Clinical and Hematologic Characteristics of Temporomandibular Disorders Patients

Seo Eun Park[1], Ji Rak Kim[2], Jung Hwan Jo[3], Ji Woon Park[1]

[1]Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute,
Seoul National University, Seoul, Korea
[2]Department of Dentistry and Oral Medicine, School of Medicine, Catholic University of Daegu, Daegu, Korea
[3]Department of Oral Medicine, Seoul National University Dental Hospital, Seoul, Korea

Correspondence to:
Ji Woon Park
Orofacial Pain Clinic, Department of
Oral Medicine and Oral Diagnosis,
School of Dentistry and Dental
Research Institute, Seoul National
University, 103 Daehak-ro, Jongno-
gu, Seoul 03080, Korea
Tel: +82-2-2072-4912
Fax: +82-2-744-9135
E-mail: ankara01@snu.ac.kr

Purpose: The aim of this study was to evaluate the possibility of utilizing blood tests for the diagnosis of temporomandibular disorders (TMDs) by investigating the hematologic characteristics of TMD patients according to the main source and level of TMD pain and analyzing their interrelationship.

Methods: Clinical examination following the research diagnostic criteria for TMD and hematological and psychological evaluations were conducted in 357 TMD patients. Patients were divided into groups according to the main source of pain (myogenous, arthrogenous, and combined pain) and the degree of pain according to the graded chronic pain scale (GCPS). Hematological differences among the groups were statistically analyzed.

Results: The C-reactive protein (CRP) level was significantly higher in the arthrogenous pain group compared to the combined pain group (p=0.032). There was no significant difference according to the GCPS classification. There were significant correlations between some of the TMD pain indices and the hematologic indices, and also between the psychological indices and the hematologic indices.

Conclusions: This study suggests the possibility of applying blood tests to the diagnosis, treatment and prevention of TMD. Further research should be conducted focusing on the role of CRP in TMD pain with more refined methodology and a longitudinal study design.

Key Words: C-reactive protein; Hematologic tests; Pain; Temporomandibular disorders

INTRODUCTION

Temporomandibular disorders (TMDs) shows characteristics, such as pain, temporomandibular joint (TMJ) sounds, and restricted mandibular movement. Many TMD patients suffer from chronic pain of the masticatory and TMJ areas. TMD is a major cause of non-odontogenic pain in the craniofacial region.[1] The prevalence of TMD is relatively high and is known to afflict around 8% to 15% of the general population.[2] The etiology of TMD is multifactorial and includes biological, environmental, and psychosocial factors while the impact of each factor depends on the unique characteristic of each individual.[3] TMD pain has a great influence on the quality of life of patients and chronic pain is known to be frequently accompanied by psychological distress which may further aggravate symptoms.[4] However the current diagnosis of TMD is mostly limited to radiologic and clinical studies, and the many studies on indicators that predict the prognosis of TMD patients are based on subjective symptoms or psychological indices. Such limitations in diagnostic tools result in patient differentiation based on symptomatology rather than etiology and extend to

symptomatic treatment that fails to eliminate the origin of the pain.

Recent studies have found that certain pain-related diseases have specific hematologic characteristics. In fibromyalgia characterized by chronic widespread pain, neutrophilic leukemoid reaction and mean platelet volume were significantly higher and platelet distribution width was significantly lower than in the healthy control group.[1] Also hematologic manifestations, such as anemia, leukopenia, and thrombocytopenia also appear in autoimmune diseases, such as systemic lupus erythematosus.[5]

In addition, studies have shown that pain in complex regional pain syndrome (CRPS) can be the result of an autoimmune process and characteristic hematologic findings may be used for the diagnosis of CRPS.[6] Based on such findings the possibility of an early diagnosis of the above-mentioned diseases through blood testing is being sought out. One common clinical characteristic of the above diseases is chronic pain regardless of its intensity. In addition many other clinical aspects are shared among such disorders and include sleep problems, psychological disorders, and sensory alterations. Thus there may be an underlying mechanism that is shared and could be identified through certain testing methods.

Hematologic testing in spite of its invasiveness is an extensively applied approach for accurate diagnosis. Blood tests are relatively simple, fast-working, routinely used and are inexpensive as diagnostic tools. If certain hematologic features appear according to different clinical characteristics in TMD patients, the possibility of its application in the diagnosis of TMD may merit further investigation. However, no previous studies have examined the general hematologic characteristics through routine blood testing of TMD patients.

This study analyzed the association between clinical features, psychological factors, pain indices, and hematologic indices of TMD patients. Based on the results, this study aimed to analyze the possibility of applying certain hematologic testing in the diagnosis and prognosis building of TMD and further seeking the possibility of applying their results to the treatment and prevention of TMD.

