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*Research Communication*

# Tumor Necrosis Factor-$\alpha$ in Temporomandibular Joint Synovial Fluid Predicts Treatment Effects on Pain by Intra-Articular Glucocorticoid Treatment

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The aim of this study was to investigate the influence of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) in temporomandibular joint (TMJ) synovial fluid and blood on the treatment effect on TMJ pain by intra-articular injection of glucocorticoid in patients with chronic inflammatory TMJ disorders. High pretreatment level of TNF-$\alpha$ in the synovial fluid was associated with a decrease of TNF-$\alpha$ and elimination of pain upon maximal mouth opening. Elimination of this TMJ pain was accordingly associated with decrease in synovial fluid level of TNF-$\alpha$. There was also a significant decrease of C-reactive protein and TMJ resting pain after treatment. In conclusion, this study indicates that presence of TNF-$\alpha$ in the synovial fluid predicts a treatment effect of intra-articular injection of glucocorticoid on TMJ movement pain in patients with chronic TMJ inflammatory disorders.



## INTRODUCTION

Glucocorticoids administered systemically or locally suppress inflammation and pain in patients with systemic inflammatory disorders such as rheumatoid arthritis (RA; [1]). Glucocorticoids act on cytoplasmic glucocorticoid receptors that upon activation inhibit the expression of genes for proinflammatory cytokines such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), while increasing the expression of genes encoding anti-inflammatory proteins such as the soluble receptor II of TNF-$\alpha$, which has been shown to reduce arthritis [2]. Glucocorticoids have an inhibitory effect on inflammatory mediator release from many cell types involved in inflammation such as macrophages, T-lymphocytes, mast cells, dendritic cells, and neutrophilic leukocytes. Glucocorticoids also reduce prostaglandin production by inhibition of the phospholipase $A_2$ enzyme [1]. TNF-$\alpha$ is elevated in plasma and synovial fluid of patients with chronic inflammatory disorders like RA [3–6]. Elevated plasma levels of TNF-$\alpha$ are considered pathological and are part of the systemic inflammatory response [7]. TNF-$\alpha$ has direct modulatory effects on pain and tissue degradation but also has indirect effects by inducing production of other proinflammatory cytokines like interleukin-1 (IL-1), IL-6, and IL-8 [8–11]. Nordahl et al [5] showed that patients with chronic inflammatory connective tissue disease and associated temporomandibular joint (TMJ) pain have elevated TNF-$\alpha$ levels in the synovial fluid compared to those without pain. Since glucocorticoids suppress pain and inflammation, systemic and peripheral TNF-$\alpha$ might be expected to influence the treatment effects of locally administered glucocorticoids.

Our hypothesis is that a difference in the peripheral expression of inflammation in the TMJ, as reflected by the proinflammatory mediator TNF-$\alpha$, is important for the local treatment response. This may explain a difference in the treatment response to, for example, glucocorticoid and that the treatment response may differ regarding symptoms and signs.

The aim of this study was to investigate the influence of TNF-$\alpha$ in TMJ synovial fluid and blood on the treatment effect on TMJ pain by intra-articular injection of glucocorticoid in patients with chronic inflammatory disorders of the TMJ.

## MATERIALS AND METHODS

### *Patients*

Twenty one female patients with chronic inflammatory TMJ disease participated (Table 1). Inclusion criteria were the presence of seropositive or seronegative RA ($n = 5$, resp), ankylosing spondylitis ($n = 3$), psoriatic arthropathy

Table 1: Demographic data for 21 female patients with chronic inflammatory temporomandibular joint (TMJ) disorders subjected to intra-articular glucocorticoid injections. The patients were asked about pain in nine joint regions besides the TMJ (neck, shoulders, elbows, hands, upper back, lower back, hips, knees, and feet) and the number of painful joint regions was recorded (score = 0–9), IQR = 75th–25th percentile, $n$ = number of patients.

