Is arthralgia a reliable clinical sign of temporomandibular joint inflammation?

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Summary

AIM

The aim of this project was to investigate if arthralgia (variables: resting pain, movement pain or tenderness to palpation) is related to the synovial fluid level of 5-HT, TNF or IL-1 and/or if arthralgia is related to blood level of 5-HT, TNF, IL-1 or CRP.

METHODS

Fifty seven patients, 10 men and 47 woman with the mean age 47,1 years, with synovial fluid analyzed for either proinflammatory mediator, 5-HT, TNF or IL-1 were selected from the data base at the department of Clinical Oral Physiology, Karolinska Institutet, Huddinge. The TMJ, right or left, with the highest pain score was included. Also blood serum samples from these patients were taken for measurement of the 5-HT, TNF and IL-1 content.

Resting pain and movement pain in the TMJ region were assessed with a numeric rating scale (NRS). Hyperalgesia/allodynia in the TMJ region was assessed as tenderness by digital palpation. Maximum voluntary mouth opening capacity (MVM) was measured in millimeters between the upper and lower right medial incisors with the vertical overbite added.

The synovial fluid and blood plasma samples were analyzed for TNF, 5-HT and IL-1 and the levels related to resting pain, movement pain, tenderness to palpation and MVM.

RESULTS AND CONCLUSIONS

The results of this study showed that the synovial fluid level of 5-HT was positively correlated to pain during mouth opening and number of painful mandibular movements and negatively correlated to MVM. SF-5-HT was neither significantly correlated to resting pain nor palpatory tenderness.

The synovial fluid level of TNF was not significantly correlated to any of the variables studied.

IL-1 was negatively correlated to MVM but not to any of the other variables investigated.

None of the clinical variables was significantly correlated to blood levels of 5-HT, TNF, IL-1 or CRP.

In conclusion the results of this study show that pain during mandibular movements are related to the synovial fluid level of 5-HT and an inflammatory reaction in the TMJ whereas resting pain and palpatory tenderness are mostly due
to other pain mechanisms. Blood levels of inflammatory markers and mediators seem to be of minor importance. Arthralgia of the TMJ in terms of resting pain and palpatory tenderness therefore seems to have multiple backgrounds and is no reliable clinical sign of TMJ inflammation.
Authors’ contributions

I am Petra Degler, a fifth year dental student at Karolinska Institutet, who has together with another dental student executed a study. 57 patients were selected and synovial fluid was analyzed for either proinflammatory mediator. I have together with my classmate studied articles, analyzed data, created tables, conducted administration work and contributed to the production of the written essay.

I am Josephine Matteoni, a fifth year dental student at Karolinska Institutet, who has together with another dental student executed a study. 57 patients were selected and synovial fluid was analyzed for either proinflammatory mediator. I have together with my classmate studied articles, analyzed data, created tables, conducted administration work and contributed to the production of the written essay.
Introduction

MECHANISMS OF PAIN

The International Association for the Study of Pain (IASP) defines pain as “A sensory and emotional experience which can be correlated to actual or potential damage or be expressed in terms of damage”. In the tissues of the body, receptors with varying sensibility for different types of stimuli can be found. Some receptors are being activated only if there is a risk for tissue damage. These receptors are called nociceptors and are free terminals. Nociceptors can be activated by mechanical, chemical or thermal stimuli. The most common pain receptors are the polymodal nociceptors which are responding to all types of stimuli (Hansson 1998).

The stimulation threshold of the nociceptor changes in relation to the surrounding chemical environment. When an inflammation is in progress proinflammatory substances are produced. These substances often activate the nociceptors or increase their sensitivity. The threshold for activation of the nociceptor decreases, and thereby the answer to the stimulus increases (Hansson 1998).

The nerves, which mediate pain, and which distal parts are nociceptors, are divided in two groups: A-delta- and C-fibers, where C-fibers are in majority. A-delta-fibers are thin, myelinated and transmit the impulses at a high speed (5-25 m/s). The pain mediated over A-delta-fibers is distinct and well-located. C-fibers are thinner than A-delta-fibers and not myelinated and therefore transmit the impulses at a lower speed (0.1-2 m/s). The experienced pain associated with these fibers is more diffuse, aching and harder to localize.

There are also silent/sleeping C-nociceptors. These receptors are not activated in their normal environment even though there is damage. In order to activate the high threshhold/silent C-nociceptors with mechanical or thermal stimulation a previous chemical influence is needed (Hansson 1998).

