Influence of sex on temporomandibular disorder pain: a review of occurrence and development

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Abstract

Aim: The aim of this study was to develop a narrative literature review using international research to present the influence of sex on occurrence and development of temporomandibular disorder (TMD) pain. **Methods**: The data sources were computer-based searches in PubMed between 1987 and Feb 2008 using appropriate keywords. For inclusion in this review, articles had to meet the following criteria: be written in English; include human and nonhuman subjects; be published a full-text paper in a peer-reviewed medical journal. **Results**: The studies considered eligible for this narrative review presented results in agreement with the difference in sex and orofacial pain. Patients were almost always adults, with particular focus on patients' sex. Clinical conditions were predominantly TDM pain. Since sexual dimorphism was detected in TMD pain, the results are focused on women. **Conclusion**: The findings of this review suggest that there is difference in the occurrence and development of pain according to the individual's sex, women being more susceptible to TMD pain.

Keywords:
Temporomandibular disorder; pain; sex difference; review.

Introduction

Being male or female is one of the most important predictors of an individual's health. Compared to women of similar age, women outnumber men for stress-related bodily complaints such as chronic pain[1]. The most common cause of chronic facial pain conditions involves temporomandibular disorder (TMD)[2]. TMD pain is the most common symptom that compels patients to seek therapy; its management, however, mostly involves a multidisciplinary approach[2]. Dentists, orthodontists, psychologists, physical therapists, and physicians work together to address the condition of the patient with TMD[3]. For a very long period, the sex of subjects used to study pain was rarely taken into account in either basic or clinical studies[4]. Epidemiological studies on nonpatient populations in the early 1970s reported that the prevalence of TMD signs and symptoms was similar for men and women. Studies of TMD signs and symptoms in nonpatients revealed either no gender difference or a somewhat greater prevalence among women. In the 1990s, a longitudinal study[5], however, showed that the course of TMD symptoms differed significantly with respect to gender: women who had reported symptoms during adolescence consistently reported symptoms 1 decade later, whereas only 60% of men reported symptoms later.

In view of the need for dealing with pain during TMD treatment, the objective of this review was to present the influence of sex on the occurrence and development of TMD pain.

Identification and Review of Studies

Computer-based searches in PubMed full-text paper electronic database were conducted using combinations of the following keywords: pain, temporomandibular disorder, orofacial pain, sex-related difference, sexual dimorphism and gender difference pain. Reference sections from published articles in the field were also used as sources. No attempt was made to contact study authors. To be included in this review, articles had to meet the following criteria: (1) be written in English; (2) include human and nonhuman subjects; (3) be published as a full-text paper in a peer-reviewed medical journal between 1987 and Feb 2008.

Occurrence of Temporomandibular Disorder Pain

Chronic orofacial pain affects approximately 10% of adults

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and up to 50% of the elderly. There is evidence that sex differences in masticatory muscle pain and tenderness emerge as early as 19 years of age[1]. Childbearing-age women, mainly those in their 40s, seek treatment for orofacial pain more frequently in comparison with men by a 2:1 ratio. Although women are more likely to seek medical care for pain, they also report more pain for which they do not seek treatment[6]. Moreover, the difference between the two sexes is multifaceted, involving the occurrence of chronic pain, the type of pain syndromes experienced, the characteristics of the complications that develop, etc. There could be several reasons for the higher reactivity of women compared to men to a similar painful stimulation, ranging from genes to hormonal and cultural influences[4].

Converging lines of evidence suggest that there are important sex-related influences on the experience of pain. Women report more pain than men and are at greater risk for developing many forms of chronic pain[7]. Laboratory studies consistently report lower pain threshold and tolerance among women, and these effects are moderate in magnitude. In addition to these human data, abundant nonhuman animal research indicates sex differences in nociceptive responses. While the clinical implications of these sex differences in pain responses are not yet precisely defined, it is becoming increasingly clear that future improvements in the effectiveness of pain management will require taking the patient's sex into account[8].

TMD refers to a group of conditions, whose principal symptom is pain in the masticatory muscles and/or temporomandibular joints on palpation and during function (e.g., chewing, mouth opening, speech)[9-10]. The classification and epidemiology of orofacial pain presents challenges because of the many anatomic structures involved, diverse causes, unpredictable pain referral patterns and symptoms, and a lack of consensus with regard to differential diagnostic criteria[6,11].

A number of aspects of the prevalence pattern of TMD suggest that reproductive hormones may play a role in these pain conditions[12]: the prevalence of TMD pain prior to adolescence is low (2-4%), and does not seem to differ for boys and girls. However, prevalence rates are higher in adult women than in adult men, and the prevalence is lower for women in the postmenopausal years than for those of reproductive age[13]. The existence of sex differences in pain and analgesia, and the fact that the developmental profile of some types of pain clearly parallels reproductive function strongly suggest that gonadal steroid hormones significantly influence pain[14].

