WRIST AND HAND

Effects of depression and inflammatory factors on chronic conditions of the wrist

M. Tatebe,
K. Iwatsuki,
H. Hirata,
T. Oguchi,
K. Tanaka,
S. Urata

From Hand and Microsurgery Center, Anjo Kosei Hospital, Japan

Aims
Chronic conditions of the wrist may be difficult to manage because pain and psychiatric conditions are correlated with abnormal function of the hand. Additionally, intra-articular inflammatory cytokines may cause pain.

We aimed to validate the measurement of inflammatory cytokines in these conditions and identify features associated with symptoms.

Patients and Methods
The study included 38 patients (18 men, 20 women, mean age 43 years) with a chronic condition of the wrist who underwent arthroscopy. Before surgery, the Self-Rating Depression Scale (SDS), Hand20 questionnaire and a visual analogue scale (VAS) for pain were used. Cytokine and chemokine levels in the synovial fluid of the wrist were measured using enzyme-linked immunosorbent assays and correlations between the levels with pain were analysed. Gene expression profiles of the synovial membranes were assessed using quantitative polymerase chain reaction.

Results
Older patients had high pre-operative Hand20 scores. One-year post-operative Hand20 and VAS scores and pre-operative VAS scores correlated with SDS scores. Post-operative VAS scores negatively correlated with the expression of nerve growth factor and SDS scores positively correlated with the expression of tumour necrosis factor-alpha and negatively correlated with the expression of tumour necrosis factor-converting enzyme.

Conclusion
There was a positive correlation between depression and chronic conditions of the wrist. Levels of some cytokines correlate with pain and depression. Additionally, cytokines may be important in the assessment and treatment of chronic conditions of the wrist and depression.

Cite this article: Bone Joint J 2016;98-B:961–8.
mediated by specific inflammatory factors and depression. We hypothesised that chronic conditions of the wrist are patient-rated evaluations of pain, function and depression. Chronic symptomatic conditions by comparing them with chronic conditions of the wrist, and to identify the features associated with depressive behaviour. Much interest has been focused on immunity, and cytokines have been shown to induce inflammatory response and the activation of cell-mediated immune mechanisms', might be involved in the pathogenesis of both pain and depression. Depression is associated with a chronic, low-grade inflammatory response and the activation of cell-mediated immunity, and cytokines have been shown to induce depressive behaviour. Much interest has been focused on the role of cytokines in the physiology and pathophysiology of joints. The mechanisms that link the immune system and the central nervous system, the so-called 'neuro-immune mechanisms', might be involved in the pathogenesis of both pain and depression.

In this study, we aimed to validate the measurement of inflammatory cytokines in patients with chronic conditions of the wrist, and to identify the features associated with chronic symptomatic conditions by comparing them with patient-rated evaluations of pain, function and depression. We hypothesised that chronic conditions of the wrist are mediated by specific inflammatory factors and depression.

Patients and Methods
Patients attending our clinic with chronic conditions of the wrist between 2010 and 2012 were asked to participate in the study. Chronic conditions were defined as those which persisted after three months of conservative treatment or those associated with post-traumatic pain at least three months after the initial trauma. We excluded patients with inflammatory disorders, such as rheumatoid arthritis, and those with inflammation as judged by a serum CRP level of > 0.4 mg/dL. We treated 45 patients with chronic wrist conditions during this time. Two declined to participate and five were lost to follow-up, leaving 38 patients in the study. There were 18 men and 20 women. Their mean age was 43 years (22 to 75). The conditions included ulnar wrist pain in 16 patients, necrosis of a carpal bone in eight, chronic post-traumatic pain in seven and degenerative disease in seven (Fig. 1). The range of movement and grip strength (measured using a Jamar grip dynamometer; Patterson Medical, Warrenville, Illinois) was assessed by physiotherapists pre-operatively and one year post-operatively.

At enrolment, the Self-Rating Depression Scale (SDS), the Hand20 questionnaire and a visual analogue scale (VAS) for pain (from 0 to 10, with 0 labelled ‘no pain’ and 10 ‘the worst possible pain’), were recorded. The psychological comorbidity status of the patients was categorised as either affected (SDS score ≥ 40, indicating mild depression) or unaffected (SDS score < 40). The Hand20 questionnaire is a 20-item questionnaire designed to measure the prevalence, degree and duration of common subjective function of the hand (from 100 (worst) to 0 (best)). The functional status and level of pain was evaluated using this questionnaire. The changes in the Hand20 and VAS scores were determined by subtracting the one year post-operative scores from the pre-operative scores.

All patients underwent arthroscopy of the wrist (surgery performed by MT), which provided a reliable assessment of the pathology. Arthroscopy is considered the reference standard, with more lesions being identifiable with arthroscopy than with arthrography. During arthroscopy, the hand was suspended with 3 kg to 5 kg of traction, and we assessed the joint for lesions of the triangular fibrocartilage complex, lesions of the articular cartilage, carpal instability and synovitis. The 16 patients with ulnar-side pain were treated according to an algorithm (Fig. 2). Their symptoms had not improved with conservative treatment (a splint for three months). The treatments which were used are shown in Table I.

