Arthritic Conditions Affecting the Temporomandibular Joint

L. G. Mercuri and S. Abramowicz

Contents

Abstract

Arthritis is the most common inflammatory joint disease in children and adults. It has multifactorial etiology resulting in joint degeneration and loss of function. Using a management classification scheme based on clinical signs, symptoms, and imaging, this chapter will present an evidence-based discussion for the management of arthritic conditions affecting the temporomandibular joint (TMJ). The common and significant signs and symptoms of TMJ arthritic conditions are pain, loss of joint function, joint instability, mandibular dysfunction, and facial deformity due to loss of posterior mandibular vertical dimension, as pathologic osteolysis decreases the height of

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the condyle. Medical management can ameliorate early-stage disease. Progressive disease may require the employment of invasive procedures, whereas in end-stage disease, joint replacement is typically required.

Keywords
Temporomandibular joint · Arthritis · Osteoarthritis · Degenerative joint disease · TMJ reconstruction · TMJ replacement · Rheumatoid arthritis · Juvenile idiopathic arthritis · Arthrocentesis · Arthroscopy · Orthognathic surgery · Synovectomy

Introduction

Worldwide statistics indicate that the incidence of arthritis is 3.2%. Arthritis affects females more than males (2.7:1) and can lead to joint destruction, deformity, and disability in 10–15% of patients. Arthritic conditions are the second most frequent cause of outpatient complaints among patients with chronic diseases (Rodrigo and Gershwin 2001). By 2030, an estimated 67 million Americans aged 18 years or older are projected to have diagnosed arthritis (Hootman and Helmick 2006). Approximately 1 in 250 children under the age of 18 have some form of arthritis or rheumatic condition; this represents approximately 294,000 children in the United States (Sacks et al. 2007).

Arthritis has many causes; however, the common result is the degeneration of the affected joint surfaces resulting in loss of joint function. The cause of the arthritic condition determines the clinical characteristics and rate of degeneration of the joint surfaces.

The prevalence of significant temporomandibular joint (TMJ) arthritis resulting in joint degeneration, dysfunction, and/or joint pain is unknown. Previous studies have provided estimates that the incidence of TMJ arthritic conditions ranges from 1% to 84% of the general population (Westesson and Rohlin 1984). Changes consistent with degenerative TMJ disease are found in approximately 70% of the patients who undergo arthroscopy for TMJ disorders; however, degenerative changes are clinically diagnosed in less than 10% of patients (Israel et al. 1991). Examination of the TMJ at autopsy reveals degenerative changes in at least 40% of specimens. However, estimates of the number of individuals in the United States seeking treatment for TMJ pain or dysfunction are substantially lower at 1.9–3.4% (Westesson and Rohlin 1984).

The diagnostic criteria used to differentiate between "arthritis" and the biologically different "osteoarthrosis" is not effective due to their shared multiple clinical signs and symptoms (Michelotti et al. 2016). There are discrepancies in estimates of the prevalence of each of these conditions because the association between pain, dysfunction, and joint morphology is complex. Gross morphologic abnormalities can be present in the absence of TMJ pain and dysfunction (Pereira et al. 1994). Furthermore, the distinction between the diagnoses of "arthralgia" and "arthritis" is difficult since the signs and symptoms overlap. "Arthralgia" may be due to intra-articular pathology (e.g., arthritis or osteoarthrosis) or extra-articular factors (e.g., joint hypermobility or sensitization, peripheral or central) (Michelotti et al. 2016).

General Principles

TMJ arthritic conditions can be classified as low-inflammatory or high-inflammatory types (Table 1) (Mercuri 2006). Table 2 describes the basic clinical, laboratory, and imaging characteristics of each of these conditions.

Table 1 Classification of TMJ arthritic conditions (Mercuri 2006)

Low-inflammatory disorders	Osteoarthritis (degenerative joint disease) Post-traumatic arthritis
High-inflammatory disorders	Infectious arthritis Rheumatoid (*ARA and JIA*) Metabolic (*Gouty arthritis, psoriatic arthritis, lupus, ankylosing spondylitis, Reiter's syndrome, arthritis associated with ulcerative colitis*)

ARA adult rheumatoid arthritis, *JIA* juvenile idiopathic arthritis

Table 2 The basic clinical, laboratory and imaging characteristics of low and high inflammatory TMJ arthritic conditions

TMJ findings	Low-inflammatory	High-inflammatory
Pain	Localized	Diffuse
TMJ involvement	Unilateral or bilateral	Bilateral
Clicking	Rare	Absent
Crepitation	Present	Rare
Rheumatoid factor	Rare	Present
ESR	Often normal	Elevated
CPP	Normal	Elevated
CRP	May be elevated	Elevated
Imaging	Erosive and exophytic	Erosive
	Asymmetric bone loss	Symmetric bone loss

ESR erythrocyte sedimentation rate, *CPP* cyclic citrullinated peptide antibody, *CRP* C-reactive protein

Low-inflammatory arthritic conditions are purported to begin in the matrix of the articular surface of the joint, with the subcondylar bone and capsule becoming secondarily involved. The two classic types of low-inflammatory arthritis are: first, degenerative joint disease, or primary osteoarthritis (OA), produced by intrinsic degeneration of articular cartilage typically the result of age-related functional loading; and second post-traumatic arthritis.

Even though these low-inflammatory arthritic conditions often involve the TMJ, these seldom require invasive surgical intervention provided they are managed appropriately in the early stages (Henderson et al. 2015; Tanaka et al. 2008; Wang et al. 2012). Patients with low-inflammatory type have been shown to have low leukocyte counts in the synovial fluid and laboratory findings consistent with low-level inflammatory activity (e.g., erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), and the affected joint shows focal degeneration on imaging (Fig. 1) (Mercuri 2006).

High-inflammatory arthritic conditions primarily involve both the synovial cells and bones of the joint. The classic type of high-inflammatory arthritis is rheumatoid arthritis (RA). Other types of high-inflammatory arthritic conditions include metabolic arthritic diseases such as gout (Oliveira et al. 2014), pseudogout (Laviv et al. 2015), psoriatic arthritis (Crincoli et al. 2015), lupus erythematosus (Jordan and D'Cruz 2016), ankylosing spondylitis (Arora et al. 2013), infectious arthritis (Gayle et al. 2013), Reiter's disease (Mansour et al. 2013), and the arthritis associated with ulcerative colitis (Sarlos et al. 2014).

Although these arthritic disorders may be histologically and pathologically different, clinical findings and management are often similar. In all instances the TMJ can be involved, and surgical intervention may be required to alleviate symptoms and correct associated end-stage functional and esthetic problems. Patients with high-inflammatory type arthritis have high leukocyte counts in the synovial fluid, laboratory findings consistent with high-inflammatory activity (e.g., rheumatoid factor [RF] and cyclic citrullinated peptide antibody [CCP]) and show diffuse degeneration of the involved joints on orthopantogram or computed tomography (CT) imaging (Figs. 2, 5, and 6) or bone marrow edema and effusion on magnetic resonance imaging (MRI) (Figs. 7 and 8) (Mercuri 2006).

Signs and Symptoms of Arthritis

The most common symptom of TMJ arthritic conditions is pain. The pain arises from the soft tissues around the affected joint that are under tension, as well as the masticatory muscles that are in reflex protective co-contraction because of Hilton's Law. This orthopedic principle states that the neural supply innervating a joint is the same as that innervating the muscles that move that joint and the overlying skin (Hébert-Blouin et al. 2014). This law provides for the protection of an injured or pathologically affected joint by causing the surrounding musculature to reflexively contract in response to intra-articular injury or pathology, thus safeguarding it from further damage. Pain has also been postulated to arise from the subchondral bone that is undergoing destruction as the result of the arthritic process (Mercuri 2006).

Other common and significant signs and symptoms of TMJ arthritic conditions are loss of

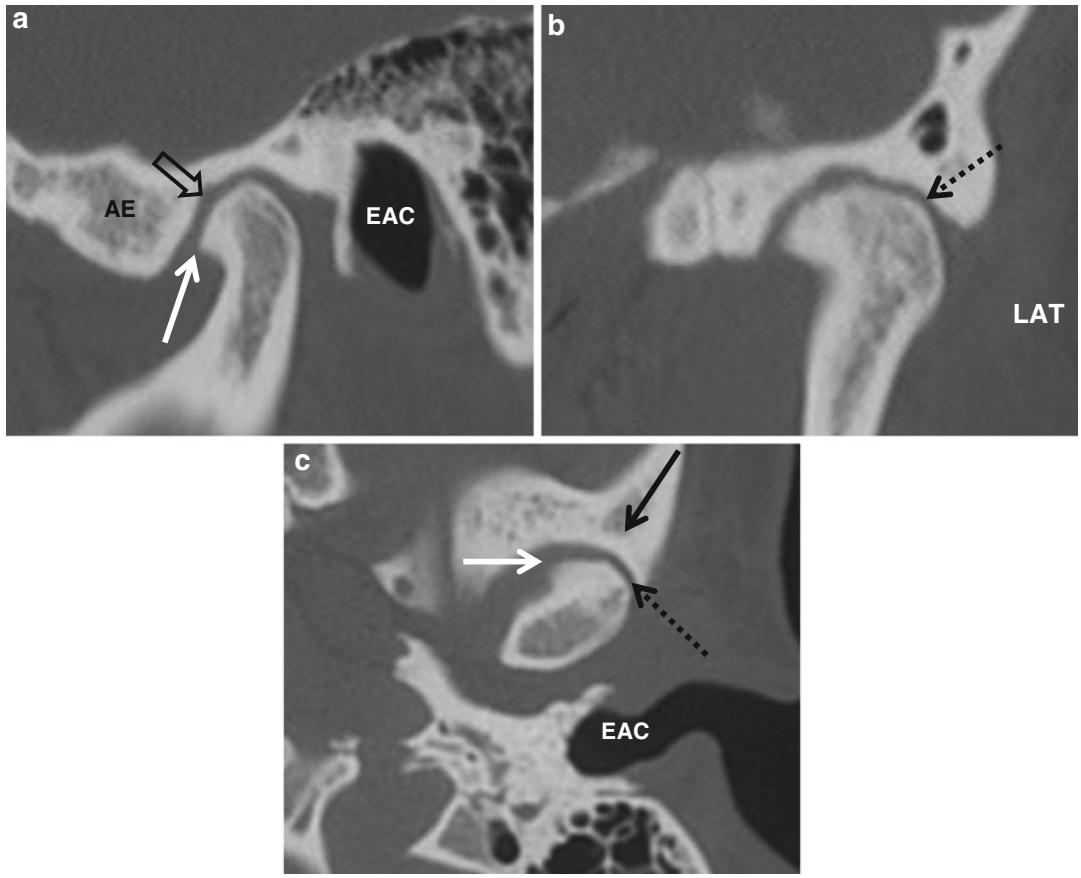

Fig. 1 Sagittal (**a**), coronal (**b**) and axial (**c**) reconstructions of the left TMJ from a multi-detector CT scan demonstrating articular surface remodelling and early, low-inflammatory, osteoarthritis. There is joint-space narrowing which is most marked anterolaterally (dotted black arrows), articular surface flattening and sclerosis (open black arrow) with a small anterior osteophyte (white arrows). Where EAC= external auditory canal and LAT = lateral. (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

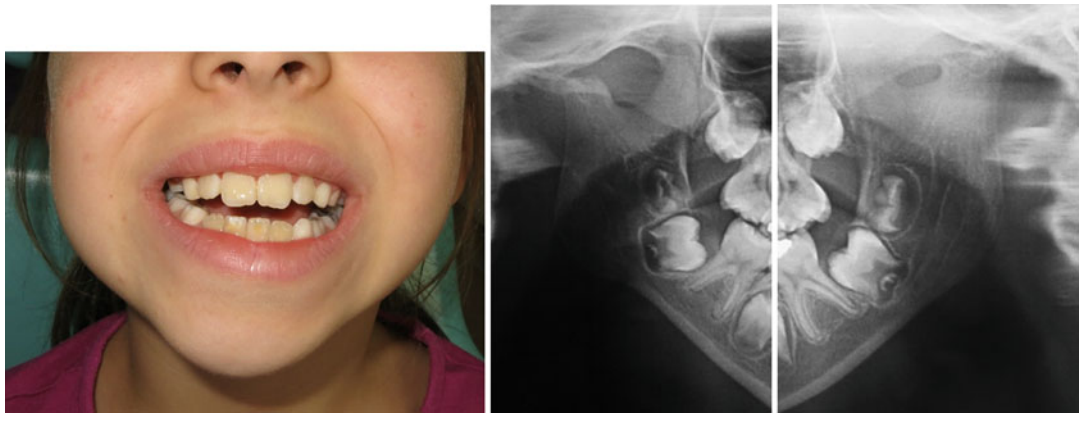

Fig. 2 Patient with JIA demonstrates open bite deformity of high-inflammatory arthritis due to diffuse degeneration of the involved joints

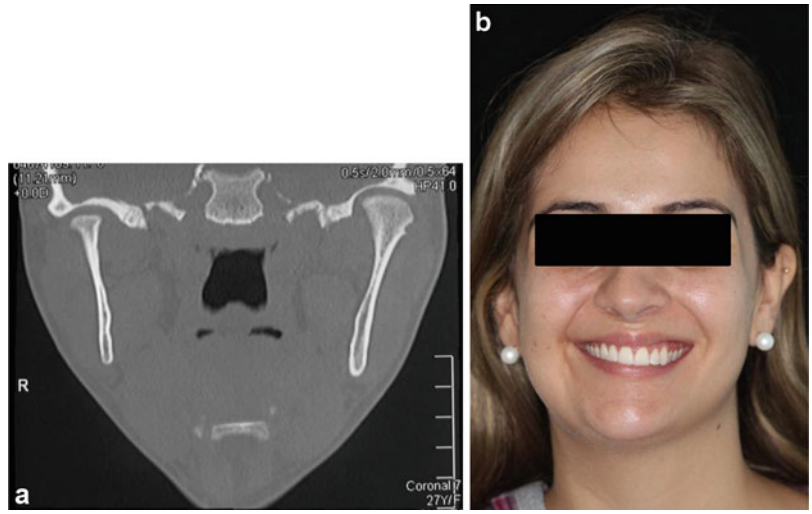

Fig. 3 Facial deformity due to loss of posterior mandibular vertical dimension (**a**) as pathologic osteolysis decreases the height of the right condyle (**b**) resulting to the right mandibular deviation

joint function, joint instability, and facial deformity due to loss of posterior mandibular vertical dimension as pathologic osteolysis decreases the height of the condyle(s) (Figs. 2, 3, and 9) (Mercuri 2006).