| | | Median | IQR | $n$ |
|---|---|---|---|---|
| Age | (years) | 48 | 22 | 21 |
| Duration of general joint involvement | (years) | 10 | 19 | 21 |
| Duration of local TMJ involvement | (years) | 3 | 9 | 20 |
| Number of painful joint regions | (0–9) | 7 | 3 | 21 |

($n = 3$), chronic unspecific polyarthritis ($n = 2$), Marfan's syndrome ($n = 2$), or osteoarthritis ($n = 1$) with unilateral or bilateral presence of TMJ inflammatory disorder according to the diagnostic classification by the American Academy of Orofacial Pain [12] with the modification that pain with mandibular function or point tenderness on TMJ palpation was mandatory. An additional criterion was that at least one of the proinflammatory mediators TNF-$\alpha$, IL-1$\beta$, or serotonin or a pathological level (90th percentile 348 pg/mL) of the anti-inflammatory mediator interleukin-1 receptor antagonist (IL-1Ra) was present in the synovial fluid directly before or after treatment. The purpose of the use of several inflammatory mediators was to validate the clinical diagnosis of local arthritis for inclusion in this study. No difference in the composition of mediators in the synovial fluid was observed between the clinical diagnostic subgroups. The exclusion criterion was intra-articular glucocorticoid treatment of the TMJ within 3 months before treatment. All patients were referred to the clinic from rheumatologists or general medical practitioners who determined the primary diagnosis before enrollment in this study except for the patient with osteoarthritis. Eight patients regularly used nonsteroidal anti-inflammatory drugs (Celecoxib, Diclofenac, Ibuprofen, Ketoprofen, Nabumetone, or Naproxen), five patients used oral glucocorticoid (Prednisolone), six patients used disease-modifying antirheumatic drugs (Sulfazalasine, Methotrexate), whereas eight patients had no current anti-inflammatory treatment. The study was approved by the Local Ethical Committee at Karolinska University Hospital in Huddinge, Sweden (142/02 and 176/91).

### *Clinical examination*

The current TMJ pain intensity at rest was assessed with a 100 mm visual analogue scale on paper with endpoints denoted by "no pain" (0 mm) and "worst pain ever experienced" (100 mm). The presence or absence of TMJ pain on maximum mouth opening was also recorded. Change from presence to absence of movement pain thus means a total elimination of pain. Absence or presence of tenderness and palpebral pain reflex to digital palpation of the lateral and posterior (through the acustic meatus) aspects of the TMJ were assessed with the mandible in rest position.

The pressure-pain threshold over the palpable lateral pole of the TMJ condyle with the patient's mandible in a rest position was determined with a single measurement by a handheld electronic pressure algometer (Somedic Production AB, Sollentuna, Sweden), consisting of a pressure transducer probe connected to a pistol grip with a display unit. The tip of the pressure transducer has a flat, circular rubber tip with an area of 1 $cm^2$. A linearly increasing pressure rate (50 $kPa/s^2$) [13–15] was applied until the subject responded to the first pain sensation by pressing a button on a device connected to the probe that froze the current pressure-pain threshold level on the display. The pressure-pain threshold was defined as the minimum pressure needed to evoke a painful sensation recognizable by the subject.

### *Synovial fluid sampling from the temporomandibular joint*

TMJ anesthesia was achieved by blocking the auriculotemporal nerve with 2 mL 2% lidocain (Xylocain, Astra-Zeneca, Södertälje, Sweden). The TMJ was punctured with a standard disposable needle (diameter = 0.65 mm) inserted into the posterior part of the upper joint compartment. TMJ synovial fluid samples were obtained by washing the joint cavity with saline using a push and pull technique [16]. Briefly, the washing solution, consisting of 78% saline (NaCl 9 mg/mL, Pharmacia Upjohn, Uppsala, Sweden) and 22% hydroxocobalamin (Behepan 1 mg/mL; Pharmacia Upjohn, Uppsala, Sweden), was slowly injected into the posterior part of the upper joint cavity approximately 1 mL at a time and then aspirated. The total volume of the washing solution injected was 4 mL. The hydroxocobalamin was included in order to determine the volume of synovial fluid recovered in the aspirate by comparing the spectrophotometric absorbance of the aspirate with that of the washing solution. The synovial fluid level was then calculated. Only samples that fulfilled previously established sample quality criteria were included in the statistical analysis [16].