Synovial fluid was collected from the wrist during arthroscopy. Using a 10 mL syringe with a 21-gauge needle, approximately 4 ml to 5 ml of saline were introduced to fill the radiocarpal joint and then withdrawn. The samples were centrifuged at 10 000 rpm for ten minutes, and the supernatants were stored at −80°C. Freeze-thaw cycles were avoided. The levels of IL-1β, IL-6, NGF, TNF-α, and ADAM-17 were measured in the synovial fluid using enzyme-linked immunosorbent assay (ELISA; Abnova, Taipei, Taiwan).

Total RNA was isolated from crushed synovial membranes obtained from the ulnar dorsal capsule (from portal 4 to 5) and the radiocarpal joint using an RNeasy Lipid Tissue Mini Kit (Qiagen, Valencia, California), and cDNA was synthesised using the High Capacity RNA-to-cDNA
Master Mix (Applied Biosystems, Foster City, California). Specific primers for TNF-α, IL-6, IL-1β, ADAM-17 and NGF were used, and the levels of TNF-α, IL-6, IL-1β, ADAM-17 and NGF in the crushed synovial membranes were measured. Samples were subjected to 40 cycles of amplification at 95°C for 15 seconds and 60°C for one minute, with period held at 50°C for two minutes and at 95°C for ten minutes, and the relative levels of mRNA expression were determined by calculating ΔCTs (CT for each target minus CT β-actin for each sample). Crushed synovial membranes were homogenised in Tris-buffered saline containing 1% Nonidet P-40, 10% glycerol, and protease inhibitors. Samples were diluted to the same protein concentration. The data of gene expressions were analysed after log transformation.

**Statistical analysis.** All variables are reported as means with ranges. The Mann–Whitney U test was used to compare the VAS and Hand20 scores, the percentage grip strength and the range of movement; the Wilcoxon signed-rank test was used to compare the measurements pre-operatively and one year post-operatively. The Kruskal–Wallis test was used to compare the variables among the four conditions. We used a Spearman rank correlation coefficient analysis for comparison of the questionnaires and

---

**Table I. The groups, by diagnosis**

<table>
<thead>
<tr>
<th>Ulnar wrist pain 16</th>
<th>Carpal bone necrosis 8</th>
<th>Post-trauma 7</th>
<th>Degenerative 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar shortening</td>
<td>11</td>
<td>Carpal ligament injury: 2</td>
<td>Gallion: 3</td>
</tr>
<tr>
<td>osteotomy TFCC repair 3</td>
<td>Radial osteotomy</td>
<td>Ligament reconstruct</td>
<td>Synovectomy</td>
</tr>
<tr>
<td>TFCC debridement</td>
<td>2</td>
<td>Traumatic osteoarthritis: 2</td>
<td>Partial wrist arthrodesis</td>
</tr>
<tr>
<td>Kienböck’s disease: 7</td>
<td>Vascularised bone graft</td>
<td>Scaphoid nonunion: 1</td>
<td>Screw fixation with bone graft</td>
</tr>
<tr>
<td>Preiser’s disease: 1</td>
<td></td>
<td>Malunited distal radial fracture: 2</td>
<td>Corrective osteotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arthritis: 4</td>
</tr>
</tbody>
</table>

TFCC, triangular fibrocartilage complex
assessments. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, New York). The level of significance was set at a p-value < 0.05.

The study had ethical approval and all patients gave informed consent.

