Arthrocentesis and viscosupplementation as treatment modalities for arthralgia of the temporomandibular joint
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 29-01-2020
Chapter 1

General introduction
The temporomandibular joint

The articulation of the mandible with the cranium consists of two synovial joints, bilaterally located anteriorly of the external auditory meatus. In each temporomandibular joint (TMJ), the mandibular condyle articulates with the squamous part of the temporal bone (figure 1). The TMJs control the position and growth of the mandible.

Figure 1. Sagittal section of the right TMJ. (A) temporal bone, (B) mandibular condyle, (C) external auditory meatus, (D) articular disc with 1) anterior attachment, 2) anterior band, 3) intermediate zone, 4) posterior band, 5) retrodiscal tissue.

Glenoid fossa

In its resting position, the mandibular condyle is seated within the glenoid fossa (also termed mandibular fossa), a concavity within the temporal bone. The anterior boundary of the squamous part of the glenoid fossa is formed by the articular eminence. The posterior boundary of the fossa is formed by the tympanic plate, which also forms the anterior boundary of the external auditory meatus. The roof of the glenoid fossa is a relatively thin part of the temporal bone, suggesting that this is not likely to be the major load bearing part with regard to the masticatory forces.

The articular eminence is strongly convex in sagittal direction and moderately concave in transversal direction. During wide opening the complex of the articular condyle and intraarticular disc slides anteriorly towards the top of the eminence and onto the preglenoid plane. Laterally of the articular eminence the articular tubercle serves as an attachment area for the temporomandibular ligament, and unlike the articular eminence is not an articular surface.
**Mandibular condyle**
The articular surface of the condyle is located at the upper and anterior side. The condyle is convex in both the sagittal and transversal plane. The articular disc is attached to the lateral pole and medial pole of the condyle. The temporomandibular ligament is also attached to the lateral pole. The condyle is covered by fibrous tissue, which is derived from, and continuous with, the periosteum of the mandible.

**Articular disc**
The articular disc can be subdivided into five parts (figure 1):
- the anterior attachment of the disc, which fuses into the capsule of the TMJ;
- the anterior band which, together with the anterior attachment, forms the anterior part of the disc;
- the intermediate zone, which forms the thin central part of the disc, is seated between the antero-superior part of the mandibular condyle and the postero-inferior slope of the articular eminence;
- the posterior band forms the thick posterior part of the disc;
- the retrodiscal tissue, which is the posterior attachment of the disc and also frequently referred to as ‘bilaminar zone’, because posteriorly it splits into two layers of highly vascularized tissue: the superior stratum, which is a fibro-elastic layer that attaches to the postglenoid process, posterior articular lip, and the tympanosquamosal fissure; and the inferior stratum, which consists of fibrous tissue, and attaches to the posterior portion of the condylar neck immediately below the articular surface. These two layers are separated by an intermediate layer of loose connective tissue that is attached to the posterior wall of the joint capsule and is richly vascularized and innervated. ¹²

Unlike anteriorly and posteriorly, the articular disc is not attached to the capsule medially and laterally. Instead, the disc is attached to the medial and lateral poles of the mandibular condyle, permitting it to passively follow the condyle along the eminence.

**TMJ cartilage and synovial fluid**
The articular surfaces are lined with cartilage, which prevents bone contact during articulation. The articular cartilage consists of chondrocytes and a matrix of collagen (mostly type I or type II) and hydrophilic proteoglycans, and glycoproteins. In most synovial joints the articulating surfaces are covered with hyaline cartilage, whereas the articular surfaces of the TMJ are lined with fibrocartilage. Compared to hyaline cartilage, fibrocartilage has a lower water content (60-70% vs 68-85% by mass), a higher collagen content (15-25% vs 10-20% by mass) and a lower proteoglycan content (1-2% vs 5-10% by mass). ³ In healthy TMJs the fibrocartilage mainly consists of type I collagen. The superficial layer may contain more collagen type II than the inner part, especially with regard to the articular disc. ⁴ Hyaline cartilage has relatively high contents of collagen type II.
Synovial joints are surrounded by an articular capsule. The inner sides of the TMJ capsule and disc, except the articulating surfaces, are lined with a synovial membrane. This membrane allows diffusion of a plasma filtrate and components of its own to produce synovial fluid (SF). One of the main functions of the SF is lubrication of the joint. Several theories have been proposed to explain the remarkably low friction in synovial joints. Currently, the two most prominent and mutually complementary views are referred to as hydrostatic lubrication, which involves interstitial fluid pressurization from the cartilage and is thought to form a layer which separates the articular surfaces, and boundary lubrication, which assumes the existence of a substance that binds to the cartilage surface separating these more permanently. Since the fibrocartilage lining is avascular, and its cells have limited ability for self repair, the circulating SF also provides for nutrient distribution and waste removal. Furthermore, SF is an important protector of the articular surfaces, largely by means of surface-active phospholipids. The water-soluble glycoprotein lubricin functions as a carrier for the highly insoluble surface-active phospholipids and contributes to the achievement of very low coefficients of friction.

