unique and dominant factors in defining TMJ pain. High signal intensity and prominent enhancement of the posterior disk attachment on fat saturation T2-weighted imaging and dynamic MR imaging with contrast material are closely correlated with the severity of TMJ pain. Magnetic transfer contrast, MR spectroscopy, diffusion tensor imaging, and ultrasonography findings have helped identify intramuscular edema and contracture as one of the causes of MM pain and fatigue. Recently, changes in brain as detected by functional MR neuroimaging have been associated with changes in the TMJ and MM regions. The thalamus, the primary somatosensory cortex, the insula, and the anterior and mid-cinglate cortices are most frequently associated with TMD pain.

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Contents

1. Introduction

Pain is the most common symptom of temporomandibular disorders (TMDs) [1,2]. Pain symptoms in the temporomandibular joint (TMJ) and masticatory muscle (MM) regions are the main complaints of TMD patients seeking treatment. However, the causes of pain symptoms in the TMJ and MM regions are not yet fully understood. In the orofacial, TMJ, and MM regions, pain can have various origins, including musculoskeletal, vascular, neurovascular, neuropathic, psychogenic, and infectious diseases. In general, the causes of pain symptoms may not be determined by clinical examination alone. Ideally, the diagnosis of TMD pain is reached by a combination of clinical manifestations and diagnostic imaging confirmation.

Computed tomography (CT) and magnetic resonance (MR) are useful tools for imaging the TMJ region of TMD patients, particularly for assessing degenerative bony changes, disk position and configuration, inflammatory pathological changes in the posterior disk attachment, the presence of effusion in joint spaces, and bone marrow edematous involvement. MR imaging with contrast material studies provide additional information regarding soft-tissue changes in the posterior disk attachment of the TMJ and the TMJ capsule. Recently, MR sequences such as magnetization transfer contrast (MTC) imaging, magnetic resonance spectroscopy (MRS), diffusion tensor imaging, and ultrasonography (US) have been applied to evaluate masticatory muscle changes such as edema and fibrosis.

This review focuses on the characteristics of the imaging findings for various pain symptoms seen in TMDs.

2. Internal derangement-related joint pain

Pain symptoms frequently arise in patients with TMJ internal derangement (ID) instead of TMDs. The articular disk of the TMJ is composed of a biconcave fibrocartilaginous structure. TMJ ID is defined as an abnormal positional relationship between the articular disk and the mandibular condyle and the articular eminence, and it signifies an interference with smooth joint movement [3]. According to Wilkes [4] and Al-Moraissi [5], TMJ ID was classified into the following five stages: patients with early stage ID (stage 1) complain of clicking sounds upon jaw opening and closing. There is no pain or dysfunction at this stage. Early/intermediate stage of ID (stage 2) manifests with clicking of the joint, intermittent locking episodes, and transient pain. Intermediate stage ID (stage 3), also known as accurate closed lock, manifests with limited mouth opening, deviation of jaw upon opening to the affected side, and pain in the involved joint. The disorder usually has an acute onset of symptoms. Intermediate/late stages of ID (stage 4) are characterized by limited mouth opening and various degrees of pain. Chronic closed lock is the term commonly used to describe this stage. Late stage ID (stage 5) signifies the development of advanced degenerative changes in the joint, and clinically manifests with crepitus and grinding sounds, episodic or continuous pain, and difficulty with function.

MR imaging for ID could be used when clinical examination cannot predict the true position of the disk [6]. Disk positional changes have been regarded as the main factor contributing to the development of abnormal mechanical trauma/microtrauma and secondary inflammatory disorder within the TMJ [7]. Many investigators have reported that anterior disk displacement (ADD) is an important source of joint pain [8—12]. ADD without reduction may produce more mechanical stress, and stretch the posterior disk attachment and joint capsule more than ADD with reduction, causing more painful joints [8,10,11]. According to Sano et al. [13], the majority of asymptomatic individuals show normal disk position, but one-third show ADD. Some publications have demonstrated that ADD of the TMJ does not necessarily correlate with joint pain [14—16]. The study of the relationship between sideways disk displacement and joint pain has yielded controversial results [17,18].

Dynamic motion MR imaging for ID complements static MR imaging by providing additional information about disk and condyle mobility, disk reduction, and topographic changes in the disk—condyle relationship between various stages of the open-mouth movement [19—23]. It has been reported that ADD using pseudo-dynamic MR imaging, particularly ADD without reduction, is an important source of TMJ pain [23].

