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Review article

# Cytokine profile in the synovial fluid of patients with temporomandibular joint disorders: A systematic review

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ABSTRACT

The aim of this study was to review the cytokine profiles in the synovial fluid (SF) of patients with temporomandibular joint disorders (TMJD). Databases were searched from 1965 till September 2015 using different combinations of the following key words: "Temporomandibular joint"; "Cytokine"; "disorder"; and "synovial fluid" and "inflammation". Titles and abstracts of studies identified using the above-described protocol were screened and checked for agreement. Full-texts of articles judged by title and abstract to be relevant were read and independently evaluated. Hand-searching of the reference lists of potentially relevant original and review articles was also performed. The pattern of the present systematic review was customized to mainly summarize the relevant data. Fifteen studies were included. In 12 studies, cytokine profile of patients with TMJD was assessed using enzyme linked immunosorbent assay; and in 2 studies, histological analysis was performed to assess the cytokine profile of patients with TMJD. Patients with TMJD presented raised levels of interleukin (IL)-6 in 8 studies, IL-1beta (1β) in 5 studies and tumor necrosis factor-alpha (TNF-α) in 5 studies. Two studies showed no significant difference in TNF-α levels in patients with and without TMJD; and IL-1β levels were comparable in patients with and without TMJD in 2 studies. Raised levels of IL-6, TNF-α, IL-1β, IL-8, and IFN-γ in the SF have been associated with inflammation in patients with TMJD. Cytokines IL-10, osteoclastogenesis inhibitory factor/osteoprotegerin (OCIF/OPG), and VEGF found in the SF of TMJs could have an anti-inflammatory effect.



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## 1. Introduction

Temporomandibular joint disorders (TMJD) are characterized by muscle-skeletal conditions and craniofacial pain in the masticatory system involving the joint, masticatory muscles or muscle innervations. Factors that have been associated with the etiology of TMJD include growth and developmental anomalies [1], trauma [2], detrimental body posture [3], parafunctional habits and bruxism [4], and stress [5]. Disc internal derangement (characterized by abnormal anatomic relationship between the articular disc and the articulating surfaces) and osteoarthritis (abnormal anatomic relationship between the articular disc and the articulating surfaces abnormal anatomic relationship between the articular disc and the articulating surfaces) are the most common forms of TMJD [6].

The degenerative changes in the TMJ are associated to osteoclastogenesis [7], however the molecular process associated to these changes are unclear. Studies [8–11] have shown that concentrations of monocyte-macrophage derived cytokines are raised in the synovial fluid (SF) of patients with TMJD. It has been reported that cytokines such as (interleukin [IL]-1beta [β], IL-6 and tumor necrosis factor-alpha [TNF-α]) may promote the release of proteinases and stimulate the expression of degrading enzymes and inflammatory mediators, resulting in TMJ inflammation and bone and cartilage degradation [12]. These results indicate a possible role of cytokines in the pathogenesis of TMJD. Recent studies [13–15] have suggested that the alteration of osteoprogeterin (OPG) and factor-kappa B ligand (RANKL) ratio can induce bone-destructive diseases like periodontal disease and rheumatoid arthritis. Wakita et al. [16], suggested a decrease in the concentration of OPG, in contrast to an unchanged concentration of RANKL in the SF from patients with TMJD. Other inflammatory mediators, bone-destruction associated cytokines and metallo-proteinases (MMPs) have been associated to TMJD, including: Interferon-gamma (IFN-γ), Prostaglandin $E_2$ ($PGE_2$), IL-17, MMP-2, MMP-9, aggrecanase-1 and aggrecanase-2 [8,9,17–19]. Therefore, the cytokine equilibrium, including their receptors and receptor antagonist are key factors for the beginning, progression and clinical expression of TMJDs. It is pertinent to systematically review the cytokine profile in the SF of patients with TMJD in an attempt to appraise the immunological biomarkers expressed in the SF of patients with TMJD. Hence, the aim of the present systematic review was to determine the cytokines profile in the SF of patient with and without TMJD.

## 2. Materials and methods

### 2.1. Focused question

Based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, a specific question was constructed. The focused question addressed was "Is there a difference in the cytokines profile in the SF of patients with and without TMJD?"

### 2.2. Eligibility criteria

The following eligibility criteria were entailed: (a) original clinical studies; (b) patients with TMJD; (c) inclusion of control group; and (d) intervention: patients with and without TMJD. Letters to the editor, historic reviews, case reports, case-series and unpublished articles were excluded.