Hyaluronic acid, one of the main components of SF, has been assumed to separate the articular surfaces under low loads because of its high molecular weight, which gives SF its high viscosity. Degradation of hyaluronic acid likely reduces the viscosity of the SF. However, this does not appear to affect the SF as a lubricant. Rather, it mainly impairs the protective function of the SF. Hyaluronic acid adheres to the surface-active phospholipids and protects them from lysis by phospholipase A₂.

Arthralgia of the temporomandibular joint

Arthralgia literally means ‘joint pain’. Many events may provoke arthralgia, including various systemic diseases and traumatic overloading. Possible causes may be subchondral micro fractures, stimulation of periosteal free nerve endings, synovitis and stretching of the capsule. In some cases the cause of the pain is known, allowing causal therapy to be applied. If the pain persists beyond the normal tissue healing time, it may become chronic. Every pain complaint involves somatic, cognitive, emotional, behavioural and social components. While in acute pain the somatic component is dominant, chronic pain is characterized by more prominent involvement of cognitive, emotional, behavioural and social components, thus significantly affecting the patient’s quality of life. Therefore, chronic or persistent pain is usually more difficult to treat than acute pain. Therefore, an important aim of the treatment of arthralgia is to prevent the pain from becoming chronic. Arthralgia may present as an arthritis with distinct features of inflammation, but often the presentation is more subtle. Furthermore, TMJ arthritis is often accompanied with tendomuscular symptoms. The most common form of TMJ arthritis is osteoarthritis, which is rarely accompanied by acute inflammatory symptoms, except for pain and function impairment.
Osteoarthritis

Osteoarthritis (OA) is one of the most common causes of arthralgia in the TMJ. This type of arthritis is related to joint loading and is also known as “wear-and-tear” arthritis or degenerative joint disease. Because of its chronic nature, the disease often has considerable impact on the patient’s quality of life and may be associated with depression, anxiety, and somatisation, which lead to further limitation of daily activities. Patients with arthralgia appear to make more use of health care services and consequently generate higher costs compared to healthy controls. Unlike osteoarthritis in large synovial joints, where OA usually affects the older population (i.e., older than 50 years of age), in the TMJ the disease generally occurs at the age of 20 to 40 years. Women are more frequently affected than men.

The disease is a degenerative process affecting the joint and its surrounding tissues. Pain and restriction of the mandibular range of motion are the main symptoms. Although the cause of the pain is not always clear, it originates from the non-articular tissues since the articular cartilage is not innervated. Quite commonly, OA occurs in combination with internal derangements like disc displacements, which can lead to joint sounds like clicking and crepitation and can lead to locking of the joint. Especially in older patients with a long duration of locking and a small interincisal opening, adhesion formation in the upper joint space may contribute to a restricted range of motion of the mandible. Under normal conditions, loading of the articular surfaces results in proteoglycan proliferation thereby increasing the elasticity of the cartilage as a repair mechanism. The spin off for the pathologic process is when the equilibrium between mechanical load and the adaptive capacity of the joint’s tissues is disturbed and degradation of the articular tissues dominates regeneration. Moreover, progressive degradation of the components of the extracellular matrix of articular cartilage occurs mainly by matrix metallo proteinases and interleukins. Initial changes in OA include microscopic breakdown of the articular cartilage and chondrocyte clustering, followed by substantial matrix degradation, i.e. proteoglycan depletion and altering of the collagen network architecture. As a result, subsequent vertical and horizontal splitting occurs as well as fibrillation and thinning, which eventually may lead to denuding and destruction of the subchondral bone. Furthermore, in the articular disc transformation of cartilage seems to occur. In the articular surfaces collagen type II synthesis appears to be significantly higher than in the inner part of the TMJ disc.