Diagnosis

The diagnosis of TMJ involvement in a patient with a widespread late-stage arthritic condition is usually obvious, since other joints will manifest the disease process. The diagnostic challenge occurs if the first affected joint is the TMJ. A comprehensive history and clinical examination are essential. If there is minimal correlation between the history and physical findings, imaging and laboratory examination may be helpful (Mercuri 2006).

Low-Inflammatory Arthritis

Among individuals with TMJ disorders (TMJD), 11% have symptoms of low-inflammatory arthritis (Mejersjö and Hollender 1984). The characteristic radiographic imaging features of low-inflammation arthritis or post-traumatic arthritis are focal joint bony degeneration and the appearance of osteophytes (Fig. 1). The image may be characterized by hypertrophic changes about the affected joint as opposed to atrophic changes seen in high-inflammatory types of arthritis (Figs. 2, 5, and 6). Subchondral focal degeneration, the so-called Ely's cyst may also be seen on low-inflammatory arthritis imaging (Fig. 4) (Mercuri 2006).

It is rare that a patient with a low-inflammatory arthritic condition presents with an acute attack unless there is a recent history of trauma that has aggravated preexisting disease. In those situations, imaging helps to determine the contribution of any long-standing articular degeneration to the traumatic episode. However, minimal flattening of the condyle and/or eminence has been demonstrated in 35% of persons with asymptomatic TMJs. Therefore, it has been concluded that minimal flattening is probably of no clinical significance (Brooks et al. 1992; Campos et al. 2008).

High-Inflammatory Arthritis

The characteristic CT imaging features of high-inflammatory arthritic conditions include diffuse narrowing of the entire joint surface and the appearance of multiple peri-articular cysts (Fig. 5). These cysts are thought to be the result of erosion from the inflamed synovium at its reflection near the insertion of the joint capsule. The margins of these cysts are "fuzzy" during the

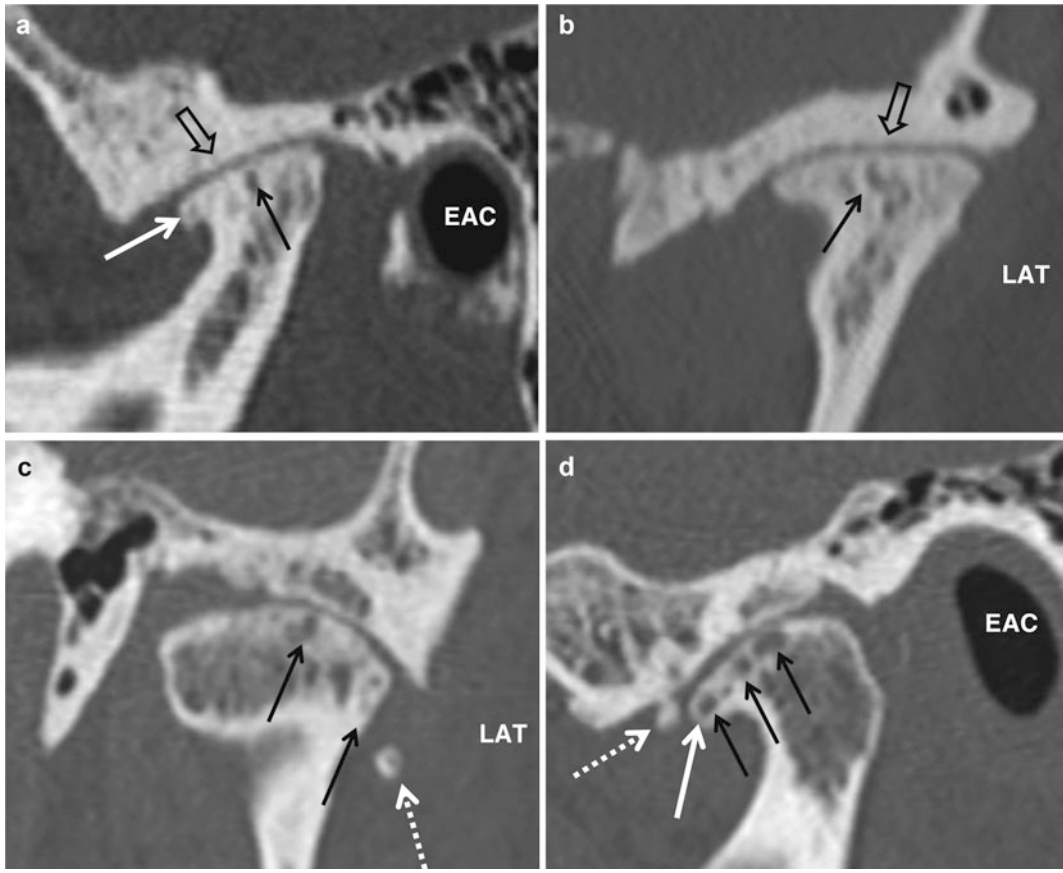

Fig. 4 Low inflammatory osteoarthritis of moderate to marked severity in the left TMJ demonstrated on sagittal and coronal reconstructions from multi-detector CT scans in two patients. Images **a** and **b** show diffuse joint space narrowing and articular surface flattening (open *black arrows*), articular and sub-articular sclerosis and an anterior osteophyte (*white arrow*). There is a small subcortical (Ely's) cyst in the condyle (*black arrow*). Images **c** and **d** are from a different patient and demonstrate similar features including multiple subcortical cysts (*black arrows*), marked loss of joint space in the superolateral aspect of the joint and a calcified intra-articular body (*dotted white arrows*). Where EAC = external auditory canal and LAT = lateral. (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

acute stage and become sclerotic during the chronic stage. The uniform narrowing of the joint space is thought to be due to enzymatic digestion of the cartilage surface (Mercuri 2006). There is characteristic erosion and flattening of the anterior and posterior condylar surfaces and a generalized osteopenia of the condyle and temporal bony components (Figs. 6, 7, and 8) (Tamimi and Hatcher 2016).

Serum rheumatoid factor is positive in only 70–80% of adult RA patients and is rarely positive in juvenile idiopathic arthritis (JIA). The lupus erythematosus test demonstrates a polymorphonuclear cell filled with antinuclear antibody (ANA) complexes. More frequently used tests are the fluorescent ANA tests, the results of which are classified as homogeneous, shaggy, or speckled. Homogeneous, the most common ANA pattern, is seen primarily in lupus erythematosus but occurs in other diseases as well; shaggy (peripheral or rim) is more specific to lupus erythematosus and is often associated with increased disease activity; speckled is characteristic of mixed connective tissue disease. In lupus erythematosus, the titers are higher than those in other rheumatic diseases (Rodrigo and Gershwin 2001).

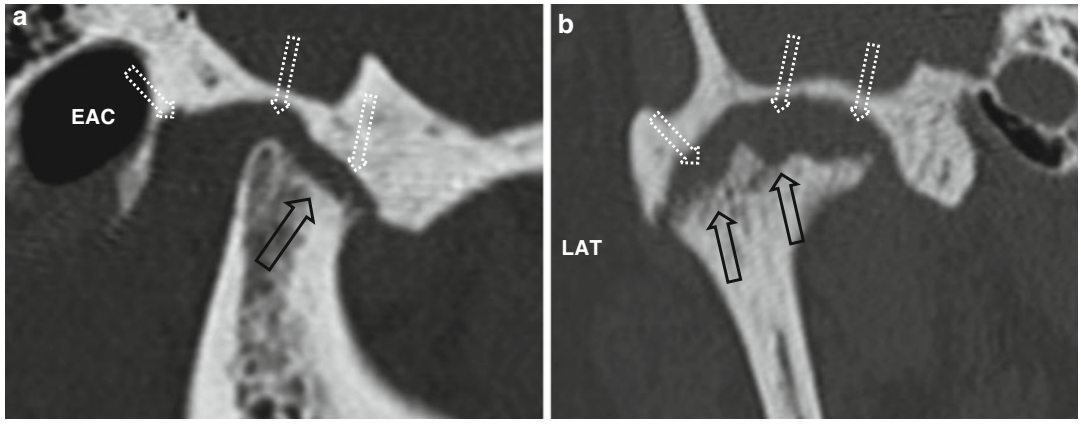

Fig. 5 Sagittal (**a**) and coronal (**b**) reconstructions of the right TMJ from a multi-detector CT scan in a patient with high inflammatory arthritis. There is diffuse erosion of both sides of the joint (open black arrows) giving a grossly irregular condylar contour and a more smoothly expanded glenoid fossa and articular eminence (dotted, open white arrows). Where EAC = external auditory canal and LAT = lateral. (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

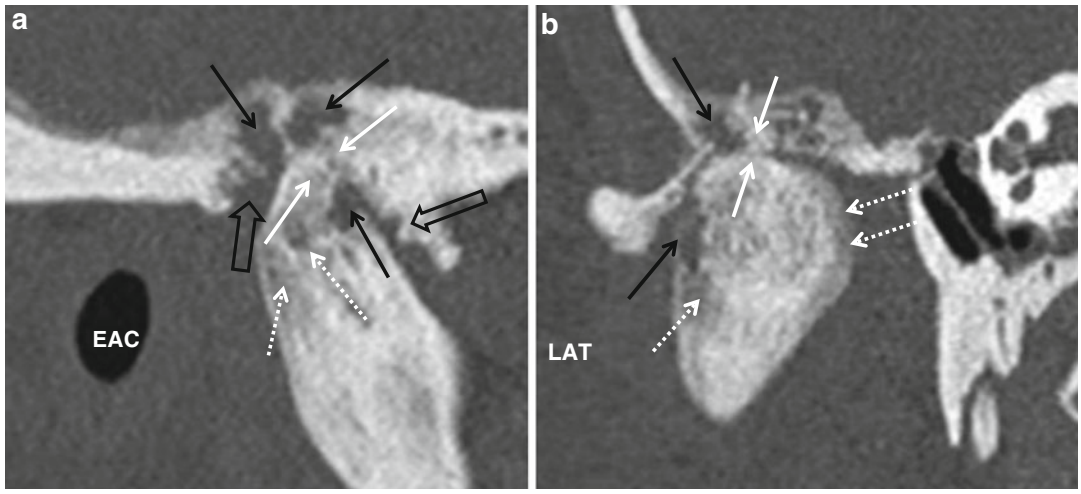

Fig. 6 Multi-detector CT with sagittal (**a**) and coronal (**b**) reconstructions of the right TMJ. In addition to extensive erosion and deformity of both articular surfaces (open, black arrows), there is "bone on bone" contact (white arrows) suggesting focal bony ankylosis. Ill-defined lucencies (black arrows) represent synovial proliferation extending into subcortical bone. In addition to patchy sclerosis which is marked in the condylar neck, there is scattered ill-defined osteopenia (radiolucency) in both the condyle and glenoid fossa (dotted white arrows). (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

Anti-cyclic citrullinated peptide (anti-CCP) antibody testing is particularly useful in the diagnosis of RA, with high specificity, presence early in the disease process, and ability to identify patients who are likely to have severe disease and irreversible damage. However, its sensitivity is low, and a negative result does not exclude disease. Anti-CCP antibodies have not been found at a significant frequency in other diseases to date and are more specific than rheumatoid factor for detecting RA (Niewold et al. 2007).

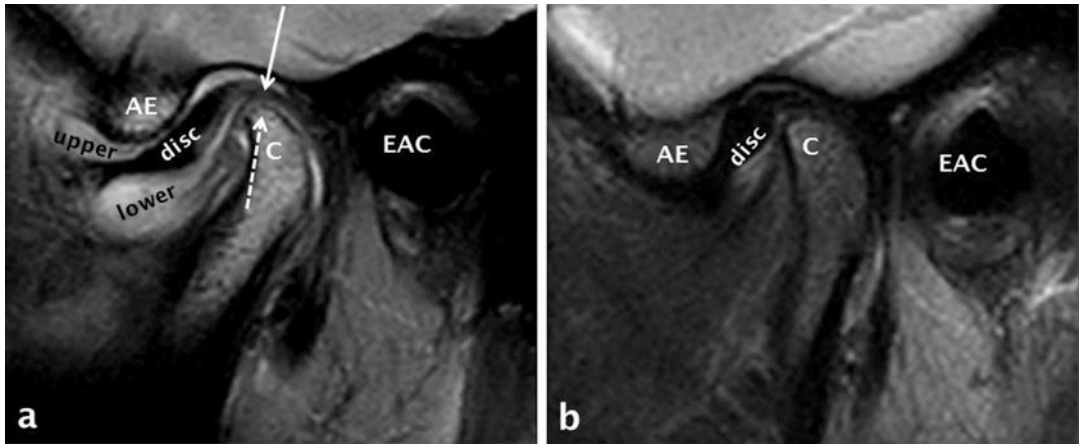

Fig. 7 Seronegative inflammatory arthritis of the right TMJ. (**a**) Right TMJ: The disc is anteriorly displaced. The lower and to a lesser extent, upper joint spaces are markedly distended by high signal fluid/synovial proliferation. There is erosion of the superior condylar cortex (*white dashed arrow*) and edema of the bilaminar zone (*white arrow*). High signal marrow edema is present in the condyle (*C*) and articular eminence. Disc displacement can occur in inflammatory arthritis secondary to weakening of the disc attachments by inflammation. (**b**) Left TMJ: Minimal anterior disc displacement is present. There is no evidence of intra-articular inflammation, the cortices are intact, and there is no marrow edema. *C* condyle, *AE* articular eminence and *EAC* external auditory canal (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most commonly diagnosed high-inflammatory rheumatologic condition in children. It is diagnosed based on medical history, clinical presentation, radiographic findings, and laboratory abnormalities. There are seven categories of JIA: (1) systemic onset, (2) oligoarthritis, (3) rheumatoid factor positive polyarthritis, (4) rheumatoid factor negative polyarthritis, (5) psoriatic arthritis, (6) enthesitis (inflammation at tendon/ligament insertion into bone) related arthritis, and (7) undifferentiated arthritis (Petty et al. 2004) (Table 3).

Clinical findings vary and depend on the location, subtype of arthritis, and duration of disease (i.e., limp, morning stiffness, difficulty walking/running). Children may exhibit extremity overgrowth, undergrowth, or asymmetries such as leg length discrepancies in the axial skeleton. Depending on the duration of symptoms, patients may have muscular atrophy around the affected joints and contractures. Detection of synovitis is a key aspect of JIA diagnosis and management and may prevent long-term disability (Abramowicz et al. 2016).

