Interleukin-6 in Synovial Fluid and HLA-DR Expression in Synovium From Patients With Temporomandibular Disorders

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Interleukin-6–dependent mouse hybridoma cell line KD83 was used to test the biologic activity of interleukin-6 in synovial fluid from 37 patients with temporomandibular disorders. The results showed that the interleukin-6 level was greater than 100 U/mL in 13 of 18 patients with degenerative joint disease and in five of 12 patients with temporomandibular disc displacement. However, the interleukin-6 level was less than 100 U/mL (range, 20 to 75 U/mL) in all patients with masticatory muscle disorder. It has been found that degenerative joint disease tends to have acute and chronic stages, and interleukin-6 activity was probably related to the acute stage in the patients. Histologic studies of the synovium from seven patients with degenerative joint disease showed a variable degree of hyperplasia of the synovial lining cells and chronic inflammation in five of eight specimens. Immunostaining studies clearly showed the presence of significantly more HLA-DR–expressing cells (human leukocyte antigen–D-related) in synovium. Although it is unlikely that immune responses play an important primary role in initiating synovial inflammation and cartilage destruction, immune reactions may be one important factor in the maintenance and severity of some patients with temporomandibular disorders.
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key words: interleukin-6, HLA-DR, synovial fluid, synovium, temporomandibular joint

Several cytokines are known to be mediators of the destructive processes of rheumatoid arthritis. Interleukin-1 (IL-1) has been consistently detected in synovial fluid samples from patients with osteoarthritis (OA).[1,2] The processes initiating OA are unknown, and it is unclear if the end stage of cartilage failure is due mainly to proteoglycan, collagen, subchondral bone, or vascular defects. It is known that increased levels of degradative enzymes such as collagenase and stromelysin are present in osteoarthritic cartilage.[3,4] Interleukin-1 has many properties, such as stimulation of stromelysin, collagenase and prostaglandin E_2 (PGE_2) synthesis, and direct bone resorbing activities that might account for many of these changes. Tumor necrosis factor α (TNFα) produces similar changes and has also been found in some osteoarthritic synovial fluids.[5] In addition to their catabolic effects, IL-1 has anabolic effects, such as increasing fibroblast collagen synthesis,[6] which might account for other changes, such as osteophyte formation.

Interleukin-1 and TNFα have been found in synovial fluid from patients with temporomandibular disorders (TMD).[7,8] These findings suggest that cytokines may play a role in the pathogenesis of TMD as they do in other synovial joints. In addition, IL-1 and TNFα have been shown to be potent inducers of interleukin-6 (IL-

6) synthesis, and IL-6 levels in synovial fluid appear to correlate with disease activity.[9,10] With this background, IL-6 activity was measured in synovial fluids from 37 patients with TMD for the present study. Histologic findings and HLA-DR (human leukocyte antigen–D-related) expression in synovium from seven patients with TMD were also studied.

Materials and Methods

Synovial Fluid Samples

Thirty-seven temporomandibular joint (TMJ) fluid samples from 37 patients with TMD were included in the study. These patients were divided into three groups, according to the classification suggested by Ma et al[11,12]: *(1)* Masticatory muscle disorder. This type is actually an extra-articular disorder. Plane radiographs show no evidence of bony changes. *(2)* Disc displacement. Various kinds of disc displacement are included. There is also no evidence of bony changes on plane radiographs. In indolent and deferred cases, the pathologic changes of the condyle and disc are early degenerative changes. *(3)* Degenerative joint disease. A characteristic is secondary degenerative arthritis. Bony changes of the joint and/or perforation in disc are present.

Specimens were obtained during arthrography of the TMJ. For each patient, 1.0 mL of Hank's solution was injected into the superior joint space. The patients were asked to open and close their mouths to mix the Hank's solution with the synovial fluid, which was next aspirated. Synovial fluid samples were centrifuged (1,500 rpm for 10 minutes) to remove cells and were stored at −70°C until assayed.

Seven specimens were from patients with masticatory muscle disorder (two males and five females with a mean age of 31.6 years; range, 20 to 56 years). Twelve specimens were from patients with disc displacement (three males and nine females with a mean age of 26.6 years; range, 15 to 40 years). The other 18 specimens were from patients with degenerative TMJ disease (three males and 15 females with a mean age of 30.6 years; range, 15 to 40 years). Those who complained of pain in the TMJ area while opening and/or chewing were considered as patients with painful TMD. They all felt tenderness on palpation of the joint area. Of the 18 patients with degenerative joint disease, 10 patients were regarded as having painful TMD. The radiographic presentation of degenerative joint disease could be divided into two types. Type I represented destructive changes including condylar erosion. Type II proliferative changes included thickness of cortex, formation of osteophytes, and condyle flattening with sclerosis.