Besides tissue destruction, also degradation of SF components occurs. SF is an important protector of the articular tissues, and degradation of its components reduces this function. Consequently, this leads to accumulation of intra-articular stress and friction, which results in more wear of the articular surfaces, changes in the proteoglycan aggregation, and inadequate cartilage repair. Furthermore, there seems to be a decline in lubricin concentrations in osteoarthritic joints, indicating an adverse contribution to the essential boundary lubrication mechanism. Therefore, the SF of inflamed TMJs often contains elevated levels of degradation products, proinflammatory cytokins, matrix degrading enzymes, and reactive cytokines.
Several theories have been proposed to explain at least a part of the processes that may be involved in TMJ OA. In 1998 Milam et al. proposed the theory that mechanical stresses lead to the accumulation of damaging free radicals in affected articular tissues of susceptible individuals.\(^{26}\) This condition was referred to as reactive oxidative stress. Further research seemed to confirm this theory.\(^{27}\) One of the most prominent theories of how highly reactive free radicals are formed is the hypoxia-reperfusion theory. This theory is based on the assumption that when the TMJ is loaded, hypoxia occurs in the vascularised articular, particularly retrodiscal tissues. When the joint unloads again, the tissues are re-perfused during which free radicals are formed.\(^{26}\) The hypothesis that this mechanism occurs in TMJ OA may form a theoretical basis for treatment modalities focusing on load reduction of the joint and elimination for damaging molecules from the joint.

### Treatment approaches for TMJ arthralgia

Because the pathophysiology and risk factors for TMJ arthralgia are not yet clear,\(^{28}\) treatment is usually focused on pain relief and functional recovery. However, pain of the TMJ is complicated, and multiple factors are believed to contribute to the conscious perception of pain.

In case of TMJ pain caused by acute inflammation, the treatment of preference is usually pain reducing and anti-inflammatory medication, for example Ibuprofen 600mg three times daily during two weeks.\(^{29,30}\) In most cases this approach appears to be sufficient. However, despite this treatment the pain may persists and the inflammation process appears to be more chronic. The initial treatment usually is non-invasive and pursues force reduction on the joint surfaces in order to prevent further cartilage degeneration. It usually focuses on reduction of the joint loading, by prescribing a soft diet, physiotherapy, functional/behavioural education, and oral appliances.\(^{31,32}\)

Recuperation of the joint initiated by this pursued force reduction, starts with fagocytosis of proteoglycan and collagen degradation products and proteolytic enzymes.\(^{33}\) This process takes time, is dependent on patient compliance, and its outcome and duration are clinically unpredictable.

Several treatment modalities, frequently referred to as minimally invasive techniques, include arthrocentesis, arthroscopic surgery and intra-articular application of substances that may reduce inflammation and pain and improve mandibular function. Currently, these minimally invasive techniques are applied after conservative, non-invasive treatment has failed. Open joint surgery, including discectomy, menisceplasty, eminectomy, and adhesiolysis, may be indicated when minimally invasive techniques have been insufficiently effective to manage pain, restricted mandibular movement, and locking.\(^{34,36}\)
Arthrocentesis and viscosupplementation as treatment modalities for osteoarthritis of the temporomandibular joint

Arthrocentesis

In 1975 Ohnishi introduced arthroscopy as an invasive technique allowing direct visualization of the joint structures and lysis and lavage of the upper joint space. To date, TMJ arthroscopy has been reported to be an effective and reliable technique for the treatment of closed lock. Arthrocentesis of the TMJ consists of lavage of the upper joint space with saline without performing arthroscopy, using only two communicating needles that are introduced in the upper joint compartment. During lavage of the joint space, elevated levels of degradation products, proinflammatory cytokines, matrix degrading enzymes, reactive cytokines and pain mediators are flushed out. This procedure can be performed under local anaesthesia or under general anaesthesia and has proven to be highly effective for resolving pain of the TMJ which is thought to be related to the molecular events referred to earlier. For arthrocentesis in joints with anterior disc displacement without reduction success rates up to 91% have been reported. Although the evidence is not conclusive, it seems that arthrocentesis has a beneficial effect on pain and impairment of mandibular motion. Al-Belasy and Dolwick concluded that arthrocentesis is a highly efficient procedure with low morbidity. In the past decade, arthroscopy and arthrocentesis have been applied with increasing frequency to treat TMJ internal derangements that have failed to improve after non-surgical treatment.