### *Blood sampling*

Venous blood was collected in a sodium citrate tube (0.105 mol/L) to determine the erythrocyte sedimentation rate and in an EDTA tube that was immediately cooled and centrifuged (1500 g for 10 minutes at +4°C) and then frozen (−70°C), and later examined for TNF-$\alpha$ in plasma. In addition, venous blood was collected without additives for analysis of thrombocyte particle count and CRP level in serum. Time from freezing to analysis varied between 1 and 6 months for the samples.

### *Treatment and examination schedule*

The glucocorticoid methylprednisolone (40 mg/mL) with lidocaine (10 mg/mL) added (Depo-Medrol cum lidocaine; Pfizer AB, Täby, Sweden) was injected in a volume of 0.7 mL into the upper joint compartment of the TMJ. In the patients

with bilateral TMJ pain, who were subjected to bilateral treatment, data from the most painful TMJ was used in the statistical analysis. The most painful TMJ was that with the highest pain intensity at rest before treatment.

The patients were examined before and after treatment. The median (interquartile range, IQR) interval between the first and second examinations was 40 (40) days. At the first visit, the glucocorticoid was injected into the TMJ after clinical examination and synovial fluid sampling. At the second visit, clinical examination and synovial fluid sampling were performed.

### *Analysis of tumor necrosis factor-α*

Plasma TNF-α was determined with an immunoenzymometric assay (Medgenix TNF-α EASIA kit, BioSource Europe Sa, Zoning Industriel B-6220, Fleurus, Belgium) with a detection limit of 3 pg/mL. The intra-assay coefficient of variation for this assay is 3.7%–5.2% and the inter-assay variation is 8%–9.9% according to the manufacturer. The median (75th/90th percentile) level of TNF-α in blood plasma from healthy individuals examined in our laboratory is 10 (12/18) pg/mL, while TNF-α is undetectable in TMJ synovial fluid in healthy individuals. The concentration of synovial fluid levels of TNF-α was analyzed as the same assay used for plasma, but it was modified to compensate for hydroxocobalamin interactions with the assay by using a standard curve with hydroxocobalamin. The small hydroxocobalamin interaction was completely compensated for by this procedure.

### *Statistical analyses*

Nonparametric descriptive and analytical statistics were applied since some of the investigated variables were not normally distributed or measured on interval scales. The Kolmogorov-Smirnov test was used to test if the variable TMJ pressure-pain threshold was normally distributed. The central tendency and the variation of the variables are presented as median and IQR (75th–25th percentile). The significances of the differences between the variables before and after treatment were calculated by the Wilcoxon test. The significances of the differences between the patient groups with a followup interval shorter than 40 days and with a longer followup interval regarding the synovial fluid level of TNF-α were tested with Mann-Whitney $U$ test. Spearman's ranked correlation test was used to calculate the significance of the correlations between the variables. A probability level below 0.05 was considered as significant.

## RESULTS

Table 2 shows the clinical, synovial fluid and blood variables before and after treatment.

### *Tumor necrosis factor-α*

TNF-α was detectable in the synovial fluid from seven patients before treatment and seven patients after treatment, that is, 33% of the patients had detectable level at each occasion but only one patient had detectable levels at both occasions (Figure 1). Seven patients showed decreased, six increased, and eight showed unchanged levels after treatment. All patients with detectable pretreatment synovial fluid level of TNF-α showed a reduction of the mediator from a median of 65 to a median of 0 ($P = .018$).

All plasma samples showed detectable pretreatment level of TNF-α. Seven of the 12 patients with plasma samples showed decreased TNF-α levels after treatment and five showed increased levels. There was thus no consistent or significant change in plasma level of TNF-α after treatment.