### 2.3. Search strategy and study selection

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE, Scopus, Web of knowledge and Google-Scholar databases were searched from 1965 up to and including September 2015 using the following combination of keywords; (a) temporomandibular joint disorder + cytokines + synovial fluid; (b) temporomandibular joint disorder + cytokines + synovial fluid + inflammation; (c) disc internal derangement + temporomandibular joint + cytokines + synovial fluid; (d) interleukin + temporomandibular joint disorders + inflammation; (e) interleukin + temporomandibular joint disorders + inflammation + synovial fluid; (f) tumor necrosis factor alpha + temporomandibular joint disorders + inflammation; (g) tumor necrosis factor alpha + temporomandibular joint disorders + inflammation + synovial fluid; (h) osteoarthritis + temporomandibular joint disorders + inflammation; (i) osteoarthritis + temporomandibular joint disorders + inflammation + cytokines + synovial fluid.

Titles and abstracts of studies identified using the above-described protocol were screened by two authors (SVK and FV) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify any studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors (Fig. 1).

The initial search yielded 33 studies. Eighteen studies, which did not fulfill the eligibility criteria, were excluded (see Appendix A). In total, 15 studies [6,11,16,20–31] were included and processed for data extraction (Tables 1 and 2).

### 2.4. Methodological study quality assessment

The Newcastle–Ottawa Scale [32] (NOS) was used to grade the methodological quality of each study assessed in the present systematic review. In summary the NOS scale uses a systematic approach based on 3 specific criteria: Selection (S), Comparability

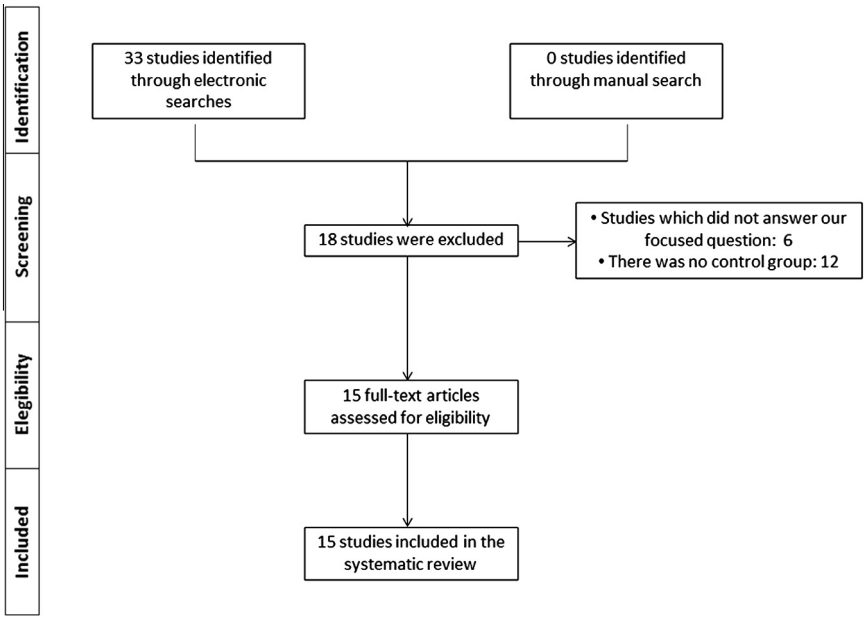


**Fig. 1.** Article selection flow chart for the systematic review according to PRISMA guidelines.

(C) and Exposure (E), which are subdivided in 9 criteria: (S1) adequate case definition; (S2) representativeness of the cases; (S3) selection of control; (S4) definition of control; (C1) comparability of cases; (C2) controls on the basis of the analysis; (E1) ascertainment of exposure; (E2) same method of ascertainment for cases and controls; (E3) non-response rate. Each criterion was given a response of either "Yes", "No", or "cannot tell,". Each study could have a maximum score of 9 (Table 3).

## 3. Results

### 3.1. Characteristics of included studies

#### 3.1.1. General characteristics

All studies [6,11,16,20–31] had a case – control design. Twelve studies [6,11,16,20,21,23–26,29–31] reported the numbers of study participants, which ranged from 6 to 130 subjects, with a mean age ranging between 25.4 and 62.3 years. Thirteen studies [6,11,16,20–29] reported the number of TMJs analyzed which ranged between 8 and 130. In all studies [6,11,16,20–31] the SF was collected with arthrocentesis using 1–4 mL of saline infiltration. Only 2 studies [20,21] reported the use of arthography.