In 1996 Fridrich investigated the effect on pain reduction of lavage of the TMJ with and without arthroscopy. Arthroscopy and arthrocentesis appeared to be equally effective in reducing pain, which has been confirmed by more recent studies as well. However, not all of these studies were properly designed, and most of them lacked a control group. Furthermore, Guo et al. were the first to systematically search for the effectiveness of arthrocentesis of the TMJ compared to arthroscopy. The main outcome of this study was that arthroscopy and arthrocentesis are equally effective with regard to pain reduction, although the included studies lacked a non-surgical control group.

Knowing this, to date a more relevant question to the patient as well as to the clinician is how effective lavage of the TMJ (i.e. arthrocentesis or arthroscopy) is compared to non-surgical therapy. If non-surgical therapy appears to be more effective than TMJ lavage, this may support the current treatment approach. However, if TMJ lavage turns out to be more effective than non-surgical therapy, this may justify reconsideration of the current treatment approach. If lavage of the TMJ and non-surgical therapy appear to be equally effective in reducing the symptoms, the indication for arthrocentesis would be doubtful and would become more dependent on factors like cost-effectiveness and treatment duration.

In addition to the arthrocentesis procedure different supplements are used in order to improve the clinical outcome. Corticosteroids are commonly used in an attempt to further reduce pain and jaw stiffness caused by synovitis of the joint capsule. Corticosteroids modify the vascular response during the inflammatory process and inhibit enzymes and the actions of inflammatory cells. However, the use of corticosteroids also has a potential
negative influence on chondrocyte activity, and may accelerate the degradation process of articular cartilage. Their use in the TMJ remains controversial with regard to their efficacy and unknown duration.

One of the substances of current interest is hyaluronic acid as mono-therapy as well as in combination with arthrocentesis. In large synovial joints, such as the knee joint and the ankle, application of this substance as mono-therapy has shown to be superior in the treatment of osteoarthritis with regard to pain relief and function improvement. However, with regard to minimally invasive treatment of the TMJ there is a paucity of high level evidence. Hyaluronic acid can be combined with arthrocentesis in order to improve cartilage protection of the TMJ after lavage of the joint space. Guarda-Nardini et al. performed a pilot study on the efficacy of arthrocentesis combined with viscosupplementation. However, this study lacked a (placebo) control group and neither the patients nor the treating clinicians were blinded. Nevertheless, the results were promising. The indication for the use of hyaluronic acid and the dosing regimen in addition to arthrocentesis have not yet been established.

At the start of the arthrocentesis procedure, saline is injected into the joint space and the mixture of SF en saline is aspirated in order to confirm the position of the first needle. This aspirate contains diluted concentrations of degradation products, proinflammatory cytokins and matrix degrading enzymes which can easily be used for analysis in order to investigate the disease activity or severity. Since the diagnosis and treatment of TMJ arthralgia are usually based on clinical and radiologic examination, whereby severity of cartilage degeneration and activity of the degenerative process remain largely unknown, there is a growing interest in markers for degeneration in SF. Many markers have been investigated in the TMJ as well as in other synovial joints. The current understanding of articular maintenance and degradation is derived from large, load-bearing joints, in particular the knee joint. The serum level of cross-linked carboxy-terminal telopeptides of collagen type II (CTX-II) is believed to be an important marker for destruction of hyaline cartilage, which consists mainly of type II collagen. However, with regard to SF CTX-II, the importance of this marker is still ambiguous. Since the cartilage lining of the articular surfaces of the TMJ predominantly consists of collagen type I, SF concentrations of CTX-II may be less informative for cartilage degeneration in the TMJ. Serum concentrations of CTX-I are generally seen as an important marker for bone degeneration in the knee joint. However, degradation of fibrocartilage may result in high concentrations of CTX-I in SF because of the degradation of collagen type I, especially in an early stage of the disease. Serum concentration levels of cartilage oligomeric matrix protein (COMP) are considered to be a biomarker of both hyaline cartilage and fibrocartilage degradation.