3. Effusion-related joint pain

Joint effusion, which is defined as a large collection of fluid in the joint space, has been detected as hyperintense signal

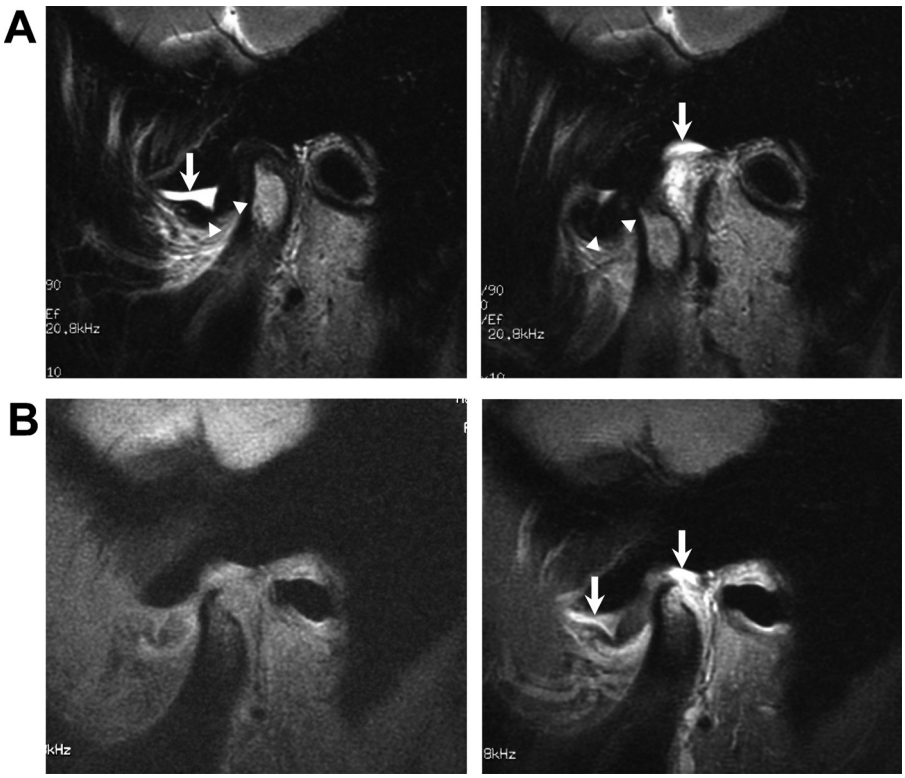

Figure 1 (A and B) A 47-year-old man with a recent history of left TMJ pain and MM pain. (A) Sagittal T2-weighted closed- (left) and open-mouth (right) MR images show marked effusion (arrows) above the displaced disk (arrowheads) and mandibular condyle. (B) Sagittal dynamic fat-suppressed T1-weighted pre- (left) and postcontrast (right) MR images demonstrate areas of enhancement corresponding to effusion (arrows). TMJ, temporomandibular joint; MM, masseter muscle.

on T2-weighted MR images and has been associated with inflammatory response [12,24,25]. Numerous researchers reported a positive relationship between joint effusion and TMJ pain [3,26—30]. Marked effusion has been particularly associated with increased intra-articular pain in ADD without reduction [31—33]. Several reports showed that only a certain type of TMJ pain is associated with joint effusion [34—37]. According to Güler et al. [36], there is a correlation between spontaneous pain and joint effusion, but not between the severity of joint pain and joint effusion. Takahashi et al. [15] showed a relationship between provoked pain and joint effusion. Conversely, only chewing pain and joint effusion showed a positive correlation in patients with TMJ closed lock. Provoked pain visual analog scale scores, such as those of pain on mouth opening and pain on palpation of the masticatory muscles, do not correlate with joint effusion [34].

The detection rate of joint effusion by frequency-selective fat saturation (FS) T2-weighted sequences is significantly greater than that by conventional T2-weighted sequences [38]. This high rate of effusion detection may be related to the suppression of the high signal of surrounding fatty tissue. The correlation between joint effusion on FS sequences and TMJ pain is significantly stronger than that between conventional methods and TMJ pain [38]. The relationship between gadolinium enhancement of joint effusion and TMJ pain is considerably stronger than that between the extent of effusion and TMJ pain (Fig. 1). Painful joints are more likely to demonstrate contrast enhancement of the joint effusion. Although some or marked effusion was observed in asymptomatic joints, contrast enhancement of effusion is not visible [31]. Given these findings, the absence of enhancement may not necessarily indicate inflammatory changes in the TMJ but rather reflect a low rate of fluid washout due to chronic changes in the synovium [31].

Other researchers have questioned and failed to correlate joint effusion and TMJ pain [25,36,39,40]. It is difficult to correctly assess joint effusion as a predictor of TMJ inflammatory process and pain when focal or spot-like areas of signal intensity are detected on plain T1/T2-weighted images [41]. As a consequence, the interpretation of joint effusion is often too subjective.

In a longitudinal study of MR imaging, TMJ pain was improved or absent in all joints in which the joint fluid was decreased [37]. Yano et al. [42] reported that the joint fluid might be a key factor in the outcome of disk recapture treatment as well as in the evaluation of joint pain.

It has been suggested that the synovial fluid concentrations of molecular markers such as total protein [35], proinflammatory cytokines [27], nitric oxide [31], prostanoids [43], seratonin, bradykinin [44], and neuropeptides [45] are increased in TMJs with joint pain, disk displacement, and osteoarthrosis. Therefore, joint effusion may reflect the intra-articular inflammatory status of TMJs.

