Circulating Omentin-1 and Chronic Painful Temporomandibular Disorders

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Aims: To investigate the relationship between omentin-1 levels and painful temporomandibular disorders (TMD). **Methods:** In a case-control design, chronic painful TMD cases (n = 90) and TMD-free controls (n = 54) were selected from participants in the multisite OPPERA study (Orofacial Pain: Prospective Evaluation and Risk Assessment). Painful TMD case status was determined by examination using established Research Diagnostic Criteria for TMD (RDC/TMD). Levels of omentin-1 in stored blood plasma samples were measured by using an enzyme-linked immunosorbent assay. Binary logistic regression was used to calculate the odds ratios (ORs) and 95% confidence limits (CLs) for the association between omentin-1 and painful TMD. Models were adjusted for study site, age, sex, and body mass index. **Results:** The unadjusted association between omentin-1 and chronic painful TMD was statistically nonsignificant (P = .072). Following adjustment for covariates, odds of TMD pain decreased 36% per standard deviation increase in circulating omentin-1 (adjusted OR = 0.64; 95% CL: 0.43, 0.96; P = .031). **Conclusion:** Circulating levels of omentin-1 were significantly lower in painful TMD cases than controls, suggesting that TMD pain is mediated by inflammatory pathways. *J Oral Facial Pain Headache 2016;30:203–209. doi: 10.11607/ofph.1608*

Keywords: *chronic pain, epidemiology, etiology, inflammation mediators, temporomandibular disorders*

Idiopathic pain conditions account for a considerable proportion of chronic pain disorders. Prominent among these are temporomandibular disorders (TMD), chronic headaches, irritable bowel syndrome (IBS), interstitial cystitis/bladder pain syndrome (IC/BPS), low back pain, and widespread bodily pain such as fibromyalgia.[1] Because these conditions share etiologic factors, individuals with idiopathic chronic pain commonly experience more than one chronic pain disorder.

Painful TMD is the most common chronic orofacial pain condition.[2,3] In the 2002 National Health Interview Survey, an estimated 5% of US adults reported TMD-like pain.[4] The condition is characterized by pain in one or both temporomandibular joints (TMJs) and masticatory muscles, as well as limitations in jaw function. The pathogenesis of painful TMD is multifactorial; risk factors commonly associated with chronic TMD pain include joint and muscle trauma, anatomical and pathophysiologic abnormalities, psychosocial distress/traits, and genetic variability.[1,5–7]

Much of what is known about risk factors for painful TMD comes from cross-sectional studies, but the OPPERA study (Orofacial Pain: Prospective Evaluation and Risk Assessment) used a prospective cohort design in order to evaluate the effects of baseline risk factors on the subsequent risk of developing painful TMD. According to a multivariate analysis, the greatest contributions to the risk of developing TMD came from measures of impaired general health, nonspecific orofacial symptoms, and psychological characteristics.[8]

Another promising line of evidence suggests that cytokines may contribute to the pathophysiology of painful TMD.[9] Proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor

alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) activate neuronal receptors in order to sensitize nerves and enhance pain perception.[10] An exaggerated release of proinflammatory cytokines causes immune cells to release more inflammatory mediators in response.[10–13] This peripheral sensitization process is thought to play a key role in the maintenance of local pain in conditions such as painful TMD. Results from clinical studies demonstrate that proinflammatory cytokine levels are elevated in individuals with painful TMD,[9,14–17] headache, IBS,[18–20] pelvic pain,[18,21,22] and widespread pain.[12,23–26]

Abnormalities in proinflammatory cytokine levels are often accompanied by alterations in levels of anti-inflammatory cytokines. Anti-inflammatory cytokines serve as negative feedback to control potentially pathologic events initiated by proinflammatory cytokines.[27] Reduced levels of anti-inflammatory cytokines are observed in TMD and other painful conditions. For example, the anti-inflammatory cytokines transforming growth factor β1 (TGFβ1) and interleukin-1 receptor antagonist (IL-1RA) are lower in individuals with painful TMD than in those without TMD.[9] Similarly, decreased expression of cytokine interleukin-10 (IL-10) has been observed in individuals with chronic fatigue syndrome and fibromyalgia.[28]