THE INNERVATION OF JOINTS

The innervation of the joint is dominated by A-delta- and C-fibers. The nociceptors are located in the capsule, ligament, bone, meniscus, periosteum, adipose tissue close to the joint and perivascular areas. Normal joint movements activate some afferents, others need (potential) damage to be activated. Major portions of the afferents, the silent nociceptors, are not activated at all by mechanical stimulation in normal conditions. However, in the presence of an inflammation, when the nociceptors are sensitized, they can be activated by normal joint movement (Hansson 1998).
TRIGEMINAL SYSTEM

The trigeminal nerve is the fifth cranial nerve and represents sensation from the face. From the trigeminal ganglion, which is located nearby the ear, three major branches originate: N. Ophtalmicus (N. V:1), N. Maxillaris (N. V:2) and N. Mandibularis (N. V:3). The major nerve that innervates the temporomandibular joint is n. auriculotemporalis which is a branch from N. Mandibularis and a branch from N. massetericus (McDevitt 1989, Netter 2000).

Pain from the joint is mediated by N. Mandibularis via the trigeminal ganglion to nucleus caudalis located in the brain stem (medulla oblongata), where the first synaps is located. The second synaps is located in the thalamus from which the signal is conducted to the sensory cortex where the pain can be perceived (Hansson 1998).

PERIPHERAL AND CENTRAL SENSITIZATION

When tissue is being damaged the nociceptors at the site of the injury gets an increased sensitivity. This is called peripheral sensitization and leads to spontaneous pain. The increased nociceptor activity may lead to central sensitization, which can be explained as an increased neuronal barrage into CNS, followed by functional changes in the spinal cord and brain which gives a persistant pain. Central sensitization can also arise when nerves begin to behave abnormally and fire spontaneously (Lund 2001).

HYPERALGESIA

Hyperalgesia is an increased response to a stimulus that is normally painful (Lund 2001). Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral or central sensitization, or both (Merskey and Bogduk 1994). There are two types of hyperalgesia: primary hyperalgesia and secondary hyperalgesia. Primary hyperalgesia occurs after an injury where the injured area gets a lower pain threshold and increased sensitivity of pain. An increased sensitivity of pain can also be noticed in the from appearances alone intact area around the injury, secondary hyperalgesia (Hansson 1998).

ALLODYNIA

Allodynia is a condition when every touch of the skin is experienced as painful (Hansson 1998). Allodynia can occur when the tissue has been exposed to trauma, for example sunburn or inflammation, and involves a change in the quality of a sensation (Merskey and Bogduk 1994).
ARTHRALGIA

TMJ arthralgia is defined by presence of pain and tenderness in the TMJ region (Dworkin and LeResche 1992). Some authors have inferred that the symptom of arthralgia emanates/has its origin in the joint capsule and/or the synovial lining of the TMJ. The criteria for the diagnosis arthralgia according to the research diagnostic criteria (RDC) are pain perceived in one or both joint regions during digital palpation and at least one of the following symptoms: pain in the joint region, pain in the joint during maximum unassisted or assisted opening or pain in the joint during lateral excursions (Dworkin and LeResche 1992).

DIFFERENTIAL DIAGNOSIS

There are many possible causes of arthralgia. The authors will explain possible states which can cause arthralgia.

Systemic joint disease like rheumatoid arthritis

RA is a chronic inflammation in the joints which is characterized by destruction of cartilage and bone close to the joint. The etiology is unknown (Nived and Sturfelt 2007/2008). In RA the levels of cytokines, for example TNF, are increased in the synovial fluid. TNF can also be detected in the blood but the levels are not as high as in the synovial fluid.

Systemic disease like Morbus Crohn and influenza

In condition of a systemic inflammatory disease cytokines are being produced in for example in the intestine (Morbus Crohn) and are then transported via the bloodstream to the joints and cause reactive arthritis. In this condition, the levels of cytokines are higher in the blood than in the synovial fluid.

Arthrosis and disc displacements

Microtrauma in the TMJ, for example occlusal trauma or disc displacement, can be the reason of severe pain in the joint site (Ma et al. 1994; Zhang et al 1999). Patients with disc displacement and patients with degenerative joint disease may show elevated levels of TNF in synovial fluid (Kaiyuan et al 1995).

Macrotraumatic arthritis

When a joint is exposed to a trauma a local inflammation takes place. The levels of TNF in synovial fluid of the traumatized joint are raised while the levels in the blood remain unchanged.
Microtraumatic arthritis

Bruxism is the non-functional clenching or grinding of the teeth that may occur during sleep or, less commonly in the daytime. Its etiology is not fully understood but it has been suggested to result in TMJ disorders such as arthritis and arthralgia and malocclusion (Cuccia 2008, Bedi and Sharma 2009).