All studies [6,11,16,20–31] included a control group; thirteen studies [6,11,16,22–31] used SF collected in patients diagnosed with healthy TMJs as controls; whereas, in two studies [20,21] the control groups included SF samples of patients diagnosed with masticatory muscle disorders. SF obtained from patients diagnosed with osteoarthritis (OA) or degenerative joint diseases were evaluated in 12 studies [6,11,16,20,21,23–27,29,30]. In thirteen studies [6,11,16,20–29], the SF of patients diagnosed with internal disc derangement was analyzed. Wake et al. [31] evaluated the SF collected in patients diagnosed with synovial chondromatosis.

#### 3.1.2. Methods for the assessment of cytokines

In twelve studies [6,11,16,22–29,31] cytokine levels in the SF of patients with and without TMJD were assessed using ELISA. Fu et al. [21] and Wake et al. [31], histologically assessed the tissues collected from the affected TMJs to study the synovial cells lining. Vernal et al. [30] used quantitative real-time polymerase chain reaction (PCR) to assess the messenger RNA (mRNA) expression levels of cytokines. Herr et al. [22], used isobaric tags for relative and absolute quantitation (Itraq) and Biotin-labeled-based protein arrays (BLPA) to identify protein markers in subjects with and without TMJD. Three studies [20,21,27] reported the use of additional methods to assess the cytokine level: Monotetrazolium cytotoxicity assay, immunostaining and enzymography respectively.

#### 3.1.3. Interleukin-6

The expression of interleukin-6 (IL-6) in the SF of patients with TMJD was analyzed in 10 studies [11,21,24–31]. In 9 studies [11,21,24–29,31], levels of IL-6 were significantly higher in the SF of patients with TMJD compared to controls. Vernal et al. [30] found no significant differences in IL-6 levels between patients with and without TMJD.

#### 3.1.4. Tumor necrosis factor-alpha

The levels of tumor necrosis factor-α (TNF-α) were explored in 8 studies [11,20,23,24,26,28,30,31], out of which, 6 studies [11,20,24,26,28,30] reported raised levels of TNF-α in the SF of patients with TMJD compared controls. In two studies [23,31], no significant difference in TNF-α levels in the SF of patients with and without TMJD.

#### 3.1.5. Interleukin 1-beta and interleukin-8

The concentration of IL-1β was assessed in 7 studies [11,23,24,26,27,29,30]. In 5 studies [11,24,26,27,30] higher IL-1β levels were reported in the SF of patients with TMJD compared to controls. In two studies [23,29], there was no significant difference in the IL-1β concentrations in the SF of patients with and without TMJD. IL-8 expression was assessed in 3 studies [11,24,31]. Results by Kaneyama et al. [24], and Takahashi et al. [11], reported significantly higher levels of IL-8 in the SF of patients with TMJD than controls. One study [31], reported no difference in IL-8 levels in the SF of patients with unilateral TMJD and controls.

#### 3.1.6. Interferon gamma

Interferon gamma (IFN-γ) concentration in the SF of patients with and without TMJD was assessed in 3 studies [11,30,31]. Takahashi et al. [11] and Vernal et al. [30], reported a higher expression