TMD are 1.5-2 times more prevalent in women than in men in the community, and 80% of treated cases of TMD are women[15-16]. Moreover, women are at significantly greater risk than men of experiencing TMD-related disability, which is associated with significant use of health services and increased use of opioid and sedative hypnotic medications. In addition, treatment of TMD can be associated with severe iatrogenic consequences[17]. Furthermore, chronic TMD has been found to interfere with normal social activity and interpersonal relationships and to negatively affect the ability to maintain employment[3]. Individuals react to stressful events in different ways, and differences in the physiological stress response are important determinants of health. A stressful stimulus results in the activation of several physiological pathways including the hypothalamic-pituitary-adrenal axis (HPAA) and the autonomic nervous system. A considerable body of research during recent years has linked the function of both of these systems with the pathogenesis of several common disorders, including coronary arterial disease, type 2 diabetes, metabolic syndrome, depression and stress-related bodily complaints. Importantly, both systems show a clear sex-specific pattern of response. Therefore, stress reactivity is a major candidate for a mechanism explaining why some diseases are more common in men and others in women[1].

TMD is usually manifested by one or more of the following signs or symptoms: pain, joint sounds, limitation in jaw movement, muscle tenderness, and joint tenderness. It also is commonly associated with other symptoms affecting the head and neck region such as headache, ear-related symptoms, and cervical spine disorders. Patients with chronic TMD frequently report symptoms of depression, stress, anxiety, poor sleep quality, and low energy[3,18]. Knowing what biological mechanisms underlie such profound differences may be extremely helpful in elucidating the pathogenesis of various common disorders, a crucial step in developing their prevention and treatment[1]. The prevalence of several pain conditions located in the craniofacial region and the mechanisms that underlie sex-related differences remain obscure and probably involve both physiological and psychosocial factors[9,19].

Development of Orofacial Pain

Nociception results from the activation of primary afferent nociceptors and the transmission of the nociceptive information to the spinal cord from where it is relayed to supra spinal levels. Following tissue injury and inflammation, primary afferent nociceptors are sensitized by mediators released from diseased or damaged tissue or from the immune system in such a way that previously slight or ineffective stimulation becomes effective in inducing nociception. This primary sensory nociceptor sensitization is referred to as hyperalgesia[20].

Inflammatory pain is a pervasive problem and usually results in both spontaneous pain and hyperalgesia. Although the hyperalgesic state does not necessarily involve ongoing pain, the nociceptive threshold is lowered in this state, and the application of a nonnoxious mechanical, thermal, or chemical stimulus induces a nociceptive behavior response. However, spontaneous

inflammatory pain is characterized by a continuous endogenous stimulation of nociceptors caused by the release of inflammatory mediators that directly stimulate them. Postsurgical or traumatic pain is usually referred to as spontaneous pain in a hyperalgesic state[21].

Inflammatory temporomandibular joint (TMJ) conditions can result in TMJ hyperalgesia produced by peripheral sensitization of TMJ nociceptors and by central sensitization of the nociceptive neurons of the trigeminal brainstem sensory nuclear complex. Peripheral sensitization, as well as central sensitization is characterized by an increase in the neuronal membrane excitability by inflammatory mediators released at the site of injury and by neuropeptide and excitatory amino acid released at the trigeminal brainstem sensory nuclear complex, respectively. Some of the inflammatory mediators released at the site of injury including PGE2 are present at high levels in the synovial fluid of patients with TMD. During hyperalgesic states, the nociceptive threshold is lowered and a nonnoxious stimulus such as jaw movement can induce pain, and noxious stimulus can also induce increased pain. The inflammatory mediators released at the site of tissue injury, such as prostaglandins, sensitize nociceptors. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to manage inflammatory pain. The analgesic action of these drugs results from the blockade of prostaglandins synthesis, thus preventing the peripheral sensitization of nociceptors[21-22].

The spinal cord has been shown to be a CNS region in which components of opioid analgesic pathways and their regulation manifest sexual dimorphism. For example, the density of the kappa-opioid receptor (KOR) and its distribution within axon terminals differs between the spinal cord of male and female rodents[23]. Functional KOR are located within the TMJ of rats; peripherally acting KOR agonists could be of benefit in the treatment of TMJ pain, especially in women[24], because the analgesic effect of a class of drugs, nalbuphine, pentazocine and butorphanol, which are thought to induce analgesia predominantly by action on KOR, produce greater analgesia in women[25].