There was no significant difference regarding the change of synovial fluid TNF-α levels after treatment between the patients with a followup interval shorter than the median interval (40 days) compared to a longer followup interval.

### *Changes after glucocorticoid treatment in relation to pretreatment TNF-α levels*

The pretreatment synovial fluid level of TNF-α was negatively correlated to the change in synovial fluid TNF-α level and TMJ pain upon maximum mouth opening, that is, a high pretreatment synovial fluid TNF-α level was associated with a reduction of TNF-α in TMJ synovial fluid and elimination of TMJ movement pain ($r_s = -0.86$, $n = 21$, $P < .001$ and $r_s = -0.51$, $n = 21$, $P = .017$, resp; Figure 2) after treatment.

### *Relation between changes after glucocorticoid treatment*

The change in synovial fluid TNF-α level after treatment was positively correlated to the corresponding change in TMJ pain upon maximum mouth opening ($r_s = 0.50$, $n = 21$, $P = .020$; Figure 3), that is, a decrease of TNF-α was associated with an elimination of TMJ pain.

The change in synovial fluid TNF-α showed a tendency to a positive correlation to the change in serum C-reactive protein during the study period ($r_s = 0.47$, $n = 16$, $P = .068$), that is, an increased C-reactive protein level tended to be associated with an increased synovial fluid level of TNF-α. C-reactive protein increased from already abnormal levels in four patients and from normal level in one, while it decreased in none.

### *Pretreatment relations*

The synovial fluid level of TNF-α was not significantly correlated to its plasma level ($r_s = -0.28$, $n = 14$, $P = .325$).

The synovial fluid TNF-α level was positively correlated to TMJ pain intensity at rest ($r_s = 0.59$, $n = 20$, $P = .006$; Figure 4).

The tenderness to digital palpation of the posterior aspect of the TMJ was negatively correlated to the level of thrombocyte particle concentration ($r_s = -0.56$, $n = 16$, $P = .024$), which in turn was positively correlated to erythrocyte sedimentation rate ($r_s = 0.60$, $n = 17$, $P = .012$) and C-reactive protein level ($r_s = 0.56$, $n = 17$, $P = .018$).

Table 2: General and temporomandibular joint (TMJ) variables before and after intra-articular administration of glucocorticoid (median interval 40 days) in 21 female patients with chronic inflammatory TMJ disorders. The TMJ data refer to the most painful joint if bilateral injections were performed.

| | | Pretreatment | | | | | Followup | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Median | IQR | $n$ | % > 0 | % abn | Median | IQR | $n$ | % > 0 | % abn | $P$ |
| General disease activity | | | | | | | | | | | | |
| General joint pain intensity | score | 53 | 32 | 18 | 100 | NA | 31 | 38 | 14 | 93 | NA | NS |
| Erythrocyte sedimentation rate | mm/first h | 9 | 16 | 19 | NA | 5 | 12 | 18 | 16 | NA | 13 | NS |
| C-reactive protein | mg/L | 0 | 11 | 18 | 28 | 28 | 0 | 12 | 17 | 29 | 29 | 0.043 |
| C-reactive protein > 10 mg/L | mg/L | 15 | 9 | 5 | NA | 100 | 26 | 22 | 5 | NA | 100 | NA |
| Thrombocyte particle concentration | $10^9$/L | 307 | 102 | 17 | NA | 6 | 277 | 71 | 9 | NA | 11 | NS |
| TMJ pain | | | | | | | | | | | | |
| Intensity at rest | score | 50 | 44 | 20 | 100 | NA | 28 | 66 | 18 | 80 | NA | 0.021 |
| Present upon maximum mouth opening | 0 or 1 | — | — | 21 | 86 | NA | — | — | 21 | 67 | NA | NS |
| Tenderness to digital palpation | | | | | | | | | | | | |
| Lateral | 0 or 1 | — | — | 21 | 86 | NA | — | — | 21 | 43 | NA | 0.008 |
| Posterior | 0 or 1 | — | — | 20 | 55 | NA | — | — | 21 | 29 | NA | 0.043 |
| Sum | 0–2 | 2 | 1 | 20 | 95 | NA | 1 | 0 | 21 | 52 | NA | 0.002 |
| Pain reflex to digital palpation | | | | | | | | | | | | |
| Lateral | 0 or 1 | — | — | 21 | 29 | NA | — | — | 21 | 14 | NA | NS |
| Posterior | 0 or 1 | — | — | 20 | 15 | NA | — | — | 21 | 10 | NA | NS |
| Sum | 0–2 | 0 | 1 | 20 | 30 | NA | 0 | 0 | 21 | 19 | NA | NS |
| **Pressure-pain threshold** | | | | | | | | | | | | |
| Temporomandibular joint | kPa | 123 | 58 | 21 | NA | NA | 123 | 66 | 21 | NA | NA | NS |
| **Tumor necrosis factor-$\alpha$** | | | | | | | | | | | | |
| Synovial fluid | pg/mL | 0 | 37 | 21 | 33 | 33 | 0 | 36 | 21 | 33 | 33 | NS |
| Plasma | pg/mL | 14 | 13 | 14 | 100 | 57 | 12 | 12 | 14 | 100 | 43 | NS |