Table 3 There are seven main types of juvinile idiopathic arthritis, but categorizing conditions is not easy as very often there is overlap between the different categories

The seven types of juvenile idiopathic arthritis	
Oligoarthritis	Affects four or fewer joints
Extended oligoarthritis	Affects more joints after the initial 6 months
Polyarthritis	Affects more than four joints
Enthesitis-related JIA	Affects where the tendons attach to the bones
Psoriatic arthritis	Psoriasis with associated joint inflammation
Systemic JIA	Affects the organs as well as the joints
Undifferentiated arthritis	Does not fit into a single category

JIA patients who also have TMJ involvement can have a dual diagnosis of active arthritis and muscle-related jaw pain. However, subjective finding of jaw pain is not always predictive of TMJ synovitis (Abramowicz 2013a). Limited mouth opening and deviation of jaw when opening have high sensitivity and specificity for synovitis (Abramowicz 2013b). Open bite develops as the result of disease-related condylar bone loss

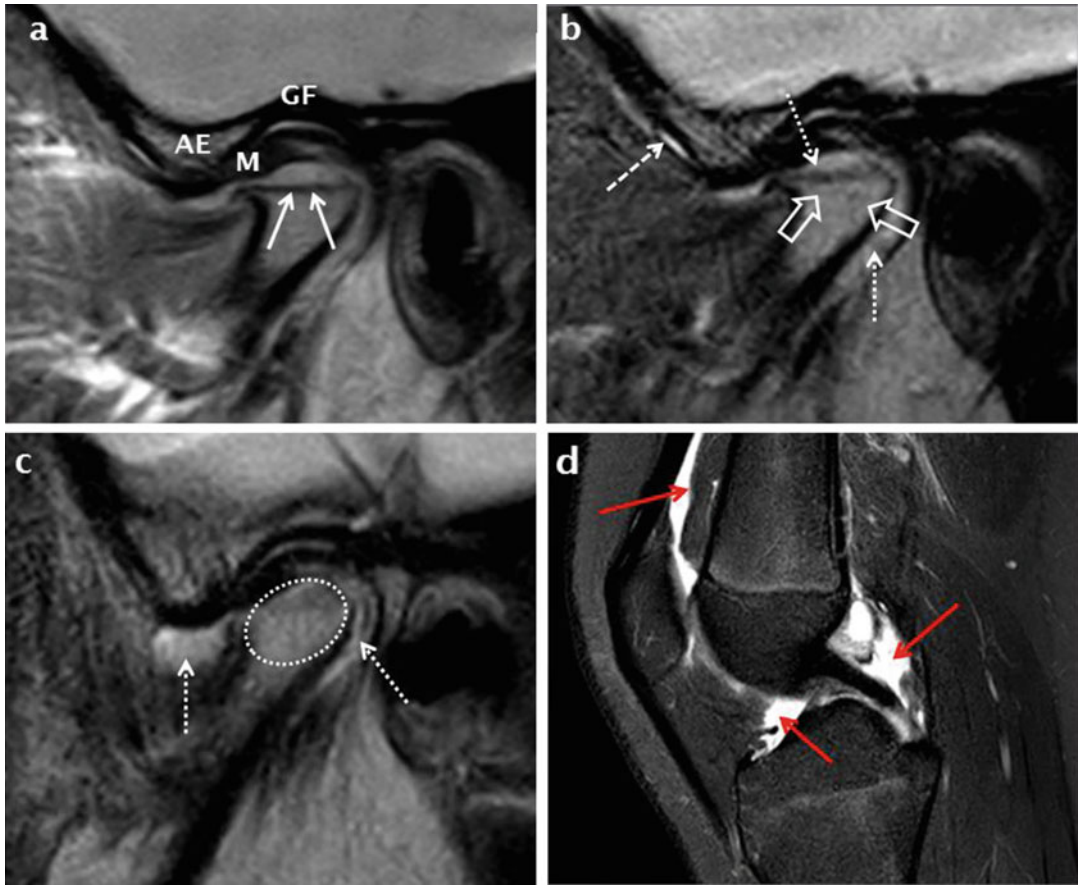

Fig. 8 Thirteen-year-old female with JIA. (**a**) Proton density, sagittal MRI scan showing a normally positioned meniscus (M); GF indicates the glenoid fossa and AE the articular eminence. (**b**) and (**c**) Fat saturation T2 sagittal of the same joint demonstrating distension of the inferior joint space by moderately hyperintense fluid and synovial proliferation (*white dotted arrows*). A trace of hyperintense fluid is present in the upper joint space (*white dashed arrow* in **b**). Diffuse erosion of the condylar cortex (*open white arrows* in **b**) and subarticular marrow edema (*dotted white oval* in **c**). (**d**) Three months later the patient represented with left knee pain and swelling. A fat saturation T2 MRI scan showed a hyperintense joint effusion with foci of synovitis (*red arrows*). JIA was confirmed (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

(Fig. 2). However, gadolinium enhanced MRI most accurately demonstrates synovitis (Fig. 8). Management of JIA depends on the severity of disease, number of joints involved, and current physical limitations (Abramowicz et al. 2011).

Condylar Resorption

Idiopathic or progressive condylar resorption (ICR/PCR) is a severe form of joint degeneration that selectively affects the TMJ of adolescent and young adult females. The period from the teen years to the early 20s appears to be the most active time for ICR/PCR. Occasionally, the disease goes into remission and "burns out" by the mid-20s. However, some patients continue to have active disease into their 30s (Handleman and Mercuri 2015).

The etiology is speculative and includes it being a variation of one of the arthritic conditions affecting the TMJ, functional overload, orthognathic surgery, or hormonal imbalance (Mercuri 2007; Handleman and Mercuri 2015).

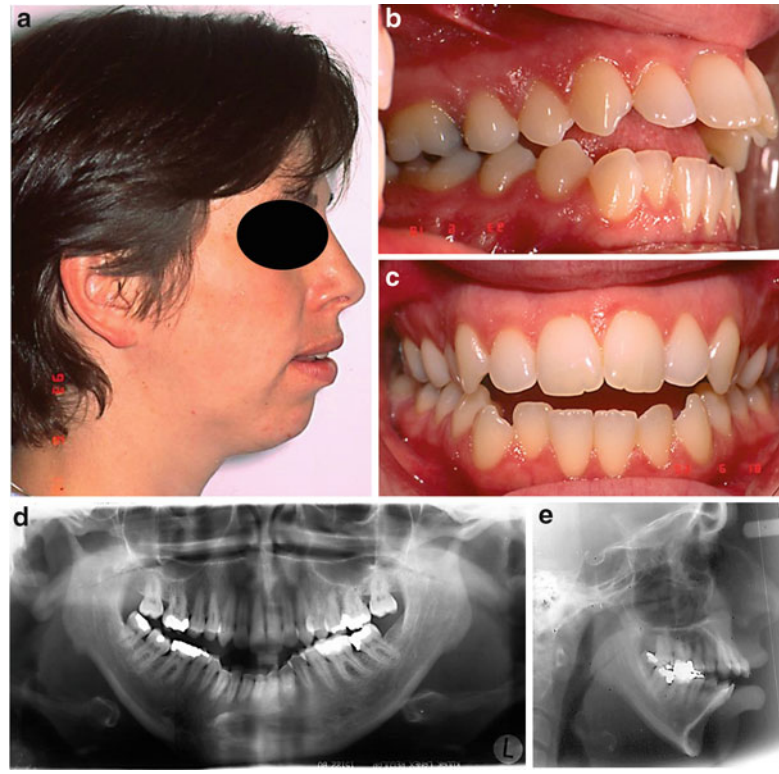

Fig. 9 Thirty-three-year-old female patient with ICR/PCR who reported that her anterior open bite developed over 2 years after a pregnancy. External lateral profile (**a**) intra-oral lateral (**b**) and frontal (**c**) views. Orthopantomogram (**d**) and lateral cephalogram (**e**) (Images courtesy of Dr Sylvain Chamberlain, Quebec City, Canada)

A history of autoimmune and collagen diseases should be documented. Referral to a physician for rheumatoid factor serology should be considered, although this is usually negative in ICR/PCR. When pain is reported, it may indicate that the disease is active (Sarver and Janyavula 2013).

A history of irregular menstrual cycles, amenorrhea, or use of oral contraceptives has been reported in female patients indicating that mid-cycle serum levels of 17β-estradiol should be measured, as low levels have been reported associated with the development of severe condylar resorption (Gunson et al. 2009).

The orthopantogram can provide gross examination of condylar anatomy in suspected cases, and features of this condition include a loss of condylar bone, thereby decreasing the height of the ramus and length of the mandible, and an opening rotation of the mandible resulting in a Class II open bite. The condyle will appear to have lost mass relative to the rest of the mandible and appear thin or shortened with flattening of the superior and/or anterior curvature (Fig. 9).

The cephalometric imaging will show mandibular divergence relative to the cranial base and maxilla, shortened posterior facial height, and increased anterior facial height with an increase in the overjet and negative overbite (Fig. 9e). CT demonstrates degeneration of condylar bone (Fig. 10). The employment of radioisotope scanning is controversial. MRI is useful in examination of the soft tissues of the TMJ, such as the chondral integrity of the condylar head surface, articular disc position and condition, joint effusion, and marrow edema (Fig. 11). MRI or cone beam CT can be used to follow progress of condylar resorption and subsequent remodeling of the condyle in ICR (Hatcher 2013). In addition to demonstrating the position and condition of a displaced disc and recapture or failure of recapture on opening, MRI is the only imaging technique that can accurately demonstrate intra-articular inflammation and sub-articular marrow edema secondary to erosion of the condylar articular surface.

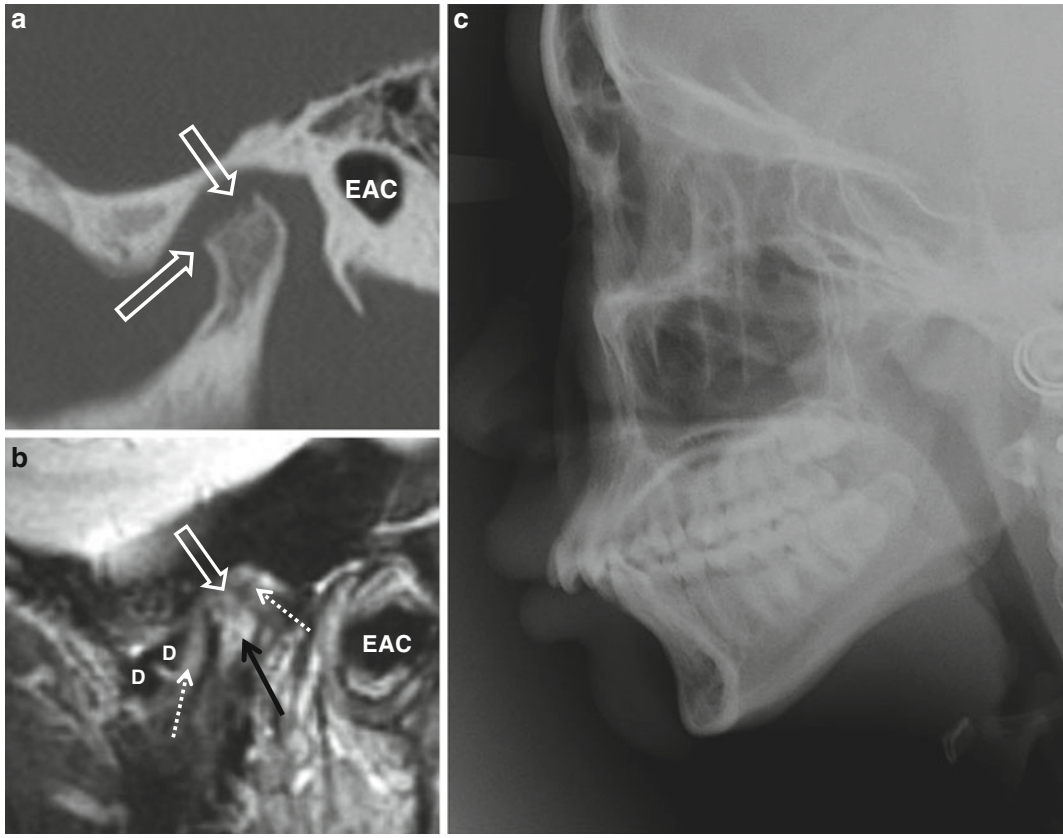

Fig. 10 A 19 year old female with bilateral ICR/ PCR. A sagittal reconstruction from a multi-detector CT of the left TMJ (**a**) is compared with a fat saturation T2 weighted sagittal MRI scan of the same joint. Extensive condylar erosion and resorption (open *white arrows*) is associated with high signal marrow edema in condylar marrow (*black arrow*) inferior joint space synovitis (dotted *white arrows*). The glenoid fossa is not involved and there is marked anterior disc displacement (D). Where EAC = external auditory canal. A lateral cephalogram of the same patient shows marked mandibular retrognathism and a high maxillary-mandibular plane angle and anterior lower facial height. (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

A biomedical and drug management approach has been proposed in which an occlusal appliance is employed for 6 months to reduce the mechanical loads on the joint, and the patient is placed on a comprehensive series of medications, such as clonazepam to relax the musculature and decrease loading from bruxism, antioxidants, tetracycline and piroxicam, and an Omega-3 fatty acid diet to decrease inflammation. A biologic, such as etanercept, is prescribed to reduce the patient's inherent bone resorption capacity (Arnett and Gunson 2013).

The approach to management of ICR/PCR cases should be individualized and based on the extent of the disease process. However, if either condylar resorption is active, in cases requiring extreme mandibular advancements, those with compromised function with severely limited movement of the joints, or failure of previous orthognathic surgery, then total alloplastic TMJ replacement (TMJR) prosthesis should be considered (Fig. 12) (Mercuri 2007; Handleman and Mercuri 2015; Mehra et al. 2016).