**Table 1**
General characteristics of included studies.

| Authors | Number of patients | Mean age/age range in years | Gender (F/M) (*N* = number) | Number of TMJs | TMJs diagnosis method | Synovial fluid collection method |
|---|---|---|---|---|---|---|
| Fang et al. [6] | 31 | Group 1: 29.6 (17–58)<br>Group 2: 39.2 (21–59)<br>Group 3: 27.7 (25–30) | NA | 38 | CE<br>Radiographs (unspecified) | Arthrocentesis with 2 mL saline solution 3 Reinjection |
| Fu et al. [21] | 37 | Group 1: 31.6 (20–56)<br>Group 2: 26.6 (15–40)<br>Group 3: 30.6 (15–40) | 29/8 | 37 | CE<br>Radiographs (unspecified) | Arthrography<br>Arthrocentesis with 1 mL saline solution<br>No reinjection |
| Fu et al. [20] | 27 | Group 1: 32.8 (23–40)<br>Group 2: 26.6 (16–40)<br>Group 3: 35.4 (25–40) | 20/7 | 27 | CE<br>Radiographs (unspecified) | Arthrography<br>Arthrocentesis with 1 mL saline solution<br>No reinjection |
| Herr et al. [22] | 6 | Group 1: NA (15–33)<br>Group 2: NA | 6/0 | 8 | CE | Arthrocentesis<br>No reinjection |
| Kaneyama et al. [24] | 124 | Group 1:29 (20–34)<br>Group 2: 30 (12–69)<br>Group 3: 42 (16–74)<br>Group 4: 30 (27–35) | 104/20 | 130 | CE<br>MRI | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Kaneyama et al. [23] | 55 | Group 1: 34 (12–69)<br>Group 2: 41 (16–74)<br>Group 3: 28 (28–30) | 44/11 | 55 | CE<br>MRI | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Kaneyama et al. [25] | 68 | Group 1: 28 (28–30)<br>Group 2: 37 (13–70)<br>Group 3: 44 (23–67) | 52/16 | 70 | CE<br>MRI | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Kaneyama et al. [26] | 60 | Group 1: 31 (28–36)<br>Group 2: 36 (14–76)<br>Group 3: 38 (15–68) | 44/16 | 60 | CE<br>MRI | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Kubota et al. [27] | 44 | Group 1: NA (15–77)<br>Group 2: NA (18–66)<br>Group 3: NA | NA | 40 | CE<br>MRI | Arthrocentesis with 2 mL saline solution >5 reinjection |
| Lee et al. [28] | 29 | NA | NA | 29 | NA | Arthrocentesis with 2–4 mL saline solution 5 reinjection |
| Shinoda and Takaku [29] | 66 | Group 1: 37.1 (±10.4)<br>Group 2: 30.1 (±10.1)<br>Group 3: 34.8 (±7.2)<br>Group 4: 39.2 (±9.8) | 42/24 | 66 | CE<br>MRI<br>Radiographs:<br>Lateral oblique transcranial and orbit-condylar | Arthrocentesis with 2 mL saline solution 3 reinjection |
| Takahashi et al. [11] | 57 | Group 1: 25.4 (17–35)<br>Group 2: 35.6 (14–61)<br>Group 3: 54.4 (20–78)<br>Group 4: 31.5 (27–39) | 46/11 | 66 | CE<br>Tomography<br>Radiographs:<br>Panoramic and transcranial<br>MRI | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Vernal et al. [30] | 18 | Group 1: 41.4 (±2.4)<br>Group 2: 39 (±2.2) | 12/6 | NA | CE<br>MRI | Arthrocentesis with 2 mL saline solution<br>No reinjection |
| Wake et al. [31] | 21 | Group 1: 62.3 (32–81)<br>Group 2: NA | NA | NA | CE<br>MRI<br>Arthroscopy | Arthrocentesis with 2 mL saline solution 10 reinjection |
| Wakita et al. [16] | 130 | Group 1: 32.4 (±2.2)<br>Group 2: 37.4 (±2.5)<br>Group 3: 42.4 (±2.6)<br>Group 4: 34.2 (±4.0) | 107/23 | 130 | CE<br>MRI | Arthrocentesis with 2 mL saline solution<br>No reinjection |

CE: Clinical Examination, MRI: Magnetic Resonance Imaging, TMJs: Temporomandibular Joints.

of IFN-γ in patients with OA; whereas, Wake et al. [31], found no detectable IFN-γ expression in patients with or without TMJD.

*3.1.7. Interleukin-2, interleukin-11, interleukin-12 and interleukin-17*

Vernal et al. [30], reported significantly higher levels of IL-2 and IL-17 in the SF of patients with TMJD compared to controls. Wake et al. [31], and Kaneyama et al. [25], reported no significant difference in IL-2 and IL-17 level respectively, in the SF of patients with and without TMJD. Kaneyama et al. [25], reported significantly higher IL-11 levels in patients with osseous changes in the condyles. Vernal et al. [30], reported a significantly higher expression of IL-12 in the SF of patients with OA compared to controls.