Pain intensity was assessed with a 100 mm visual analogue scale (VAS), tenderness or palpebral pain reflex to digital palpation of the lateral and posterior aspects of the TMJ on each side was recorded as one unit if the patient reported tenderness or if pain reflex was observed and the pressure-pain threshold was assessed over the palpable lateral pole of the TMJ condyle. IQR = 75th–25th percentile, $n$ = number of patients, % > 0 = percentage of observations exceeding 0, % abn = percentage of observations exceeding normal levels, median and IQR are not given for the 0/1 variables, NA = not applicable and NS = not significant.

Presence of a palpebral pain reflex, but not tenderness, on digital palpation of both lateral and posterior aspects of the TMJ was negatively correlated to the TMJ pressure-pain threshold ($r_s = -0.55$, $n = 21$, $P = .010$ and $r_s = -0.51$, $n = 20$, $P = .021$, resp; Table 3).

## DISCUSSION

This study indicates that local TNF-$\alpha$-related mechanisms influence the treatment effect of glucocorticoids on TMJ movement pain and that presence of TNF-$\alpha$ in synovial fluid predicts a positive treatment response in patients with chronic inflammatory TMJ disorders. TMJ movement pain is the clinical variable with the strongest relation to an inflammatory condition of the TMJ as determined by presence of inflammatory mediators in the synovial fluid [5, 17] and therefore the most valid clinical sign of TMJ arthritis.

High synovial fluid TNF-$\alpha$ level before treatment was associated with elimination of TMJ pain on maximum mouth opening after treatment. A decrease of synovial fluid TNF-$\alpha$ level after treatment was accordingly associated with elimination of TMJ pain on maximum mouth opening. Indeed, high synovial fluid level of TNF-$\alpha$ has previously been shown to be associated with pain on maximum mouth opening [5]. Synovial fluid TNF-$\alpha$. therefore seems to be predictive for glucocorticoid treatment outcome of this particular TMJ pain entity, which most probably is due to inhibition of intra-articular pain mechanisms provoked by joint movement and modulated by TNF-$\alpha$. At the same time, patients with detectable, that is, pathological, synovial fluid TNF-$\alpha$ levels had higher TMJ pain intensity in the TMJ at rest than those with undetectable levels, which indicates that synovial TNF-$\alpha$ is involved in modulation of resting pain as well. The plasma level of TNF-$\alpha$ was not associated with TMJ pain in this