4. Pathological posterior disk attachment-related joint pain

The assessment of synovial proliferation in the posterior disk attachment by T1-weighted MR imaging with contrast material provides a more accurate diagnosis than that obtained by conventional MR sequences [46—49]. Fatty tissue within the posterior disk attachment and lateral pterygoid muscle has high signal intensity on T1-weighted MR images and occasionally obscures anatomic structures in the TMJ region by means of chemical artifact [50]. Therefore, dynamic fat-suppressed MR imaging with contrast material appears to be highly sensitive for the diagnosis of posterior disk attachment abnormalities. Many investigators have reported that the pattern of rapid enhancement and higher degree of contrast enhancement may reflect the inflammatory pathology caused by mechanical stress on the intra-articular tissues [41,47,51,52]. Prominent contrast enhancement of the posterior disk attachment, suggestive of synovial proliferation (synovitis), helps differentiate intra-articular from extra-articular causes of pain in and around the TMJ (Fig. 2). In patients with joint pain, ADD without reduction is closely associated with prominent enhancement [47]. In the same line of thought, Tasali et al. [52] demonstrated that different disk malpositions (i.e., normal disk position, partially disk displacement, total disk displacement with reduction, and total disk displacement without reduction) created different enhancement patterns. And it may be due to different degrees of vascularization and/or fibrosis in the posterior disk attachment region. As mentioned above, synovial enhancement with contrast material is probably secondary to passive diffusion of the contrast material molecules into this tissue and mixing with the synovial fluid. Furthermore, contrast enhancement of the posterior disk attachment may be due to flow into this region and with movement through capillary pores into the interstitial tissues.

A higher T2 signal intensity, due to a higher degree of vascular supply, has been found in the posterior disk attachment of painful joints compared to pain-free joints [53—55]. A frequency-selective fat-saturated T2-weighted imaging technique has been reported to precisely detect pathological posterior disk attachment [56]. It is problematic that the signal intensity of the posterior disk attachment differs in each individual owing to differences in the space between the posterior aspect of the mandibular condyle and the posterior wall of the mandibular fossa. Nevertheless, T2-weighted MR sequence is a noninvasive method compared to MR imaging with contrast material. The blood-flow volume changes according to joint space. Consequently, it may be difficult to quantitatively measure the signal intensity of the posterior disk attachment on T2-weighted MR images. It is not commonly accepted that MR imaging with contrast material has a significant indication for the assessment of TMJ pain. There is a risk in administering contrast material and it increases the cost and time of the examination, however, MR imaging with contrast material provides an accurate information such as synovial proliferation and fibrosis in the posterior disk attachment.

High signal intensity and contrast enhancement in the posterior disk attachment may be consistent with the increased vascularity or inflammatory response of the posterior disk attachment based on histological studies [57,58].

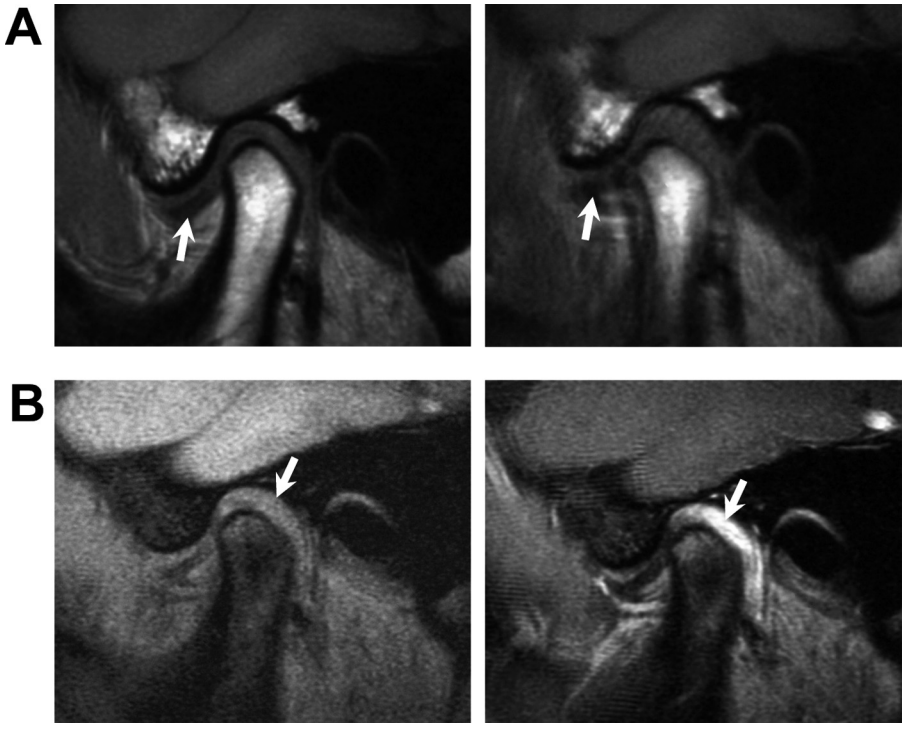

Figure 2 (A and B) A 18-year-old woman with a recent history of right TMJ pain and clicking. (A) Sagittal T1-weighted closed- (left) and open-mouth (right) MR images show anterior disk displacement without reduction (arrows). (B) Sagittal dynamic fat-suppressed T1-weighted pre- (left) and postcontrast (right) MR images demonstrate inhomogeneous prominent enhancement of the posterior disk attachment (arrows). TMJ, temporomandibular joint.

