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# Circulating Omentin-1 and Chronic Painful Temporomandibular Disorder

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## Abstract

**AIMS—**The biological basis for painful temporomandibular disorder (TMD) remains unclear. An emerging literature implicates circulating inflammatory cytokines in the development of pain sensitivity and painful TMD. One newly discovered anti-inflammatory adipokine, omentin-1, has decreased expression in several inflammatory conditions including osteoarthritis. The aim of this study was to investigate the relationship between omentin-1 levels and painful TMD.

**METHODS—**Using a case-control design, chronic painful TMD cases (n=90) and TMD-free controls (n=54) were selected participants in the multisite OPPERA study (Orofacial Pain: Prospective Evaluation and Risk Assessment). Painful TMD case status was determined by

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examiner using established Research Diagnostic Criteria for TMD. Levels of omentin-1 were measured in stored blood plasma samples using an enzyme-linked immunosorbent assay. Binary logistic regression calculated the odds ratios (ORs) and 95% confidence limits (CLs) for the association between omentin-1 and painful TMD. Models adjusted for study site, age, sex, and body mass index (BMI).

**RESULTS—**The unadjusted association between omentin-1 and chronic painful TMD was statistically non-significant (P=.072) Following adjustment of the negative confounding bias of covariates, odds of painful 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 painful TMD pain is mediated by inflammatory pathways.

### Keywords

Inflammation mediators; Epidemiology; Chronic Pain; Etiology; Temporomandibular disorders

## INTRODUCTION

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 etiological factors, individuals with 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 five percent of U.S. adults reported TMD-like pain.[4] The condition is characterized by pain in one or both temporomandibular joints and masticatory muscles, as well as limitations in jaw function. The pathogenesis of painful TMD is multifactorial, and risk factors commonly associated with chronic TMD pain include joint and muscle trauma, anatomical and pathophysiological 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. In contrast, the OPPERA study (Orofacial Pain: Prospective Evaluation and Risk Assessment) used a prospective cohort design to evaluate effects of baseline risk factors on subsequent risk of developing painful TMD. In multivariable analysis, the greatest contributions came from measures of impaired general health, non-specific orofacial symptoms and psychological characteristics.[8]

Another promising line of evidence suggests that small intracellular proteins, called 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 so as to sensitize nerves and enhance pain perception.[10] An exaggerated release of pro-inflammatory cytokines in turn activates immune cells to release more inflammatory mediators. [10–13] This

process of peripheral sensitization 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 cytokines are often accompanied by alterations in levels of anti-inflammatory cytokines. Anti-inflammatory cytokines serve as negative feedback regulators 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, anti-inflammatory cytokines transforming growth factor β1 (TGFβ1) and interleukin-1 receptor antagonist (IL-1RA) are lower in individuals with painful TMD than controls[9] Similarly, decreased expression cytokine interleukin-10 (IL-10) is observed in individuals with chronic fatigue syndrome and fibromyalgia.[28] Several studies provide evidence of decreased expression of omentin-1 in chronic conditions including coronary heart disease[29,30] type 2 diabetes[30] impaired glucose tolerance,[31] and in the synovial fluid of people with rheumatoid arthritis.[32] While not well studied, emerging evidence suggests that omentin-1 may play a role in regulating pain-relevant processes. Omentin, also known as intelectin, is an anti-inflammatory cytokine 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, 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. Cross-sectional studies have linked obesity to chronic headaches, abdominal pain, and arthritis. These conditions may also occur in a state of chronic low-grade inflammation, similar to painful TMD. Obesity is an expression of systemic inflammation, making plausible an association between obesity and painful TMD. In fact, in OPPERA, individuals with a higher body mass index (BMI) at baseline were at higher risk of developing first-onset painful TMD than those with lower BMI.[35] If omentin-1 plays a role in inflammation, and if inflammation is associated with the mechanism 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 were lower among individuals with painful TMD than among 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, to participate in the study. The parent study, OPPERA, is an ongoing multisite study of painful TMD.[6] OPPERA's objectives are to identify

physiological, psychological, clinical, and genetic risk factors for the incidence of painful TMD.[36] At baseline OPPERA enrolled 3,263 participants with no lifetime experience of TMD and 185 participants with chronic painful TMD.[37] 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 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 was obtained by venipuncture from OPPERA study participants at enrollment for further DNA investigation and genotyping.[37] Anthropometric measurements were also determined.