Additionally, several studies have provided evidence of the decreased expression of the anti-inflammatory cytokine omentin-1 in chronic conditions including coronary heart disease,[29,30] type 2 diabetes,[30] and impaired glucose tolerance,[31] as well as in the synovial fluid of individuals with rheumatoid arthritis.[32] While not well studied, emerging evidence suggests that omentin-1 may play a role in regulating processes related to pain. Omentin, also known as intelectin, is an adipokine since it is secreted mainly by cells of visceral adipose tissue.[33] It exists in two forms, omentin-1 and omentin-2. Decreased expression of omentin-1, the major circulating form, is associated with the pathophysiology of obesity and obesity-associated disorders.[34] In addition, as noted above, omentin-1 is also found in lower levels in the synovial fluid of patients with rheumatoid arthritis.[32] Therefore, the downregulation of omentin-1 is likely to undermine its protective anti-inflammatory action.

Since decreased omentin-1 is related to obesity, it is intuitive to expect that obesity might be associated with chronic pain. Indeed, cross-sectional studies have linked obesity to migraine,[35] abdominal pain,[36] and arthritis.[37] These conditions may also occur in a state of chronic low-grade inflammation similar to TMD, and since obesity is an expression of systemic inflammation, an association between obesity and painful TMD is plausible. In fact, in the OPPERA study, individuals with a higher body mass index (BMI) at baseline were at higher risk for developing first-onset, painful TMD than those with lower BMI.[38] If omentin-1 plays a role in inflammation and if inflammation is associated with the mechanisms of obesity and painful TMD, then adipokines may play a role in the pathophysiology of painful TMD.

The aim of this study was to investigate the relationship between omentin-1 levels and painful TMD. The authors tested the hypothesis that circulating levels of omentin-1 are lower in individuals with painful TMD than in TMD-free controls.

Materials and Methods

Parent Study: OPPERA

Institutional review boards at each study site approved the study and all subjects provided informed, written consent. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC). The parent study, OPPERA, is an ongoing multisite study of painful TMD.[6] The OPPERA study's objectives are to identify physiologic, psychological, clinical, and genetic risk factors for the incidence of painful TMD.[39] At baseline, the OPPERA study enrolled 3,263 participants with no lifetime experience of TMD and 185 participants with chronic painful TMD.[40] Adults were recruited from communities in: Baltimore, Maryland; Buffalo, New York; Chapel Hill, North Carolina; and Gainesville, Florida. Recruitment took place around these study sites between May 2006 and November 2008 by using newspaper and radio station advertisements, university emails, flyers, and word of mouth. Eligible adults were aged 18 to 44 years, had no history of 10 major health conditions, no recent history of facial trauma or surgery, and were not pregnant. At baseline, all participants completed questionnaires evaluating behavioral, social, and psychological characteristics related to painful TMD. A 20-mL sample of peripheral blood from OPPERA study participants at enrollment was obtained by venipuncture for further DNA investigation and genotyping.[40] Anthropometric measurements were also determined.

Omentin Ancillary Study

Subjects in this ancillary case-control study were drawn from the population of the OPPERA case-control study of chronic painful TMD. Chronic painful TMD cases (n = 90) had experienced TMD pain symptoms for at least 6 months and examiners confirmed clinical TMD by using the Research Diagnostic Criteria for TMD (RDC/TMD). A total of 38 controls (n = 55) were chosen from a random sample of enrollees in the prospective cohort OPPERA study who were verified by an examiner as not having painful TMD.

TMD Classification

All OPPERA participants underwent a clinical examination that was based on the RDC/TMD[41] and performed by trained and calibrated examiners. Confirmation of a diagnosis of painful TMD was based on: *(1)* pain experienced for at least 5 days per month in masticatory structures and *(2)* confirmation of painful TMD arthralgia (pain of either TMJ during jaw movement or digital palpation) and/or myalgia (pain during jaw movement in at least three of the eight muscle groups based on evaluation of temporalis, masseter, lateral pterygoid, and submandibular muscles).