Whiplash associated disorder (WAD)

Patients suffering from WAD after trauma may show central sensitization due to brainstem injuries. This can lead to allodynia or hyperalgesia in the trigeminal system. Subnucleus caudalis in the brain stem may be damaged and constantly sensitised to even normal stimuli, which leads to nociceptor activation and thereby an experience of pain.

MEDIATORS (SIGNAL SUBSTANCES) OF PAIN

In pain conditions, several mediators can be found in the tissues of the temporomandibular joint. These mediators have stimulatory or inhibitory biological effects. Each mediator links to a specific receptor at the afferent nerve ending. The authors of this report will focus on following mediators: Serotonin (5-HT), interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF).

Tumor Necrosis Factor (TNF)

TNF is a very potent cytokine, e.g. it activates macrophages, neutrophiles and eosinophiles (Kopp 2001). Besides linking to receptors attached to afferent nerve endings and other effector cells TNF also links to the soluble receptor TNF$sRII$. Normally there is a balance between the amount of biologically active TNF and the soluble TNF$sRII$ (Duff 1994). If the amount of TNF increases and the balance is disturbed there will be an inflammatory response with consequences for nociception and connective tissue turn over.

TNF has effect on the acute phase response by increasing the production of C-reactive protein (CRP) in the liver, which is used as an inflammatory marker. Increased levels of TNF and CRP and the resulting acute phase response can lead to fever and malaise.

Clinical aspects: In many medical conditions, e.g. RA, internal derangement of the TMJ, unspecified TMJ disorders, TNF has been detected in the synovial fluid. TNF has direct modulatory effects on pain, e.g. by sensitization of the X receptor on peripheral nerves. TNF also has effects on cartilage and bone degradation and may increase the production and release of other pain mediators, for example IL-1β, IL1-6 and serotonin in the inflamed synovial tissues and thereby cause further nociceptor sensitization (Watkins et al. 1994, Fredriksson 2006, Kopp and Alstergren 2008).
Infliximab is an artificial antibody against TNF which is used as a treatment modality. Infliximab works by binding to TNF with high affinity and prevents the effective binding of TNF with its receptor and neutralizes TNF at the inflammatory site (Elliot et al. 1994, Choy and Panayi 2001). Intravenous infusion with Infliximab in patients also taking Methotrexate, a drug used in treatment of autoimmune disease, has been shown to reduce disease activity and joint destruction in RA patients by increasing the levels of anti-inflammatory cytokines such as IL-1ra and IL-10 and the soluble cytokine receptors e.g. TNFsRII and IL-1sRII in the synovial tissues including plasma and synovial fluid (Lipsky et al. 2000, Kopp et al 2005). The effect of Infliximab primary depends of the increased levels of anti-inflammatory cytokines in the synovial tissue, while the changed levels in synovial fluid and plasma are secondary.

**Serotonin (5-HT)**

Peripheral serotonin (5-HT) is a mediator of nociceptive pain. 5-HT is produced in enterochromaffin cells in the gastrointestinal mucosa and is immediately uptaken and stored in platelets, the nervous system and is also released from activated mast cells. There are seven different classes of receptors for 5-HT identified so far (Fredriksson 2006, Ernberg 2008). Within these classes, several receptor subclasses have been identified (Ernberg 2008). The effect of the linking is dependent on the type of receptor. In inflammatory conditions of peripheral tissues 5-HT is an important endogenous proinflammatory mediator and regarding pain the 5-HT\(_3\) receptor is the most studied. The 5-HT\(_3\) receptor is widely distributed in the peripheral nervous system but is only located on neurons. It is associated with inflammatory pain and 5-HT\(_3\) receptor antagonists reduce inflammatory pain. Granisetron is a 5-HT\(_3\) receptor antagonist which reduces resting as well as movement pain of the TMJ (Voog et al. 2000, Kopp 2001, Fredriksson 2006).

*Clinical aspects:* Patients with arthritic conditions of the TMJ show detectable levels of 5-HT in their synovial fluid while healthy individuals do not. Alstergren and Kopp showed that there is a positive correlation between 5-HT in the synovial fluid and pain in the arthritic TMJ upon movement (Alstergren and Kopp 1997, Fredriksson 2006).