The posterior disk attachment is composed of collagen fibers, elastic fibers, fat, blood vessels and nerves. Kurita et al. [57] reported that in the posterior disk attachment of pathologic TMJs, the vascular structures increased in number. Holmlund et al. [58] observed hyperemia and perivascular inflammatory response at the posterior disk attachment of patients with symptomatic disk pathologies. There is controversy regarding the changes in the vascular structures of the posterior disk attachment in painful TMJs [59,60]. In one study, the wall of the capillary artery and veins was constricted and obliterated with extravasated erythrocytes [59]. On the other hand, Hall et al. [60] demonstrated the presence of thickened arterial walls, suggesting a decrease in blood flow. These results may reflect two different phases of the histological changes that develop in the posterior disk attachment. The painful phase is characterized by increased inflammatory response in the posterior disk attachment accompanied by higher contrast enhancement, whereas the painless phase is characterized by decreased vascularization, probably due to fibrosis [52].

At follow-up examination after manipulation and splint therapy combined with occlusal adjustment, the resolution or reduction of TMJ pain is associated with a decrease in contrast material of the posterior disk attachment on dynamic MR imaging with contrast material [61]. This MR sequence may be a valuable method for evaluating TMJ treatment outcome in patients with TMJ pain and dysfunction.

Epidemiological studies of TMDs suggest a high female-to-male predilection for TMJ symptoms [62]. Indeed, TMJ pain is a common condition that has its highest prevalence among woman of productive age [63]. The estrogen receptors and estrogen that contribute to symptomatic TMJ disease have been shown to be abundantly present in the human TMJ region [64]. Therefore, the amount and binding activity of estrogen receptor and estrogen may play an etiologic role in TMJ pain of TMDs. It has been reported that estrogen increases at the proliferative phase during the menstrual cycle (menstrual, proliferative and secretory phases), and protects against acute TMJ pain [65,66]. According to Suenaga et al. [67], there is a strong statistical difference in the degree of TMJ pain between each phase. TMJ pain has a tendency to decrease at the proliferative phase and increase at the menstrual and secretory phases. Significantly less contrast enhancement of the posterior disk attachment is observed in the proliferative phase than in the secretory or menstrual phases, that is to say, an increase of estrogen decreases inflammatory changes in the posterior disk attachment. Moreover, ADD without reduction of the TMJ is closely associated with TMJ pain. In women with TMJ pain, the contrast enhancement of the posterior disk attachment of the joints with ADD is higher than that of the joints with normal disk position. Thus, the positional changes of the disk and female hormonal changes during the menstrual cycle synergistically result in increased or decreased TMJ pain and inflammatory pathology of the posterior disk attachment [67].

5. Bone marrow abnormalities-related joint pain

MR appearance of bone marrow abnormalities of the mandibular condyle is classified into two types based on histological findings: edema and osteonecrosis (Fig. 3). Bone marrow edema and osteonecrosis are defined as decreased T1 signal or proton density signal and increased T2 signal, and decreased T1 signal or proton density signal and decreased T2 signal (sclerosis pattern), respectively [68—70]. Sano et al. [71] suggested that there was more severe pain in joints with bone marrow edema of the mandibular condyle than in those with osteonecrosis. Marrow edema pattern may be a precursor condition in osteonecrotic development of the TMJ as suggested by the observation that patients with marrow edema are younger [68,72]. Signal intensity abnormalities in the mandibular condyle marrow are not observed in asymptomatic volunteers [73,74].

It has been stated that fat-suppressed T2-weighted MR imaging is useful for the detection of the marrow edema pattern in the mandibular condyle associated with TMJ-related pain [75,76]. Furthermore, Kodama et al. [77] referred to the usefulness of fluid-attenuated inversion recovery (FLAIR)-sequence MRI to detect such minimal bone marrow changes. Signal intensity on FLAIR images is significantly higher in painful than in non-painful TMJs [77]. A significant and positive association between TMJ pain, joint effusion, and bone marrow abnormalities has also been reported [32,78].

On the other hand, according to a longitudinal study of MR imaging by Chiba et al. [79], a reduction in joint pain does not correlate with disappearance of bone marrow edema pattern in most joints. Therefore, they concluded that bone edema pattern does not always contribute to the occurrence of joint pain in patients with TMDs [79].

Thus, the correlation between condylar bone marrow edema and TMJ pain remains a matter of dispute.

6. Osteoarthritis and degenerative joint diseases-related joint pain

Degenerative bony changes are more frequent in the mandibular condyle than in the mandibular fossa or the articular eminence and are characterized by the development of pathological bony changes (erosion, osteophytes and deformity) and adaptive bony changes (marginal proliferation, flattening, concavity, sclerosis and subchondral cysts) [80—83]. These abnormalities are considered to be radiological signs of osteoarthritis (OA) and are frequently observed in joints with long-standing ADD without reduction [81]. Osteochondritis dissecans is frequently associated with avascular necrosis [84].