Bioassay for IL-6 Activity

The IL-6 was determined by the specific IL-6–dependent mouse hybridoma cell line KD83 (DNAX Research Institute, Palo Alto, CA). The cells were washed three times and suspended in a medium (5×10^4 cells/mL) consisting of DMEM (GIBCO, Grant Island, NY) with 10% fetal calf serum. A total of 100 µL of the medium was added to each well of the 96-well microplates (Sigma, St Louis, MO), and 100 µL of different dilutions of synovial fluid samples or recombinant IL-6 (1×10^7 U/mg, DNAX Research Institute) in DMEM was added to the culture wells. Interleukin-6–free DMEM was used as a control. Each sample was examined in triplicate in final solutions of 1:2, 1:4, and 1:8. Recombinant IL-6 as standard was retested in triplicate in final solutions of 1:2, 1:4, 1:8, 1:16, and 1:32. After 72 hours of incubation at 37°C, 50 µL of MTT (Sigma) at a concentration of 1 mg/mL in serum-free RPMI1640 (GIBCO), with no phenol red indicator, was added and further incubated for 4 hours at 37°C. After the supernatant from the wells was aspirated, 120 µL of isopropanol with 0.04 N of HCl was added to each well, which resulted in the formation of dark blue crystals. After the crystals were dissolved, the plates were read on a Dynatech MR 5000 microplate reader, using a test wavelength of 570 nm and a reference wavelength of 630 nm. The concentration of IL-6 giving half of the maximal optical density signal was defined as 1 U/mL.

Histologic and Immunostaining Procedures

Synovial membranes (n = 8) were obtained during discectomy in seven patients (eight joints) diagnosed with degenerative joint disease. All seven patients were females, with a mean age of 36.3 years (range, 26 to 42 years). Although patients had previously been treated nonsurgically, pain and/or limitation of mandibular movement still remained. Seven of the 8 joints showed disc perforation by arthrography. Synovium specimens were dissected from the bilaminar zone of the disc. Tissue samples were embedded in embedding medium used for frozen tissue specimens (Cryoform, International Equipment, Needham,

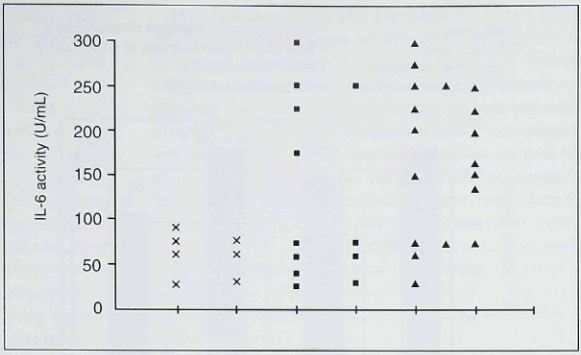

Fig 1 Levels of IL-6 in synovial fluid. × = specimens from patients with TMD masticatory muscle disorder; ■ = specimens from patients with disc displacement; ▲ = specimens from patients with degenerative joint disease.

MA), immediately frozen in liquid nitrogen, and stored at –60°C. Cryostat sections of 5 μm were cut on each specimen, air dried, and fixed in acetone. Specimens were processed using the avidin-biotin complex (ABC) method for frozen tissue. The assay was performed using the monoclonal mouse antihuman HLA-DR (dilution, 1:25; DAKO Japan, Kyoto, Japan) in combination with the Vectastain ABC kit (Vector, Burlingame, CA). The color was developed by diaminobenzidine containing nickel chloride and hydrogen peroxide. Each section was examined under a light microscope. Negative control sections were treated with normal mouse serum together with the tissues stained with the antibody to HLA-DR. Tissue specimens for histologic studies were stained with hematoxylin-eosin.

Results

Clinical Findings

No positive change was found on radiographs, and the disc position was normal in seven joints from the patients with masticatory muscle disorder. The 12 joints diagnosed with disc displacement included eight joints with anterior disc displacement with reduction and four joints with anterior disc displacement without reduction. Eighteen joints with degenerative joint disease had degenerative changes in condyles on radiographs, and disc perforation was found in 10 of the 18 joints. Radiographic features of the condyle could be divided into two types: one characteristic of destruction (13 of 18 joints); the other, of proliferation (five of 18 joints).