Coexisting Pain Conditions

Other pain conditions such as headache, chronic back pain, and IBS were evaluated using the Comprehensive Pain and Symptom Questionnaire (CPSQ). Participants were asked whether they had any headaches in the past year (yes/no). Participants were asked questions to characterize their headaches in order to measure headache severity and type. Questions regarding pain other than pain in the face, current back pain, and number of back pain episodes in the past 12 months were also asked. Participants answered four questions about abdominal pain by using the Rome III classification for IBS.[42] Information was also collected on IBS symptoms over the period of the last 3 months.

Body Mass Index

Body mass index (BMI) was calculated as weight divided by height (kg/m^2) and categorized using standard World Health Organization (WHO) categories of: underweight and normal combined (< 25.00); overweight (25.00 to 29.99); and obese (≥ 30.0).

Blood Plasma Collection and Storage

Blood samples were centrifuged for at least 12 minutes and plasma was immediately frozen and stored at −80°C in 5-mL polyethylene vacutainers.

Omentin-1 Assessment

Plasma omentin-1 protein levels were measured by a colorimetric ELISA kit (BioVendor Research and Diagnostic Products) according to kit instructions. All plasma samples were diluted at 40×. Following a series of incubation and wash steps, ELISA 96-well plates were read on a Victor3 microplate reader (PerkinElmer) at 450 nm. Background noise measured at 630 nm was subtracted from each well. Following microplate readings, omentin-1 standards provided in the kit were plotted using a 4-point logarithmic algorithm to generate a standard curve. Omentin-1 protein concentrations were then calculated by assessing optical density values for plasma samples by using the standard curve. Samples were run in duplicate and the average value of omentin-1 concentration was used for statistical analysis.

Statistical Power and Sample Size

The sample size calculation was guided by estimates of serum omentin-1 levels in obstructive sleep apnea (OSA) cases and healthy controls reported by Wang et al[43] where the median (interquartile range [IQR]) serum omentin-1 level was 11.29 ng/mL (0.02 to 15.13) for cases and was 22.62 ng/mL (18.71 to 27.21) for controls, which is a two-fold difference. To permit a less extreme effect size, a two-sample means test was specified in setting the mean for controls as 22.0 ng/mL and allowing the means for cases to be 10.0, 12.0, 14.0, or 16.0. Assuming equally sized groups, an alpha of 0.05, power of 0.8, and a pooled standard deviation of 13.0, the minimum number of subjects required for the case and control groups combined was 40, 56, 86, and 150, respectively. A sample size of 150 (n = 75 subjects per group) was chosen, allowing the detection of a difference of 6 ng/mL between cases and controls. Because only 10% of TMD cases had arthralgia alone and 5% had myalgia alone,[44] there was insufficient power to conduct subgroup analyses of possible differences between patients with muscle pain and patients with joint pain.

Statistical Analyses

Statistical analyses were conducted using STATA (StataCorp, College Station, Release 13.1). The dependent variable was painful TMD case status and the exposure was plasma omentin-1 levels. Omentin-1 values were standardized as *z* scores to aid in the interpretation of statistical estimates. Binary logistic regression was used to calculate the unadjusted odds ratio values (ORs) and 95% confidence limits (CLs) for painful TMD. Finally, multivariate analysis was used to adjust for potential confounding covariates including study site, age, sex, and BMI.

Results

One study participant was omitted from analysis due to an inadequate amount of blood plasma needed to measure omentin-1 levels, and so a total of 144 participants comprised the final sample (Table 1). As reported previously,[40] most TMD cases (71%) had a history of facial pain spanning at least 3 years with the majority (75%) reporting recurrent bouts that lasted at least 15 days per month. Mean pain intensity was 7.8 ± 4.8 and mean pain unpleasantness was 7.2 ± 4.3, both measured using Gracely scales[45] that ranged from 0 to 20. Nearly half (47%) of the TMD

Table 1 Characteristics of Chronic Painful TMD Cases and Pain-free Controls (n = 144)

	n	%	Painful TMD cases (n = 90)	Controls (n = 54)	*P* value
Sex					
Male	38	26.4	21.1	35.2	.064
Female	106	73.6	78.9	64.8	
Age (y)					
18–24	55	38.2	32.2	48.2	.452
25–29	32	22.2	24.4	18.5	
30–34	20	13.9	15.6	11.1	
35–39	18	12.5	13.3	11.1	
40–44	19	13.2	14.4	11.1	
Body mass index (kg/m^2)					
Underweight/ normal (< 25.00)	83	57.6	57.3	61.5	.691
Overweight (25.00–29.99)	34	23.6	23.6	25.0	
Obese (≥ 30.00)	24	16.7	19.1	13.5	
Missing	3	2.1			