### Omentin Ancillary Study

Subjects in this ancillary case-control study were drawn from the OPPERA case-control study of chronic painful TMD. Examiner-classified chronic painful TMD cases (n = 90) had experienced TMD pain symptoms for at least 6 months and examiners confirmed clinical TMD using Research Diagnostic Criteria. [38] Controls (n = 55) were a random sample of enrollees in the prospective cohort study who were examiner-verified to not have painful TMD.

### TMD Classification

All OPPERA participants underwent a clinical examination based on the Research Diagnostic Criteria for TMD[38] performed by trained and calibrated examiners. Painful TMD case status was confirmed 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 temporomandibular joint during jaw movement or digital palpation) and/or myalgia (pain during jaw movement in at least 3 of the 8 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). To measure headache severity and headache types, participants were asked questions for initial characterization. Questions regarding pains other than 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 using the Rome III IBS classification for irritable bowel syndrome.[39] Information was also collected on IBS symptoms over the referent period of the last 3 months.

### Body Mass Index

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

### Blood Plasma Collection and Storage

Blood samples were centrifuged for at least 12 minutes and plasma was quickly 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 (BioVendor Research and Diagnostic Products; Asheville, NC) according to kit instructions. All plasma samples were diluted at 40x. Following a series of incubation and wash steps, ELISA 96-well plates were read on a Victor3 microplate reader (PerkinElmer; Waltham, MA) 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 four-point logarithmic algorithm to generate a standard curve. Omentin-1 protein concentrations were then calculated by assessing optical density values for plasma samples 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 for obstructive sleep apnea (OSA) cases and healthy controls reported by Wang et al.[40] where the median (IQR) serum omentin-1 level was 11.29 ng/mL (0.02–15.13) for cases and 22.62 ng/mL (18.71–27.21) for controls: 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. Assuming equal size 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 for a difference between cases and controls of 6 ng/ml. Because only 10% of TMD cases had arthralgia alone and 5% had myalgia alone[41], there was insufficient power to conduct sub-group analysis of possible differences according to muscle pain versus joint pain.

### Statistical Analysis

Statistical analyses were conducted using STATA (StataCorp., College Station, TX, USA, 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, multivariable analysis adjusted for potential confounding covariates of study site, age, sex, and BMI.

### IRB

Institutional review boards at all four study sites approved study procedures for OPPERA, and participants provided informed consent. This study was approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC).

## RESULTS

One study participant was omitted from analysis due to an inadequate amount of blood plasma needed to measure omentin-1 levels. The final sample comprised 106 females and 38 males (Table 1). As reported previously,[37] most TMD cases (71%) had a history of facial pain spanning at least three years, with the majority (75%) reporting recurrent bouts that lasted at least 15 days per month. Mean pain intensity was 7.8 and mean pain unpleasantness was 7.2, both measured using Gracely scales [42] that range from 0 to 20. Nearly one half (47%) of TMD cases reported having experience other types of chronic pain (i.e., aside from facial pain) compared to only 13% of controls.[41]

In unadjusted analysis, mean omentin-1 levels in TMD cases (413.5 μg/ml) were not statistically significantly lower than in controls (464.8 μg/ml), (P=.072, Table 2). Furthermore, there were no significant differences in sex, age, and BMI between cases and controls. However adjustment for study site, age, sex, and BMI revealed a significant association between omentin-1 and painful TMD. This indicated the presence of confounding of the unadjusted association in the direction of a null association. In the unadjusted logistic regression model (Table 3), odds of painful TMD were not significantly associated with omentin-1 (OR=0.73, 95% CL: 0.52, 1.03). However in the multivariate analysis (Table 3), odds of 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, ancillary to OPPERA, omentin-1 levels were lower in chronic painful TMD cases than controls after adjusting for the confounding bias of covariates in the multivariable analyses. The fact that omentin-1 was measured in plasma from peripheral blood, indicates that heightened inflammation in painful TMD is not confined locally to the temporomandibular tissues, but is present systemically.