In current initial therapeutic strategies for TMJ arthralgia, in which conservative treatment is offered first, duration and clinical outcome are unpredictable and are dependent on patient compliance. Consequently, this approach includes multiple visits to the outpatient clinic in order to monitor the clinical course and to optimize patient compliance. If patients are non-responsive to this approach and the arthralgia appears to persist, conservative therapy is usually followed by minimally invasive techniques such as arthrocentesis. Improvement during the conservative therapy phase usually occurs
slowly. Furthermore, there is no definite evidence that loading of the articular surfaces is reduced by conservative therapy, and since arthrocentesis seems to be highly efficient in patients who did not benefit sufficiently from conservative treatment, this treatment modality could be applied at an earlier stage. Adequate reduction of TMJ pain may prevent the development of chronic pain, reduce the impact on daily activities, and reduce the need for additional health care utilization. \(^{72}\) Therefore, using arthrocentesis as an initial therapy for TMJ arthralgia, may reduce medical and non-medical costs, both directly and indirectly, as it seems to immediately reduce inflammatory and pain mediators and may ultimately prevent the disease from remaining symptomatic.

**Viscosupplementation**

Viscosupplementation is the repeated intra-articular administration of a highly viscous fluid e.g. sodium hyaluronate. In large synovial joints, such as the knee joint, this treatment has shown to be superior in the treatment of OA with regard to pain reduction and improvement of joint function. \(^{58,60}\) However, despite the assumed similarity between OA of the knee and OA of the TMJ, viscosupplementation as treatment modality for TMJ OA has not been investigated thoroughly before. \(^{73}\) Bertolami et al. performed a randomized, double blind, placebo controlled trial on this topic in the TMJ, but how blinding of the patients and the clinician was obtained was not mentioned. \(^{74}\) Guarda-Nardini et al. performed a pilot study on the effectiveness of arthrocentesis combined with viscosupplementation, \(^{61}\) but this study lacked a (placebo) control group and neither the patients nor the treating clinicians were blinded. Nevertheless, the results were promising. Furthermore, Tang et al. investigated the effect of hyaluronate on the synovial fluid from the TMJ. \(^{75}\) Their results confirm the possible usefulness of hyaluronate injections in the treatment of TMJ arthropathy.

**Aims and outline of the thesis**

In this thesis the clinical effectiveness and cost effectiveness of arthrocentesis for the treatment of arthralgia of the TMJ are studied. Furthermore, relevant TMJ pathology with regard to the development of new treatment modalities, in particular viscosupplementation, are investigated.

The effectiveness of TMJ arthrocentesis (with or without arthroscopy) with regard to pain reduction and improvement of the mandibular range of motion compared to non-surgical treatment modalities is systematically reviewed in chapter 2. In the literature, arthrocentesis is usually applied following insufficiently effective non-invasive treatment. In chapter 3 the clinical effectiveness of corticosteroid administration following arthrocentesis of the TMJ is investigated in a randomized placebo controlled trial. In this trial arthrocentesis was applied as initial treatment. However, this study was not designed to investigate the effectiveness of arthrocentesis as initial treatment. In order to thoroughly test this new treatment strategy, in chapter 4 the clinical effectiveness of arthrocentesis as initial treatment is compared to ‘care as usual’ in a randomized controlled trial. The cost-
effectiveness of these treatment options is studied in chapter 5.

With regard to the pathophysiology of degenerative processes involved in arthralgia of the TMJ, hypoxia-reperfusion injury is one of the most prominent theories. Chapter 6 is a systematic review of the literature to determine the available evidence to support or reject this theory. The degenerative process is characterized by the progressive loss of articular cartilage and subchondral bone. Degradation of these tissues may result in detectable concentrations of breakdown products in the SF, of which CTX-I, CTX-II, COMP are specific markers. In chapter 7, relative SF concentrations of CTX-I, CTX-II, COMP and PGE₂ are determined in arthralgic TMJs compared to knee joints. In chapter 8, these markers are studied comparing arthritic TMJs with healthy, symptom free TMJs.

For the investigation of (future) intra-articularly applied therapeutic agents it is important to test these agents in a double blind manner. However, proprioceptive information during application of substances with different viscosities has not been eliminated successfully in previous studies. In chapter 9 the feasibility of a double blind study design with regard to intra-articular fluid or drug administration is explored.

In the general discussion the results of this thesis are discussed and placed into clinical and economical perspective. Furthermore, future research directions are considered, especially with regard to intra-articular fluid application in the diagnosis of TMJ arthralgia and the role of minimally invasive treatments of arthralgia of the TMJ.
References