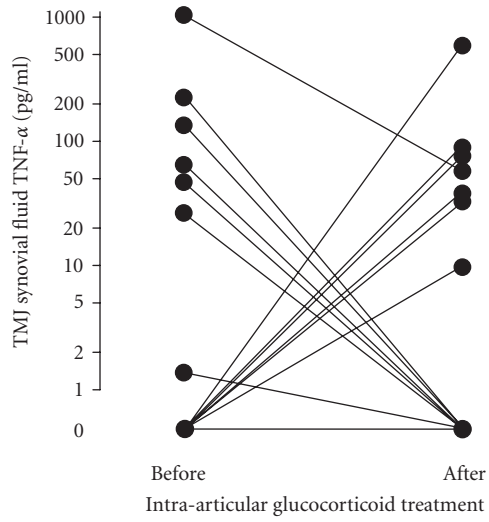


Figure 1: Individual changes in temporomandibular joint (TMJ) synovial fluid levels of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) before and after (median interval: 40 days) intra-articular glucocorticoid treatment in 21 female patients with chronic inflammatory TMJ disorder. Eight patients had undetectable synovial fluid levels of TNF-$\alpha$ at both occasions. The patients with detectable pretreatment synovial fluid level of TNF-$\alpha$ showed a reduction of the mediator from a median of 65 to a median of 0.

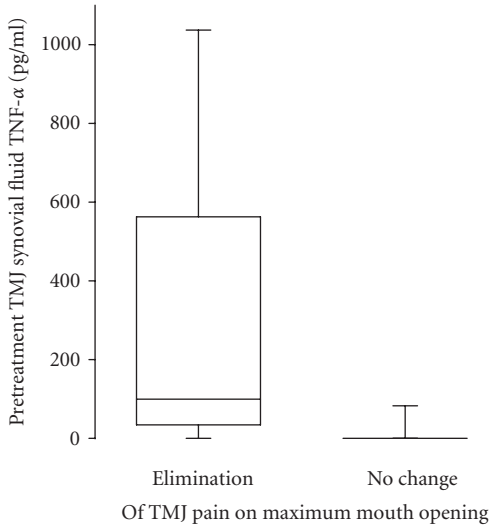


Figure 2: Box-plot (10th, 25th, 50th, 75th, and 90th percentiles) showing the relation between pretreatment TMJ synovial fluid level of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and the change in temporomandibular joint (TMJ) pain upon maximum mouth opening after intra-articular glucocorticoid treatment in 21 female patients with chronic inflammatory disorders of the TMJ ($r_s = 0.51$, $n = 21$, $P = .017$). Four patients had an elimination and 17 had no change of TMJ pain upon maximum mouth opening. In the 7 patients with detectable pretreatment levels, 3 experienced an elimination and 4 no change in TMJ pain upon maximum mouth opening.

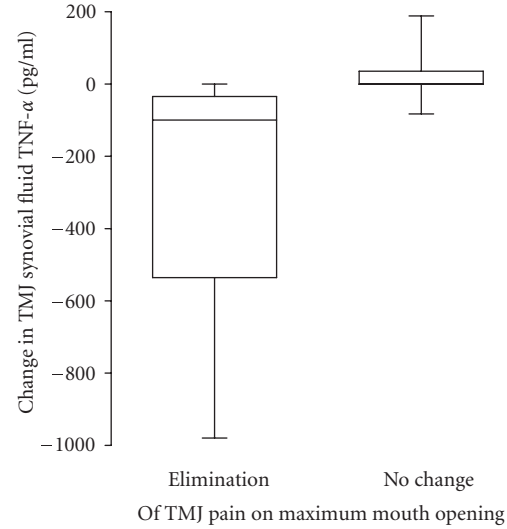


Figure 3: Box-plot (10th, 25th, 50th, 75th, and 90th percentiles) showing the relation between change in presence of temporomandibular joint (TMJ) pain upon maximum mouth opening and change in synovial fluid level of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) after intra-articular glucocorticoid treatment in 21 female patients with chronic TMJ inflammatory disorders ($r_s = 0.50$, $n = 21$, $P = .020$). Four patients had an elimination and 17 had no change of TMJ pain upon maximum mouth opening. In the 7 patients with detectable pretreatment levels, 3 experienced an elimination and 4 no change in TMJ pain upon maximum mouth opening.

