Int. J. Oral Maxillofac. Surg. 2016; 45: 323–331
http://dx.doi.org/10.1016/j.ijom.2015.10.007, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
TMJ Disorders

ESRRB polymorphisms are associated with comorbidity of temporomandibular disorders and rotator cuff disease

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Abstract. Temporomandibular disorders (TMD) are associated with comorbidity. Shoulder pain is among the symptoms associated with TMD. The purpose of this study was to investigate the association between TMD and rotator cuff disease (RCD) and related genetic aspects. All subjects underwent orofacial and shoulder examinations. The control group comprised 30 subjects with no pain. Affected subjects were divided into three groups: RCD (TMD-free, $n = 16$), TMD (RCD-free, $n = 13$), and TMD/RCD (patients with both RCD and TMD, $n = 49$). A total of eight single nucleotide polymorphisms in the *ESRRB* gene were investigated. A chemiluminescent immunoassay was used to measure estradiol levels. Surface electromyography recorded head and cervical muscle activity. The χ^2 test and Student *t*-test/Mann–Whitney test were used to assess the significance of nominal and continuous variables. A *P*-value of <0.05 was considered significant. TMD subjects were seven times more susceptible to RCD than controls. The rs1676303 TT ($P = 0.02$) and rs6574293 GG ($P = 0.04$) genotypes were associated with RCD and TMD, respectively. TMD/RCD subjects showed associations with rs4903399 ($P = 0.02$), rs10132091 ($P = 0.02$), and CTTCTTAG/CCTCTCAG ($P = 0.01$) haplotypes and lower muscle activity. Estradiol levels were similar among groups. This study supports TMD as a risk factor for RCD. *ESRRB* haplotypes and low muscle activity are common biomechanical characteristics in subjects with both diseases.

Keywords: temporomandibular disorder; rotator cuff disease; polymorphism; disease susceptibility; estradiol.

Accepted for publication 8 October 2015
Available online 14 November 2015

Temporomandibular disorders (TMDs) are the most common source of non-odontogenic pain of musculoskeletal origin. These disorders affect the temporomandibular joint (TMJ) and masticatory muscles.[1] TMDs are heterogeneous in presentation and multifactorial in aetiology.[2] However, it has been hypothesized that persistent TMD pain conditions result from a 'central sensitization syndrome',[3] disregarding other important etiological factors, such as

trauma, pro-inflammatory states, and a genetic basis.[2]

The overlap of physical symptoms of TMD with those of other comorbid disorders involving pain in the muscles and joints has recently been reported.[4,5] The facial pain may radiate to surrounding areas triggering jaw pain, earache, tinnitus, headache, cervical/shoulder pain, neuralgia, and toothache.[4] Among these, shoulder pain is one of the main symptoms in TMD patients.[5] However, the most common cause of chronic shoulder pain in adults is rotator cuff disease (RCD), which is a spectrum of disorders varying from reversible tendinopathy to frank tear,[6] affecting 30–50% of the population.[4] The specific aetiology of RCD has not been fully elucidated, but it is considered to be the result of articular degeneration,[7] hypovascularity, collagen abnormalities, tensile overload,[8] and genetic factors[9] – all common to the development of TMD.[2,10]

The mechanical aetiology of chronic facial and shoulder pain has been related to poor posture of the head–neck–shoulder complex.[4] However, the masticatory and cervical muscle activities in patients with TMD associated with RCD have not been studied previously in order to elucidate the mechanical basis of these comorbid pain conditions.

Epidemiological data have shown that women are predominantly affected by RCD[9] and TMD.[11] This gender difference could be explained on the basis of sex hormones and their receptors.[12] In humans, 17β-estradiol decreases sensitivity to noxious subcutaneous stimuli over the TMJ region.[2] Low oestrogen or rapid changes in oestrogen concentration result in an increase in articular pain,[13] explaining the greater pain intensity observed in women with TMD and RCD.[14]

Endogenous oestrogen can act directly on monocytes, increasing the production of pro-inflammatory cytokines, which promotes cartilage resorption, inhibits the synthesis of proteoglycans, and causes inflammation.[15] This hormone can also increase type III collagen content and lead to a decrease in the type I/III collagen ratio, affecting the healing process.[11]