MATERIALS AND METHODS

1. Subjects

We analyzed the data obtained from all consecutive patients who visited the Department of Oral Medicine of Seoul National University Dental Hospital complaining of TMD symptoms from May 2013 to July 2015. A total of 357 patients (70 men and 287 women; age range, 20-81 years; mean age, 29.54±7.52 years) were included in the study. Patients were diagnosed as TMD according to the research diagnostic criteria for temporomandibular disorders (RDC/TMDs).[7] The clinical examination was performed by a single specialist on TMD and orofacial pain (JWP). Venous blood was harvested from the antecubital vein of the patients included in the study on their first visit. Patients were classified into three groups with no, low, and high disability due to TMD pain according to the graded chronic pain scale (GCPS) reflecting their level of pain.[8] GCPS of the RDC/TMD axis II was obtained using two indicators, "pain intensity" and "degree of disability". Pain intensity was calculated by averaging current pain intensity, maximum pain intensity and recent 6-month average pain intensity. Degree of disability was assessed with disability points. Disability points are calculated by the disability score (the mean ratings of how much the pain has interfered in performing activities in the last 6 months) and disability days (the number of days that usual activities were avoided due to pain in the last 6 months). The total score is divided into five grades from 0 to IV. And it is divided into 3 groups as GCPS no disability group (Grade 0 with no TMD pain for the past 6 months), low disability group (grade I and II), and high disability group (grade III and IV).

Also, depending on the source of pain, patients were classified into three groups: myogenous, arthrogenous, and combined pain. Patients with myogenous pain were defined as group I, arthrogenous pain as group II, and patients with both as group III.

Patients with active inflammations in the orofacial region, such as periodontitis with spontaneous bleeding, myositis, abscess of the maxillofacial region and inflammatory diseases of other body parts, intake of analgesics with anti-inflammatory effects within 4 months prior to the study that could affect the test results, history of trauma and history

of psychiatric or immune diseases were excluded from the study. Also those who refused blood testing were excluded.

This study was approved by the Institutional Review Board of Seoul National University Dental Hospital (IRB no. CRI15018). The IRB authorized the exemption of informed consent.

2. Clinical and Hematologic Assessment

All patients completed the RDC/TMD axis II questionnaire and the Symptom Checklist-90-Revision (SCL-90-R) evaluation. The pain interview included demographic features, such as age, sex, and pain-related characteristics (quality, duration, and intensity), overall health status (cardiovascular, musculoskeletal, psychological and medication usage), and the presence of comorbidities of TMD (headache, sleep disturbance, neck and shoulder pain, lower back pain, arm and leg pain, and gastrointestinal disorder).

Clinical examination based on RDC/TMD included clinical parameters, such as comfortable mouth opening (CMO), maximum mouth opening (MMO), pain on palpation of masticatory and cervical muscles and TMJ capsule, pain on mouth opening and eccentric mandibular movements (protrusion and laterotrusion). Overall TMD pain intensity was scored by the patient on a 0-10 numeric rating scale (NRS). Clinical parameters were analysed at the initial visit and at 6 months after treatment initiation.

Psychological evaluations were based on RDC/TMD axis II and SCL-90-R.[9]

Plasma samples were obtained from the antecubital vein and stored in Lavender tubes coated with ethylenediaminetetraacetic acid (BD Vacutainer SST; Becton, Dickinson and company, Franklin Lakes, NJ, USA).

Concentrations of C-reactive protein (CRP) were analyzed by means of a highly sensitive immunoturbidimetric assay autoanalyzer (Hitachi 7180; Hitachi High-Technologies Corp., Tokyo, Japan). Comprehensive laboratory assessments consisted of complete blood cell counts with white blood cell (WBC) differential, red blood cell (RBC) indices, and blood chemistry.

3. Statistical Analysis

All statistical analyses were performed using IBM SPSS Stastistics ver. 25.0 software (IBM Co., Armonk, NY, USA).

The results were expressed as mean±standard deviation. ANOVA was used for the comparison of hematologic indices, psychological indices, and clinical indices among the patient groups. Bonferroni tests were also carried out for post-hoc analysis. Correlations of each dimension of TMD clinical parameters and laboratory findings were analyzed by Spearman's correlation coefficients.

Results were considered statistically significant at a probability level of p<0.05.

RESULTS

1. Clinical Characteristics

According to GCPS, among the total 357 patients there were 39 patients in the no disability group, 152 patients in the low disability group, and 166 patients in the high disability group. According to the source of pain, 36 were diagnosed as group I, 126 as group II, and 141 as group III, excluding the 54 patients who had not been definitely diagnosed at the first visit.