Imaging modalities such as CT [80,85,86], CBCT [83,87,88], and MR [81,89—91] have been used for diagnosing degenerative joint diseases such as TMJ OA. CBCT is a fairly new imaging modality that can produce images of high diagnostic quality using a lower radiation dose than CT [88]. According to the specific value of CBCT by Fu et al. [72], CBCT is very useful for depicting abnormal changes such as the cortical margin of the surface and the subchondral cancellous trabecular structure in the mandibular condyle which are difficult to show completely with conventional radiography. Detailed assessment of changes in surface morphology of the condyle and fossa is difficult in conventional tomography, since the thickness of the slices in

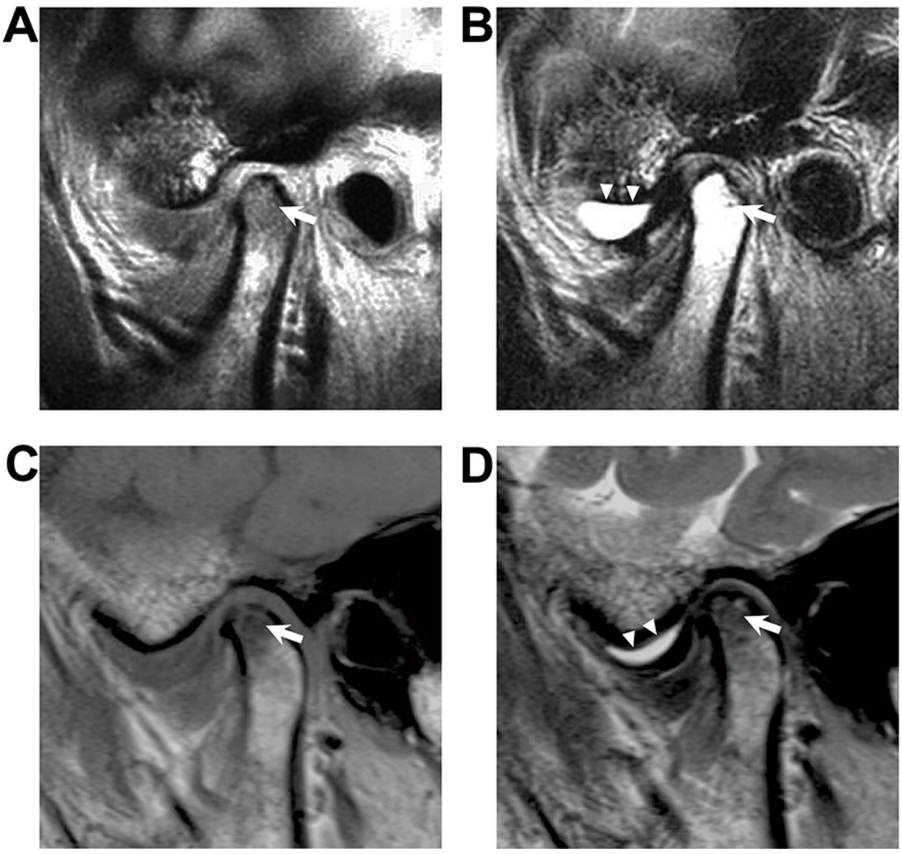

Figure 3 (A and B) Bone marrow edema pattern in the mandibular condyle. (A) Sagittal T1-weighted closed-mouth MR image shows an ill-defined area of abnormal decreased signal in the subchondral bone marrow (arrow). (B) Sagittal T2-weighted closed-mouth MR image demonstrates abnormal increased signal in the corresponding area (arrow) and effusion (arrowheads) in the superior joint space. (C and D) Bone marrow osteonecrosis pattern in the mandibular condyle. (C and D) Both sagittal T1-weighted and T2-weighted closed-mouth MR images show an ill-defined area of abnormal decreased signal in the mandibular bone marrow (arrow) and effusion (arrowheads) in the superior joint space.

this modality is 1.0—3.0 mm [92]. It is generally known that 2-dimensional radiographs cannot be sufficient for evaluating the condylar position. On the other hand, Hintze et al. [93] compared CBCT with multidirectional tomography in detection of morphological TMJ changes, and no significant differences in diagnostic accuracy were found between the two techniques. On these imaging modalities, condylar morphology correlates with pronounced differences between OA and asymptomatic condyles [87], and resorptive bone changes correlate with pain severity [81,85,87,89]. Erosion of the bone surface is more common among patients with TMJ pain or mouth opening limitation than among those without [82,87,94]. Conversely, there is a poor correlation between condylar bony changes including pathological bony changes, adaptive bony changes and/or remodeling and pain symptoms in OA of the TMJ [90,91,95—97]. TMJ remodeling is difficult to distinguish from a post mechanical injury inflammatory process. OA is frequently related to bone marrow abnormalities, and a symptomatic TMJ is accompanied by bone marrow changes with an osteoarthritic mandibular condyle, showing an increasing signal intensity on proton density-weighted MR images [79,98].

Some investigators evaluated the usefulness of bone scintigraphy for the diagnosis of OA in the TMJ [99—102]. The correlation of signs and symptoms with scintigraphy showed sensitivity 100%, specificity 90.91%, and accuracy 96.97% [100]. Bone scintigraphy had a positive effect on the osseous reaction and TMJ pain [101]. In contrast, although there were significant differences in uptake between the OA and non-OA groups, no significant differences in uptake associated with pain and bone changes were seen [102].

The radiographic changes of the follow-up CBCT suggested that osteonecrosis may be a precursor of OA [72]. The MRI findings and radionuclide imaging supported the initial diagnosis of osteonecrosis as a disease involving the bone marrow. In the late stage of osteonecrosis, differentiation from OA may not be possible even if using conventional radiographs, medical CT and CBCT [72].