Table 2 Mean and Standard Deviation (SD) of Circulating Omentin-1 Concentration (µg/ml)

	Mean	SD	*P* value
Painful TMD case status			
Case	413.5	145.9	.072
Control	464.8	191.8	
Sex			
Male	436.8	149.3	.861
Female	431.3	172.0	
Age (y)			
18–24	408.4	141.4	.174
25–29	452.9	181.7	
30–34	496.4	224.5	
35–39	383.8	106.2	
40–44	448.7	167.7	
Body mass index (kg/m^2)			
Underweight/normal (< 25.00)	423.6	159.2	.289
Overweight (25.00–29.99)	469.7	194.8	
Obese (≥ 30.00)	407.8	137.6	

Table 3 Multivariate, Adjusted Association Between Standardized Omentin-1 Concentration and Painful TMD (n = 141)

	Unadjusted OR (95% CL)	*P* value	Multivariate-adjusted[a] OR (95% CL)	*P* value
Standardized omentin-1 (z score)	0.73 (0.52, 1.03)	.077	0.64 (0.43, 0.96)	.031
Sex				
Male			Ref	
Female			2.74 (1.13, 6.68)	.026
Age (y)				
18–24			Ref	
25–29			1.76 (0.63, 4.92)	.280
30–34			2.94 (0.79, 10.95)	.108
35–39			1.31 (0.37, 4.67)	.681
40–44			2.17 (0.59, 7.93)	.242
Body mass index (kg/m^2)				
Underweight/normal (< 25.00)			Ref	
Overweight (25.00–29.99)			1.29 (0.50, 3.33)	.603
Obese (≥ 30.00)			1.51 (0.48, 4.73)	.482
Intercept	0.60 (0.26, 1.40)	.239	0.17 (0.04, 0.62)	.008

[a] = Adjusted for study site, sex, age group, and body mass index.
OR = odds ratio; CL = confidence limits; Ref = reference category.

cases reported having experienced other types of chronic pain aside from facial pain, which was reported by only 13% of controls.[44]

In the unadjusted analysis, mean omentin-1 levels in TMD cases (413.5 µg/ml) were not significantly lower than in controls (464.8 µg/ml) (*P* = .072, Table 2). There were also no significant differences in sex, age, and BMI between cases and controls. However, when adjusted for study site, age, sex, and BMI, the analysis revealed a significant association between omentin-1 and painful TMD. This indicated the presence of confounding factors. In the unadjusted logistic regression model (Table 3), the odds of having painful TMD were not significantly associated with omentin-1 (OR = 0.73; 95% CL: 0.52, 1.03; *P* > .05). However, in the multivariate analysis (Table 3), the odds of having painful TMD were 36% lower per standard deviation increase in circulating omentin-1 (OR = 0.64; 95% CL: 0.43, 0.96; *P* = .031).

Discussion

In this case-control study, which was ancillary to the OPPERA study, omentin-1 levels were lower in chronic painful TMD cases than in controls after adjusting for the covariates in the multivariate analyses. The fact that omentin-1 was measured in plasma from peripheral blood indicates that heightened inflammatory-related cytokines in painful TMD are not confined locally to the temporomandibular tissues but are present systemically.

These findings build on earlier work. In several in vitro studies, omentin-1 inhibited TNFα-induced vascular inflammation in human endothelial cells.[46] In another study, omentin-1 was shown to play a similar anti-inflammatory role by preventing the TNFα-induced inflammatory responses in vascular smooth muscle cells.[47] Kim et al further showed that TNF-α, along with several interleukin cytokines, were detected in the synovial fluid of painful TMD cases in significantly greater amounts than in healthy controls.[48] These studies suggest that in addition to its systemic effect, omentin-1 inhibits a specific inflammatory cytokine that is present in the joint in painful TMD cases.