Management of TMJ Arthritic Conditions

The goals for the management of TMJ arthritic conditions consist of pain relief, improvement of joint function, diminishing further joint damage,

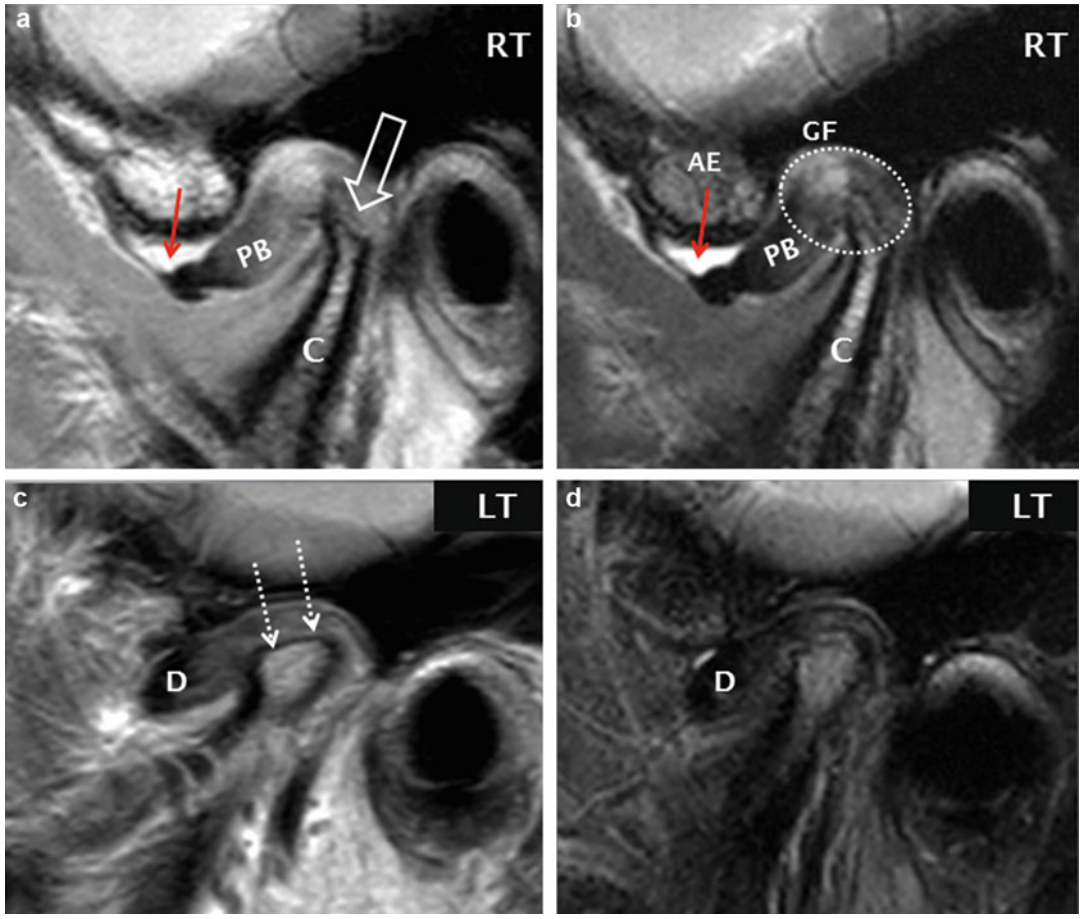

Fig. 11 Bilateral idiopathic condylar resorption (ICR) in a 16-year-old female with mandibular retrognathism, asymmetry, alteration in occlusion, right TMJ pain, and suspected internal derangement. Proton density (**a**) and fat saturation T2 (**b**) sagittal images of the symptomatic right TMJ. A hyperintense effusion distends the anterior recess of the upper joint space (*red arrows*). There is marked anterior disc displacement with swelling and myxoid degeneration of the posterior band (PB). There is extensive resorption of the condylar head (*open white arrow* in **a**) associated with marked synovitis (*white dotted oval* in **b**). A tapered condylar stump remains (*C*) with diffuse hyperintense, marrow edema when compared to the normal, low-signal marrow, in the articular eminence (AE) and glenoid fossa (GF) in image **b**. Mature articular surface remodeling of the left TMJ with flattened articular surfaces and intact cortices (*white dotted arrows*) as shown on proton density (**c**) and fat saturation T2 sagittal (**d**) sequences. The disc (*D*) is anteriorly displaced and deformed and there is only low grade intra-articular inflammation. This joint had been symptomatic 2 years previously (Images courtesy of Clinical Associate Professor Andy Whyte, Perth Radiological Clinic, Perth WA, Australia)

and prevention of disability and disease related morbidity (Mercuri 2006).

An escalating scale for management of TMJ arthritic conditions exists. Noninvasive modalities consist of education, physical therapy, oral appliance therapy, diet control, and pharmacologic agents. Minimally invasive procedures can also include arthrocentesis, arthroscopy, and/or viscosupplementation. Surgical interventions consist of invasive procedures (e.g., bone and joint procedures such as arthroplasty and osteotomy) or salvage procedures such as autogenous or alloplastic joint replacement (Fig. 13). A classification and management scheme based on clinical signs, symptoms, and imaging was proposed many years ago (Steinbrocker et al. 1949), clarified in

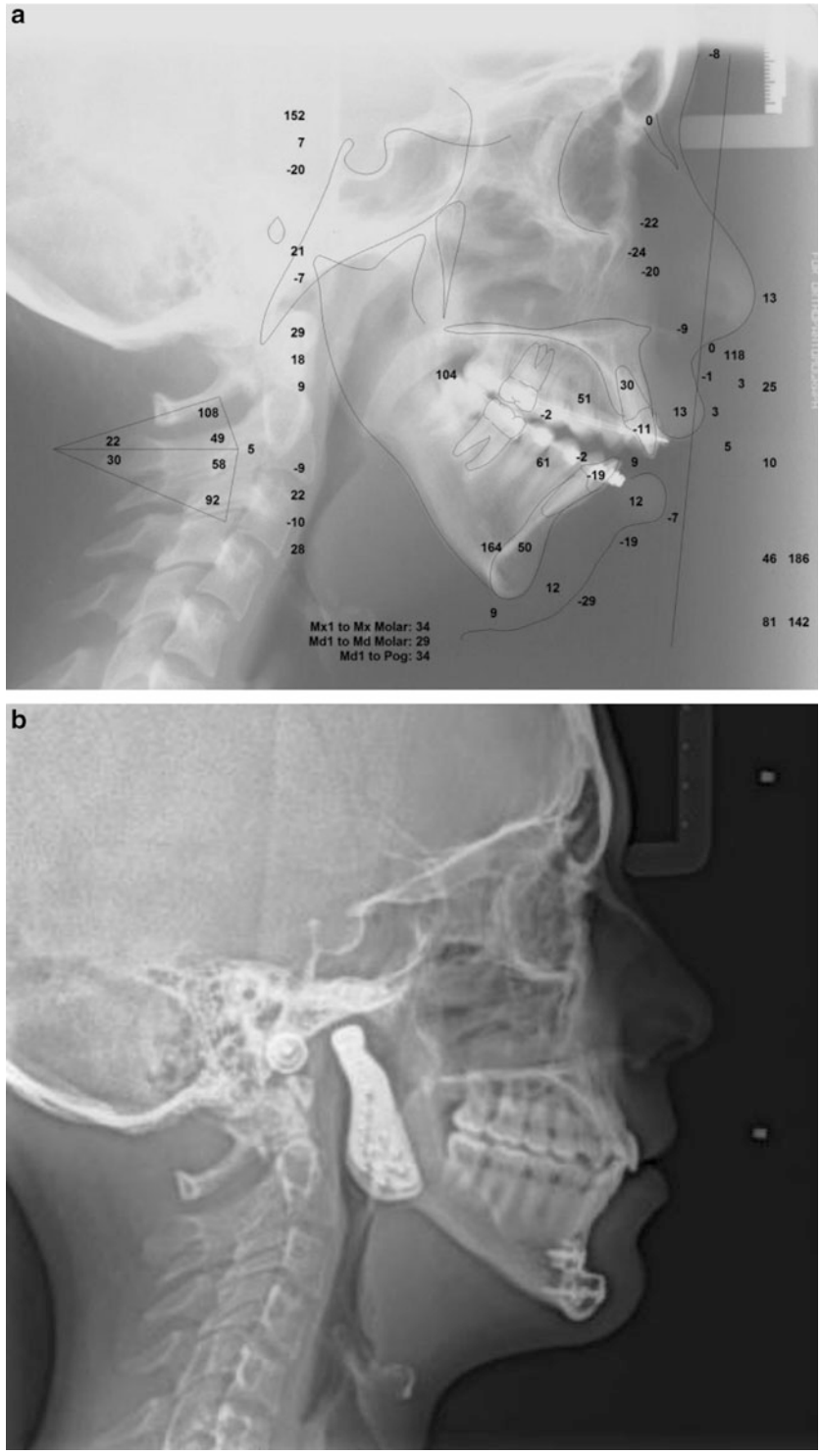

Fig. 12 Lateral cephalogram of a 15-year-old female with ICR/PCR pre- (**a**)- and 6 years post (**b**)-bilateral patient-fitted alloplastic joint replacement (TMJ Concepts, Ventura, CA) and genioplasty (Images courtesy of Dr Donald Kalant, Naperville, Illinois, USA)

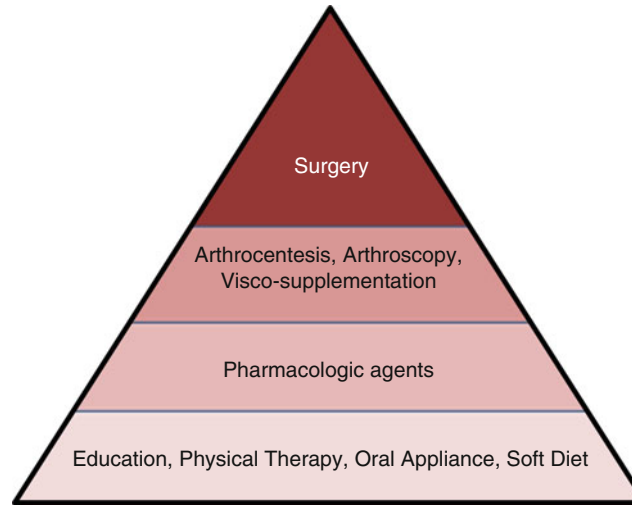

Fig. 13 Arthritic condition management pyramid (Hochberg 2012)

Table 4 Management classification scheme for TMJ arthritic conditions based on signs, symptoms, and imaging (Mercuri 2006; Steinbrocker et al. 1949; Kent et al. 1986)

Stage	Symptoms	Signs	Imaging	Manage
I Early disease	Joint pain Muscle pain Limited function Crepitus	Little or no esthetic or occlusal changes	Mild/moderate erosion of condyle/ fossa and eminence	Noninvasive ↓ Minimally invasive
II Arrested disease	Some joint pain Muscle pain Some joint dysfunction Crepitus	Class II malocclusion Open bite	Flattening of condyle and eminence	Invasive ↓ Salvage
III Advanced disease	Joint pain Muscle pain Dysfunction Retrognathia	High angle Class II Open bite Ankylosis	Gross erosion Loss of height Ankylosis Coronoid hyperplasia	Salvage[a]

[a]Orthognathic surgery or total joint replacement should be considered in a patient with JIA

the 1980s (Kent et al. 1986), and enhanced and modified recently (Table 4) (Mercuri 2006).

Noninvasive Modalities

Education, Physical Therapy, Oral Appliance Therapy, and Diet Control

One of the most difficult problems for patients with arthritic conditions is acceptance that the disease is chronic, with little likelihood of spontaneous complete resolution. Patients with arthritic conditions must live with their disease. Therefore, accurate diagnosis and appropriate patient education are critical to the successful management and quality of life (Mercuri 2006).

Physical modalities can reduce inflammation and pain. Superficial moist heat or localized cold may relieve pain sufficiently to permit exercise. Therapeutic exercises are designed to increase muscle strength, reduce joint contractures, and maintain a functional range of motion. Ultrasound, electro-galvanic stimulation, and massage techniques are also helpful in reducing inflammation and pain (Mercuri 2006). In an informative study, active and passive jaw movements, manual therapy techniques, correction of body posture, and relaxation techniques were used in the

management of 20 consecutive TMJ arthritis patients. After treatment (mean 46 days) pain at rest was reduced by 80% and there was no impairment in 37% of patients (Nicolakis et al. 2001). In pursuing physical therapy, patients should avoid heavy loading exercises that compress the joint. For this reason, isometric muscle strengthening exercises, done so as not to cause pain, are best. Assisted, passive range of motion exercises such as with one of the commercially available jaw exercising devices, such as the Therabite (Atos Medical, Milwaukee, WI) is recommended (Fig. 14) (Oh et al. 2002; Salter et al. 1984).

Soft diet and the use of an oral appliance have been demonstrated to aid in decreasing the load across the articulating surfaces of the joint (Casares et al. 2014). A flat plane processed acrylic maxillary stabilization occlusal appliance can be worn 24/7 for 1 month, except while eating, during the initial acute phase, then at night thereafter. This appliance should be full coverage, opening the bite 2–3 mm posteriorly. It should allow freedom of movement in all excursions of the mandible with cuspid rise or group function in lateral excursions and incisal guidance in protrusion (Fig. 15) (Mercuri 2006).

Pharmacologic Agents

There are multiple pharmacologic agents employed to decrease pain and inflammation in the management of arthritic conditions. Acetaminophen, opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, biologics, nonacetylated salicylate, diclofenac sodium, and/or glucosamine have all been used with varying results.

Fig. 14 Therabite jaw exercising device. Atos Medical, Milwaukee, WI

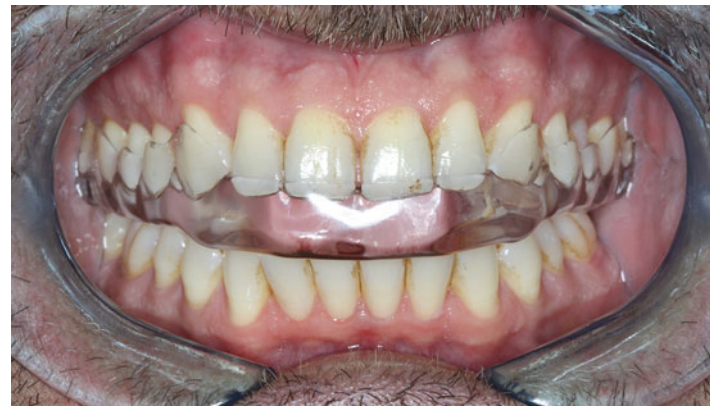

Fig. 15 Flat plane processed acrylic maxillary, full coverage, stabilization appliance (Image courtesy of Clinical Associate Professor Ramesh Balasubramaniam, Perth Oral Medicine & Dental Sleep Centre, Perth WA, Australia)

Low-Inflammatory Arthritic Condition Pharmacologic Management

Acetaminophen (paracetamol), NSAIDs, and opioids are effective in relieving pain but are incapable of reversing cartilage damage and are frequently associated with adverse events. Current research focuses on the development of new drugs (such as sprifermin/recombinant human fibroblast growth factor-18, tanezumab/monoclonal antibody against β-nerve growth factor), which aim for more effectiveness and less incidence of adverse side effects (Zhang et al. 2016).