Traditionally, it has been thought that oestrogen acts only through oestrogen receptors α and β.[16] However, another subfamily within the nuclear receptor subfamily – the oestrogen-related receptors (ERRs) – shares sequence similarity, co-regulatory proteins, and action sites with oestrogen receptors. This subfamily contains three members: ERR α, β, and γ.[16] The oestrogen-related receptor β (ESRRB) is involved in oestrogen-regulated pathways because it can bind the oestrogen response element, activate transcription independent of exogenous ligands, and share co-activators with oestrogen receptors α and β.[17]

There is evidence that genetic factors act as intrinsic risk factors for RCD.[18] In a recent report, different mutations, single nucleotide polymorphism (SNP) functions, and haplotypes of the *ESRRB* gene were associated with RCD.[9] However, genetic effects on TMJ derangement have not been fully clarified. Since oestrogen alterations are associated with TMD, an investigation of the *ESRRB* gene may help to gain insights into the pathogenesis of TMD and explore its correlation with RCD.

Taking into account that TMD and RCD are common multifactorial diseases modulated by numerous biological processes, it was hypothesized that the aetiology of TMD/RCD comorbidity is influenced by mechanical muscle activity, oestrogen levels, and the *ESRRB* gene. Therefore, the purpose of this study was to investigate the association between TMD and RCD comorbidity symptoms and the biomechanical basis. Once a combined diagnosis of TMD and RCD is made, treatment options must be considered. Greater knowledge of these comorbid diseases may help in the identification of therapeutic targets and procedures, providing better strategies to optimize the outcomes of RCD and TMD therapies.

Materials and methods

Subject selection

This cross-sectional study was conducted in accordance with the recommendations of the Ethics Committee of the National Institute of Traumatology and Orthopedic Research; informed consent was obtained from each subject. One hundred eight Brazilian volunteers, of both sexes, were selected from an outpatient pool during the course of 1 year. Subjects reported their personal and medical histories. They underwent routine consultations in a specialized care center for shoulder and elbow disorders in order to evaluate their shoulder and TMJ conditions. Inclusion criteria for subjects were the following: Brazilian citizen, age >45 years, and no previous surgery or neoplasm in the TMJ or shoulder.

Subjects with a history of trauma, bursitis, rheumatoid arthritis, or autoimmune diseases, chronic use of systemic corticosteroids, hyperlaxity, or who were pregnant were excluded. The control group comprised 30 subjects without pain and with no signs or symptoms of TMD or RCD. Subjects diagnosed as having RCD and/or a TMD were divided into three groups: RCD subjects (TMD-free, $n = 16$), TMD subjects (RCD-free, $n = 13$), and TMD/RCD affected subjects (patients with both RCD and TMD, $n = 49$). The baseline clinical parameters for the subject population are shown in Table 1.

Diagnosis of temporomandibular disorders

All participants were examined clinically by the same dentist (L.L.B.) according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I[19] in order to investigate the three groups of TMD: group I, muscle disorder; group II, disc displacement; and group III, arthralgia, arthritis, and arthrosis. The RDC/TMD were used to assess these three groups of TMD using well-validated techniques, including palpation at 20 specified muscle sites.[19] Self-reported symptoms pertaining to jaw impairment and associated pain were also recorded during the evaluation.

Clinical characteristics were noted, which included the following clinical symptoms: ear pain, toothache, burning sensation in the mouth, limited mouth opening, and noises (clicking, crepitation) in the TMJ, as well as diagnosed bruxism. Of the 108 patients examined, 62 showed a TMD.

Diagnosis of rotator cuff disease

Sixty-five subjects were diagnosed with RCD. The diagnosis of RCD was based on the protocol of Motta et al.,[9] by clinical examination and imaging of the involved shoulder (radiography and magnetic resonance imaging). Subjects considered to be RCD-free had a negative history for shoulder pain, a negative specific test result for impingement syndrome in a complete physical examination of the shoulders,[20] and an absence of tendinopathy. All clinical evaluations were performed by one of the authors from the specialized care center (M.V.A.).

The records of the orthopedist who carried out the RCD diagnosis and the dentist performing the orofacial examination were independent of one another.

Oestrogen-related receptor β genotyping

DNA from all participants was extracted from buccal cells after vigorously rinsing with 5 ml of saline solution for 60 s, as described previously.[21] A NanoDrop