There were significant differences in the pain intensity and pain on mouth opening after 6 months of treatment between the groups according to the source of TMD pain. Pain intensity was significantly lower in group II (arthrogenous pain group) than in group I (myogenous pain group) (p=0.021) and group III (combined pain group) (p=0.038). Pain on mouth opening after 6 months of treatment was significantly higher in group III than group I (Table 1). Number of areas with positive responsiveness on capsule palpation was significantly higher in group III than group II (p=0.005). Number of areas with positive responsiveness on masticatory muscle palpation was significantly lower in group II than in group I (p<0.001) and group III (p<0.001). Number of area with positive responsiveness on neck muscle palpation was significantly higher in group III than in group I (p=0.022) and group II (p=0.00). There was a significant difference in the pain intensity and pain on mouth opening between the groups according to GCPS classification. Pain intensity was significantly higher in the high disability group compared to the low disability group (p=0.000) and no disability group (p=0.000). Pain on mouth opening was significantly higher in the high disability group (p=0.034) compared to the no disability group (data not

Table 1. Clinical characteristics according to source of TMD pain

Clinical parameter	Group I (n=36)	Group II (n=126)	Group III (n=141)	p-value	Multiple comparison
Pain duration	21.906±21.906	16.962±16.962	21.159±21.159	0.518	
Pain intensity	52.720±19.564	42.399±20.609	48.368±19.542	0.007**	(I, II), (II, III)
NRS first	5.083±2.430	4.349±2.445	4.949±2.399	0.074	
CMO	41.194±10.612	39.679±10.689	38.956±9.934	0.485	
MMO	45.389±8.550	44.557±8.857	44.038±8.031	0.660	
Capsule palpation	1.167±1.699	0.679±1.198	1.222±1.575	0.006**	(II, III)
Muscle palpation, face	4.139±3.474	1.069±1.642	5.177±2.892	0.000**	(I, II), (II, III)
Muscle palpation, neck	1.056±1.739	0.466±1.139	2.139±2.282	0.000**	(I, III) (II, III)
Pain on open	0.500±0.507	0.588±0.494	0.551±0.499	0.611	
Eccentric movement pain	0.639±0.833	0.794±0.966	0.703±1.000	0.604	
DJD	0.444±0.504	0.382±0.488	0.405±0.492	0.782	
Pain on open 6	0.111±0.319	0.252±0.436	0.323±0.469	0.029*	(I, III)
CMO 6	47.042±6.727	43.734±9.302	42.726±8.183	0.068	
MMO 6	47.958±6.118	45.651±8.217	44.788±6.671	0.129	
Capsule palpation 6	0.375±0.576	0.147±0.381	0.514±2.257	0.220	
Muscle palpation, face 6	0.375±0.711	0.193±0.481	0.774±2.708	0.068	
NRS 6	0.850±1.089	0.850±0.788	0.959±0.089	0.668	

TMD, temporomandibular disorder; NRS, numeric rating scale; CMO, comfortable mouth opening; MMO, maximum mouth opening; DJD, degenerative joint disease.
Values are presented as mean±standard deviation.
Group I, muscular pain group; Group II, joint pain group; Group III, muscular and joint pain group.
NRS first, NRS score before treatment initiation; Palpation, number of capsule/muscle areas that showed a positive response on palpation; Pain on open, whether there is pain on mouth opening (0: without pain, 1: with pain); Eccentric movement pain, Whether there is pain on eccentric movement (0: without pain, 1: with pain); Pain on open 6, whether there is pain when mouth opening after 6 months of treatment; CMO 6, CMO following 6 months of treatment; MMO 6, MMO following 6 months of treatment; NRS 6, NRS score after 6 months of treatment.
Pain intensity scores were calculated based on answers to the research diagnostic criteria/TMD Axis II questionnaire (mean score of question #7, 8, 9, 10).
*p<0.05, **p<0.01.

shown).

Psychological profiles were significantly different in several indices according to the source of TMD pain. RDC SOM (somatization scores of RDC/TMD axis II) (p<0.001), RDC PSOM (somatization score of RDC/TMD axis II without pain items) (p=0.001), RDC DEP (depression score of RDC/TMD axis II) (p=0.004), along with somatization (p=0.002), obsessive compulsive (p=0.015) and depression (p=0.020) scores of the SCL-90-R were significantly higher in group III than in group II (Table 2). Also, there were significant differences in psychological indices between groups according to GCPS classification. RDC SOM (p=0.000), RDC PSOM (p=0.000), RDC DEP (p=0.000), along with somatization (p=0.003), obsessive compulsive (p=0.012), interpersonal sensitivity (p=0.047) and depression (p=0.004) scores of the SCL-90-R were significantly higher in the high disability group compared to no disability group and low disability group (data not shown).

2. Hematologic Characteristics

Hematologic characteristics of patients with TMD were significantly different only in the CRP level. CRP level was significantly higher in group II (p=0.032) than in the group III (Table 2). However, there was no significant difference in all hematologic indices among the groups according to graded pain score classification (Table 3).