Interleukin-6 Activity in Synovial Fluid

Interleukin-6 activity was detected in all of the synovial fluid samples tested (Fig 1). This level of IL-6 activity could be neutralized by polyclonal rabbit antihuman IL-6 (GIBCO). The level of IL-6 was less than 100 U/mL (range, 20 to 75 U/mL) in all patients with masticatory muscle disorder. However, the IL-6 level was much greater than 100 U/mL in 13 of 18 patients with degenerative joint disease and in five of 12 patients with TMJ displacement (Fig 1). In addition, the IL-6 level was considerably higher in the synovial fluids obtained from the patients with degenerative joint disease (mean ± SEM, 175.4 U/mL ± 85.5 U/mL) than in those with masticatory muscle disorder (joint area 59.4 U/mL ± 29.4 U/mL) ($P < .05$, Student-Newman-Keul's multiple comparisons test). There was no statistically significant difference between the levels for degenerative joint disease and disc displacement, and no statistically significant difference between those for disc displacement and masticatory muscle disorder ($P > .05$).

Correlation Between IL-6 Level in Synovial Fluid and Clinical Characteristics in Patients With TMD

As shown in Fig 2, IL-6 level in synovial fluid was positively correlated with pain in the joint area and findings of radiographs in 18 patients with degenerative joint disease (t test). The IL-6 activity in three of 12 synovial fluid samples from patients with disc displacement was considerably high (229 U/mL, 264 U/mL, 303 U/mL). The three patients complained of marked pain in the joint area exacerbated by function.

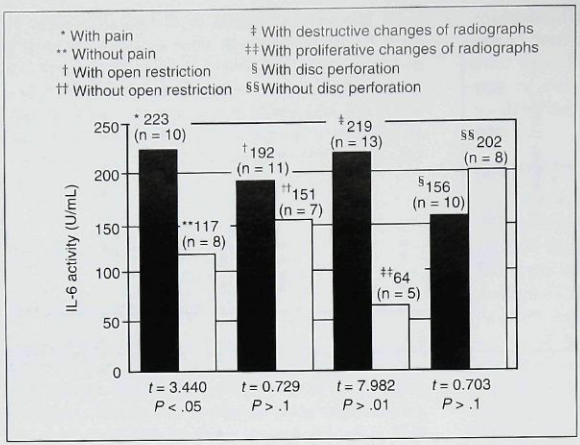

Fig 2 Correlation between IL-6 level in synovial fluid and clinical indexes from 18 patients with degenerative joint disease.

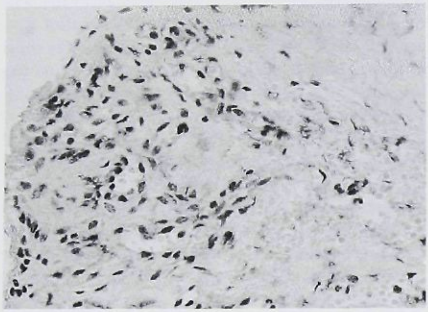

Fig 3 Hematoxylin-eosin staining reveals the presence of a synovial lining cell hyperplasia in the synovial membrane. (Original magnification × 480.)

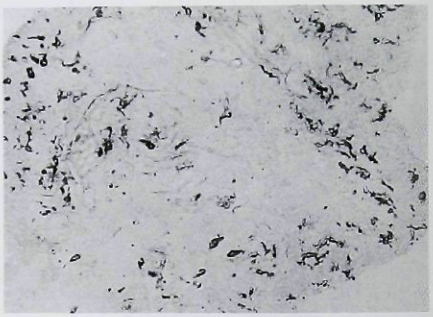

Fig 4 Immunostaining of the synovial membrane using a mouse monoclonal antibody antihuman HLA-DR shows the presence of HLA-DR antigen. (Original magnification × 240.)

Histologic and Immunohistologic Studies

Histologic studies showed that the synovial lining cells exhibited hyperplasia in five of eight specimens with degenerative joint disease (Fig 3). Mononuclear cell infiltration in seven of eight subsynovial tissue specimens was also seen. The HLA-DR–expressing cells were found in the layer of synovial lining in all specimens examined. Five of eight synovium specimens showed significantly more HLA-DR–expressing cells in the layer of synovial lining as well as in the deeper interstitium (Fig 4).