These findings build on earlier work. In *in vitro* studies, omentin-1 inhibited TNFα-induced vascular inflammation in human endothelial cells.[43] In another study, omentin-1 played a similar anti-inflammatory role by preventing the TNFα-induced inflammatory responses in vascular smooth muscle cells.[44] Kim and colleagues further showed that TNF-α, along with several interleukin cytokines, were detected in the synovial fluid of painful TMD cases as compared to healthy controls.[45] These studies suggest that omentin-1, in addition to its systemic effect, inhibits a specific inflammatory cytokine that is present in the joint of painful TMD cases.

This finding of decreased omentin-1 levels in cases with conditions 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 inflammatory bowel disease. [46] In another study, decreased secretion of omentin-1 in the synovial fluid of painful knee osteoarthritis was ten times lower than omentin-1 levels in the serum of these patients.[47] Lower omentin-1 concentration was found in blood plasma (taken via venipuncture) for those subjects with TMD only. Potential confounding effects of other cytokines may provide

the answer as to why omentin-1 levels of the painful TMD plus another pain group were more similar to the control group. Therefore, the etiology of a single pain disorder versus comorbid pain disorders is likely distinct.

In this study of omentin-1 and painful TMD, the absence of association in unadjusted analysis warrants explanation. Confounding occurs when extraneous factors, e.g. 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, i.e. positive confounding. However, in this study the opposite effect was apparent. Confounding by 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 multivariable analysis by adjusting for these covariates. Specifically, adjustment for age categories and BMI strengthened the association between omentin-1 and painful TMD, which also resulted in a statistically significant relationship.

The magnitude of confounding bias was substantial. The odds ratio for the crude association of 0.73 (95% CL: 0.52, 1.03, p = .077) was considerably closer to the null than the odds ratio for the adjusted association of 0.64 (95% CL: 0.43, 0.96, p = .031). 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 the finding supports the general hypothesis of a biological 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 and colleagues found that cytokine profiles differed among cases 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 painflul 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 temporomandibular joint inflammation has been examined.[9,48] The release of TNF-α along with interleukins occurs in conjunction with temporomandibular joint inflammation.[48] These proinflammatory cytokines play a role in articular cartilage remodeling and deterioration as seen in osteoarthritis. Changes in the cartilage become noticeable via swelling and redness due to the nociceptors of the temporomandibular joint being stimulated by these inflammatory mediators. Moreover, Slade et al. showed that in painful TMD cases and widespread pain, levels of the anti-inflammatory cytokine IL-1RA were lower.[9]

Based on the emerging collective evidence for omentin-1 in epidemiologic studies, low levels of omentin-1 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 persistent pain and development of pain. This information could motivate development of effective interventions to 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, protocols and rich dataset of the OPPERA parent study. Multiple study sites and community recruitment optimized the diversity and representativeness of the study population to improve the generalizability of the findings.

Potential limitations of this study merit consideration. First, the total number of participants in the ancillary case-control study was small. This limited exploration of potential variation in the association between omentin-1 levels and 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 painful TMD pain is mediated by anti-inflammatory pathways.

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**Table 1**

Characteristics of chronic painful TMD cases and pain-free controls (column percentages), n=144

| | N | Percent | Painful TMD Case (n=90) | Control (n=54) | P-value |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male | 38 | 26.4 | 21.1 | 35.2 | .064 |
| Female | 106 | 73.6 | 78.9 | 64.8 | |
| **Age (years)** | | | | | |
| 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$^2$)** | | | | | |
| Unweight/healthy (<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 | | | |

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**Table 2**

Mean (std. dev.) circulating omentin-1 concentration (μg/ml)

| | Mean | Std. dev. | 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 (years)** | | | |
| 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$^2$)** | | | |
| Unweight/healthy (<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 (odds ratio (OR) and 95% confidence limits (CL), 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 (years)** | | | | |
| 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$^2$)** | | | | |
| Unweight/healthy (<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