7. Myositis and muscle edema/contracture-related myofascial pain, muscle pain, and fatigue

Myofascial pain and muscle pain are very common. The fatigue and muscle pain are caused by the edematous changes in the muscles, the mechanical disruption of the

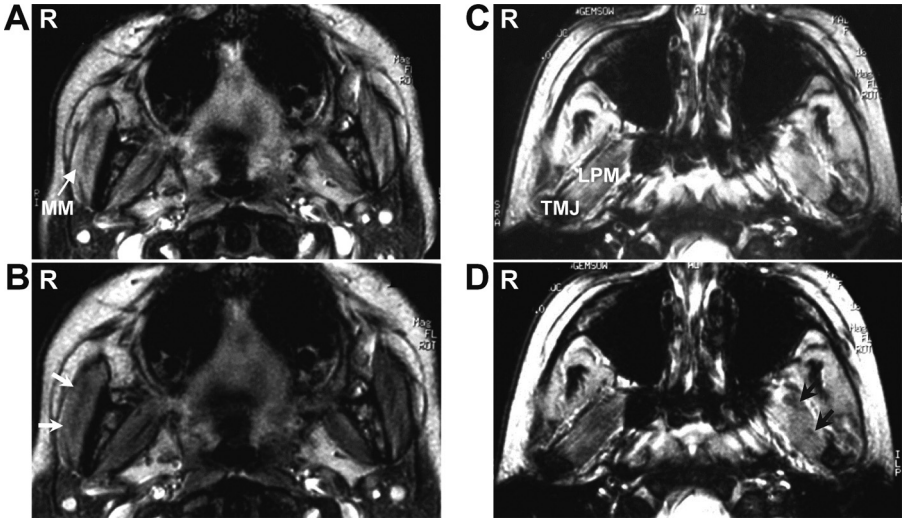

Figure 4 (A and B) A 28-year-old man with a recent history of right masseter muscle pain. (A) Axial GRE and (B) MTC-GRE images show less signal loss in the right masseter muscle (arrows). (C and D) A 14-year-old female with left TMJ pain and opening limitation. (C) Axial GRE and (D) MTC-GRE images show less signal loss in the left lateral pterygoid muscle (arrows). GRE, gradient-recalled echo; MTC, magnetization transfer contrast; MM, masseter muscle; TMJ, temporomandibular joint; LPM, lateral pterygoid muscle.

muscular fibers and of the connective tissue and inflammatory processes of the muscular fibers and/or membranes. However, the mechanisms and effects of the muscle fatigue and pain have not been fully described. The relation between the muscle fatigue and pain is still unclear. Some researchers reported that the patients diagnosed with myofascial pain had more severe depressive and nonspecific physical symptoms than patients diagnosed with TMJ ID (i.e., disk displacement) [103,104]. Laskin [105] distinguished myofascial pain, which is of muscular origin and more diffuse in nature, from TMJ pathology such as disk displacement and other joint conditions. Both are typically diagnosed by an initial clinical examination [25]. In the past recent years, MR sequences such as MTC imaging, MRS, diffusion tensor imaging, and US also started being used to evaluate muscular pathological changes associated with pain symptoms.

MTC imaging has been described as a possible means to obtain additional contrast information to better distinguish between normal and pathological tissues [106]. The MTC technique is considered to be sensitive to the rapid interaction between tissue water and bound protons by selective saturation with an off-resonance radio frequency pulse [107]. These bound protons normally show very short T2 times and therefore are not generally imaged with conventional MR sequences. MTC can easily detect excessive water content within the muscles, thus improving the contrast between the active and the surrounding inactive muscles. The signal intensity changes of masticatory muscles by clenching exercise and inflammatory process have previously been reported using T2-weighted FSE MR imaging [108,109]. MTC images of the maxillofacial region show superior fluid conspicuity in the TMJ compared to conventional MR images [110]. In TMD patients, the MT ratios (MTRs; calculated as $(Mo - Ms)/Mo$, where Mo and Ms are the signal intensities of each muscle tissue before and after the saturation pulse is applied, respectively) of masseter muscles with pain symptoms caused by edematous changes are significantly lower than those of healthy muscles. A decrease and an increase of MTRs in masticatory muscles may represent edematous and ischemic changes, respectively. MTC imaging has improved the contrast between intramasticatory muscle lesions and their surrounding healthy muscle regions, thus allowing the characterization of tissues (Fig. 4). The abovementioned study was the first to suggest that MTC images are effective for detecting inflammatory changes in painful masticatory muscles [111].

^{31}P MRS is a non-invasive biochemical method for analyzing the intramuscular metabolism of high-energy phosphate compounds such as adenosine triphosphate (ATP) and phosphocreatine (PCr), which act as energy sources to produce ATP [112—114]. In a clinical study of the MRS method, Okada et al. [115] performed the ^{31}P MRS measurements before and after hot pack application, and the PCr/β-ATP ratio was analyzed. Their results demonstrated that changes in blood flow volume influenced the energy metabolism in masseter muscles and that blood flow increased because the hot pack increased the energy levels in masseter muscles, thus providing an advantage for relieving muscle fatigue. According to the ^{1}H MRS reports by Gerstner et al. [116], glutamate levels are significantly lower in all individuals after pain testing. Among those with TMDs, insular glutamine levels are related to pain symptoms; posterior insular *N*-acetylaspartate and choline levels are significantly higher at baseline than in control individuals; and *N*-acetylaspartate levels are significantly correlated with symptom duration, suggestive of adaptive changes [117,118]. These results suggest that significant central cellular and molecular changes occur in TMD patients.