Discussion

Interleukin-6 is a 26-kd cytokine that is produced by monocytes, T lymphocytes, and fibroblasts.[13] Both IL-1 and TNFα induce the synthesis and secretion of IL-6. Furthermore, the biologic activities of IL-6 are similar to those of IL-1 and TNFα. Interleukin-6 differs from IL-1 and TNFα in its failure to stimulate PGE_2 and collagenase production in chondrocytes and synovial fibroblasts.[14] However, IL-6, synergistically with IL-1, stimulates bone resorption by osteoclasts.[15] Both IL-1 and IL-6 promote a number of other proinflammatory

effects. Increased production of IL-6 may contribute to the immunologic hyperactivity observed in diseases such as rheumatoid arthritis and related disorders.[16] Other studies have shown that IL-1 and TNFα could be detected in synovial fluid from patients with TMD.[7,8] Our findings indicate that the level of IL-6 activity is elevated in the synovial fluid of patients with degenerative joint disease and some patients with disc displacement, suggesting that excessive production of IL-1, TNFα, and IL-6 does exist locally in the TMJs of most patients with degenerative joint disease and some patients with disc displacement. It is possible that excessive production of these cytokines contributes to the pathogenesis of some patients with TMD, resulting in synovitis, cartilage destruction, and bone resorption.

Recent investigations have revealed that prominent inflammatory changes of the synovial membrane are also present in osteoarthritis.[17,18] Evidence for synovitis was also shown in patients with internal derangement of the TMJ.[19,20] Quinn and Bazan[21] reported the identification of PGE_2 and leukotriene B_4 in 19 samples of synovial fluid from patients with internally deranged TMJs. In our study, synovium from the patients with degenerative joint disease showed hyperplasia of synovial lining cells and inflammation in subsynovial tissue. Osteoarthritis usually has a gradual onset, but the disease tends to have acute and chronic stages. During the acute stage, pain may be present, and it likely corresponds to the period of regressive remodeling. The pain may be due to the presence of inflammation of the synovium.[22] Of the 18 patients with degenerative joint disease, 10 patients who complained of pain in the TMJ area had greater than a 100-U/mL level of IL-6 activity (see Fig 2). Radiographs of those 10 patients showed destructive changes in the condyle. Thirteen of 18 patients with destructive changes in the condyle had higher IL-6 levels than did those with changes of proliferation (Fig 2). Therefore, the results indicated that degenerative TMJ disease may have acute and chronic stages, and the high IL-6 levels were probably related to the acute stage of the disease. It has been reported that IL-6 in synovial fluid is related to disease activity in patients with rheumatoid arthritis.[9,10] In addition, of the 12 patients with disc displacement, five patients complained of pain in the TMJ area. Three fluid samples from the patients with pain contained a high level of IL-6 (229 U/mL, 264 U/mL, 303 U/mL). Synovitis was suspected in the patients with TMJ pain, so it was thought that a high level of IL-6 in synovial fluid might be due to synovitis of TMJ.

Immune complexes and complement were found in the superficial areas of articular cartilage in a group of patients with osteoarthritis.[23] These immune complexes may play a pathologic role in cartilage damage. In experimental antigen-induced arthritis in rabbits, sequestered immune complexes were seen to be able to activate complement and to induce acute and chronic inflammatory reactions.[24] The infused collagen antibodies have been shown to localize in the superficial areas of articular cartilage, and the identical anatomic location was found in osteoarthritis and rheumatoid arthritis.[25] The possible role of collagen antibodies in a relatively noninflammatory process such as osteoarthritis is more difficult to surmise, but the evidence from the animal models of collagen autoimmunity indicate that these autoantibodies could play a major role in the maintenance of chronic inflammatory process and in the modulation of disease severity. Immune complexes in the articular cartilage and collagen antibodies in synovial fluid from patients with TMD were also found.[26] Therefore, it is possible that autoimmune reactions may be present in TMJ tissues of some patients with TMD. Our findings that cytokines were detected in synovial fluid and that significant amounts of HLA-DR–expressing cells were shown in the synovium of some patients with TMD supported the conclusion mentioned above. It should be pointed out, however, that a limitation of this study is that a substantial amount of variability exists in retrieving synovial washings, such that the dilution factor of the synovial fluid may vary substantially from joint to joint. Normalizing the samples by total protein concentration would probably decrease the variability in the results and increase their reliability as a measure for disease activity.

One of the major histocompatibility complex (MHC) class II–transplantation antigens that are found on the surface of specialized cells such as macrophages, Langerhans cells, and dendritic cells is HLA-DR. Increased expression of MHC class II molecules has been shown in autoimmune thyroiditis and in insulin-dependent diabetes.[27,28] In rheumatoid arthritis, MHC class II–determinant expression by cells belonging to the common system, or by synoviocytes and other connective tissue cells, appears to be common,[29] although the precise role of these cells in arthritides is not yet clear. Antigen presentation by connective tissue cells expressing MHC class II determinants may contribute to the chronicity of the diseases. The present data suggest that it is possible that a number of stimuli, including nonspecific stimulation such as trauma, may lead to a selective accumulation in