3. Relationship between Hematological and TMD Pain-Related Indices

Significant correlation was shown between ESR with CMO ($\gamma=-0.14$, p<0.01), MMO ($\gamma=-0.216$, p<0.01), CMO at 6 months after treatment ($\gamma=-0.133$, p<0.05), MMO at 6 months after treatment ($\gamma=-0.184$, p<0.01), pain duration ($\gamma=0.122$, p<0.05) and pain intensity ($\gamma=0.116$, p<0.05).

Table 2. Hematological characteristics according to source of temporomandibular disorder pain

Hematological parameter	Group I (n=36)	Group II (n=126)	Group III (n=141)	p-value	Multiple comparison
CRP (mg/dL)	0.086±0.08	0.127±0.247	0.073±0.077	0.032*	(II, III)
ESR (mm/h)	10.417±10.5	8.687±7.57	7.544±5.536	0.068	
Total protein (g/dL)	7.517±0.39	7.591±0.379	7.574±0.097	0.599	
White blood cell (10^3/μL)	6.663±1.584	6.145±1.708	5.989±1.734	0.103	
Red blood cell (10^6/μL)	4.501±0.434	4.537±0.471	4.488±0.382	0.618	
Hemoglobin (g/dL)	13.531±1.33	13.732±1.419	13.520±1.182	0.361	
Hct (%)	40.197±3.381	40.544±3.502	40.037±3.037	0.420	
MCV (fL)	89.536±5.234	89.637±3.705	89.309±3.705	0.815	
MCH (pg)	30.111±2.00	30.305±1.889	30.173±1.468	0.746	
MCHC (g/dL)	33.633±0.87	33.811±1.062	33.761±0.836	0.600	
Platelet (10^3/μL)	251.750±46.553	250.275±54.962	252.722±61.324	0.937	
PCT (%)	0.244±0.056	0.237±0.056	0.241±0.06	0.702	
MPV (fL)	9.536±0.661	9.482±0.838	9.416±0.745	0.623	
Absolute neutrophil count (/μL)	3,897.361±1,382	3,603.244±1,502.287	3,411.722±1,530.756	0.183	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCT, platelet crit; MPV, mean platelet volume.
Values are presented as mean±standard deviation.
Group I, muscular pain group; Group II, joint pain group; Group III, muscular and joint pain group.
*p<0.05.

Table 3. Hematological characteristics according to GCPS group

Hematological parameter	No disability group (n=39)	Low disability group (n=152)	High disability group (n=166)	p-value
CRP (mg/dL)	0.135±0.275	0.104±0.183	0.083±0.112	0.187
ESR (mm/h)	8.692±6.092	7.283±5.899	8.651±7.869	0.178
Total protein (g/dL)	7.623±0.367	7.524±0.422	7.587±0.386	0.235
White blood cell (10^3/μL)	6.436±1.161	6.119±1.721	6.085±1.759	0.515
Red blood cell (10^6/μL)	4.569±0.472	4.512±0.421	4.485±0.417	0.527
Hemoglobin (g/dL)	13.687±1.5	13.664±1.243	13.543±1.333	0.663
Hct (%)	40.392±3.662	40.383±3.183	40.036±3.307	0.608
MCV (fL)	88.754±6.58	89.668±3.932	89.413±4.147	0.505
MCH (pg)	30.059±2.651	30.352±1.525	30.202±1.588	0.567
MCHC (g/dL)	33.844±1.169	33.825±0.938	33.787±0.948	0.915
Platelet (10^3/μL)	254.79±54.676	242.901±49.795	255.355±61.295	0.121
PCT (%)	0.233±0.066	0.232±0.052	0.245±0.060	0.140
MPV (fL)	9.577±0.772	9.472±0.785	9.436±0.762	0.586
Absolute neutrophil count (/μL)	3,866.487±1,193.416	3,534.921±1,516.136	3,474.675±1,552.078	0.341

GCPS, graded chronic pain scale; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCT, platelet crit; MPV, mean platelet volume.
Values are presented as mean±standard deviation.

Total protein showed significant correlation with CMO (γ=0.106, p<0.05) and number of positive muscles on palpation (γ=0.126, p<0.01). WBC showed significant correlation with pain duration (γ=0.12, p<0.05). RBC showed significant correlation with NRS at before treatment (γ=−111, p<0.05), CMO (γ=0.237, p<0.01), MMO (γ=0.287, p<0.01), CMO at 6 months after treatment (γ=0.306, p<0.01), MMO at 6 months after treatment (γ=0.345, p<0.01), and pain intensity (γ=−0.126, p<0.05). Hemoglobin concentration showed significant correlation with CMO (γ=0.229, p<0.01), MMO (γ=0.276, p<0.01), CMO at 6 months after treatment (γ=0.295, p<0.01) and MMO at 6 months after treatment (γ=0.343, p<0.01). Significant correlation was shown between haematocrit with NRS at before treatment (γ=−0.114, p<0.05), CMO (γ=0.247, p<0.01), MMO (γ=0.298, p<0.01), CMO at 6 months after treatment (γ=0.333, p<0.01) and