Regenerative therapies (such as autologous chondrocyte implantation (ACI), new generation of matrix-induced ACI, cell-free scaffolds, induced pluripotent stem cells (iPS cells or iPSCs), and endogenous cell homing) are also emerging as promising alternatives, as they have potential to enhance cartilage repair, and ultimately restore healthy tissue. However, despite currently available therapies and research advances, there remain unmet medical needs in the treatment of low-inflammatory arthritic conditions (Zhang et al. 2016).

The following review highlights current knowledge, research progress on pharmacologic and regenerative therapies for low-inflammatory arthritic conditions and includes key advances and potential limitations of these agents.

Acetaminophen (Paracetamol) Due to its relative safety and effectiveness, acetaminophen is recommended as the first-line oral analgesic for mild-to-moderate low-inflammatory arthritic conditions by most guidelines. The American College of Rheumatology (ACR) and the Osteoarthritis Research Society International (OARSI) guidelines recommend up to 4000 mg per day is an effective initial treatment for mild-to-moderate knee or hip low-inflammatory arthritic conditions (Hochberg 2012).

Due to the risk of liver damage, the US Food and Drug Administration (FDA) limited the amount of acetaminophen in prescription combination products to no more than 325 mg per dosage unit (US FDA 2015). Consistent with the change made by the FDA, the latest 2013 American Academy of Orthopedic Surgeons (AAOS) guideline downgraded the acetaminophen recommendation level to inconclusive and reduced the daily dosage from 4000 to 3000 mg (AAOS 2013). For patients with severe symptoms or who do not respond to acetaminophen, more potent drugs should be considered, such as NSAIDs.

NSAIDs NSAIDs provide anti-inflammatory and analgesic effects, and have long been used as an important remedy for moderate-to-severe low-inflammatory arthritic conditions. Acetaminophen is not regarded as an NSAID as it has little anti-inflammatory effect. In a meta-analysis comparing the safety and efficacy between acetaminophen and NSAIDs, the NSAIDs were better overall than acetaminophen in terms of pain relief. Although the efficacy of NSAIDs for management of low-inflammatory arthritic conditions has been well documented, their potential adverse biological affects often restrict their extensive application (Zhang et al. 2004).

It is estimated that adverse effects occur in approximately 30% of those who take NSAIDs (Pirmohamed et al. 2004). One percent to two percent of people using NSAIDs develop gastrointestinal (GI) complications per year, which is much higher than those not using NSAIDs (Garcia and Jick 1994). Although selective COX-2 inhibitors appeared safer than traditional NSAIDs, several commercial drugs have been placed under scrutiny or withdrawn by the FDA. The first approved COX-2 inhibitor, Celecoxib (Celebrex, Pfizer, New York, NY) received an FDA alert for the potential risk of serious adverse cardiovascular events (US FDA 2005a). Rofecoxib (Vioxx, Merck, Kenilworth, NJ) and Valdecoxib (Bextra, Pfizer, New York, NY) were withdrawn from the market for associated cardiovascular risks and other side effects (US Food and Drug Administration 2004, 2005b).

Therefore, there is a balance between the efficacy and safety of NSAIDs, and the benefit/risk ratio should be considered when employing these drugs. It is recommended by OARSI that NSAIDs be used at the minimum effective dose and prolonged use should be avoided as much as possible (Zhang et al. 2008).

Opioid Analgesics Opioids are used for the management of moderate-to-severe low-inflammatory arthritic pain when NSAIDs and acetaminophen are ineffective or contraindicated (Zhang et al. 2008).There has been an increased use of opioids in arthritic disease management (31% in 2003 to 40% in 2009) (Wright et al. 2014). However, the frequent adverse effects associated with opioids, including nausea, vomiting, dizziness, constipation, sleepiness, tiredness, and headache, may outweigh the benefits in pain relief (Beaulieu et al. 2008). Opioid abuse is another potential risk of using these drugs. Routine use should be avoided, and low effective and tolerated doses are recommended if these drugs must be used (Bouloux 2011).

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) SNRIs are primarily used in the treatment of depression and other mood disorders. In 2010, the FDA approved duloxetine, a selective SNRI, for the management of chronic musculoskeletal pain including low-inflammatory arthritic pain (US Food and Drug Administration 2010). It may be a promising and efficacious way to alleviate low-inflammatory arthritic pain for patients who are unable to take other more commonly used drugs. However, AAOS and OARSI have not included duloxetine in their low-inflammatory arthritic pain management guidelines as more large-scale longitudinal studies to further investigate the safety and efficacy for arthritic condition management should be performed (Zhang et al. 2016).

Potential Pharmacologic Management for Low-Inflammatory Arthritic Condition

The unsatisfactory effects and unacceptable side effects associated with traditional drugs warrants a continued search for potential new medications. Although few of them have received the regulatory approval for routine clinical use, a variety of new low-inflammatory arthritic condition management drugs have shown promising results in clinical trials. Based on the potential therapeutic targets, they can be classified as chondrogenesis inducers, osteogenesis inhibitors, matrix degradation inhibitors, apoptosis inhibitors, and anti-inflammatory cytokines (Zhang et al. 2016).

Bone Morphogenetic Protein-7 Recombinant human bone morphogenetic protein-7 (BMP-7), also called osteogenic protein-1 (OP-1), was a FDA-approved biologic for the treatment of bone nonunions and spine fusion (Ong et al. 2010). A Phase 1 safety and tolerability study first reported the use of BMP-7 in symptomatic low-inflammatory knee arthritic disease. Thirty-three patients (mean age 60 years) were injected intra-articularly with four doses of BMP-7 or placebo. Participants who received 0.1 and 0.3 mg of BMP-7 showed greater symptomatic improvement and higher OARSI response rate. No dose-limiting toxicity was found. Phase 2 study with 0.1 and 0.3 mg dosing cohorts would be further conducted in future (Zhang et al. 2016).

Interleukin-1β Two randomized, double-blind, placebo controlled studies attempted interleukin (IL)-1β inhibitor for low-inflammatory knee arthritic disease management (Chevalier et al. 2009; Cohen et al. 2011). Although IL-1β receptor antagonist/antibody was well tolerated, no significant clinical improvements were reported compared with placebo in either study.

β-Nerve Growth Factor Tanezumab, a monoclonal antibody against β-nerve growth factor, has been tested clinically against low-inflammatory arthritic conditions. As compared with the placebo treatment, treatment with tanezumab significantly reduced knee pain while walking and improved the patients' global assessment (Lane et al. 2010). However, 68% of patients receiving tanezumab were recorded with adverse events. Sixteen subjects developed rapidly progressive end-stage low-inflammatory arthritic disease requiring total joint replacements. These findings prompted the FDA to request the suspension of the trials of tanezumab. However, from subsequent assessments, the risk of rapidly progressive arthritic disease with tanezumab was lower than that with tanezumab/NSAID combination therapy, and the rate of joint replacement was comparable between tanezumab monotherapy and placebo treatment. Therefore, the FDA has agreed to continue the clinical trials of tanezumab for low-inflammatory arthritic pain management in

conjunction with appropriate safety monitoring (US Food and Drug Administration 2012).

Fibroblast Growth Factor A proof-of-concept study has been conducted to evaluate the efficacy and safety of intra-articular sprifermin (recombinant human fibroblast growth factor-18) to manage symptomatic low-inflammatory knee arthritic pain with 180 patients. Sprifermin treatment significantly reduced the loss of total and lateral femorotibial cartilage thickness and volume, as well as the joint space width narrowing in the lateral femorotibial compartment in a dose-dependent manner. No significant difference in serious adverse events was recorded between groups (Lohmander et al. 2014). More basic and clinical studies should be performed to fully investigate this novel low-inflammatory arthritic condition management biologic drug (Zhang et al. 2016).

Pharmacologic Management for High-Inflammatory Arthritic Condition

Over the past two decades, the management of systemic high-inflammatory arthritic conditions has been revolutionized by advances in the understanding of their pathologic mechanisms and the development of drugs which directly target them. These newer medications have shown great promise at improving disease outcomes, but they come with notable side effects which can pose long-term treatment challenges, as well as difficulties in the perioperative arena (Kahlenberg and Fox 2011).

NSAIDs NSAIDs are used often in the management of high-inflammatory arthritic conditions in conjunction with other medications or as monotherapy for acute gout or the seronegative spondylo-arthropathies. There is not one NSAID medication or dose recommended over other medications (Bays and Gardner 2016).

Corticosteroids Steroids are used commonly in the management of the high-inflammatory arthritic conditions. Glucocorticoids act through the cytosolic steroid hormone receptor, resulting in increased expression of anti-inflammatory proteins and decreased production of proinflammatory proteins (Stahn and Buttgereit 2008).

The underlying principle in prescribing steroids is that patients should be on the lowest dose possible for the least amount of time. Some consequences of steroid usage include bone loss, hypertension, weight gain, steroid psychosis, impaired glucose tolerance, avascular necrosis, and increased rate of infection. In addition, severe hypokalemia may occur from pulse dose steroids. Important adjunctive therapy includes calcium and vitamin D, and in some situations, prophylactic bisphosphonate therapy and prophylaxis against pneumocystis. Special considerations include patients with high infectious risk, patients with diabetes, and patients with surgical wound healing. In addition, steroid usage may increase the risk of GI bleed in a hospitalized patient setting, and prophylactic proton pump inhibitors should be considered (Narum et al. 2014).

Disease modifying anti-rheumatic drugs (DMARDs) became the mainstay of RA management in the 1970s. Examples of conventional DMARDs are methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine.

As a group, these drugs have been shown to decrease inflammation and slow radiographic progression of the disease's effect on articulations; but the degree to which this is accomplished is variable. The timing of DMARD initiation has been debated, but current consensus suggests that the earlier treatment can be initiated, the better the overall outcome for clinical improvement and prevention of erosive disease (Verstappen et al. 2003).

A major difficulty in managing patients with high-inflammatory arthritic conditions is that it is currently impossible to predict which patients will respond to which medication regimen. Current research is ongoing to develop patient-specific disease signatures via genetic and proteomic approaches. However, the practical application of such advances has not been achieved. Thus, practice guidelines typically recommend starting with conventional DMARD treatment before addition or substitution of biologic DMARD medications. Importantly, the use of DMARDs in combination rather than monotherapy has been reported more effective in achieving improved

clinical outcomes as well as slowing radiographic progression of the disease (Ma et al. 2010).

Biologic DMARDs The availability of medications targeted toward specific abnormalities of the immune system, the so-called biologic DMARDs, has revolutionized the management of high-inflammatory arthritic conditions. This expanding collection of drugs targets molecules which have been shown to play important roles in the pathology of these diseases.

Because of their cost and side effect profile, the use of biologic DMARDs is typically recommended after patients have failed the use of single or combination conventional DMARD therapy. However, in patients who present with aggressive, erosive high-inflammatory arthritic conditions, the biologic DMARDs can be considered as a component of first-line therapy (Kahlenberg and Fox 2011).

The initial choice of a biologic DMARD is typically a tumor necrosis factor (TNF) blocking agent, which includes infliximab, adalimumab, etanercept, and the newer golimumab and certolizumab. These agents have varied effects on a molecular level including binding soluble TNFα and induction of apoptosis of TNFα expressing cells. Each of these drugs has a distinct dosing schedule or mode of administration. However, all appear to have similar benefits in high-inflammatory arthritic conditions (Statkute and Ruderman 2010). Other biologic DMARDs found to be effective in inhibiting the immune and cytokine systems in high-inflammatory arthritic conditions include rituximab, abatacept, anakinra, and tocilizumab (Kahlenberg and Fox 2011).

By their nature, high-inflammatory arthritic conditions confer an elevated risk of infection. DMARD and biologic therapies suppress the immune system through various targets, increasing this risk. Bacterial infections, particularly pneumonia and soft tissue infections, are increased with the use of methotrexate, and this is increased 2–4-fold with the addition of an anti-TNF medication. Similar infectious risks have been found with other biologic DMARDs as well (Mushtaq et al. 2011).

Because of the nature of their disease, patients with high-inflammatory arthritic conditions have many features that can impact perioperative management. Thus, consultation with a patient's rheumatologist prior to surgery may help to identify unique risks for that patient and prevent perioperative morbidity and mortality. High-inflammatory arthritic patients have an increased risk of infection after joint replacement surgery (Bongartz et al. 2008). The use of corticosteroids, DMARDs, and biologic DMARDs all can increase the risk of infection and theoretically impair wound healing. There is ongoing debate regarding which medications to interrupt perioperatively. Current recommendations for perioperative use of these medications are summarized in Table 5 (Kahlenberg and Fox 2011).

Table 5 Recommendations for perioperative management of medications used to treat high-inflammatory arthritis (Kahlenberg and Fox 2011)

Medication	Perioperative management
Steroids	Continue at lowest dose possible; stress dose steroids as indicated
Methotrexate	Hold doses immediately before and after surgery
Leflunomide	Hold at least 1 week prior to surgery
Hydroxychloroquine	Continue perioperatively
Sulfasalazine	Hold only on day of surgery
Anti-TNF drugs	Hold for one dose perioperatively
Rituximab	Optimal timing of surgery when CD20 counts have rebounded (3–6 months after last dose)
Abatacept	Hold 1 month prior to surgery
Anakinra	Hold 1 week before and after surgery
Tocilizumab	Hold dose prior to surgery

Minimally Invasive Procedures

A Cochrane Database meta-analysis concluded that there was a paucity of high level evidence for the effectiveness of interventions for the management of TMJ arthritic conditions. Large parallel groups of randomized clinical trials which include participants with a clear diagnosis of TMJ arthritic conditions should be encouraged, especially studies evaluating some of the

possible surgical interventions (de Souza et al. 2012).

Intra-articular Medications

Localized drug delivery via intra-articular injections can minimize ectopic effects while directly alleviating joint pain and other symptoms. Intra-articular injection of corticosteroids and hyaluronic acid are selectively used in the management of arthritic conditions.