synovial tissue of helper T lymphocytes that preferentially locate close to HLA-DR–expressing cells potentially capable of antigen presentation to T cells. Such an event might be a prerequisite for an activation of helper T lymphocytes and a subsequent elicitation of a delayed type cell reaction[30] and stimulation of antibody synthesis.[31] Activated helper T lymphocytes could induce macrophages, B cells, other T cells, and synoviocytes to release cytokines, growth factors, and lytic enzymes, which contribute to joint damage.[32] The arthropathy of TMD with degenerative changes was found to have an extravasation of lymphocytes as well as a thickening and increase in the numbers of MHC class II–expression cells in synovium tissue, which may lead to the release of cytokines. These cytokines would further enhance synovitis, cartilage destruction, and bone resorption. It is well known that cytokines may themselves, or in synergy with each other, induce MHC class II expression in the synovium as well as on chondrocytes within the cartilage.[32] Interleukin-6 may be a general stimulus for antibody synthesis and may also contribute to recruitments of cells that participate in the localized inflammatory process.[14] Thus, a vicious cycle is formed because immunopathogenic mechanisms may play a role in both the maintenance and the severity of the disease process.

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Resumen

La Interleucina-6 en el Fluido Sinovial y la Expresión del Antígeno del Leucocito Humano-RD (ALH-RD) en la Membrana Sinovial de Pacientes con Desórdenes Temporomandibulares

Se utilizó la interleucina-6 dependiente de la linea celular del hibridoma KD83 del ratón, para examinar la actividad biológica de la interleucina-6 en el fluido sinovial de 37 pacientes con desórdenes temporomandibulares (DTM). Los resultados demostraron que el nivel de interleucina-6 fue mayor de 100 U/mL en 13 de los 18 pacientes con enfermedad degenerativa de la articulación y en cinco de 12 pacientes con desplazamiento del disco temporomandibular. Sin embargo, el nivel de interleucina-6 fue menor de 100 U/mL (rango, 20 a 75 U/mL) en todos los pacientes afectados por el desorden muscular masticatorio. Se encontró que la enfermedad degenerativa de la articulación tiende a presentar estados crónicos y agudos, y que la activadad de la interleucina-6 estaba probablemente relacionada al estado agudo en los pacientes. Los estudios histológicos de la membrana sinovial de siete pacientes con enfermedad degenerativa de la articulación presentó un grado variable de hiperplasia del revestimiento de las células de la membrana sinovial e inflamación crónica en cinco de ocho espécimenes. Los estudios de colorantes immunológicos demuestran claramente la presencia de células que expresan el ALH-RD en la membrana sinovial. Aunque es improbable que las respuestas inmunes jueguen un papel primario importante en la iniciación de la inflamación sinovial y la destrucción del cartílago, las reacciones inmunes pueden ser un factor importante en el mantenimiento y severidad de algunos pacientes con DTM.

Zusammenfassung

Interleukin 6 in der Synovialflüssigkeit und HLA-DR Expression in der Synovia von Patienten mit Myoarthropathien des Kausystems

Die Interleukin 6-abhängige Maus Hybridom Zellinie KD 83 wurde verwendet, um die biologische Aktivität von Interleukin 6 in der Synovialflüssigkeit von 37 Patienten mit Myoarthropathien des Kausystems (MAP) zu überprüfen. Die Resultate zeigten, dass bei 13 von 18 Patienten mit degenerativen Gelenkerkrankungen und bei fünf von 12 Patienten mit Diskusverlagerung im Kiefergelenk das Interleukin 6 Niveau höher als 100 U/mL war. Bei allen Patienten mit muskulär bedingter MAP hingegen war der Interleukin 6 Niveau unter 100 U/mL(20–75 U/mL). Man konnte feststellen, dass degenerative Gelenkerkrankungen akute und chronische Zustände haben können, und dass Interleukin 6-Aktivität möglicherweise mit dem akuten Stadium in Verbindung gebracht werden kann. Histologische Studien der Synovialmembranen der sieben Patienten mit degenerativen Gelenkerkrankungen ergaben einen unterschiedlichen Grad von Hyperplasie der auskleidenden Synoviazellen und chronische Entzündung in fünf von acht Proben. Studien mit Immunmarkern ergaben signifikant mehr HLA-DR-exprimierende Zellen in der Synovia. Obwohl es unwahrscheinlich scheint, dass Immunantwort eine wichtige primäre Rolle im Entstehen einer Synoviaentzündung und Knorpelzerstörung spielt, können Immunreaktionen bei Patienten mit MAP einen wichtigen aufrechterhaltenden und beeinflussenden Faktor darstellen.