Table 4. Relationship between hematological and TMD pain-related indices

Hematological parameter	NRS first	CMO	MMO	Capsule palpation	Muscle palpation	CMO 6	MMO 6	Capsule palpation 6	Muscle palpation 6	NRS 6	Pain duration	Pain intensity
CRP (mg/dL)	0.055	-0.065	-0.087	-0.053	-0.072	-0.002	-0.019	-0.041	-0.043	-0.029	0.074	0.047
ESR (mm/h)	0.104	-0.140**	-0.216**	-0.026	-0.043	-0.133*	-0.184**	-0.035	-0.052	0.062	0.122*	0.116*
Total protein (g/dL)	-0.030	0.106*	0.066	0.004	-0.126*	0.033	0.014	0.031	0.005	0.027	0.069	-0.025
White blood cell (10^3/μL)	0.006	-0.074	-0.063	0.023	-0.001	0.003	-0.031	-0.057	-0.049	-0.046	0.120*	-0.001
Red blood cell (10^6/μL)	-0.111*	0.237**	0.287**	-0.065	-0.090	0.306**	0.345**	-0.034	-0.051	-0.063	0.080	-0.126*
Hemoglobin (g/dL)	-0.074	0.229**	0.276**	-0.046	-0.099	0.295**	0.343**	-0.003	-0.022	-0.042	-0.011	-0.089
Hct (%)	-0.114*	0.247**	0.298**	-0.036	-0.077	0.333***	0.383***	-0.005	-0.015	-0.031	0.017	-0.097
MCV (fL)	0.014	-0.033	-0.049	0.062	0.044	-0.046	-0.039	0.060	0.076	0.057	-0.127*	0.077
MCH (pg)	0.062	-0.003	-0.007	0.019	-0.015	-0.031	-0.019	0.053	0.054	0.039	-0.154**	0.060
MCHC (g/dL)	0.106*	0.052	0.075	-0.053	-0.101	0.030	0.048	0.003	-0.023	-0.031	-0.083	0.003
Platelet (10^3/μL)	0.011	-0.107*	-0.066	-0.009	0.037	-0.047	-0.046	-0.045	-0.036	0.004	0.024	-0.001
PCT (%)	-0.004	-0.053	-0.041	0.067	0.076	0.000	-0.028	-0.014	-0.033	0.059	0.008	-0.037
MPV (fL)	-0.042	0.009	0.036	0.054	0.044	0.018	0.044	0.030	0.002	0.067	-0.026	-0.080
Absolute neutrophil count (/μL)	-0.027	-0.076	-0.073	0.017	-0.008	-0.008	-0.050	-0.058	-0.052	-0.098	0.134*	-0.049

TMD, temporomandibular disorder; NRS, numeric rating scale; CMO, comfortable mouth opening; MMO, maximum mouth opening; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCT, platelet crit; MPV, mean platelet volume.

Palpation, number of muscle that showed a positive response on palpation; CMO 6, CMO following 6 months of treatment; NRS first, numeric rating scale score before treatment initiation; the of treatment; MMO 6, MMO following 6 months of treatment.

Pain intensity scores were calculated based on answers to the research diagnostic criteria/TMD Axis II questionnaire (mean score of question #7, 8, 9, 10).

*p<0.05, **p<0.01.