*3.1.8. Growth factors*

Fang et al. [6], suggested an increased level of transforming growth factor beta 1 (TGF-β1) in patients with OA. Herr et al. [22], assessed endocrine gland derived vascular endothelial growth factor (EG-VEGF) levels, suggesting lower concentrations in healthy controls, compared to patients with TMJD. One study [16] reported a lower osteoclastogenesis inhibitory factor/osteoprotegerin (OCIF/OPG) concentration in patients with OA,

**Table 2**
Cytokines profile in the TMJs synovial fluid among study groups.

| Authors | Study Groups | Measure of cytokine levels | Cytokines studied | Outcomes of study |
|---|---|---|---|---|
| Fang et al. [6] | Group 1: DID ($n$ = 12)<br>Group 2: OA ($n$ = 15)<br>Group 3: Control ($n$ = 4) | ELISA | IL-1RA<br>IL-10<br>TGF-β1 | No cytokines in Group 3. Significantly higher TGF-β1 levels in group 2 versus group 1. No significant difference in IL-1RA between groups 1 and 2. IL-10 undetectable in all the groups |
| Fu et al. [21] | Group 1: MOM disorder. ($n$ = 7)<br>Group 2: DID. ($n$ = 12)<br>Group 3: Degenerative joint disease. ($n$ = 18) | Histology<br>Immunostaining | IL-6 | Group 3 presented significantly higher IL-6 levels compared to group 1. No significant difference between group 1 and 2 |
| Fu et al. [20] | Group 1: MOM disorder. ($n$ = 5)<br>Group 2: DID. ($n$ = 11)<br>Group 3: Degenerative joint disease. ($n$ = 11) | MTT | TNF-α | Higher TNF-α levels in group 3, compared to group 2. No detectable TNF-α levels in group 1 |
| Herr et al. [22] | Group 1: Stage II and III TMJD. ($n$ = 4)<br>Groups 2: Control ($n$ = 2) | iTRAQ<br>BLPA<br>ELISA | EG-VEGF | Group 2 had a mean EG-VEGF concentration higher than group 1 |
| Kaneyama et al. [24] | Group 1: DID with clicking. ($n$ = 8)<br>Group 2: DID with locking. ($n$ = 52)<br>Group 3: OA. ($n$ = 57)<br>Group 4: Control. ($n$ = 7) | ELISA | IL-1β<br>TNF-α<br>IL-6<br>IL-8 | IL-1β TNF-α IL-6 and IL-8 concentrations were significantly higher in groups 1, 2 and 3, compared to group 4. IL-6 level was significantly higher in group 3, compared to the rest of the groups |
| Kaneyama et al. [23] | Group 1: DID ($n$ = 24)<br>Group 2: OA ($n$ = 26)<br>Group 3: Control ($n$ = 5) | ELISA | OCIF/OPG<br>IL-1β<br>TNF-α | OCIF/OPG concentration in group 2 was significantly lower than group 3. No significant difference with group 1. Concentrations of IL-1β and TNF-α did not differ among the groups |
| Kaneyama et al. [25] | Group 1: Control ($n$ = 7)<br>Group 2: DID ($n$ = 39)<br>Group 3: OA ($n$ = 22) | ELISA | IL-6<br>IL-11<br>IL-17 | No cytokines detected in group 1. IL-6 and IL-11 levels in groups 2 and 3 were significantly higher in joints with osseous changes in the condyle |
| Kaneyama et al. [26] | Group 1: Control ($n$ = 5)<br>Group 2: DID ($n$ = 41)<br>Group 3: OA ($n$ = 14) | ELISA | IL-1β, IL-6, 6sR, 1sR, 1RA<br>TNF-α<br>sTNFR-I<br>sTNFR-II | IL-1β, TNF-α, IL-6, sTNFR-I and sTNFR-II concentrations were significantly lower in group 1 compared to groups 2 and 3. TNF-α level was positively correlated with those of IL-6, sTNFR-I and sTNFR-II |
| Kubota et al. [27] | Group 1: DID and OA ($n$ = 22)<br>Group 2: Control ($n$ = 12)<br>Group 3: OA of Knee ($n$ = 10) | ELISA<br>EZG | IL-1β<br>IL-6 | Higher levels of IL-1β and IL-6 in group 1 compared to group 2. TMJs with OA contained significantly higher levels of IL-lβ and IL-6 than those with DID |
| Lee et al. [28] | Group 1: Control ($n$ = 5)<br>Group 2: Pain ($n$ = NA)<br>Group 3: Limited mouth opening ($n$ = NA)<br>Group 4: Clicking ($n$ = NA) | ELISA | TNF-α<br>IL-6 | Group 1 presented significantly lower levels of IL-6 and TNF-α compared to the other groups |
| Shinoda et al. [29] | Group 1: Control ($n$ = 18)<br>Group 2: TMJD without osseous changes ($n$ = 28)<br>Group 3: TMJD with osseous changes ($n$ = 10)<br>Group 4: TMJD with osseous changes and damaged discs ($n$ = 10) | ELISA | IL-1β<br>IL-6<br>TIMP-I | No significant difference in IL-1β level between the 4 groups. In group 1, IL-6 and TIMP-1, levels were lower compared to groups 2, 3 and 4. A correlation was noted between the presence of IL-6 and pain upon joint movements. The IL-6 level was correlated with the TIMP-1 level |
| Takahashi et al. [11] | Group 1: DID with clicking ($n$ = 8)<br>Group 2: DID with locking ($n$ = 25)<br>Group 3: OA ($n$ = 18)<br>Group 4: Control ($n$ = 6) | ELISA | IL-1β<br>TNF-α<br>IL-6<br>IL-8<br>IFN-ϫ | No cytokines were detected in group 4. Group 1, 2 and 3 presented at least 1 of the cytokines in 64.5% of the cases. IL-1β and IFN-ϫ presented the higher incidence, TNF-α the lower. Strong correlation between the presence of IL1β and TMJ pain in groups 1, 2 and 3 |
| Vernal et al. [30] | Group 1: OA ($n$ = 12)<br>Group 2: Control ($n$ = 6) | CRNAIRT<br>PCR | IL: 1β, 2, 4, 5, 6, 10, 12p35, 12p40, 17<br>IFN-γ<br>TNF-α<br>TNF-β | Group 1 presented higher expression of IL-1β, IL-2, IL-12p35, IL-12p40, IL-17, IFN-γ, TNF-α and TNF-β mRNAs compared to group 2. In group 1 the IL-12 was the predominant cytokine expressed. In group 2, IL-10 mRNA levels were higher versus group 1 |
| Wake et al. [31] | Group 1: TMJ chondromatosis ($n$ = 10)<br>Group 2: Control ($n$ = 11) | ELISA<br>Histology | Aggrecan<br>IL: 2, 4, 5, 6, 8, 10<br>IFN-γ<br>TNF-α<br>VEGF-A | In group 1 the concentrations of aggrecan, IL-6 and VEGF-A were significant higher compared to group 2 |
| Wakita et al. [16] | Group 1: DID with reduction ($n$ = 25) | ELISA | RANKL | No significance difference in RANKL |