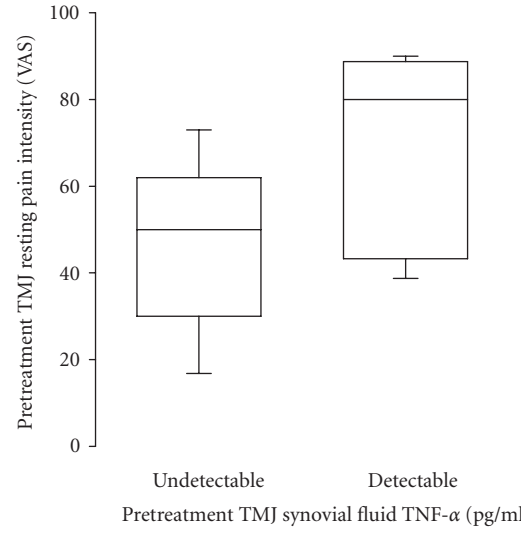


Figure 4: Box-plot (10th, 25th, 50th, 75th, and 90th percentiles) showing the pretreatment relation between temporomandibular joint (TMJ) synovial fluid level of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and TMJ resting pain intensity in 20 female patients with chronic inflammatory TMJ disorders ($r_s = 0.59$, $n = 20$, $P = .006$). Fourteen patients had undetectable synovial fluid TNF-$\alpha$ levels, whereas seven had detectable levels.

Table 3: Pressure-pain threshold in relation to tenderness and palpebral pain reflex to palpation before and 40 days after intra-articular administration of glucocorticoid in 21 female patients with chronic inflammatory temporomandibular joint (TMJ) disorders. Median (IQR) in kPa and number of observations. Absence or presence of tenderness and palpebral pain reflex to digital palpation of the lateral and posterior (through the acoustic meatus) aspects of the TMJ were assessed with the mandible in rest position (all patients with a pain reflex had tenderness to palpation) and the pressure-pain threshold was recorded over the palpable lateral pole of the TMJ condyle, NA = not applicable and IQR = 75th–25th percentile.

| | Tenderness to palpation | | | |
|---|---|---|---|---|
| Palpebral pain reflex to palpation | Lateral | | Posterior | |
| | No | Yes | No | Yes |
| | Before treatment | | | |
| No | 147 (73) | 142 (70) | 123 (49) | 147 (84) |
| | 3 | 12 | 9 | 8 |
| Yes | NA | 90 (53) | NA | 82 (68) |
| | 0 | 6 | 0 | 3 |
| | After treatment | | | |
| No | 120 (75) | 129 (103) | 123 (85) | 74 (47) |
| | 12 | 6 | 15 | 4 |
| Yes | NA | 98 (56) | NA | 76 (-) |
| | 0 | 3 | 0 | 2 |

study, which indicates a primarily local, rather than systemic, influence of TNF-$\alpha$ on the reduction of TMJ pain by glucocorticoid treatment and supports the previous finding that TNF-$\alpha$ mediates pain in the synovial tissues of the TMJ [5].

TMJ resting pain and tenderness to digital palpation decreased after intra-articular glucocorticoid treatment, which is in accordance with several previous studies [18–20]. In this study, the tenderness to digital palpation of the posterior aspect of the TMJ was negatively correlated to the level of thrombocyte particle concentration which in turn was associated with the inflammatory markers, erythrocyte sedimentation rate, and C-reactive protein. This suggests that posterior tenderness is not directly related to systemic inflammatory activity. Instead, local pain mechanisms are probably more important, which would favour a response of this pain entity to intra-articular glucocorticoid administration.

One explanation for the observed absence of treatment effect on pain on maximum mouth opening may be the large proportion of patients with undetectable levels of synovial fluid TNF-$\alpha$ before treatment since detectable pretreatment levels of synovial fluid TNF-$\alpha$ were found to predict reduction of pain on maximum mouth opening.