Diffusion-weighted imaging and diffusion tensor imaging methods can be used to evaluate changes that accompany skeletal muscle contraction [119]. The coefficients for diffusion of the masseter muscles are sensitive to change by clenching—one possible cause of TMDs [120]. In the future,

the relationship between the diffusion coefficients and pain symptoms in the masticatory muscles should be elucidated.

US is an acceptable diagnostic tool for the detection of ID, OA, and intramuscular edema [121,122]. In low-level contraction, muscular edema plays an essential role in provoking pain and fatigue [123]. There are significant differences in the thickness at rest and the increase in contraction between patients with TMDs and control subjects [124]. Edema is caused by increased blood-flow filtration spaces of the masticatory muscles. For this reason, many investigators have investigated blood-flow in and around muscles in an attempt to clarify the mechanism of myofascial pain, muscular pain, and fatigue [124—127]. Ariji et al. [127] reported intramuscular changes of the masseter muscles after low-level static contraction by sonographic elastography. The thickness of muscles and their surrounding tissues on sonographic elastography corresponded to the water content, indicating edematous pathology, and the hard area contributed to the total hardness of the masseter muscle [127]. The results of US and sonographic elastography may be useful for the evaluation of myofascial and muscular pain in TMD patients.

8. Relationship between joint pain, muscle pain, and brain activation

TMD pain is reported to be affected by emotional and cognitive factors [128]. Therefore, TMD pain is considered to be associated with changes in the central pathophysiological process [129]. Recently, changes in brain neuroimaging have been widely investigated [116,130—132]. Chronic orofacial pain changes the brain's structure and pain-related network [133—135]. In addition, cognitive and affective factors such as anxiety and depression have been considered to form the experience of pain in the brain [136,137]. The thalamus, the primary somatosensory cortex (S1), the insula, and the anterior and mid-cingulate cortices (ACC/MCC) are most associated with TMD pain, while the secondary somatosensory cortex (S2) has been less commonly reported. Both the thalamus and the S1 are important regions of the trigeminal nerve system [138] that play a major role in the thalamocortical pathway for TMD pain [139]. Both insular and ACC/MCC activation are associated with noxious stimuli; they encode pain experience [140,141] and are part of the brain connectivity network [142]. The S2 with the insula and the MCC are key regions evoked by noxious stimuli [140], and S2 activation has been reported to respond to the experience of acute pain [141,143]. In addition to the above-mentioned regions, other reports have shown that TMD pain changes the prefrontal cortex (PFC) and the basal ganglia in the limbic system associated with the cognitive and affective network [144,145]. The PFC plays a role in coping with and modulating pain [136,146], and the basal ganglia is the neural substrate for motivation and future reward [147,148]. However, the crosswise difference and the detailed role of each region associated with TMD pain within connection circuit remain unclear. Therefore, we have examined the regions of brain activation in TMD patients with unilateral MM pain and unilateral TMJ pain, when the patient feels pain by chewing and/or clenching (Fig. 5). In the future, more studies are warranted to understand the neural mechanisms of MM pain and TMJ pain.