Table 5. Relationship between hematological and psychological indices

Hematological parameter	RDC SOM	RDC PSOM	RDC DEP	SOM	OC	IS	DEP	ANX	HOS	PHOB	PAR	PSY	GSI	PSDI	PST
CRP (mg/dL)	-0.059	-0.046	-0.029	-0.045	-0.022	0.014	-0.004	0.003	0.032	-0.015	0.084	0.033	-0.015	-0.012	-0.007
ESR (mm/h)	0.064	0.052	0.106*	-0.027	0.080	0.081	0.104	0.061	-0.005	-0.015	0.109*	0.084	0.079	0.025	0.090
Total protein (g/dL)	0.062	0.061	0.068	-0.010	0.045	0.059	0.043	0.105*	0.034	0.117*	0.034	0.048	0.033	0.023	0.047
White blood cell ($10^3/\mu L$)	0.011	0.010	-0.010	-0.046	-0.028	0.059	0.026	0.021	0.036	0.092	0.074	0.056	0.028	-0.005	0.042
Red blood cell ($10^6/\mu L$)	-0.084	-0.084	-0.063	0.027	0.014	0.029	0.006	0.100	0.054	0.148**	0.030	0.066	0.018	0.033	0.006
Hemoglobin (g/dL)	-0.096	-0.091	-0.084	0.006	-0.010	0.023	-0.005	0.048	0.023	0.161**	0.047	0.053	-0.014	0.007	-0.008
Hct (%)	-0.081	-0.087	-0.078	0.033	0.003	0.026	0.011	0.062	0.028	0.158**	0.046	0.051	0.001	0.007	0.012
MCV (fL)	-0.012	-0.006	-0.021	-0.018	-0.007	0.008	0.013	-0.078	-0.054	-0.032	0.023	-0.029	-0.029	-0.087	0.026
MCH (pg)	-0.057	-0.026	-0.039	-0.031	-0.008	0.002	0.004	-0.050	-0.045	0.025	0.037	-0.016	-0.037	-0.053	0.000
MCHC (g/dL)	-0.077	-0.044	-0.058	-0.057	-0.026	0.004	-0.034	0.006	0.023	0.065	0.027	0.013	-0.046	-0.010	-0.052
Platelet ($10^3/\mu L$)	0.030	0.017	0.047	0.007	0.003	0.002	0.019	0.010	-0.084	0.027	0.009	0.017	0.001	0.031	0.004
PCT (%)	0.044	0.046	0.080	0.021	0.057	0.049	0.090	0.057	-0.012	0.039	0.061	0.083	0.057	0.029	0.071
MPV (fL)	-0.061	-0.044	-0.069	-0.080	-0.080	-0.072	-0.061	-0.053	0.002	-0.073	-0.059	-0.054	-0.051	-0.047	-0.042
Absolute neutrophil count (/μL)	-0.027	-0.035	-0.041	-0.101	-0.098	-0.011	-0.035	-0.032	-0.025	0.038	0.008	-0.006	-0.054	-0.046	-0.048

RDC, research diagnostic criteria; SOM, somatization; PSOM, somatization score without pain items; DEP, depression; OC, obsessive compulsive; IS, interpersonal sensitivity; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI, global severity index; PSDI, positive symptom distress index; PST, positive symptom total; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCT, platelet crit; MPV, mean platelet volume.

RDC SOM, somatization score of RDC/temporomandibular disorder [TMD] axis II; RDC PSOM, somatization score of RDC/TMD axis II without pain items; RDC DEP, depression score of RDC/TMD axis II.

RDC SOM, PSOM, and DEP scores were calculated based on answers to the RDC/TMD Axis II questionnaire.

Items not designated with RDC were based on the Symptom-Checklist-90-Revised.

*p<0.05, **p<0.01.

MMO at 6 months after treatment (γ=0.383, p<0.01). MCV (γ=−0.127, p<0.05) and MCH (γ=−0.154, p<0.01) showed significant correlation with pain duration. MCHC showed significant correlation with NRS at before treatment (γ=0.106, p<0.05). Platelet showed significant correlation with COM (γ=−0.107, p<0.05). And absolute neutrophil count showed significant correlation with pain duration (γ=0.134, p<0.01) (Table 4).

4. Relationship between Hematologic and Psychological Indices

Significant correlation was shown between ESR with depression score of RDC/TMD axis II (γ=0.106, p<0.05) and paranoid ideation (γ=0.109, p<0.05). Total protein showed significant correlation with anxiety (γ=0.105, p<0.05) and phobic anxiety (γ=0.117, p<0.05). RBC (γ=0.148, p<0.01), hemoglobin (γ=0.161, p<0.01) and hematocrit (γ=0.158, p<0.01) showed a significant correlation with phobic anxiety (Table 5).

DISCUSSION

This study investigated the hematologic characteristics of TMD patients. The purpose of this study was to present the tentative diagnostic usefulness of hematologic testing in TMD diagnosis. The results of this study suggest that CRP levels in patients with TMD may be useful in predicting the source and prognosis of a patient's pain. We found that CRP was significantly higher in the arthrogenous pain group compared to the combined pain group. There were also significant correlations between TMD pain related indices and hematological indices.

When analyzing clinical characteristics according to the source of TMD pain, pain intensity was significantly lower in the arthrogenous pain group compared to the 2 other groups. In the case of arthrogenous pain, medication and physical therapy are known to efficiently alleviate the pain in a relatively short period of time. Therefore, the duration of the pain could be shorter than in the myogenous pain group and hence the less disability days.[10] When classifying the patients by GCPS, pain intensity and pain on mouth opening were significantly higher in the high disability group. This is an expected result and shows that GCPS

accurately reflects the degree of TMD pain of the patient.