**Table 2** (*continued*)

| Authors | Study Groups | Measure of cytokine levels | Cytokines studied | Outcomes of study |
|---|---|---|---|---|
| | Group 2: DID without reduction ($n$ = 39)<br>Group 3: OA ($n$ = 53)<br>Group 4: Control ($n$ = 13) | | OPG | concentration between group 4 compared to the rest of groups. Group 4 presented higher OPG levels versus groups 1, 2 and 3. RANKL/OPG ratio in group 3 was increased |

MOM: muscles of mastication, SF: synovial fluid, PCR: polymerase chain reaction, ELISA: enzyme-linked immunosorbent assay, BLPA: biotin-labeled-based protein arrays, MTT: monotetrazolium cytotoxicity assay, iTRAQ: isobaric tags for relative and absolute quantitation, IL: interleukin, TGF: transforming growth factor, CRNAIRT: cytoplasmic RNA isolation reverse transcription, TNF: tumor necrosis factor, RA: receptor antagonist, IFN: interferon, EZG: enzymography, EG-VEGF: endocrine gland derived vascular endothelial growth factor, sTNFR: soluble tumor necrosis factor receptor, OCIF: osteoclastogenesis inbitory factor, OPG: osteoprotegerin, sR: soluble receptor, OA: osteoarthritis, TIMP: tissue inhibitor of metalloproteinases, RANKL: receptor activator of nuclear factor kappa-B ligand, DID: disc internal derangement.