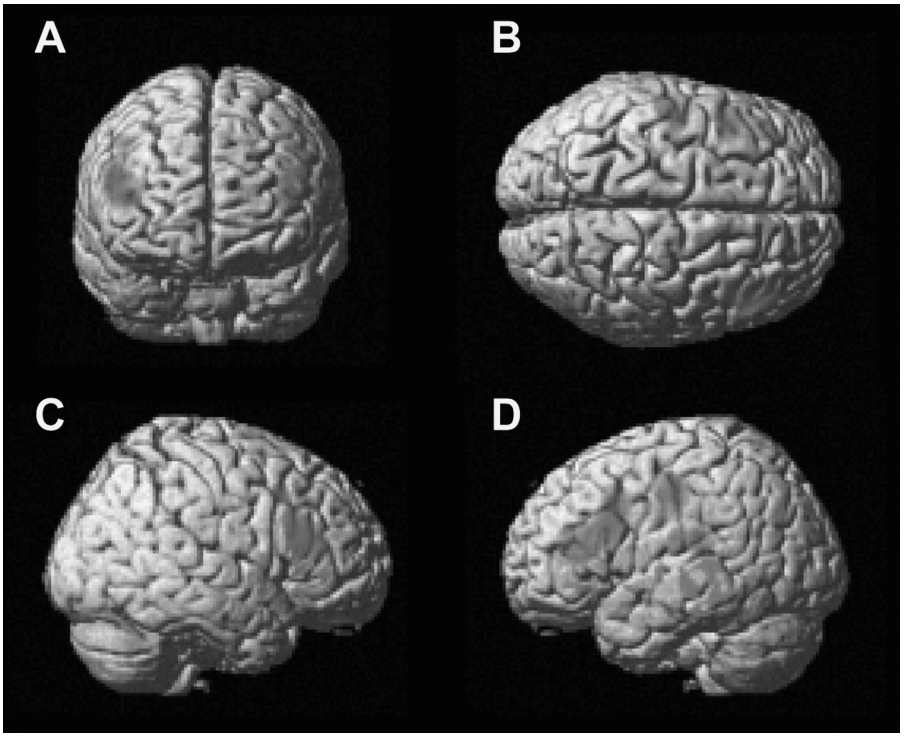

Figure 5 Surface projection of regional brain activity in a TMD patient with right masseter muscle pain when the patient feels the pain by clenching. (A) Frontal view, (B) upper view, (C) right side view, and (D) left side view. The clenching task activated the left sensorimotor cortex, while it did not activate the right one.

Table 1 A rating of the usefulness of each imaging modality related to TMJ pain, MM pain and fatigue.

Imaging modality	Imaging findings
Medical CT and cone beam CT	• Pathological bony changes such as erosion, osteophyte and deformity • Osteochondritis disseccans
Static MR imaging	• Disk positional abnormalities (1) ADD without reduction (2) ADD with reduction (3) Sideways disk displacement • Joint effusion presence of marked effusion • A higher T2 signal of the posterior disk attachment • Bone marrow abnormalities (1) Bone marrow edema (2) Bone marrow osteonecrosis • Tumor involvement and inflammatory diseases into the TMJ region and the surrounding structures • Autoimmune processes such as rheumatoid arthritis • A closer proximity between the TMJ disk and the mandibular nerve
Dynamic MR imaging with contrast material	• Prominent contrast enhancement of the posterior disk attachment • Contrast enhancement of effusion
Magnetization transfer contrast imaging	• Detection for the edematous and ischemic changes in the muscles
Magnetic resonance spectroscopy	• Ascending of insular glutamine levels by ^{1}H MRS
Functional MR imaging	• The regions and the network of brain activation associated with TMD
Ultrasonography	• Muscular edema by low-level contraction
Bone scintigraphy	• Detection for early changes on the osseous reaction of OA

TMJ, temporomandibular joint; MM, masticatory muscle; ADD, anterior disk displacement; TMD, temporomandibular disorders; OA, osteoarthritis.

9. Tumor involvement, inflammatory process and autoimmune disease-related orofacial and joint pain

MR imaging and enhanced CT allows for an accurate evaluation of the relationship between the masticatory muscle spaces and the TMJ, as well as the surrounding structures, such as the parotid gland, skull base, and parapharygeal space [149,150].

Tumor involvement and inflammatory diseases in the head and neck region are difficult to diagnose because of their deep location and presence of pain symptoms mimicking those of TMDs or other orofacial pain disorders [151]. Dental clinicians must consider the possibility of unusual causes, including benign and malignant tumors, and infectious or inflammatory disease, in particular when patients experience increasing pain and worsening of extreme limitation and, finally, do not respond to treatment appropriately [152,153]. Metastatic tumor invasion into the TMJ region is rare. It is important for clinicians to differentiate tumor involvement from musculoskeletal disorders such as TMDs [154,155]. In addition, a cause of TMJ pain is autoimmune processes such as rheumatoid arthritis characterized by symmetric, erosive synovitis, pannus formation and sometimes multisystem involvement [156,157].

TMDs may be associated with the onset of neuropathic pain [158]. Although TMJ pain seems to correlate with the presence of internal derangement, joint effusion, OA, and bone marrow edema within the TMJ, the possible causes of neuropathic pain in patients with TMDs are less clear [3,28,53]. Pedullà et al. [158] suggested that a closer proximity between the TMJ disk and the mandibular nerve could be one of the causes of the onset of neuropathic pain in TMD patients.

The significance of positron emission tomography in the assessment of pain symptoms in neoplasm-related TMJs should be studied in the future.

10. Conclusions

A rating of the usefulness of each imaging modality related to TMJ pain, MM pain and fatigue is summarized in Table 1. This paper reviews the relationship between pain symptoms in the TMJ and MM regions and MR imaging findings for ID, joint effusion, and bone marrow edema. Nonetheless, several reports have denied the relationship between pain symptoms and imaging findings for several different conditions. Fat-saturated T2-weighted and dynamic fat-suppressed MR imaging with contrast material methods have provided a better understanding of the sources of TMJ pain, but not masticatory muscle pain. These imaging techniques are able to detect the presence of synovial inflammatory process in the TMJ, and high signal intensity and strong contrast enhancement of the posterior disk attachment are closely related to the severity of TMJ pain. MM pain is associated with MM pathological changes such as edema, fibrosis,

and contracture on MTC, MRS, diffusion tensor imaging, and US images. Recently, changes in brain neuroimaging have been investigated in an attempt to identify the causes of pain symptoms. The thalamus, the primary somatosensory cortex, the insula, and the anterior and mid-cingulate cortices are most frequently associated with TMD pain. In the future, the development of alternative imaging techniques is expected to better diagnose the bony and soft-tissue abnormalities in the TMJ and MM regions.

Conflict of interest statement

The authors declare no conflicts of interest.

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