Results
The flexion-extension arc of the wrist and grip strength were significantly better post-operatively than pre-operatively (pre-operative arc/grip = 77.1 (33 to 115)/72.6 (19 to 130) %normal, post-operative arc/grip = 87.2 (45 to 108)/85.9 (50 to 109) %normal, p-values were: 0.013, grip: 0.030). Additionally, the overall mean Hand20 score significantly improved from 40.0 (2 to 93) pre-operatively to 23.3 (1 to 76) post-operatively (p = 0.000), and the overall VAS score significantly improved from 6.1 (1 to 10) pre-operatively to 2.9 (0 to 9) post-operatively (p = 0.000). The mean change in the Hand20 score was 16.8 (-35 to 59) and in the VAS score was 3.2 (1 to 8). The mean pre-operative SDS score was 39.2 (25 to 51) (Table II). The pre-operative Hand20 scores and age were significantly lower among men than women (Hand20: p = 0.04, age: p = 0.003). The Hand20 and VAS scores were not significantly different among the various conditions (Table II). The one-year post-operative Hand20 and VAS scores correlated with the pre-operative scores (Hand20 scores: r = 0.597, p = 0.000; VAS scores: r = 0.498, p = 0.011). The changes in these scores correlated with NGF expression (Hand20 scores: r = 0.344, p = 0.034; VAS scores: r = 0.472, p = 0.004). The pre-operative Hand20 scores were higher in older patients than in younger patients (r = 0.434, p = 0.006) (Fig. 3). The one year post-operative Hand20 and VAS scores and the pre-operative VAS scores correlated with the SDS scores (post-operative Hand20 scores: r = 0.415, p = 0.01; post-operative VAS scores: r = 0.380, p = 0.019; pre-operative VAS scores: r = 0.330, p = 0.043) (Fig. 4). Additionally, the one year post-operative VAS scores correlated moderately negatively with NGF expression (r = –0.497, p = 0.002) (Fig. 5). Moreover, the SDS scores correlated mildly positively with TNF-α expression and negatively correlated with ADAM-17 expression in the synovial fluid (TNF-α: r = 0.374, p = 0.021; ADAM-17: r = –0.403, p = 0.012). Of the 38 patients, 19 had a mild depressive tendency and 19 were unaffected. The pre-operative and one year post-operative VAS scores, one year post-operative Hand20 scores, and TNF-α expression in the synovial fluid were higher in the patients with a mild depressive tendency than in those who were unaffected (Table III).

Discussion
We found a positive association between depression and chronic conditions of the wrist, suggesting that psychological factors may contribute to the pain experienced by the patient. The treatment of chronic low back pain is often multidisciplinary, consisting of rehabilitation, treatment with drugs and psychological support.29 The assessment of depression aids the treatment of the low back pain and this might be similarly applied to chronic disorders of the wrist. We recommend considering the psychological status in the treatment of these disorders.

The pre-operative Hand20 scores and age were significantly lower among men than women and higher in older patients than in younger patients. Age correlated with pre-operative function and a depressive tendency correlated with pre-operative pain. In older patients, the main causes...
of pain are related to the locomotor system. In a previous study, the Hand20 scores of asymptomatic volunteers tended to be higher in women and older people than in men and younger people. Basic motor control deteriorates and the prevalence of musculoskeletal disorders increases with age. The range of movement also decreases with age; however, the causes of such age-related changes remain unclear. Our findings were similar to those of these previous studies. We found that the function of the hand decreased with age. Additionally, we found that pre-operative function and pain correlated with post-operative function and pain, indicating that function improves and pain decreases after surgery, and the changes were influenced by age and a depressive tendency.

The SDS scores mildly correlated with the levels of some cytokines, and this may support a relationship between inflammatory diseases and depression. A depressive tendency was found to affect post-operative function and pain.
Some anti-depressants have been approved for the treatment of diabetic peripheral neuropathic pain, fibromyalgia and chronic low back pain. There may be a relationship between depression and pro-inflammatory cytokines. The inflammatory hypothesis of depression postulates that elevated circulating levels of pro-inflammatory cytokines might promote the development and persistence of depressive symptoms. Meta-analyses have indicated that in the absence of infection, peripheral levels of pro-inflammatory cytokines, especially IL-6 and TNF-α, were higher in non-medicated patients with depression than in non-depressed individuals. However, our data were limited and the correlation was mild. Further studies are needed on the associations between pain, depression, and inflammation.

The one year post-operative VAS scores moderately correlated with the expression of NGF. Additionally, we found that the changes in the Hand20 and VAS scores correlated with the expression of NGF. The production of NGF is...
upregulated in inflammation, and it can increase pain in arthritic joints through various mechanisms.\textsuperscript{41-45} The expression of NGF regulates pain and the healing of ligaments and decelerates chondrocyte differentiation \textit{in vitro}.\textsuperscript{46} Additionally, NGF is considered therapeutically valuable for ligament injuries.\textsuperscript{47} Therefore, high levels of NGF in the synovial membrane may indicate its potential to achieve a good clinical outcome with appropriate treatment.

This study has limitations. First, the cohort of patients was heterogeneous, and the number in each group and one year post-operatively was relatively small. The small sample size limits the statistical power of the data. Secondly, the levels of cytokines and SDS scores were only evaluated at surgery. Thirdly, our analysis was retrospective, and the results can only provide evidence for an association.

In conclusion, however, we found a positive association between depression and chronic conditions of the wrist. The levels of some cytokines correlate with pain and depression. These findings suggest that psychological factors are important in the treatment of these conditions. Additionally, cytokines may be important in not only chronic conditions of the wrist, but also depression.

**Take home message:**

Psychological factors are important in the treatment of chronic wrist conditions.

**References**

23. Zung WW. A SELF-RATING DEPRESSION SCALE. *Arch Gen Psychiatry* 1965;12:63–70.
40. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J Affect Disord* 2012;139:230–239.


42. Forsgren S. New data favouring that neurotrophins are of importance in arthritis. *Arthritis Res Ther* 2009;11:122.