The receptors of gonadal steroids are referred to as the hormones produced by the ovaries and testes (gonads). They are present in many brain areas including some involved in pain transmission and modulation[4]. The man products of the tests are the androgens: testosterone and dihydrotestosterone. The ovaries primarily produce two types of steroid hormones: estrogens (e.g., estradiol, estriol, estrone) and progestins (e.g., progesterone; so-called because it promotes gestation and pregnancy). Testosterone is a precursor to estradiol, so the ovaries also make testosterone. Conversely, estradiol is a metabolite of testosterone, so the testes also produce some estrogens. The aromatization of testosterone to estradiol is greatly facilitated by the enzyme aromatase. This means that tissues containing aromatase can convert testosterone to estrogen and thereby make use of estrogen through estrogen receptors. In women, testosterone is produced in the adrenal cortex (25%) and ovaries (25%) and by transformation (50%) in the liver, kidneys, bowel, lungs, adipose tissue, and CNS[26]. Furthermore, since TMJ pain in women is highest at times of lowest estrogen, the effects of peripherally acting kappa opioid receptor agonists on the treatment of TMJ pain in women across the menstrual cycle should be better evaluated[24].

The physiological basis for the sex-related difference in analgesic response to a KOR agonist is not completely known. It is possible that a male related hormone, such as testosterone, interacts negatively with KOR agonists; or that female-related hormones, such as progesterone or estrogen, potentiate the action of KOR[27]. Thus, the treatment of choice for TMD is conservative because the symptomatology of the condition is often improved by the use of medication, occlusal splints, physical therapy, and orthodontic treatment[3].

Influence of female gonadal hormones on orofacial pain

During the menstrual cycle, serum levels of estrogen and progesterone fluctuate. In women, estrogen and progesterone levels are both relatively low at the beginning of the cycle. During the follicular phase, estrogen levels gradually increase, peaking prior to ovulation, and then moderately decrease during the luteal phase. Progesterone levels rapidly increase after ovulation, peaking during the middle of the luteal phase. At the end of the luteal phase, both estrogen and progesterone levels drastically decrease[28]. However, menopause induces changes in the endogenous hormone balance: ovarian production of estrogens dramatically decreases. Thereafter, the adrenal cortex is responsible for estrogen production via aromatization of androgens to estradiol in peripheral tissue (e.g., fat), which is significant in obese postmenopausal women. Nevertheless, few researchers determine testosterone and estradiol blood concentrations in their experimental subjects at the time of testing[14].

Several mechanisms by which hormones could influence TMD pain can be postulate[29]. Peripherally, hormones could act directly on the temporomandibular joint and associated soft tissues. For example, estrogen is known to increase joint laxity, at least during pregnancy, and laxity of the temporomandibular joint is thought to play a role in the development of some of these disorders[30]. Another possibility is that estrogen enhances a number of specific inflammatory responses in the TMJ, and estrogen receptors have been found only in the TMJ tissues of female primates, but not in males[31].

The classic animal experiment testing the relationship between hormones and nociception involves ovarectomizing female animals to examine the effects of

hormone deficit, and then replacing hormones exogenously and observing the effects of hormone replacement. Such studies are obviously not feasible in humans. However, the natural experiment of postmenopausal hormone replacement therapy presents an interesting parallel to the animal model: hormones are depleted (either slowly with the natural aging process, or more abruptly by surgery) and then replaced from exogenous sources. If female reproductive hormones increase the risk of a particular pain condition, those post-menopausal women who replace their depleted endogenous hormones from exogenous sources would be hormonally more similar to younger women than those postmenopausal women, who chose not to use hormone replacement therapy, and the users of hormone replacement therapy would be expected to be at higher risk of the specific pain condition[31].

Few studies have investigated the role of hormonal fluctuations in the frequency or intensity of musculoskeletal pains, such as TMD, where episodes tend to be longer than for headache. There was a report on the variability of myofascial pain of TMD over three menstrual cycles in 12 female subjects. Users of oral contraceptives tended to show less variable pain intensity levels, and fewer pain-free days than women experiencing hormonal fluctuations related to their naturally occurring menstrual cycles. However, the differences were not statistically significant and a predominant temporal pattern could not be discerned in this small sample[13].

TMD pain, abdominal pain, migraine and tension-type headache are more prevalent in adult women than in men. Epidemiological studies have also found higher prevalence of these conditions, and sometimes back pain, among adolescent girls when compared to boys. Recently, use of hormone replacement therapy in postmenopausal women has been identified as a risk factor for back pain and TMD pain[32].

Concluding, the findings of this narrative literature review suggest that there is difference in the occurrence and development of pain according to sex, women being more susceptibly to orofacial pain. However, the conclusions drawn from these studies have considerable methodological limitations and this area requires further assessment using stricter randomized controlled trials to assess the difference between sexes. It is hoped that this review will highlight the fact that the patient's sex should be taken into account during TMD therapy.

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ERRATUM

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