As a major result of this study, the CRP level was found to be significantly higher in the arthrogenous pain group compared to the combined pain group. CRP levels are known to show a rapid and distinct increase following an acute inflammatory challenge. Therefore CRP is a valuable index of systemic inflammation that is produced in the liver in response to increases in inflammatory cytokines, such as interleukin-6.[11] CRP is currently recognized as a valuable marker of active and persistent inflammation in the body. Also many previous studies have shown that CRP can act as a biomarker of various diseases. CRP levels are known to predict cardiovascular events and are used as an indicator for its prevention.[12-14] In addition, studies have suggested that CRP can be an index of disease activity in inflammatory bowel syndrome,[15] rheumatoid arthritis[16] and diabetes mellitus.[17]

Inflammation may exist according to the state of the TMJ in conditions, such as synovitis, capsulitis, and retrodiscitis, depending on which structure is involved. And osteoarthritis (OA) is also known as a state of inflammation associated with destructive changes of the bone.[18] In studies on OA, CRP levels were significantly higher in OA patients than in the healthy control group,[19-21] and high CRP levels could predict incidents of OA.[20] However, the relationship between synovitis and OA is not well established yet.[22] Synovial fluid analysis results of patients with TMJ arthralgia revealed an increase in inflammatory cytokines.[23-26] CRP has a pro-inflammatory effect, so it is understandable that the increased level of CRP may worsen pain in patients with arthralgia. Myogenous pain was traditionally considered to be related to contraction and ischemia of the masticatory muscles.[27] However recent studies tell us that myofascial pain is highly associated with psychological disorders and can be initiated and prolonged by abnormalities of the pain control system in the central nervous system.[10] In addition, the mechanism underlying the development of chronic pain is much more intricate and involves both biologic and psychologic factors.[28] Therefore, it could be said that myogenous pain is affected by more various factors compared to pain that is resulting from an acute inflammation.

There are previous studies based on the analysis of TMJ synovial fluid. However, it is difficult to aspirate a sufficient

amount of synovial fluid from the TMJ due to its small volume and the specimen is easily contaminated by blood causing distortion of the analysis results. Compared to this, blood tests are relatively simple and the analysis results are generally accurate. Therefore, the possibility applying blood tests to the diagnosis of TMD pain is feasible and merits further consideration. Especially considering the current lack of diagnostic tools that are available.

ESR is known to show low specificity but reflects an inflammatory state. Thus, an increased ERS level means the possible existence of an inflammatory condition that is closely related to an increased pro-inflammatory cytokine level. Therefore, ESR levels may show a certain level of association with several TMD-related symptoms.[29] In this study, ERS level was highly correlated with various TMD pain-related indices including CMO, MMO, CMO at 6 months after treatment, MMO at 6 months after treatment, pain duration, and pain intensity. In the pathogenesis of certain immune mediated inflammatory diseases, an increase in platelet derived factors and platelet activation can be observed.[30] In the results of this study, there was a significant correlation between CMO and platelet levels. All these results indicate a relationship between pain and inflammation. In liver cirrhosis, multiple myeloma, and lymphoma, an increase in total protein level can be observed. Total protein is also known to be increased in chronic inflammatory states. CMO and number of positive muscles on palpation were highly correlated with the total protein level. This fact may indirectly support the possible presence of a chronic inflammatory condition in myalgia. Increased WBC levels indicate the presence of an inflammatory condition. WBC is also known to be increased in psychological states, such as depression.[31] The relationship between depression and TMD pain has already been revealed through many previous studies.[29] In this study, there was a significant correlation between WBC level and pain duration. Unexpectedly, as the RBC, hemoglobin, and hematocrit level increased, the pain level tended to decrease. Although study results with sickle cell disease show that high hematocrit levels affect pain, the mechanism is yet to be defined.[32]

There are various studies on the hematological features of psychological disorders. Shafiee et al.[31] reported that depression and anxiety are associated with an increased WBC

and red cell distribution width (RDW) indicating an increased inflammatory state. Köhler-Forsberg et al.[33] reported that high CRP levels in women were associated with the symptom severity of depression. Many other studies also supported the association between CRP and depression.[34-36] This study also supports the positive correlation between depression and inflammation.

There are some limitations of this study to be considered in the interpretation of the results. First, this study did not consider gender and age in the analysis of blood samples. Although there are no consistent data suggesting different hematologic levels studies exist that do show diversity according to gender and age, and some of the results of this study may have been affected. In addition, in the case of female subjects, the menstrual cycle may have caused further inconsistencies. Second, there may be bias in the data since we could not conduct blood testing on all TMD patients visiting the clinic. However, whether the blood test was performed was not based on the severity of disease, age, and gender. So we believe that results were not largely affected. Third, the number of arthrogenous pain patients was relatively small. It could have lowered the statistical power resulting in insignificant results. This study was conducted to tentatively suggest the possibility of using hematologic tests in the diagnosis of TMD. And the results indicated that the usage of CRP should be assessed through future studies with more refined study designs.

This study suggests the possibility of diagnosing TMD pain using an easy and accurate blood test. Such early differentiation of patients based on the etiology of pain could offer backgrounds to establish a cause targeting treatment plan which will result in better prognosis. Although the results of this study do not provide direct evidence of the relationship between hematologic and clinical indices of TMD pain, the results suggest the need of future studies to verify hematologic indices that could be recognized as markers of TMD pain.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Aktürk S, Büyükavcı R. Evaluation of blood neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol 2017;36:1885-1889.