**Interleukin-1 (IL-1)**

Interleukin-1 (IL-1) is a cytokine that is mainly derived from macrophages and takes part in the mediation of acute and chronic inflammation. This leads to destruction of connective tissue as well as activation/sensitization of nociceptors. There are two subtypes of IL-1, IL-1\(\alpha\) and IL-1\(\beta\). The function of IL-1\(\alpha\) is to work as an autocrine messenger inside the cell or on the surface of the cell membrane. IL-1\(\beta\) acts locally outside the cell or systemically by entering the blood circulation.
IL-1 links to two receptors: IL-1RI and IL-1RII. Both healthy individuals and patients with inflammatory disorders have soluble forms of the receptors (IL-1sRI and IL-1sRII) in their extracellular matrix and blood. For patients with inflammatory joint disease the levels of IL-1sRII are increased (Kopp and Alstergen 2001). When IL-1β links to this soluble receptor it becomes inactivated and IL-1sRII therefore has an anti-inflammatory effect.

The IL-1 receptor antagonist (IL-1ra) competes with IL-1α and IL-1β for receptor binding and is produced in much higher concentrations than IL-1β. When IL-1ra links to the IL-1RI receptor no biological response is elicited and IL-1ra therefore works anti-inflammatory. In an inflamed tissue the production of IL-1ra increases, but not enough to inhibit the effect of IL-1β (Kopp 2001, Alstergren and Kopp 2001).

Clinical aspects: IL-1β is not detected in synovial fluid from healthy individuals. However, synovial fluid from patients with polyarthritis or TMJ arthritis can show detectable levels of IL-1β (Fredriksson 2006, Kopp and Alstergren 2008).

SYNOVIAL FLUID

Serotonin and IL-1 are normally not detected in healthy TM-joint tissues (Alstergren and Kopp 1997, Alstergren et al 1998), and are therefore of special diagnostic interest when investigating the origin of pain in the TMJ. IL-6 and TNF are present in normal tissues at very low levels to stimulate remodeling of bone and cartilage and to control growth. By analyzing synovial fluid from patients with pain from the TMJ region, important information can be received. Presence of the mediators (5-HT and IL-1) above in the synovial fluid indicates ongoing/current inflammation in the joint. If the mediators are not to be found the pain likely originates from other sources e.g. surrounding muscles.

PRESSURE-PAIN THRESHOLD (PPT)

Pressure-pain threshold is the point at which pain begins to be recognizable by the subject. The minimum pressure needed varies from individual to individual as well as over time. Studies suggest that TMJ pressure-pain threshold is modulated by systemic mechanisms, e.g. level of 5-HT in the blood (Fredriksson et al 2008). High levels of 5-HT in serum from healthy persons and patients with TMJ disorders have been associated with low pressure-pain threshold (Fredriksson et al 2008). Patients with fibromyalgia/whiplash, endometriosis, low back pain and RA have also been reported to show lower pressure-pain threshold (Fredriksson 2006).
THE SITUATION OF TODAY

Today many patients are suffering from temporomandibular disorders (TMD). One subgroup of these patients experience pain in the temporomandibular joint, some of them spontaneously, i.e. at rest, while others only experience pain on provocation. The provocation can be mechanical such as movement of the joint or external pressure such as palpation of the joint. Many patients are being treated inefficiently because knowledge is lacking whether the pain has its origin in the temporomandibular joint or in the surrounding muscles.

**Aim**

The aim of this project is to determine if arthralgia is a reliable clinical sign of local TMJ inflammation (synovitis/arthritis) and thereby to give answers to the following questions:

Is arthralgia (variables: resting pain, movement pain or tenderness to palpation) related to the synovial fluid level of 5-HT, TNF or IL-1?

Is arthralgia (variables: resting pain, movement pain or tenderness to palpation) related to blood level of 5-HT, TNF, IL-1 or CRP?

**Materials and methods**

**PATIENTS**

Fifty seven patients with synovial fluid analysed for either proinflammatory mediators 5-HT, TNF or IL-1 were selected from the data base at the department of Clinical Oral Physiology and the TMJ, right or left with the highest pain score was studied. These criteria resulted in a patient sample comprising Twenty-three patients with a diagnosis of RA, of which 16 were positive for the rheumatoid factor, nine patients with ankylosing spondylitis, 4 with osteoarthritis, 8 with psoriatic arthropaty, 2 chronic juvenile arthritis, 1 with chronic unspecific polyarthritis, 2 with common variable immunodeficiency 2 with Marfan´s syndrome and 1 reactive arthritis. The demographic and background data of these patients are shown in Tables 1-4.
Table 1. Demographic and background data for all 57 patients with analysed levels of serotonin (5-HT), tumor necrosis factor (TNF) or interleukin 1 (IL-1) in the synovial fluid of the temporomandibular joint.