The finding that omentin-1 levels are decreased in patients with conditions that are believed to have an inflammatory basis is consistent with results from other studies. A recent study revealed that omentin-1 levels were significantly lower in patients with IBS.[49] In another study, decreased secretion of omentin-1 in the synovial fluid of patients with painful knee osteoarthritis was 10 times lower than omentin-1 levels in the patients' serum.[50] Potential confounding effects of other cytokines may provide the answer as to why omentin-1 levels in the painful TMD plus another pain group were more similar to the control group. Therefore, the etiologies of a single pain disorder and comorbid pain disorders are likely distinct.

The absence of an association in unadjusted analysis warrants explanation. Confounding occurs when extraneous factors (eg, age and BMI in this instance) are associated with exposure (omentin-1) and outcome (painful TMD). Most often, confounding inflates the true association between the exposure and outcome (positive confounding). However, the opposite effect was apparent in this study. Confounding with age and BMI underestimated the true association between omentin-1 and chronic painful TMD. The bias arising from this negative confounding was corrected in the multivariate analysis by adjusting for these covariates; specifically, adjustment for age categories and BMI strengthened the association between omentin-1 and painful TMD and also resulted in a statistically significant relationship.

The magnitude of confounding bias was substantial. The OR for the unadjusted association of 0.73 (95% CL: 0.52, 1.03) was considerably closer to the null hypothesis than the OR for the adjusted association, which was 0.64 (95% CL: 0.43, 0.96). Although the authors do not claim the association between omentin-1 and chronic painful TMD to be of particular importance clinically, what it is noteworthy is that this finding supports the general hypothesis of a biologic basis for painful TMD that likely involves inflammatory pathways.

There is a growing interest in identifying potential diagnostic biomarkers for pain in patients with painful TMD. For example, Slade et al found that cytokine profiles differed among cases that were stratified on the basis of comorbid, widespread palpation tenderness.[9] Elevated levels of various circulating inflammatory markers such as cytokine IL-8 were associated with painful TMD and widespread pain, whereas MCP-1 levels were associated with painful TMD only in the absence of widespread pain.

Recently, the relationship between proinflammatory cytokines and TMJ inflammation has been examined.[9,51] The release of TNF-α along with interleukins occurs in conjunction with TMJ inflammation.[51] These proinflammatory cytokines play a role in the remodeling and deterioration of articular cartilage as seen in osteoarthritis. Changes in the cartilage become noticeable via swelling and redness due to the nociceptors of the TMJ being stimulated by these inflammatory mediators. Moreover, Slade et al showed that levels of the anti-inflammatory cytokine IL-1RA were lower in painful TMD cases and in cases of widespread pain.[9]

Based on emerging collective evidence in epidemiologic studies, low levels of omentin-1 seem to exacerbate the putative effects of proinflammatory mediators. Therefore, it is conceivable that a decrease in omentin-1 levels may be involved in the pathophysiology of painful TMD. Further studies are needed to clearly elucidate the plausible mechanism by which omentin-1 may contribute to the development of pain and persistent pain. This information could motivate the development of effective interventions that increase omentin-1 levels and other anti-inflammatory cytokines in an attempt to decrease inflammation, thereby reducing existing pain or preventing the development of new pain.

Strengths and Limitations

This ancillary study took advantage of the established infrastructure and protocols and the rich dataset of the OPPERA parent study. Multiple study sites and community recruitment optimized the diversity and representativeness of the study population, improving the generalizability of the findings.

Potential limitations of this study merit consideration. First, the total number of participants in this

case-control study was small. This limited exploration of any potential variation in the association between omentin-1 levels and painful TMD based on clinical subtypes of the condition or occurrence of comorbid pain conditions. In addition, factors with the potential to affect inflammation such as alcohol, smoking, and medications were not controlled for during statistical analyses.

Conclusions

Circulating levels of omentin-1 were lower in painful TMD cases than controls, suggesting that TMD pain is mediated by inflammatory pathways.