Hyaluronic Acid Sodium hyaluronic acid (HA) is an injectable, large, linear glycosaminoglycan that is a component in both healthy and arthritic joint fluid. Intra-articular injection of HA is recommended by OARSI as a management option for painful knee or hip arthritic conditions (Zhang et al. 2008). However, the efficacy of HA injection varies. The 2013 edition of the AAOS guideline downgraded the recommendation on HA from an inconclusive level to a nonaffirming level after excluding the lower strength evidence of its effectiveness (Felson 2006).

For TMJ arthritic conditions, there was no difference in outcomes of measured variables between the HA group and the placebo and saline control groups. It was concluded that HA did not appear to be an effective means of treating TMJ arthritic conditions (Bertalomi et al. 1993).

HA injections into an experimentally induced sheep TMJ low-inflammatory arthritic disease model over a 14-month period suggested a possible role for HA in preventing the progression of the disease. The HA-injected TMJs revealed minimized osteoarthritic changes when compared to control joints injected similarly with saline (Neo et al. 1997).

In humans, it has been reported that after a 24-month follow-up period after arthrocentesis either with or without the addition of HA, that although both groups benefited from these procedures, those patients having arthrocentesis with the addition of HA had superior results (Alpaslan and Alpaslan 2001). An in vivo rabbit study compared intra-articular injections of 1.6-mg prednisolone and 1.3-mg hyaluronate weekly for 1 month for TMJ low-inflammatory arthritic disease. The HA injected joints demonstrated limited cartilage change, less fibrillation, and the presence of clusters of chondrocytes in deficit areas. The prednisolone treated joint exhibited worsening of the cartilage destruction (Shi et al. 2002).

A systematic review and meta-analysis of all randomized, controlled trials of intra-articular HA injections for TMJ disorders concluded that the existing evidence was insufficient to either support or refute the benefit of HA injections (Shi et al. 2003). Nevertheless, the usefulness of serial HA injections performed after arthrocentesis for the treatment of TMJ low-inflammatory arthritic disease and for the maintenance of improvements over a 6-month follow-up period was reported (Manfredini et al. 2009).

The US FDA has only approved intra-articular HA formulations for knee arthritic conditions. However, these formulations are currently being used "off label" (Stafford 2008) to manage pain in several other joints, including the TMJ (Tanaka and Detamore 2008; Salk et al. 2006).

Corticosteroids Corticosteroid injection is recommended by OARSI for patients with moderate-to-severe pain who do not respond to oral analgesic and anti-inflammatory agents (Zhang et al. 2008). The American College of Rheumatology and AAOS conditionally recommended corticosteroids for management of early knee and/or for hip arthritic conditions (Hochberg et al. 2012).

The main limitations of repeated intra-articular steroid injections are the risks of infection and the destruction of articular cartilage, tendon, or ligament attachments. Repeated intra-articular corticosteroid injections have been implicated in the "chemical condylectomy" phenomenon in the TMJ of adults (Møystad et al. 2008; Moskowitz et al. 1970; Ringold et al. 2008; Slater et al. 1967; Toller 1977). Single injections of steroids into the TMJ may be helpful for patients over 30 years of age but are not indicated in younger patients (Toller 1977).

A review of an extensive experience of over 7000 injections of hydrocortisone into synovial cavities concluded that such treatment was a safe and effective palliative procedure in the local management of arthritic condition (Hollander 1953). However, almost concurrently, caution

was recommended with this treatment since the steroid might interfere with a local protective mechanism and encourage further damage with joint function (Chandler and Wright 1958).

Experimental evidence of histological damage to the articular surfaces of the mandibular condyles of healthy *Macaca irus* monkeys was reported after six injections of hydrocortisone (Poswillo 1970). Intra-articular injections of steroids are not routinely recommended in patients with low-inflammation arthritic conditions. Injections should be considered only with evidence of acute high-inflammation of the joint. In all cases after intra-capsular injection of steroids, decreased activities within pain free limits should be recommended to prevent acceleration of the degenerative process from overactivity and joint overload (Tanaka and Detamore 2008). The accuracy of the placement of intra-articular injections depends upon the experience of the practitioner. An estimated one-third to one-half of all steroid and HA injections are inaccurately placed, although the impact of this extra-articular placement on therapeutic efficacy and clinical outcome remains unclear (Jackson et al. 2002; Jones et al. 1993).

Nano- and microparticles developed from a variety of natural and synthetic materials are being investigated for intra-articular sustained release applications (Gerwin et al. 2006; Larsen et al. 2008). Novel systems for sustained release will increase the resident time of medications within the joint, reducing the need for repeated intra-articular injections and thus minimizing iatrogenic damage. Tighter control over release kinetics would reduce the required medication dosage and decrease the risk of ectopic effects (Mountziaris et al. 2009).

There has been reluctance to use intra-articular steroid injections for arthritic TMJs in children because of initial studies reporting cartilage damage and avascular necrosis. However, these adverse outcomes occurred in adults with arthritic conditions, not in children with JIA. Intra-articular injections can be indicated as an adjunct to systemic treatment of JIA, if the TMJs exhibit persistent active arthritis despite systemic therapy. TMJ injections may also be of use in patients not responsive to systemic medication to provide relief during a change in drug therapy (Abramowicz et al. 2016).

Intra-articular steroid injections for management of TMJ symptoms in JIA have had recent success using triamcinolone acetate or triamcinolone hexacetonide. Adverse reactions have been reported to be rare, but they included transient facial swelling (Arabshahi et al. 2005), and/or reversible subcutaneous atrophy at the injection site (Ringold et al. 2008). These studies reported that most patients demonstrated an increase in mouth opening. However, repeated injections only yield minimal further benefits (Ringold et al. 2008). If there is recurrence of TMJ involved despite intra-articular injections, additional systemic therapy may be indicated (Abramowicz et al. 2016).

In a study of 24 consecutive adult patients with TMJ low-inflammatory arthritic conditions treated randomly with either arthrocentesis alone (control group) or arthrocentesis plus corticosteroid injection (CS group) where outcome variables were visual analog scale evaluations (i.e., masticatory efficiency, joint sounds, and pain complaints), maximal interincisal opening, and mandibular motions recorded at baseline and at 12 months postoperatively, concluded that arthrocentesis plus intra-articular CS injection produced no better outcomes in terms of range of motion and clinical symptoms in patients with TMJ low-inflammatory arthritic conditions, as compared with those undergoing arthrocentesis alone (Kiliç 2016).

Platelet-Rich Plasma Platelet-rich plasma (PRP) contains several kinds of growth factors including transforming growth factor β1 platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor-1, and hepatocyte growth factor (Sánchez et al. 2008). Positive trends and safety profile of PRP have been reported in other studies, suggesting a feasible and potential treatment for low-inflammatory arthritic conditions (Kon et al. 2010; Smyth et al. 2016).

In one study, surgical defects were created bilaterally in the TMJ condylar fibrocartilage, hyaline cartilage, and bone to induce osteoarthritic changes in rabbits. PRP was applied to the

right joints of the rabbits (PRP group), and the left joints received physiologic saline (control group). After 4 weeks, the rabbits were sacrificed for histologic and scanning electron microscopy (SEM) examinations. The authors found new bone regeneration was significantly greater in the PRP group ($P < .011$). Although the regeneration of the fibrocartilage and hyaline cartilage was greater in the PRP group, no statistically significant difference was found between the two groups. SEM showed better ultrastructural architecture of the collagen fibrils in the PRP group. They concluded that PRP might enhance the regeneration of bone in TMJ low-inflammatory arthritic conditions (Kütük et al. 2014).

When injected into patients with TMJ low-inflammatory arthritic conditions, PRP was reported to have performed better than HA in follow-up in terms of pain reduction and increased interincisal mouth opening (Hegab et al. 2015).

In cell culture, the effects of PRP on non-chondrocyte cell lineages within synovial joints, such as fibroblast-like synoviocytes, which produce cytokines and matrix metalloproteinases (MMPs) that mediate cartilage catabolism were studied. Platelet-rich plasma was shown to contain a mixture of anabolic and catabolic mediators. These authors found that synoviocytes treated PRP responded with substantial MMP secretion, which may increase cartilage catabolism. Therefore, future studies must focus on the synergistic actions of PRP in the management of TMJ low-inflammatory arthritic conditions (Browning et al. 2012).

Arthrocentesis

Arthrocentesis is defined as the instillation or removal of fluid or injection of medication into a joint. In the TMJ, arthrocentesis has been used to "wash out" TMJ inflammatory mediators, release the "anchored" disc, disrupt joint adhesions, and deliver drugs to the joint (e.g., HA, corticosteroids, PRP) to manage pain (Fig. 16). Typically, manual TMJ manipulation to the extremes of function is performed during this procedure. The procedure may be performed under local analgesia, conscious sedation, or general anesthesia.

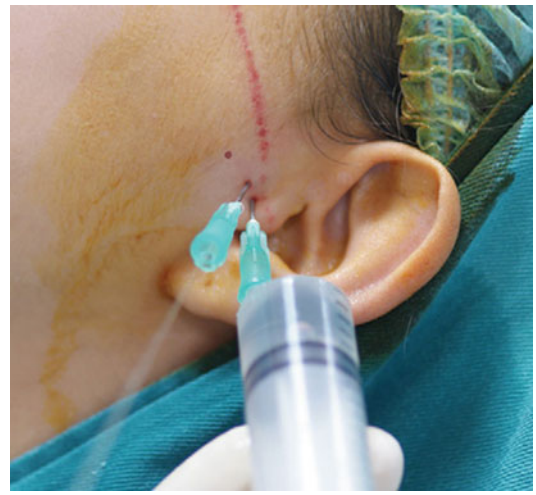

Fig. 16 Arthrocentesis lavage of the left TMJ superior joint space. The upper joint space is undergoing a lavage with lactated Ringer's solution in a patient with an acute disc displacement, limited mouth opening and pain

TMJ arthrocentesis provided a statistically significant short-term improvement of pain and enhanced function in low-inflammatory arthritic patients for 6 weeks after TMJ arthrocentesis (Trieger et al. 1999). A possible explanation for the relief of symptoms being that debris and inflammatory cytokines were removed during the procedure (Quinn and Bazan 1990).

The long-term outcome of arthrocentesis in 79 patients (83 joints) with symptomatic TMJ low-inflammatory arthritic disease was studied. These patients had not responded to nonsurgical interventions. In this study cohort, arthrocentesis offered long-term favorable outcomes for symptomatic TMJ low-inflammatory arthritic patients who had not responded to nonsurgical treatments and otherwise would have required surgery. Severity of preoperative clinical and computerized tomographic findings did not predict the success of arthrocentesis. This finding and the lack of correlation between the clinical and radiologic findings negates the commonly held belief that the clinical signs and symptoms deteriorate together with radiologic changes (Nitzan et al. 2016).

In another study, arthrocentesis plus intra-articular corticosteroid injection produced no better outcomes in terms of range of motion and clinical symptoms in patients with low-inflammatory TMJ

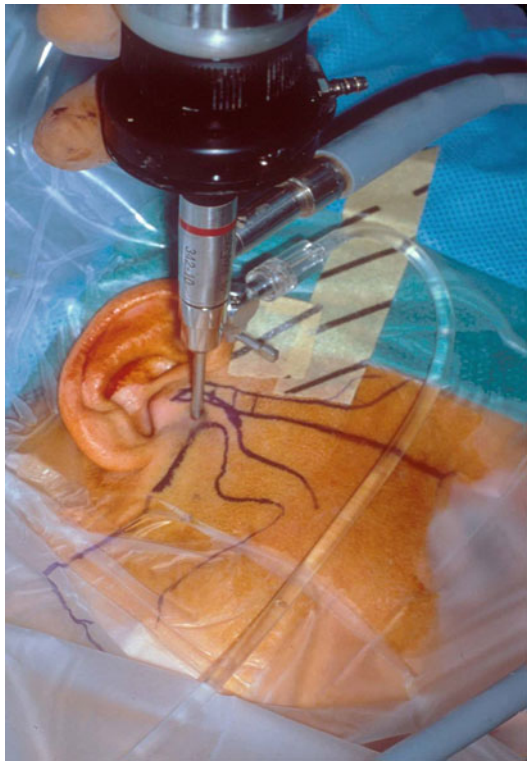

Fig. 17 Arthroscope in the superior joint space of a right TMJ

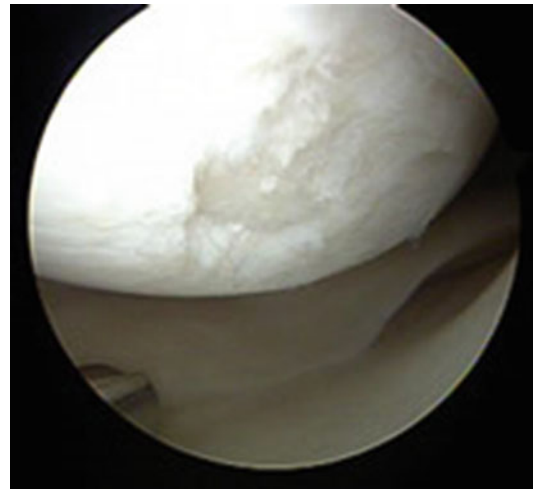

Fig. 18 Arthroscopic examination of the superior joint space of a right TMJ demonstrating early osteoarthritic changes at the posterior slope of the articular eminence. Note the loss of cartilage and exposed bone

arthritic conditions, as compared with those undergoing arthrocentesis alone (Kiliç 2016).

Arthroscopy

Arthroscopy is a procedure for diagnosing and managing intra-articular joint problems. A surgeon inserts a narrow tube attached to a fiber-optic video camera through a small incision. The view inside the joint in question is transmitted to a high-definition video monitor (Figs. 17 and 18).

The value of TMJ arthroscopy lies in the early diagnosis and management of arthritic conditions. However, the incidence of low-inflammatory arthritic conditions on magnetic resonance images (38%) was reported to be significantly lower than that in arthroscopic findings (78%). There was no significant agreement between these two findings ($p = .108$). The κ coefficient was 0.154. Therefore, they concluded that the diagnostic accuracy of magnetic resonance images for TMJ arthritic condition was low and that the early arthritic condition could not be diagnosed from magnetic resonance images. These authors stated that the diagnostic accuracy of low-inflammatory arthritic conditions without arthroscopy is not always high.

The arthroscopic picture varies widely depending on when during the arthritic process the procedure is performed and whether disease-modifying therapeutic agents are concurrently used (Holmlund 1991). For patients with rheumatoid arthritis, the early features of synovial involvement may be increased vascularity and capillary hyperemia and the more severe the disease, the more these features will be observed. The same is true of the cartilage, in which the findings may vary from early superficial changes such as localized areas with fibrillation, to lesions and exposure of subchondral bone. Late-stage marked fibrosis or ankylosis makes arthroscopy impossible and contraindicates its usefulness.