<table>
<thead>
<tr>
<th>Percentiles</th>
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<th>75th</th>
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<td>57</td>
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Table 2. Demographic and background data for 28 patients with analysed serotonin (5-HT) in the synovial fluid of the temporomandibular joint.

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Table 3. Demographic and background data for 28 patients with analysed levels of tumor necrosis factor (TNF) in the synovial fluid of the temporomandibular joint.

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Table 4. Demographic and background data for 16 patients with analysed IL-1 in the synovial fluid of the temporomandibular joint.

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<td>16,0</td>
<td>19,5</td>
<td>16</td>
<td>9778</td>
<td>18,5</td>
</tr>
<tr>
<td>P-IL-1</td>
<td>pg/mL</td>
<td>3</td>
<td>0</td>
<td>8,3</td>
<td>0</td>
<td>18</td>
<td>5,3</td>
</tr>
</tbody>
</table>
PAIN ASSESSMENT

Resting pain and movement paint in the temporomandibular joint region (arthralgia) were assessed with a numeric rating scale (NRS; 0-10). The patients were asked to express the level of pain in the TMJ during rest and mandibular movement (Alstergren et al 1998).

Hyperalgesia/allodynia (arthralgia) in the temporomandibular joint region was assessed as tenderness by digital palpation laterally and posteriorly over the TMJ (Kopp et al 2005).

MAXIMUM VOLUNTARY MOUTH OPENING (MVM)

MVM was measured in millimeters between the upper and lower right medial incisors with the vertical overbite added (Kopp et al 2005). This variable was included to assess the influence of pain and mediators on mandibular function.

SYNOVIAL FLUID SAMPLING

Anesthesia of the TMJ was achieved before the TMJ was punctured with a standard disposable needle. Synovial fluid samples were obtained using a push-and-pull technique with one syringe for the washing solution to be injected and one syringe for aspiration. The concentration of TNF, 5-HT and IL-1 were determined using the formula \( C_{SF} = C_{Asp}/(1-Abs_{Asp}/Abs_{Wash}) \) where \( C_{SF} \) is synovial fluid concentration, \( C_{Asp} \) is aspirate concentration and \( Abs_{Wash} \) is washing solution absorbance (Nordahl et al 2000, Alstergren et al 2003).

INFLAMMATORY MEDIATOR ANALYSIS

Mediators 5-HT (synovial fluid and serum), TNF (synovial fluid and plasma) and IL-1 (synovial fluid and plasma) were determined by commercially available enzyme-linked immunoassays (ELISA) with highly specific antibodies to detect each mediator (Alstergren et al 2008).

STATISTICS

Univariate correlations were tested by Pearson's correlation coefficient (r) when variables were normally distributed and by Spearman's rank correlation coefficient (r_s) when not. A P-value < 0.05 was considered significant.
Results

The values of the main variables are shown in Table 5.

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>Median</th>
<th>25th</th>
<th>75th</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity (0-10)</td>
<td>0-10</td>
<td>4.5</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>10</td>
<td>4.3</td>
</tr>
<tr>
<td>Pain on mouth opening</td>
<td>Q1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Number of painful movements (0-5)</td>
<td>0-5</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>2.6</td>
</tr>
<tr>
<td>SF-5-HT</td>
<td>pg/mL</td>
<td>950</td>
<td>653</td>
<td>1321.5</td>
<td>9</td>
<td>9778</td>
<td>854.8</td>
</tr>
<tr>
<td>SF-TNF</td>
<td>pg/mL</td>
<td>15</td>
<td>11.3</td>
<td>18.8</td>
<td>0</td>
<td>250.3</td>
<td>24.3</td>
</tr>
<tr>
<td>SF-IL-1</td>
<td>pg/mL</td>
<td>0</td>
<td>0</td>
<td>1.8</td>
<td>0</td>
<td>49</td>
<td>2.9</td>
</tr>
<tr>
<td>S-CRP</td>
<td>mg/L</td>
<td>0</td>
<td>0</td>
<td>13.5</td>
<td>0</td>
<td>66</td>
<td>8.3</td>
</tr>
</tbody>
</table>

SYNOVIAL FLUID LEVEL OF SEROTONIN (SF-5-HT)

SF-5-HT was positively correlated to pain during mouth opening ($r_s = 0.45$, $n= 28$, $p= 0.014$) and number of painful mandibular movements ($r = 0.55$, $n=28$, $p= 0.002$) and negatively correlated to MVM ($r = -0.54$, $n= 27$, $p= 0.002$). SF-5-HT was neither significantly correlated to resting pain nor palpatory tenderness.