There were no treatment effects observed on presence of palpebral pain reflex to digital TMJ palpation or TMJ pressure-pain threshold. These variables were accordingly related to each other but not to the presence of tenderness to palpation. The findings presented indicate that different pain mechanisms modulate tenderness to digital palpation on the one hand and pain reflex to digital palpation and pressure-pain threshold over the TMJ on the other. Consequently, glucocorticoid actually seems to have different effects on different pain entities, which in part may be due to different origins of these pain entities. TMJ pain on maximum mouth opening is probably related to intra-articular pain mechanisms [17], whereas TMJ pressure-pain threshold as well as palpebral pain reflex probably are related to pain mechanisms in the lateral periarticular tissues. It therefore seems that there is a difference in mechanisms between pain reflex and tenderness to palpation of the joint, which is difficult to explain but may include activation of different subsets of nociceptors. There are reasons to consider pain on maximum mouth opening as intra-articular allodynia, which corroborates earlier findings [17]. It has previously been hypothesized that pressure-pain threshold and resting pain of the TMJ are modulated by different pain mechanisms [20], which is supported by the results of this study since there was no relation between these variables which responded differently to local administration of glucocorticoid. Future studies should investigate whether tenderness to digital palpation represents intra-articular pain or periarticular pain or both.

The synovial fluid TNF-$\alpha$ levels decreased consistently after treatment in the patients with detectable pretreatment levels. The clinical effect of glucocorticoid on TMJ pain may thus be explained by its well-documented inhibiting effect on TNF-$\alpha$ production [1]. Besides its direct effects, TNF-$\alpha$ also induces production of, for example, IL-1$\beta$, IL-6, IL-8, and prostaglandins in the inflamed synovial tissues [8, 9, 21, 22]. In addition, activated glucocorticoid receptors increase the expression of genes encoding anti-inflammatory proteins [1]. The observed treatment effect on TMJ resting pain and tenderness to digital palpation may thus be accomplished by reduction of several local pain mediators or increased local expression of anti-inflammatory proteins modulated by TNF-$\alpha$.

In this study, 33% of the patients had detectable levels of TNF-$\alpha$ in the synovial fluid at each sampling occasion, which is in agreement with other studies of similar patient categories [5, 23]. However, in six of the patients, the synovial fluid level of TNF-$\alpha$ increased from undetectable to detectable levels during the study period after treatment. The small but significant increase in C-reactive protein observed in the whole patient sample indicates a slight increase in the systemic inflammatory activity over the followup period. The observed increase in synovial fluid TNF-$\alpha$ levels is probably related to this increased systemic inflammatory activity. This is supported by the tendency to an association between the increase of synovial fluid TNF-$\alpha$ and C-reactive protein. The local release of TNF-$\alpha$ in the TMJ is thus most likely increased by increased systemic inflammation and higher concomitant C-reactive protein level. Another but less likely explanation is that the length of the time period between treatment and followup was too long for a reasonable possibility to detect a temporary reduction in synovial fluid TNF-$\alpha$ after treatment. However, no difference could be observed between patients with shorter intervals compared to longer intervals regarding the treatment effect on synovial fluid TNF-$\alpha$. In addition, those patients with a detectable pretreatment level of synvial fluid TNF-$\alpha$, who possibly could show a reduction of the mediator, did so significantly.

In this study, all patients had mediators in the TMJ synovial fluid indicating an inflammatory process, which supported the clinical diagnosis of "TMJ inflammatory disorder" as to whether there was a true intra-articular inflammatory condition. The synovial fluid mediator profile observed in this study was similar among the various clinical diagnostic subgroups.

In conclusion, this study indicates that presence of TNF-$\alpha$ in the synovial fluid predicts a treatment effect of intra-articular injection of glucocorticoid on TMJ movement pain in patients with chronic TMJ inflammatory disorders.

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