In early-stage RA, arthroscopic lysis and lavage has been reported to alleviate symptoms in both the knee (Jayson and Dison 1968) and the TMJ (Holmlund et al. 1986). The explanation for the relief of symptoms being that debris and other inflammatory products are removed (Gynther and Holmlund 1998). In cases with only minor areas of synovial inflammation, sometimes found in

early-stage RA, subsynovial injection of small volumes of corticosteroids during arthroscopy and/or HA has been reported as helpful in reducing symptoms and increasing function (Kopp et al. 1987; Vallon et al. 2002).

Advanced arthroscopic surgical techniques have been reportedly used to perform synovectomy in more advanced-stage RA where hypertrophic synovium or granulation tissue is found. The removal of such tissue may arrest the disease process in that joint. These techniques demand considerable skill and must always be performed under direct vision. Bleeding can obscure the visibility and these procedures should be limited to patients with well-defined lesions in the hands of highly skilled arthroscopists (Holmlund 1991; Bjornland and Larheim 1995).

Diagnostic and surgical arthroscopy has decreased the morbidity and cost of invasive TMJ procedures; nevertheless, it is essential to understand that there are limitations to their use. In certain stages of TMJ arthritic conditions, it is contraindicated to attempt to insert an arthroscope. These include cases with marked clinical impairment of mobility due to fibrosis or bony ankylosis (Fig. 19). Such cases, as well as those exhibiting imaging consistent with pronounced granulation tissue or suspected villus formation, are all best managed by open TMJ procedures (Heffez 1991; Holmlund 1991; Murakami 1992).

Surgery

End-stage disease represents the worst condition or disease state of an organ system, at which point in time, the organ is functioning minimally or not at all. Systemic examples include end-stage renal disease, in which the kidneys have essentially shut down and the patient requires dialysis or renal transplantation to accomplish the essential roles of the kidney; and end-stage cardiac disease, in which the heart is functioning very poorly with minimal cardiac output and a compromised ejection fraction, and may need mechanical support (e.g., left ventricular assist device) or cardiac transplantation for the patient to survive, considering the vital role of the cardiovascular system (Mercuri 2012).

Applying the term "end-stage" to disorders affecting the functional joints of the human body, end-stage joint disease indicates a joint that is so negatively affected architecturally by disease or injury that severe functional

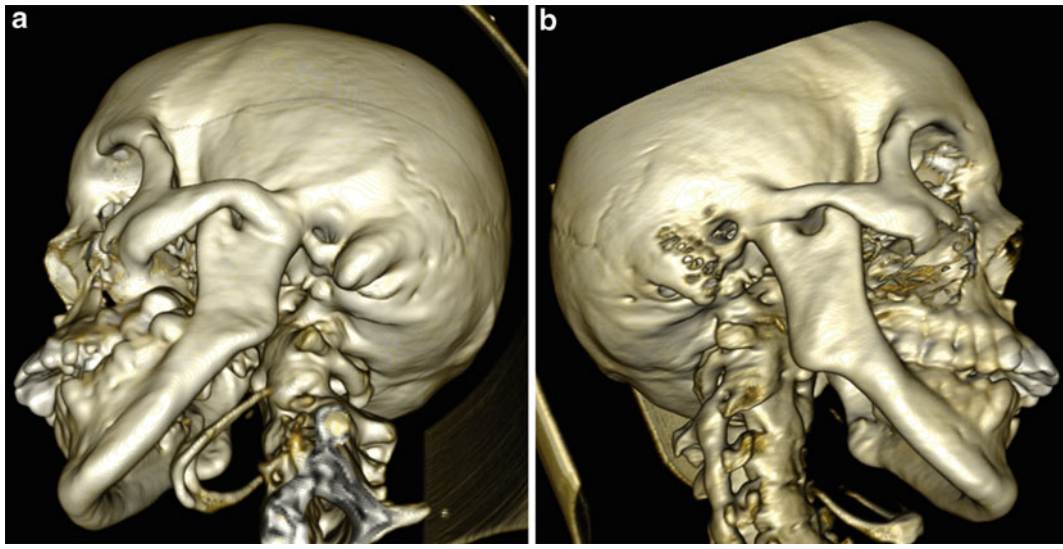

Fig. 19 3 Dimensional CT reconstruction of bilateral TMJ ankylosis secondary to ankylosing spondylitis, a high-inflammatory arthritic condition (Images courtesy of Dr Adriano R Germano, Sao Paulo, Brazil)

impairment is the result for the patient. As with all other joints in the body, the TMJ is affected by all the end-stage joint diseases such as developmental disorders, neoplasia, trauma, failed prior joint surgery, fibrous or bony ankylosis, or arthritic conditions (Mercuri 2012).

When considering surgical management of end-stage TMJ arthritic conditions, multiple factors should be evaluated. First, a check for any effects the patient's medication might have on coagulation and wound healing. Positioning the patient for a long anesthetic due to joint deformities may lead to pressure necrosis of overlying fragile skin. Cervical spine involvement and potential for cervical myelopathy in arthritic patients requires critical care in the positioning of the head for surgical access and can add to the hazard of cervical cord injury (Mercuri 2006).

For functionally unacceptable open bites in early-Stage II cases (Table 4), the management options of arthroplasty or orthognathic surgery to close the open bite can be considered. In patients with an end-stage TMJ arthritic condition combined with an open bite, total joint replacement (TJR) should be considered (Mercuri 2006).

Arthroplasty

High condylar shave; a procedure incorporating limited removal of the damaged articular surface of the condyle, while maintaining the height of the ramus, the articular disc, and the surrounding soft tissue including the lateral pterygoid muscle attachments superiorly and inferiorly, has been advocated in severe, unremitting TMJ low-inflammatory arthritic conditions (Henny and Baldridge 1957). Reshaping the articular surfaces to eliminate osteophytes, erosions, and irregularities found in TMJ low-inflammatory arthritic condition refractory to other modalities of treatment has also been employed for these cases (Dingman and Grabb 1966).

While both techniques reportedly provided pain relief, there are concerns about resultant mandibular dysfunctions, dental malocclusions, facial asymmetries, and the potential for development of further bony articular degeneration, disc disorders or loss and ankylosis, and led to the development of techniques for interposing autogenous tissues and alloplastic materials (Figs. 20, 21, 22, and 24) (Mercuri 2006).

Osteotomy

Preexisting TMJ pathology with or without symptoms that can lead to unfavorable orthognathic surgery outcomes include: arthritic conditions, neoplasia, severe trauma, internal derangements, idiopathic condylar resorption, condylar hyperplasia, osteochondroma, congenital deformities, and nonsalvageable joints (Wolford 2003).

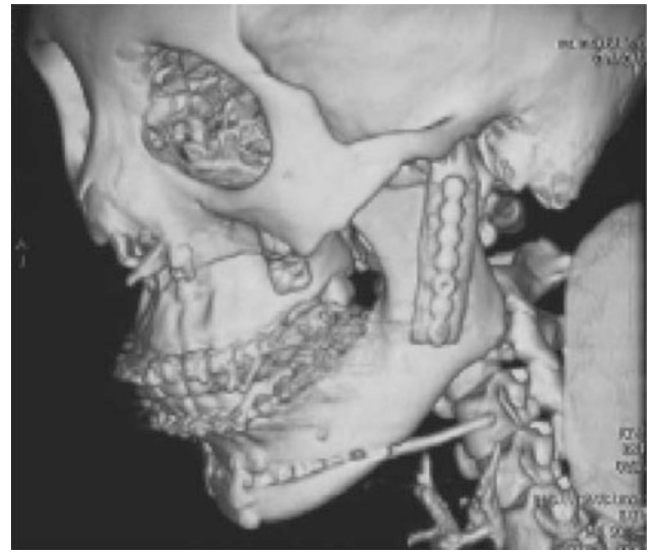

Fig. 20 CT of a left autogenous costochondral graft reconstruction (Image courtesy of Dr Michael Miloro, Chicago, Illinois, USA)

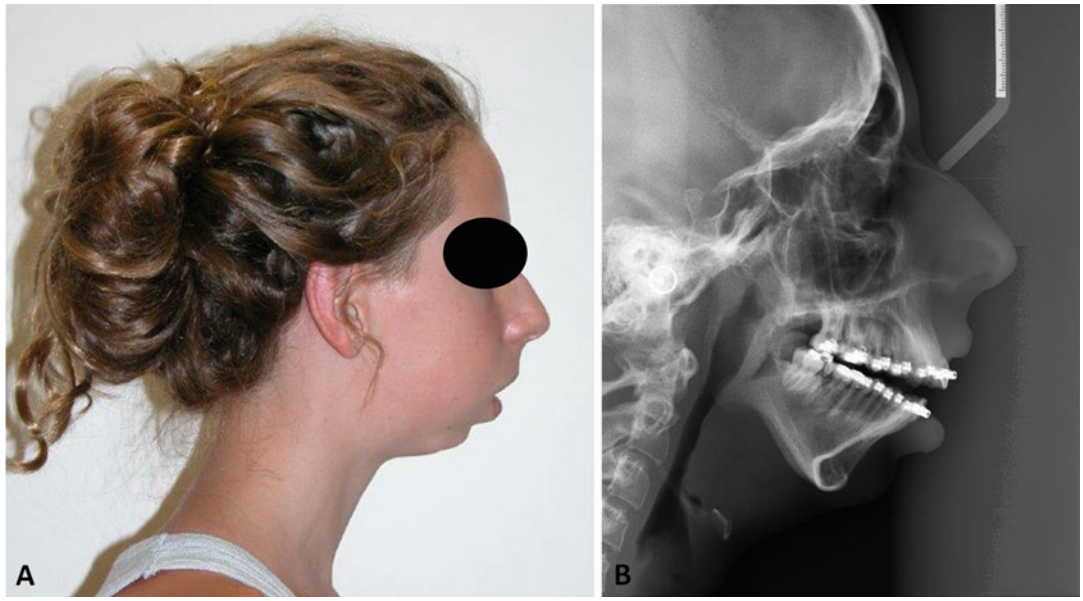

Fig. 21 "Bird Face" clinical appearance and lateral cephalometric image of a patient with JIA and TMJ involvement

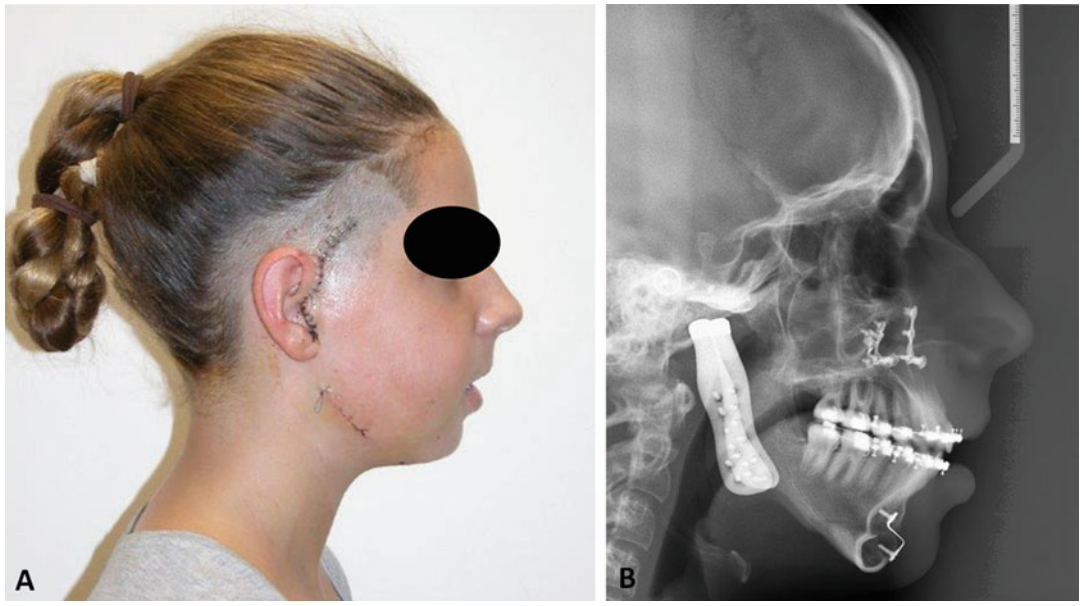

Fig. 22 Clinical appearance and lateral cephalometric image of the patient shown in (Figure 21) with JIA and TMJ involvement 1 week post bilateral alloplastic TMJ replacements, LeFort I osteotomy and genioplasty

Patients with an active low- or high-inflammatory arthritic condition, and concomitant or resultant maxillofacial skeletal discrepancies, who undergo orthognathic surgery have had mixed outcomes (DeClercq et al. 1994; Handleman and Mercuri 2015; Kerstens et al. 1990; Moore et al. 1991; Wolford et al. 2002). In those conditions, as in active, early stage TMJ

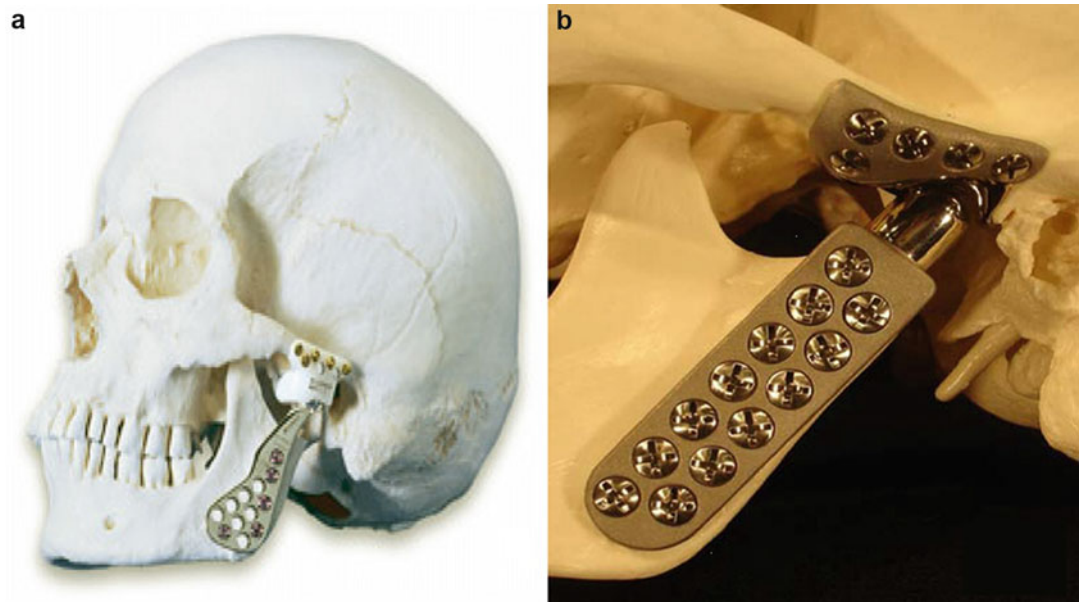

Fig. 23 Stock TMJ total joint replacement devices. (**a**) Zimmer Biomet TMJ replacement system, Jacksonville, FL, USA (cast metal-on-all UHMWPE); (**b**) Nexus CMF, Golden, CO, USA (cast metal-on-cast metal)