Acknowledgments

This study was supported by the NIDCR Cooperative Agreement/NIH grant U01 DE017018. The OPPERA program provided resources by the respective host universities: University of Maryland-Baltimore; University at Buffalo; University of North Carolina at Chapel Hill; and University of Florida. The other authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

References

1. Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--Pathways of vulnerability. Pain 2006;123:226–230.
2. Romero-Reyes M, Uyanik JM. Orofacial pain management: Current perspectives. J Pain Res 2014;7:99–115.
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. Isong U, Gansky SA, Plesh O. Temporomandibular joint and muscle disorder-type pain in U.S. adults: The National Health Interview Survey. J Orofac Pain 2008;22:317–322.
5. Carlson CR, Okeson JP, Falace DA, Nitz AJ, Curran SL, Anderson D. Comparison of psychologic and physiologic functioning between patients with masticatory muscle pain and matched controls. J Orofac Pain 1993;7:15–22.
6. Maixner W, Diatchenko L, Dubner R, et al. Orofacial pain prospective evaluation and risk assessment study--the OPPERA study. J Pain 2011;12(11, suppl):T4–T11.e1–2.
7. Vassend O, Krogstad BS, Dahl BL. Negative affectivity, somatic complaints, and symptoms of temporomandibular disorders. J Psychosom Res 1995;39:889–899.
8. Slade GD, Fillingim RB, Sanders AE, et al. Summary of findings from the OPPERA prospective cohort study of incidence of first-onset temporomandibular disorder: Implications and future directions. J Pain 2013;14(12, suppl):T116–T124.
9. Slade GD, Conrad MS, Diatchenko L, et al. Cytokine biomarkers and chronic pain: Association of genes, transcription, and circulating proteins with temporomandibular disorders and widespread palpation tenderness. Pain 2011;152:2802–2812.
10. Cheng JK, Ji RR. Intracellular signaling in primary sensory neurons and persistent pain. Neurochem Res 2008;33:1970–1978.
11. Copray JC, Mantingh I, Brouwer N, et al. Expression of interleukin-1 beta in rat dorsal root ganglia. J Neuroimmunol 2001; 118:203–211.
12. Sommer C, Häuser W, Gerhold K, et al. Etiology and pathophysiology of fibromyalgia syndrome and chronic widespread pain [article in German]. Schmerz 2008;22:267–282.
13. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45:27–37.
14. Kaneyama K, Segami N, Nishimura M, Suzuki T, Sato J. Importance of proinflammatory cytokines in synovial fluid from 121 joints with temporomandibular disorders. Br J Oral Maxillofac Surg 2002;40:418–423.
15. Matsumoto K, Honda K, Ohshima M, et al. Cytokine profile in synovial fluid from patients with internal derangement of the temporomandibular joint: A preliminary study. Dentomaxillofac Radiol 2006;35:432–441.
16. Ogura N, Satoh K, Akutsu M, et al. MCP-1 production in temporomandibular joint inflammation. J Dent Res 2010;89: 1117–1122.
17. Takahashi T, Kondoh T, Fukuda M, Yamazaki Y, Toyosaki T, Suzuki R. Proinflammatory cytokines detectable in synovial fluids from patients with temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:135–141.
18. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology 2007; 132:913–920.
19. Rana SV, Sharma S, Sinha SK, Parsad KK, Malik A, Singh K. Pro-inflammatory and anti-inflammatory cytokine response in diarrhoea-predominant irritable bowel syndrome patients. Trop Gastroenterol 2012;33:251–256.
20. Dinan TG, Clarke G, Quigley EM, et al. Enhanced cholinergic-mediated increase in the pro-inflammatory cytokine IL-6 in irritable bowel syndrome: role of muscarinic receptors. Am J Gastroenterol 2008;103:2570–2576.
21. Lindenlaub T, Sommer C. Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. Acta Neuropathol 2003;105:593–602.
22. Poole S, Lorenzetti BB, Cunha JM, Cunha FQ, Ferreira SH. Bradykinin B1 and B2 receptors, tumour necrosis factor alpha and inflammatory hyperalgesia. Br J Pharmacol 1999;126: 649–656.
23. Zhang Z, Cherryholmes G, Mao A, et al. High plasma levels of MCP-1 and eotaxin provide evidence for an immunological basis of fibromyalgia. Exp Biol Med (Maywood) 2008;233:1171–1180.
24. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: A hypothesis and pilot study. Rheumatology (Oxford) 2001;40:743–749.
25. Bazzichi L, Rossi A, Massimetti G, et al. Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. Clin Exp Rheumatol 2007;25:225–230.
26. Gür A, Karakoç M, Nas K, et al. Cytokines and depression in cases with fibromyalgia. J Rheumatol 2002;29:358–361.
27. Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: Role in biology. Annu Rev Immunol 1998; 16:27–55.
28. Amel Kashipaz MR, Swinden D, Todd I, Powell RJ. Normal production of inflammatory cytokines in chronic fatigue and fibromyalgia syndromes determined by intracellular cytokine staining in short-term cultured blood mononuclear cells. Clin Exp Immunol 2003;132:360–365.
29. Shibata R, Ouchi N, Kikuchi R, et al. Circulating omentin is associated with coronary artery disease in men. Atherosclerosis 2011;219:811–814.

