Association Between Polymorphisms in the Genes of Estrogen Receptors and the Presence of Temporomandibular Disorders and Chronic Arthralgia

Valquiria Quinelato, Letícia Ladeira Bonato,† Alexandre Rezende Vieira,‡ José Mauro Granjeiro,§ Ricardo Tesch,‖ and Priscila Ladeira Casado¶*

Purpose: The high prevalence of painful temporomandibular disorders (TMDs) in women suggests that estrogen and its receptors play a fundamental etiologic role in the development of this joint pathology through complex action mechanisms. The aim of this study was to evaluate the possible association between polymorphisms in the *ESR1* (estrogen receptor-1) and *ESRRB* (estrogen-related receptor-β) genes and the risk of simultaneous development of TMDs and pain in other joints in the body.

Materials and Methods: All participants were clinically evaluated for the presence of TMD (Research Diagnostic Criteria for TMD) and asked about the presence of chronic joint pain. The control group consisted of 72 patients without TMD and without pain. Participants with arthralgia were divided into 3 groups: with muscular TMD (n = 42), with articular TMD (n = 16), and without TMD and with systemic arthralgia (n = 82). Eight single-nucleotide polymorphisms in the *ESR1* (rs12154178, rs1884051, rs2273206, rs7774230) and *ESRRB* (rs1676303, rs4903399, rs10132091, rs7151924) genes were investigated. The χ^2 test and Student *t* and Mann-Whitney tests were used to assess the relevance of nominal and continuous variables, respectively. A *P* value less than .05 was considered significant.

Results: The TT (timin/timin) genotype for the *ESR1* (rs2273206) gene was strongly associated with the risk of developing muscle TMDs and temporomandibular joint pain (*P* = .04). For the *ESRRB* (rs1676303) gene, an association was observed between the CC (cytosine/cytosine) genotype and the presence of articular TMDs associated with other chronic arthralgia (*P* = .02). These results were confirmed by the increased risk of developing articular TMDs associated with the C allele (*P* = .04).

*Doctoral Student of Dentistry, Fluminense Federal University, Niterói, RJ, Brazil.

†Doctor in Dentistry, Fluminense Federal University, Niterói; Specialist in Temporomandibular Disorders and Orofacial Pain, School of Medicine, Petrópolis, RJ, Brazil.

‡Doctor in Oral Biology, Departments of Oral Biology and Pediatric Dentistry, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA.

§Doctor in Chemistry and Cell Therapy Center, Clinical Research Unit and Biology Institute, Fluminense Federal University, Niterói; National Institute of Metrology, Quality and Technology, Rio de Janeiro, RJ, Brazil.

‖Master of Health Sciences and Assistant Professor and Specialist in Temporomandibular Disorders and Orofacial Pain, School of Medicine, Petrópolis, RJ, Brazil; Professor of Specialization Courses in Orthodontics, Brazilian Dental Association, Petrópolis and Duque de Caxias, RJ, Brazil; Professor of Orthodontics of the Specialization Course, Pontificia Universidad Católica Madre y Maestra, Santiago de los Caballeros, Dominican Republic.

¶Doctor in Morphology and Adjunct Professor of Periodontics, Fluminense Federal University, Niterói, RJ, Brazil.

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Address correspondence and reprint requests to Dr Quinelato: School of Dentistry, Fluminense Federal University, Mario Santos Braga Street, 28, Centro, Niterói, RJ, Brazil; e-mail: valquiriaquinelato@yahoo.com.br

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Conclusions: This study supports the hypothesis that changes in the *ESR1* and *ESRRB* genes influence the presence of TMDs associated with chronic joint pain.