SYNOVIAL FLUID LEVEL OF TNF (SF-TNF)

SF-TNF was not significantly correlated to any of the variables studied.

SYNOVIAL FLUID LEVEL OF INTERLEUKIN (SF-IL-1)

IL-1 was negatively correlated to MVM ($r = -0.52$, $n= 16$, $p= 0.036$), but not to any of the other variables investigated.

BLOOD LEVELS OF INFLAMMATORY MEDIATORS

None of the clinical variables was significantly correlated to blood levels of 5-HT, TNF, IL-1 or CRP.
Discussion

Fifty seven patients, 10 men and 47 women, were selected from the data base at the department of Clinical Oral Physiology at Karolinska Institutet, Huddinge, Sweden. The criteria for being included in the study were that the patients at the first visit were subjected to analysis of synovial fluid levels of TNF, 5-HT or IL-1. The number of patients included in the study is relatively small which might influence the results. The selection resulted in a patient sample with mainly systemic inflammatory disorders but with low systemic inflammatory activity according to CRP and the results are therefore strictly valid only for this particular group.

Synovial fluid samples from the TMJ, right or left, with the highest pain score were analyzed in regard to presence of mediators (signal substances) of pain and inflammation. The technique used in this study for the synovial fluid sampling was push-and-pull aspiration with saline including vitamin B12, which is well documented. The synovial fluid samples and blood plasma were analyzed for TNF, 5-HT and IL-1 and the levels related to resting pain, movement pain, tenderness to palpation and MVM by standard methods.

This study showed that patients with detectable levels of serotonin in the TMJ presented pain during mandibular movements more frequently than patients without. These patients also have less maximum voluntary mouth opening. Levels of serotonin in the synovial fluid did not correlate to resting pain or palpatory tenderness, which has been shown in previous studies (Alstergren and Kopp 1997). This difference might be due to the modest number of patients in this study or to the impact of the patients’ diagnoses.

The study also showed that patients with increased levels of IL-1 in the synovial fluid more often have a reduced maximum voluntary mouth opening compared to those without. Increased levels of IL-1 were, however, not related to any of the other clinical variables studied.

The levels of TNF did not correlate to any of the clinical variables studied. It has previously been shown that high synovial fluid level of TNF is associated with pain on maximum mouth opening (Nordahl et al 2000). In the study made by Nordahl et al (2000) only patients with a diagnosis of chronic inflammatory connective tissue disease and TMJ pain were included, which can explain the differences in results shown. The role of TNF should be further elucidated in future studies.

None of the mediators, 5-HT, TNF or IL-1, correlated to tenderness upon digital palpation. Tenderness during palpation is one of the criteria that needs to be fulfilled for the clinical diagnosis of arthralgia (RDC; Dworkin 1992). The authors can therefore make the conclusion that arthralgia in terms of tenderness to palpation or resting pain are no reliable clinical signs of TMJ inflammation (synovitis/arthritis) and should not be used as a diagnosis with this implication.
Blood levels of 5-HT, TNF, IL-1 or CRP did not correlate to the clinical variables in this study. In terms of TNF this is in agreement with a previous study made by Fredriksson et al 2006. In terms of 5-HT, however, conflicting results have been shown in a study made by Kopp (2001). That study indicated that blood level of 5-HT is a factor involved in the modulation of pain and hyperalgesia/allodynia in the TMJ. This difference might be due to differences in diagnoses, gender or the number of patients included in the studies or most probably to the low level of systemic inflammation in this patient sample.

In conclusion the results of this study indicate that pain during mandibular movements are related to the synovial fluid level of 5-HT and an inflammatory reaction in the TMJ whereas resting pain and palpatory tenderness are mostly due to other pain mechanisms. Blood levels of inflammatory markers and mediators seem to be of minor importance in this patient sample. Arthralgia of the TMJ therefore seems to have multiple background and is no reliable clinical sign of TMJ inflammation and should not be used as a diagnosis implicating TMJ inflammation.
Acknowledgement

We would like to thank Professor Sigvard Kopp. We are grateful that he has contributed through his great knowledge and supported us throughout the project. Without him it would have been impossible for us to fulfill this study.
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