30. Greulich S, Chen WJ, Maxhera B, et al. Cardioprotective properties of omentin-1 in type 2 diabetes: Evidence from clinical and in vitro studies. PLoS One 2013;8:e59697.
31. Pan HY, Guo L, Li Q. Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. Diabetes Res Clin Pract 2010;88:29–33.
32. Senolt L, Polanská M, Filková M, et al. Vaspin and omentin: New adipokines differentially regulated at the site of inflammation in rheumatoid arthritis. Ann Rheum Dis 2010;69:1410–1411.
33. Yang RZ, Lee MJ, Hu H, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: Possible role in modulating insulin action. Am J Physiol Endocrinol Metab 2006;290:E1253–E1261.
34. de Souza Batista CM, Yang RZ, Lee MJ, et al. Omentin plasma levels and gene expression are decreased in obesity. Diabetes 2007;56:1655–1661.
35. Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology 2006;67:252–257.
36. Delgado-Aros S, Locke GR 3rd, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: A population-based study. Am J Gastroenterol 2004;99:1801–1806.
37. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;109:18–24.
38. Sanders AE, Slade GD, Bair E, et al. General health status and incidence of first-onset temporomandibular disorder: The OPPERA prospective cohort study. J Pain 2013;14(12, suppl): T51–T62.
39. Dworkin SF. The OPPERA study: Act One. J Pain 2011;12 (11, suppl):T1–T3.
40. Slade GD, Bair E, By K, et al. Study methods, recruitment, sociodemographic findings, and demographic representativeness in the OPPERA study. J Pain 2011;12(11, suppl):T12–T26.
41. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6: 301–355.
42. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480–1491.
43. Wang Q, Feng X, Zhou C, Li P, Kang J. Decreased levels of serum omentin-1 in patients with obstructive sleep apnoea syndrome. Ann Clin Biochem 2013;50(Pt 3):230–235.
44. Ohrbach R, Fillingim RB, Mulkey F, et al. Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 2011;12(11, suppl): T27–T45.
45. Gracely RH, McGrath F, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. Pain 1978;5:5–18.
46. Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y. Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. Biochem Biophys Res Commun 2011;408:339–343.
47. Kazama K, Usui T, Okada M, Hara Y, Yamawaki H. Omentin plays an anti-inflammatory role through inhibition of TNF-α-induced superoxide production in vascular smooth muscle cells. Eur J Pharmacol 2012;686:116–123.
48. Kim YK, Kim SG, Kim BS, et al. Analysis of the cytokine profiles of the synovial fluid in a normal temporomandibular joint: Preliminary study. J Craniomaxillofac Surg 2012;40:e337–e341.
49. Yin J, Hou P, Wu Z, Nie Y. Decreased levels of serum omentin-1 in patients with inflammatory bowel disease. Med Sci Monit 2015;21:118–122.
50. Li ZG, Zhao DW, Xia CJ, et al. Decreased synovial fluid omentin-1 concentrations reflect symptomatic severity in patients with knee osteoarthritis. Scand J Clin Lab Invest 2012;72:623–628.
51. Furquim BD, Flamengui LM, Conti PC. TMD and chronic pain: A current view. Dental Press J Orthod 2015;20:127–133.