The Use of Synovial Fluid Analysis for Diagnosis of Temporomandibular Joint Disorders

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KEYWORDS

• Temporomandibular joint • Synovial fluid • Cytokines • Biomarkers

KEY POINTS

- Intra-articular pathologic conditions are associated with qualitative and quantitative changes in multiple synovial fluid biomarkers.
- The biomarkers identified in any given patient may enable a specific diagnosis to be made, including internal derangement, synovitis, chondromalacia, and autoimmune arthritis.
- Biomarkers may be used to monitor disease progression and response to treatment.

INTRODUCTION

Synovial fluid in the temporomandibular joint (TMJ) is a dialysate of plasma that also contains lipids, cholesterol, phospholipids, hyaluronic acid, glycosaminoglycans, albumin, immunoglobulin, elastase, collagenase, cathepsins, proteinase inhibitors, phospholipase A_2, alpha-2-macroglobulin, cytokines, and growth factors, as well as degradation products, inflammatory cells, and mesenchymal stem cells.[1] It provides joint lubrication and stress distribution in addition to providing nutrients and removing waste products of collagen and proteoglycan catabolism.

Synovial fluid is predominantly produced by type B synovial cells that line the nonarticulating surfaces of the TMJ. Various disease states in the TMJ result in alterations in the composition of synovial fluid, including viscosity, hyaluronic acid molecular size, and cytokine levels. Changes in synovial fluid composition provides an opportunity to quantitate and qualitate composition changes in order to potentially diagnose and monitor response to treatment.

The ability to use synovial fluid analysis to diagnose TMJ pathologic conditions is predicated on 3 assumptions:

- Synovial fluid biomarkers should be unique to specific diseases, such as osteoarthritis (OA), autoimmune arthritis, reactive arthritis (ReA), and internal derangement (ID)
- Quantitative biomarker analysis should correlate with disease progression or regression
- Asymptomatic patients without TMJ pathologic condition have a biomarker profile that is different from those with symptoms and/or pathologic conditions

Synovial Fluid and the Healthy Temporomandibular Joint

Synovial fluid sampling from subjects with healthy TMJs has provided much insight into the biological milieu within the TMJ. A healthy TMJ is generally considered to be an asymptomatic TMJ without any radiographic evidence of OA. Synovial fluid from healthy subjects is known to have both

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inflammatory and anti-inflammatory cytokines.[2] The pro-inflammatory cytokines interleukin (IL-2) and tumor necrosis factor (TNF) are typically present at low levels, as is the anti-inflammatory cytokine interferon-γ (IFN-γ). Furthermore, the levels of TNF and IFN-γ appear to correlate in healthy subjects, reflecting a balance between inflammatory and anti-inflammatory cytokines in an asymptomatic TMJ.

Synovial Fluid and Temporomandibular Joint Arthropathy

Qualitative and quantitative differences in the cytokine profile between healthy subjects and those with TMJ disease have been previously described.[3–13] A positive correlation between cytokine levels and the presence of disease is generally seen in most studies. Furthermore, many studies suggest that cytokine levels correlate with the extent of the disease. Correlation has been reported for the key cytokines IL-1β, IL-6, IL-11, TNF-α, and transforming growth factor-β1 (TGF-β1).[4–6,9–12,14] These findings would suggest that inflammatory cytokines play a major role in the development and progression of diseases, including ID and OA. Although most studies support these findings, there are some that have failed to show a positive correlation for specific cytokines, including IL-1β,[8,11] IL-6,[15] IL-8,[16] IL-10,[15] and TNF-α.[8,16]

Although the inciting event may differ, the inflammatory response within the TMJ and synovial fluid is similar. Inflammatory arthropathy and ReA are thought to result from activation of the immune system resulting in complement activation and the migration and activation of macrophages and polymorphonuclear leukocytes, and the release of multiple cytokines and growth factors[17] (**Table 1**). Mechanical stress is also thought to result in a similar process, although the mechanism appears to be more complicated. Ultimately, tissue destruction occurs as a result of the generation of free radicals and reactive oxygen species by macrophages and polymorphonuclear leukocytes[18] (**Fig. 1**). The free radicals and reactive oxygen species result in the degradation of proteins and proteoglycans in the synovial fluid, cartilage, bone, and connective tissues. Synovial fluid viscosity is increased, which results in further tissue destruction and impaired lubrication and nutrition of the articular cartilage and disc. The amount of tissue destruction depends on the tissue's ability to scavenge the free radicals and reactive oxygen species (see **Fig. 1**).

Table 1
Cytokine and growth factor content of temporomandibular joint synovial fluid aspirate

Cytokine or Growth Factor	Source	Activity
IL-1α, IL-1β	IC, SC	Pro-inflammatory
IL-1Ra	IC	Anti-inflammatory
IL-2	IC	Pro-inflammatory
IL-4	IC	Pro-inflammatory
IL-6	IC, FB, ET	Pro-inflammatory
IL-6sr	IC	Pro-inflammatory
IL-8	IC, FB, ET, SC	Pro-inflammatory
IL-10	IC	Anti-inflammatory
IL-11	FB, ET, SC	Pro-inflammatory
IL-12	IC	Pro-inflammatory
IL-17	IC	Pro-inflammatory
TNFα	IC	Pro-inflammatory
TNFβ	IC	Pro-inflammatory
sTNFr	Most cells	IR
IFN γ	IC	Pro-inflammatory
TGF-β1	IC	Anabolic, IR
VEGF	Most cells	Angiogenesis
Osteoprotegerin	MSC	Inhibit osteoclasts
TIMP-1	IC	Anti-inflammatory
MMP-3	IC	Pro-inflammatory
MMP-7	IC	Pro-inflammatory
RANKL	Most cells	Bone turnover, IR
ADAMTS	Most cells	Pro-inflammatory

Abbreviations: ET, endothelial cells; FB, fibroblasts; IC, inflammatory cells; IR, immune regulation; RANKL, receptor activator of nuclear factor; SC, synovial cells; sTNFr, soluble tumor necrosis factor receptor; TIMP, tissue inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor.

Synovial Sampling

Synovial sampling is relatively simple to perform during arthrocentesis and arthroscopy. However, it remains technique sensitive in that it is important to obtain the sample without contamination with blood. Typically, a 1-mL volume of normal saline is injected into the superior joint space using a 22-gauge needle; the mandible is manipulated to ensure the saline and synovial fluid mix, and then the joint fluid is aspirated and sent for analysis. The enzyme-linked immune sorbent assay, polymerase chain reaction (PCR), isobaric tags for relative and absolute quantitation, biotin-labeled-based protein