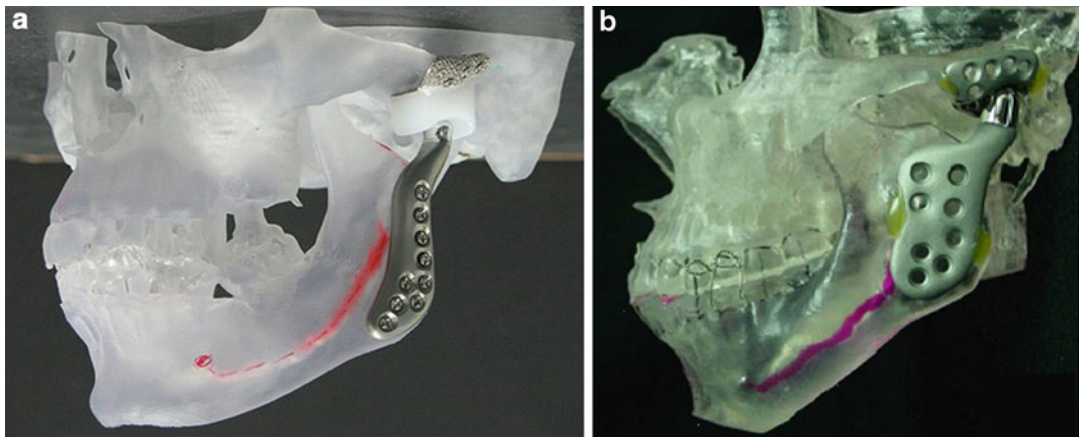

Fig. 24 Custom TMJ total joint replacement devices. (**a**) TMJ Concepts patient-fitted total TMJ replacement system, Ventura, CA, USA (wrought metal-on-UHMWPE-wrought metal mesh backed); (**b**) Nexus CMF, Golden, CO, USA (cast metal-on-cast metal)

arthritic disease, early erosive condylar and fossa bony changes result in loss of posterior mandibular height (Figs. 2 and 3). Since the TMJs are the foundation of the mandible, the resultant pathology offers a poor base upon which to build any maxillofacial functional skeletal reconstruction.

Further, the degenerative and osteolytic changes the joint components undergo in these conditions make the compromised bony components of the TMJ (condyle, eminence, and fossa) highly susceptible to failure under the new functional loading that will be developed after orthognathic surgical repositioning of the maxillofacial skeleton.

Despite this, successful outcomes have been reported using orthognathic surgical procedures

to manage maxillofacial skeletal discrepancies in patients with an arrested arthritic condition (Sinn 1992). A 10-year retrospective study of 16 children with JIA, who had mandibular advancement surgery (genioplasty and/or sagittal split ramus osteotomy), concluded that after evaluation of esthetics, TMJ pain, and mandibular function that all patients had improved and that the procedures performed were safe without complications (Oye et al. 2003).

Bioengineered Tissue

A bioengineered TMJ disc might be indicated to replace unsalvageable articular discs caused by trauma, disease, or Wilkes Stage III and IV internal derangements (Wilkes 1990), or as a component of a bioengineered total TMJ replacement unit. The utility of bioengineered discs is a point of debate because complete disc removal without disc replacement, although controversial, has yielded satisfactory long-term results (i.e., decreased pain and improved joint mobility). Also, surgical placement and attachment of the disc to surrounding structures is of the utmost concern (Detamore et al. 2007).

Because the disc must move with opening and closing of the jaw, the device might be prone to failure if it does not possess adequate mechanical integrity to oppose all the forces associated with ginglymo-arthrodial articulation. Bioengineered total joint implant constructs also might be contraindicated for use in reactive or inflammatory environments such as in the high-inflammatory arthritic conditions, where the underlying autoimmune process likely will destroy the regenerated tissue as it typically does to autogenous tissues in such cases (Salash et al. 2016).

Autogenous Total Joint Replacement

Long-term clinical results of autogenous costochondral TMJ reconstruction in adult patients have been reported as satisfactory (Fig. 20). This observation is based on a 10-year mean follow-up clinical study of 16 patients. All cases were unilateral and four were reported preoperatively as severe TMJ arthritic conditions (Lindqvist et al. 1988). There was no indication as to whether these four cases were low-inflammatory or high-inflammatory arthritis, although based on the pathophysiology of these disease processes, it is suspected that these patients had low-inflammatory TMJ arthritic conditions, which are demographically more common unilaterally than is high inflammatory TMJ arthritis.

A retrospective clinical follow-up study (mean 5-year; range 2–11 years) concluded that despite a 10% infection rate and an unpredictable growth rate in younger patients (requiring later corrective osteotomies), autogenous free costochondral grafting was also a successful method for reconstruction of portions of the mandible and its temporal articulation in the reconstruction of 22 patients (14 unilateral) (Obeid et al. 1988).

Costochondral grafts may be used to successfully construct or reconstruct the ramus-condyle unit. This observation is based on a retrospective study of 26 patients (7 growing and 19 nongrowing), with a mean follow-up period of approximately 4 years. Pre-reconstruction diagnoses included “autoimmune arthritis” and “degenerative joint disease” (Perrott et al. 1994).

The rationale for the use of autogenous costochondral grafting in the management of the functional and esthetic consequences of any end-stage TMJ arthritic condition was suggested by MacIntosh. He concluded that absolute guidelines for determining the appropriate time to operate on these patients do not exist, but reported that a quiescent period of 2 years, during which the number of affected body articulations remains stable, coupled with radiographic evidence of unaltered TMJs and unchanged jaw position-occlusion, offered reasonable expectations for postsurgical stability (MacIntosh 1992; MacIntosh 1994; MacIntosh 2000).

A study of 76 costochondral grafts in 57 patients with a mean follow-up period of 53 months (range 24–161 months) reported that a preoperative diagnosis of ankylosis was associated with a high complication rate, suggesting caution with the use of autogenous costochondral grafts in end-stage arthritic condition patients (Saeed and Kent 2003). Current orthopedic surgery literature does not discuss the use of

autogenous bone in TMJ reconstruction in a non-growing patient affected by end-stage arthritic disease. Instead total alloplastic joint replacement is recommended and utilized (Wiesel and Delahay 2011).

There are few reports discussing jaw reconstruction in JIA patients with a facial skeletal deformity. Because of improvements in early diagnosis, aggressive early treatment, and new medications, surgeons in developed countries rarely encounter severe micrognathia, open bite and clockwise rotation of the mandible (e.g., bird faces) (Figs. 21 and 22) (Abramowicz et al. 2016).

Theoretically, because JIA is a systemic disease, it is possible that even if the affected condyle is removed with the synovium, recurrence of the TMJ component of the disease may occur with relapse of systemic disease. Since most JIA patients do not have persistent disease throughout their adult lives, orthognathic surgery can be considered once skeletal growth ceases. This can be monitored with serial lateral cephalograms or an MRI with contrast. If possible, in patients with stable disease, open bite and clockwise rotation of the mandible should be treated with a Le Fort I osteotomy with autorotation of the mandible. This eliminates mandibular surgery and therefore might eliminate possible condylar resorption that can occur after bilateral sagittal split osteotomies (Abramowicz et al. 2016).

Children with JIA may require orthognathic surgery or total TMJ reconstruction including condylectomy, synovectomy, and discectomy. Autogenous replacement with temporalis flap and costochondral graft or alloplastic total joint replacement are surgical options in such cases (Abramowicz et al. 2016).

Alloplastic TMJ Replacement

Successful reconstructive surgery in large joints involves alloplastic replacement. Early problems of material failure have been resolved and most designs, regardless of their implantation sites, involve the use of convex metal (chrome-cobalt) against concave ultrahigh molecular weight polyethylene. Earlier materials were stabilized to host bone surfaces with rapid curing polymethylmethacrylate cement yielding unacceptable failure rates from latent cement-bone interface loosening and host bone osteolysis, but newer femoral implants are made to be press-fitted to achieve osseointegration and longer-term wear even in younger individuals (Herberts et al. 1989).

To date, there are two categories of TMJ TJR devices approved by the Food and Drug Administration for implantation in the United States. First, stock (off-the-shelf) devices which the surgeon must "make fit" at implantation (Zimmer Biomet TMJ Replacement System, Jacksonville, FL, USA; Nexus CMF, Golden, CO, USA). Second, custom (patient-fitted) devices which are "made to fit" each specific case (TMJ Concepts Patient-Fitted Total TMJ Replacement System, Ventura, CA, USA; Nexus CMF, Golden, CO, USA) (Figs. 23 and 24).

Alloplastic TMJ replacement is advocated because it avoids the need for a second operative site and its potential morbidity decreases operating room time and allows for simultaneous mandibular advancement with predictable long-term results and stability (Mehra and Wolford 2000). An early alloplastic total TMJ system (Vitek II – Kent, Houston, TX) was reported successful in the management of TMJ end-stage arthritic conditions (Stern et al. 1986). Alloplastic total TMJ replacement was initially discussed in two comprehensive reviews of the surgical management of TMJ arthritic condition (Zide et al. 1986; Kent et al. 1986).

In a separate study, it was reported that alloplastic TMJ reconstruction achieved statistically significant improved subjective and objective results than did reconstruction with autogenous bone. The conclusion was that alloplastic TMJ replacement was more appropriate for adult patients with low-inflammatory or high-inflammatory arthritic conditions compared to those managed with autogenous sternoclavicular or costochondral graft (Frietas et al. 2002).

TMJ replacement with an alloplastic prosthesis is advocated in cases with a major vertical dimension problem, loss of disc and the entire condylar head with chronic pain, hypomobility, malocclusion, such as seen in advanced end-stage arthritic conditions (Kent and Misiek 1994).

In a report of 86 total alloplastic joints (27 VK II (Houston, TX) and 59 TMJ, Inc. (Golden, CO)

implanted to reconstruct end-stage arthritic condition patients, with a median follow-up of 14.5 months (range 1–120 months), an overall success rate of 94% was reported. However, four patients required replacement of the VK II devices due to foreign body giant cell reactions (Speculand et al. 2000).

A series of seven high-inflammatory patients whose TMJs were replaced with TMJ, Inc. (Golden, CO) devices, with a mean follow-up of 30 months (range 8–50 months), reported improved subjective (pain and diet) and objective (inter-incisal opening) scores. The conclusion was that patients with a TMJ high-inflammatory arthritic condition should consider alloplastic TMJR to restore function and facial esthetic (Saeed et al. 2001).

In a study of six high-inflammatory patients after alloplastic TMJR to examine improvement in respiratory status and correction occlusal discrepancies reported that after surgery, symptoms of daytime sleepiness and nighttime snoring improved and each patient's ability to masticate solid foods improved significantly. Postoperative cephalograms revealed that both posterior airway space and ramus height were significantly improved as did the dental occlusion. Mean oxygen saturation significantly improved 1-month post reconstruction, whereas apnea-hypopnea indices did not change significantly (Mishima et al. 2003).

A Techmedica/ TMJ Concepts (Ventura, CA) prospective registry was reviewed to determine the outcomes of TMJR after implantation with these devices in low- and high-inflammatory arthritic patients. Sixty patients (12%) had diagnoses consistent with a low-inflammatory TMJ arthritic conditions. Twenty-seven (5%) had diagnoses consistent with high-inflammatory TMJ arthritic conditions. After a mean follow-up period of 31.8 months (range 2–48 months), the data revealed a significant improvement in subjective variable (pain, function, diet) visual analogue scores and improvement in measured maximum incisal opening in the high-inflammatory diagnosis group. There was a significant improvement in subjective variable (pain, function, diet) visual analogue scores and improvement in measured maximum incisal opening in the low-inflammatory diagnosis group (Mercuri 2006).

The subjective and objective outcomes of end-stage arthritic conditions and other patients implanted with patient-fitted alloplastic TMJR devices after 19–24 years of service. At a median of 21 years after surgery, there was a statistically significant improvement ($P < .001$) for mouth opening, TMJ pain, jaw function, and diet. The longest follow-up of patients also reported a statistically significant improved quality of life (Wolford et al. 2015).

Considering the orthopedic experience, the literature comparing autogenous versus alloplastic TMJR in end-stage arthritic conditions, and the long-term success reported in the oral and maxillofacial surgery literature with these devices (Leandro et al. 2013; Wolford et al. 2015), it appears that alloplastic TMJR should be considered appropriate management for late Stage II and Stage III TMJ arthritic conditions (Table 4).

Conclusions and Future Directions

The 2016 report from the most recent International RDC/TMD Consortium Network Workshop concluded that one of the unsolved issues regarding TMJ arthritic conditions was the lack of a reference standard. The sampling of TMJ synovial fluid to determine inflammatory mediator levels was considered a step forward. Therefore, this group recommended exploration using these results as reference standard biomarkers to improve identification of patients with early-stage TMJ arthritis (Michelotti et al. 2016).

This workgroup suggested future directions should include a systematic review of standards for the diagnosis of arthritis for all joints in collaboration with rheumatology and orthopedic colleagues. Further, after gathering scientific data, this group recommended forming a study group to propose new diagnostic criteria for TMJ arthritis (of local or systemic genesis), including a simple diagnostic flowchart. Finally, it was recommended that subgroups of arthritis, with and without pain, with and without tissue

destruction, be included in future discussions and development of diagnostic criteria (Michelotti et al. 2016).

Cross-References

- Classification of Orofacial Pain
- Clinical Evaluation of Oral Diseases
- Clinical Evaluation of Orofacial Pain
- Diagnostic Imaging Principles and Applications in Head and Neck Pathology
- Internal Derangements of the Temporomandibular Joint
- Sleep Bruxism

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