**Table 3**
Assessment of study quality with Newcastle–Ottawa Scale.

| Study | Selection | | | | Comparability | | Exposure | | | Number of star |
|---|---|---|---|---|---|---|---|---|---|---|
| | S1 | S2 | S3 | S4 | C1 | C2 | E1 | E2 | E3 | |
| Fang et al. [6] | × | | | × | × | | × | × | | 5 |
| Fu et al. [21] | × | | | × | × | | × | × | | 5 |
| Fu et al. [20] | × | | | × | × | | × | × | | 5 |
| Herr et al. [22] | × | × | × | × | | | × | × | | 6 |
| Kaneyama et al.[24] | × | × | | × | × | | × | × | | 6 |
| Kaneyama et al.[23] | × | | | × | × | | × | × | | 5 |
| Kaneyama et al.[25] | × | | | × | × | | × | × | | 5 |
| Kaneyama et al.[26] | × | | | × | × | | × | × | | 5 |
| Kubota et al.[27] | × | | | × | × | | × | × | | 5 |
| Lee et al.[28] | × | | | × | | | × | × | | 4 |
| Shinoda and Takaku [29] | × | × | | × | × | × | × | × | | 7 |
| Takahashi et al.[11] | × | × | × | × | | | × | × | | 6 |
| Vernal et al.[30] | × | × | × | × | × | | × | × | | 7 |
| Wake et al.[31] | × | × | × | × | | | × | × | | 6 |
| Wakita et al.[16] | × | × | × | × | × | × | × | × | | 8 |

compared to patients with internal derangement and healthy TMJs; meanwhile, Kaneyama et al. [23] reported higher OCIF/OPG concentrations in patients with internal derangement compared to healthy controls. One study [26] assessed the levels of soluble tumor necrosis factor receptors I and II (sTNRF-I, sTNRF-II), IL-6 soluble receptor (IL-6sR) and IL-1 soluble receptor (IL-1sR), correlating TMJD with an increased concentration of these cytokines. One study showed that IL-1 receptor antagonist (IL-1ra) concentration did not present significant difference among patients with or without TMJD. Fang et al. [6] suggested an increased level of IL-1ra in patients with TMJD and OA.

### 3.1.9. Tumor necrosis factor beta

Shinoda and Takaku [29], suggested higher tissue inhibitor of metalloproteinase (TIMP)-1 levels in patients with chronic TMJD. Vernal et al. [30], found that the levels of TNF-β, presented higher expression in patients with OA compared to healthy controls. Higher *aggrecan* and VEGF-A concentrations were reported by Wake et al. [31], in patients with chondromatosis compared with healthy TMJs. Wakita et al. [16] reported no significant difference in RANKL concentrations between control and TMJD patients.

### 3.1.10. Interleukin 10

Higher IL-10 levels in healthy TMJs compared to patients with disc derangement were reported in one study [30] Wake et al. [31] and Fang et al. [6] reported no detectable levels of IL-10 in either, control or TMJD groups, suggesting that the deficiency of IL-10 was likely to be one of the reasons for the development of OA.

## 4. Discussion

To the best of our knowledge from indexed literature, this is the first study systematically reviewing cytokine profile in the SF of patients with TMJD. The purpose of this study was to highlight the use of SF cytokine levels as an analytical tool in the diagnosis and treatment of TMJD. In the present systematic review, the main outcome of 80% (12 out of 15) of studies [11,20–22,24–31] included show a positive correlation between cytokine levels and TMJD. A possible explanation for these findings is related to the role, which pro-inflammatory cytokines play in TMJ inflammation. These cytokines are produced by macrophages and monocytes that induce protease release, accelerating the rate of cartilage degradation through proteoglycan depletion [33]. Furthermore, increased cytokine expression by chronic inflammatory cells that infiltrate the synovium, raises SF viscosity impairing nutrition and lubrication of the disc and articular cartilage [27]. These and other processes in the presence of cytokines lead to deterioration of joint ultrastructure (disc and articular surfaces) leading to internal derangement and degenerative joint disease [34].

In the studies [6,11,16,20–31] reviewed, cytokines including IL-6 [11,21,24–29,31], TNF-α [11,20,24,26,28,30], IL-1β [11,24,26,27,30], IL-8 [11,24], and IF-γ [11,3] have been identified and associated with inflammation in synovial joints and connective tissue destruction. Therefore, it is tempting to speculate that increased levels of these cytokines would be expected in the SF of TMJD patients compared to healthy TMJs. However, some studies [23,29–31] have shown a negative association between frequently isolated cytokines (IL-6 [30], TNF-α [23,31], IL-1β [23,29], IL-8 [31] and IL-10 [30] correlated with TMJD. The reasons of these controversial findings are manifolds. For instance in the study by Kaneyama et al. [23], no correlations between the IL-1 or TNF-α level and degenerative changes of the condyle, were related to the rapid turnover and consumption of cytokines within the joint cavity [9]. In addition, levels of IL-6 were comparable in SF of TMJ with OA and healthy TMJs in another study [30]. The authors of the study [30], suggested that this variability in outcome of IL-6

levels in comparison to other studies in SF of TMJD patients is due to inconsistency in sampling procedures, assay methods and the selection of patients and controls. Therefore, the hypothesis that TMJD is associated with increased levels of pro-inflammatory cytokines still remains to be established and studies with standard methodology and protocols are recommended for future research.