2. de Leeuw R, Klasser GD; American Academy of Orofacial Pain. Orofacial pain: guidelines for assessment, diagnosis, and management. 5th ed. Chicago, IL: Quintessence Publishing; 2013. pp.127-186.

3. Dworkin SF, Huggins KH, LeResche L, et al. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. J Am Dent Assoc 1990;120:273-281.

4. Barros Vde M, Seraidarian PI, Côrtes MI, de Paula LV. The impact of orofacial pain on the quality of life of patients with temporomandibular disorder. J Orofac Pain 2009;23:28-37.

5. Sasidharan PK, Bindya M, Sajeeth Kumar KG. Hematological manifestations of SLE at initial presentation: is it underestimated? ISRN Hematol 2012;2012:961872.

6. Blaes F, Schmitz K, Tschernatsch M, et al. Autoimmune etiology of complex regional pain syndrome (M. Sudeck). Neurology 2004;63:1734-1736.

7. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301-355.

8. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133-149.

9. Derogatis LR, Cleary PA. Confirmation of the dimensional structure of the SCL-90: a study in construct validation. J Clin Psychol 1977;33:981-989.

10. Maixner W, Fillingim R, Booker D, Sigurdsson A. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995;63:341-351.

11. Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279:48487-48490.

12. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-843.

13. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol 2007;49:2129-2138.

14. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363-369.

15. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004;10:661-665.

16. Gonzalez-Gay MA, Gonzalez-Juanatey C, Piñeiro A, Garcia-Porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol 2005;32:1219-1223.

17. Thorand B, Löwel H, Schneider A, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Arch Intern Med 2003;163:93-99.

18. Okeson JP. Management of temporomandibular disorders and occlusion-E-Book. 7th ed. Edinburgh: Mosby Elsevier; 2014.

19. Lee YC, Lu B, Bathon JM, et al. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res (Hoboken) 2011;63:320-327.

20. Spector TD, Hart DJ, Nandra D, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997;40:723-727.

21. Sowers M, Jannausch M, Stein E, Jamadar D, Hochberg M, Lachance L. C-reactive protein as a biomarker of emergent osteoarthritis. Osteoarthritis Cartilage 2002;10:595-601.

22. Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. Rheumatology (Oxford) 2005;44:7-16.

23. Kubota E, Kubota T, Matsumoto J, Shibata T, Murakami K. Synovial fluid cytokines and proteinases as markers of temporomandibular joint disease. J Oral Maxillofac Surg 1998;56:192-198.

24. Kubota E, Imamura H, Kubota T, Shibata T, Murakami K. Interleukin 1 beta and stromelysin (MMP3) activity of synovial fluid as possible markers of osteoarthritis in the temporomandibular joint. J Oral Maxillofac Surg 1997;55:20-27; discussion 27-28.

25. Takahashi T, Nagai H, Seki H, Fukuda M. Relationship between joint effusion, joint pain, and protein levels in joint lavage fluid of patients with internal derangement and osteoarthritis of the temporomandibular joint. J Oral Maxillofac Surg 1999;57:1187-1193; discussion 1193-1194.

26. Emshoff R, Puffer P, Rudisch A, Gassner R. Temporomandibular joint pain: relationship to internal derangement type, osteoarthrosis, and synovial fluid mediator level of tumor necrosis factor-alpha. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:442-449.

27. List T, Jensen RH. Temporomandibular disorders: old ideas and new concepts. Cephalalgia 2017;37:692-704.

28. Schmidt BL, Milam SB, Caloss R. Future directions for pain research in oral and maxillofacial surgery: findings of the 2005 AAOMS Research Summit. J Oral Maxillofac Surg 2005;63:1410-1417.

29. Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis, and treatment. J Dent Res 2008;87:296-307.

30. Pankratz S, Bittner S, Kehrel BE, et al. The inflammatory role of platelets: translational insights from experimental studies of autoimmune disorders. Int J Mol Sci 2016;17:E1723.

31. Shafiee M, Tayefi M, Hassanian SM, et al. Depression and anxiety symptoms are associated with white blood cell count and red cell distribution width: a sex-stratified analysis in a population-based study. Psychoneuroendocrinology 2017;84:101-108.

32. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. N Engl J Med 1991;325:11-16.

33. Köhler-Forsberg O, Buttenschøn HN, Tansey KE, et al. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. Brain Behav Immun 2017;62:344-350.

34. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171-186.

35. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry 2014;71:1121-1128.

36. Tayefi M, Shafiee M, Kazemi-Bajestani SMR, et al. Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study. Psychoneuroendocrinology 2017;81:63-69.