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The high prevalence of painful temporomandibular disorders (TMDs) in women, the pattern of onset after puberty, and the lower prevalence rates in the postmenopausal period suggest that female reproductive hormones play a fundamental etiologic role in the development of this pathology.[1,2] Although involving different mechanisms, it is believed that the influence of these hormones occurs directly on the metabolism and homeostasis of the temporomandibular joint (TMJ),[2] but also on pain modulation, through their action on the central nervous system (CNS) and peripheral nervous system.[3]

Estrogen is produced not only in the ovaries and adrenal glands but also in nonendocrine tissues such as bone and the CNS.[4] Its biological effects are based on genomic mechanisms (mediated by the interaction between estrogen receptors α and β [ER-α and ER-β]) and on non-genomic mechanisms that involve G protein-coupled receptors capable of activating intracellular signaling cascades.[4]

In human articular tissues, these 2 ER types are expressed by chondrocytes,[5] subchondral bone cells,[6] synoviocytes,[7] and ligament fibroblasts.[8] However, ER-α predominates in cortical bone and ER-β predominates in cartilage, cancellous bone, and synovium.[7] Estrogen acts on osteoblast differentiation, decreasing cell proliferation and altering the regulation of the extracellular matrix,[9] and on the extracellular cartilage matrix, influencing its tolerance against overloads.[10] It also produces increased sensitivity of joint structures to relaxin and activation of matrix metalloproteinases, resulting in ligament laxity and catabolism of the articular disc.[11] All these mechanisms predispose the TMJ to the development of degenerative changes.[12]

In relation to pain modulation, it is believed that estrogen can interact with N-methyl-D-aspartate (NMDA) receptors and serotonin.[4] NMDA receptors are glutamate receptors (considered the main neurotransmitter of the CNS) activated by ER-β after the neuronal sensitization process.[4-13] These receptors mediate the rapid depolarization in most synapses in the brain and spinal cord and are associated with sodium ion influx channels. Once activated, they play a key role in central sensitization by depolarizing second-order neurons and activating calcium- and calmodulin-dependent kinases, which in turn phosphorylate postsynaptic proteins, thus activating other NMDA receptors.[14] It is believed that estrogen can increase the hypothalamic excitability of the NMDA receptors and their sensitivity to glutamate through these mechanisms.[15,16] Thus, ERs in the periaduqueal substance become influential in the pro-nociceptive pathways of pain modulation.[4]

Changes in estrogen levels also can increase the concentration of serotonin and the inhibition of gene expression related to its reuptake, thus increasing the time this neurotransmitter remains available in synapses and interstitial spaces. Furthermore, ER activation can influence the distribution and actions of serotonin receptors, with the activation of ER-β resulting in activation of serotonin receptors and the activation of ER-α leading to silencing of serotonergic receptors.[13] Serotonin in combination with estrogen can exert central and peripheral effects. At the periphery, it exerts a pro-nociceptive effect[17] and is considered an inflammatory mediator that is released from platelets and mast cells after tissue injury and exerts direct action on C fibers.[18] At the central level, this substance is located in the superficial layers of the dorsal horn and has an antinociceptive effect.[17]

It is believed that genetic and epigenetic alterations might be related to estrogen and its receptors, influencing the development of TMDs and the precipitation and maintenance of painful conditions.[19,20] The gene encoding ER-α, *ESR1*, is located on chromosome 6q and includes 7 introns and 8 exons over a range of 140 kb. *ESR1* gene polymorphisms are correlated with endometriosis, uterine fibroids, breast cancer, osteoporosis, and osteoarthritis.[21] The large proportion of women with TMDs in various studies suggests genetic alteration of the *ESR1* gene as a strong candidate associated with this disorder.[22]

Estrogen-related receptor-β (ESSRB) is a group of orphan nuclear receptors that act on the establishment and maintenance of hormone production in various tissues, with expression in regions where estradiol has important physiologic functions, and share target genes in common with other ERs, such as osteopontin,[23] lactoferrin,[24] and pS2.[25] It also has been identified as a cofactor of hypoxia-inducing factor in mediating adaptation to the hypoxic environment and oxygen homeostasis.[26] In a recent study conducted in 2015, polymorphisms in the *ESRRB* gene (rs6574293, rs4903399, rs10132091) were associated with the risk of damage developing in the TMJ and the shoulder joint.[20]

Thus, it is believed that the association between TMDs and other chronic systemic arthralgias is not