The biochemical analyses of SF in TMJD mentioned in the studies [6,11,20,21,25–27,29] reviewed also suggests that cytokine levels (TGF-β1, IL-6, TNF-α, IL11 and IL-1 β) correlate with the extent of TMJ disease, including morphological changes [24,25,35], clinical symptoms [11,29] and amount of joint effusion [36–38]. For example, in the study by Kaneyama et al. [25] and Kubota et al. [27], it was concluded that levels of IL-6 & IL-11 and IL-1β & IL-6 respectively, were increased in patients with degenerative joint diseases and joints with osseous changes as compared to patients with internal derangement of TMJ. Similarly in the studies by Shinoda and Takaku [29] and Takahashi et al. [11], in addition to the increased levels of IL-6 and IL-1β in patients with degenerative joint disease, a correlation was drawn between TMJ pain and increased levels of IL-6 and IL-1β Pro-inflammatory cytokines including IL-6, IL-1β and others, are not only present in chronic inflammatory cells like machrophages but are also released by fibroblasts and chondrocytes resulting in degenerative changes in the joint cartilage. In addition it is reported that one of the roles of IL-6 and IL-11 is the induction of RANKL expression which intern stimulates osteoclast formation leading to osseous joint changes [39–41]. Therefore, significantly higher levels of a combination of cytokines (such as IL-6 and IL-11) in SF of TMJ may well be an indicator for osseous breakdown and morphological changes of the joint. However such a correlation between TMJ disease progression (extent of TMJ destruction) and significantly higher cytokine levels was unfounded in nearly 34% of the studies [24,26,28,29,33] reviewed for some cytokines including IL-6, IL-1β and TNF-α. Therefore, further randomized controlled trials to monitor the levels of pro-inflammatory cytokines and their ability to predict the extent and severity of TMJ pathology are recommended. Furthermore, cytokines (IL-6 & IL-11) known to influence osteoclastogenesis could also be investigated as therapeutic targets to resolve TMD in future trials.

An interesting observation in the present systematic review is the role of cytokines (IL-10, OCIF/OPG, VEGF) found in the SF of TMJs possibly having an anti-inflammatory effect. For instance in the study by Vernal et al. [30], levels of IL-10 in the SF of TMJs in patients with OA was down regulated as compared to healthy controls. This may be related to the role of IL10 in inhibiting synthesis of pro-inflammatory cytokines (IL1a, IL1b, IL6, IL8, IL12, TNFa) and producing anti-inflammatory cytokines such as IL1RA [42] by monocytes and macrophages minimizing TMJ inflammation. Similarly in the study by Kaneyama et al. [23] decreased OPG levels were found in the SF of TMJs with OA and degenerative disease. This is due to the fact that OPG prevents osteoclastic differentiation by inhibiting cell–cell interaction between osteoclast progenitors and bone marrow cells [43,44]. Therefore cytokines such as OPG, IL-10 and EG-VEGF have the potential to be utilized as therapeutic agents in TMJD and also act as bio-markers for TMJ response to treatment. Therefore clinical trials aimed at investigating the role of cytokines as therapeutic agents and healing biomarkers of TMJD are recommended.

It is pertinent to mention that there was a lack of standardization (in terms of the type of cytokines assessed and methods used to investigate this cytokines) among the studies included in the present systematic review. Moreover, from the literature reviewed it was difficult to estimate the severity of TMJD. The authors of the present study hypothesizes that had there been a consistency (with reference to the types of cytokines assessed, severity of TMJD and the methodology of cytokines investigation) in the studies included, it could have been possible to quantify the cytokine levels in patients with and without TMJD.

## 5. Conclusions

Levels of pro-inflammatory cytokines including IL-6, TNF-α, IL-1β, IL-8, and IF-γ have been identified and associated with inflammation in synovial joints and connective tissue destruction are raised in the SF of patients with TMJD. Cytokines IL-10, OCIF/OPG, and VEGF found in the SF of TMJs could have an anti-inflammatory effect.

## Conflict of interest and financial disclosure

The authors declare that they have no conflicts of interest and there were no external sources of funding for the present study.

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## Appendix A. List of excluded studies. Main reason for exclusion is shown in parenthesis.

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