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Review

Sex-related differences in pain

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ABSTRACT

This article provides an overview of sex-related differences in musculoskeletal pain and the role sex hormones and response to analgesic drugs may play in these differences. Some common pain conditions that include temporomandibular disorders, rheumatoid arthritis, fibromyalgia syndrome and tension-type and migraine headaches, show fairly marked sex-related differences in their occurrence, however, with the exception of rheumatoid arthritis, these pain conditions are also characterized by a lack of understanding of their basic underlying pathophysiology. The association of pain symptoms of these musculoskeletal pain conditions with the reproductive cycle of women is strongly suggestive of a role of the estrogens and/or progesterones, the main female sex hormones, in sex-related differences in pain. Nevertheless, an alternative suggestion that testosterone, the major male sex hormone, protects men from these chronic musculoskeletal pain conditions, has also been made. Indeed, emerging evidence suggests that both male and female sex hormones may contribute to the marked sex-related differences in the occurrence of certain musculoskeletal pain conditions. Men and women also appear to differ in response to pain treatment with certain analgesic drugs. The mechanistic basis for these sex-related differences is not entirely understood but sex hormones are thought to be one of the influencing factors. An improved understanding of mechanisms which underlie sex-related differences in musculoskeletal pain and response to analgesic drugs should permit improved pain management strategies for male and female musculoskeletal pain patients in the clinical setting.

Contents

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1. Introduction

Pain is the number one reason people seek medical treatment and, with an estimated annual cost of 1 trillion US dollars per year, it is the most costly health problem [1]. However, men and women are not equally represented as sufferers of a number of common, debilitating chronic pain conditions. For example, more women than men are thought to suffer from tension-type and migraine headache, temporomandibular disorders (TMD), irritable bowel syndrome, rheumatoid arthritis (RA) and fibromyalgia syndrome (FMS), whereas more men than women seek treatment for cluster headaches, ulcers, pancreatitis and trigeminal post-herpetic neuralgia [2]. When men and women suffer from the same pain condition, women often report more severe, frequent, anatomically diffuse and longer lasting pain than men. Chronic pain from the muscles and/or joints (musculoskeletal pain) is one of the most common reasons for seeking medical treatment and is one of the sources of pain where the greatest differences between women and men have been identified. The purpose of this article is to provide an overview of musculoskeletal pain conditions that exhibit pronounced sex-related differences in their prevalence and discuss biological mechanisms that may contribute to these differences. In the present article, we will refer to male–female differences as sex-related rather than gender-related, as the latter term is better applied to a person's self-representation as a male or female. The discussion of psychological and social factors, which are thought to play an equally significant role in differences in the prevalence of certain pain conditions in men and women, is beyond the scope of the current article.

2. Sex-related differences in musculoskeletal pain conditions

Some common musculoskeletal pain conditions show fairly marked sex-related differences in their occurrence, however, with the exception of rheumatoid arthritis, these pain conditions are also characterized by a lack of understanding of their basic underlying pathophysiology. The subsequent sections highlight some of the most common of these conditions.

2.1. TMD

TMD are comprised of a group of conditions which have as their principal symptom pain in the jaw muscles and/or temporomandibular (jaw) joints with palpation and during function (e.g. chewing, mouth opening, and speech). In addition to jaw muscle and joint pain, many TMD patients will also suffer symptoms of neck muscle pain and headache (particularly chronic tension-type headache) [3].

TMD affects about 10% of the population, however, 2–5 times more women than men seek treatment for TMD-related pain and dysfunction [4]. The prevalence of TMD in women appears to peak during the 3rd to 4th decade and then declines to levels comparable with men, which suggests that the increased occurrence of this disorder in women may be related to levels of female sex hormones. In particular, menstrual cycle-related variations in sex hormone levels that begin at puberty are thought to be associated with the intensity of jaw muscle pain in women TMD sufferers [4].

2.2. FMS

FMS is characterized by localized muscle tenderness as well as muscle pain and stiffness that is widespread throughout the body and a propensity for increased muscle fatigue and weakness, often exacerbated by exercise [5]. Muscle pain in FMS fluctuates and is associated with generalized symptoms of increased sensitivity to pain. FMS is commonly associated with other pain conditions such as TMD, chronic neck and back pain, and migraine headaches [5].

FMS has a prevalence in the general population of about 2–3%, however, more than 80% of the sufferers of this disorder are women [5]. Unlike TMD, FMS usually develops or worsens markedly around menopause. This may indicate that for this disorder, female sex hormones play a protective role and their decrease at menopause plays a permissive role in the development of the widespread pain associated with the disorder.

2.3. RA

RA is a chronic systemic autoimmune disease that results in significant joint inflammation and pain. RA typically affects joints of the fingers, toes, and wrists initially and eventually leads to irreversible joint destruction of these and other joints [6]. It is thought that RA pain results from increased joint pressure as a result of the profound joint swelling that occurs.

RA has a prevalence of about 0.5–1% in adults, however, 2–4 times more women than men suffer from this disorder [7]. In women, the peak incidence of RA occurs in the 4th decade, which suggests that decreased levels of female sex hormones contribute to its development [6,7]. RA improves during the postovulatory phase and pregnancy when sex hormone levels are high, but a protective role for sex hormone replacement therapy has not been conclusively established [6,8]. Although controversial, some research supports the suggestion that women with RA suffer more functional deficits at a faster rate than their male counterparts [7].

2.4. Headache

Although technically not a musculoskeletal pain condition, both migraine and tension-type headaches are often associated with tenderness of the neck/shoulder and/or temporalis muscles that, as discussed above, are also commonly reported by individuals with chronic musculoskeletal pain conditions. Tension-type headache is characterized by dull, aching, non-throbbing pain that can be distributed unilaterally or bilaterally and referred to temporal, occipital, parietal or frontal regions of the head [9]. Migraine headache is described as a severe pounding–throbbing head pain that is usually unilateral and referred to the temporal region. Migraine headache is typically associated with more severe symptoms such as nausea, light and sound sensitivity. Migraine headache is often reported to start at the back of the head or in the neck, and later move to the front of the head [10]. About 10% of migraine headaches are preceded by an aura which can involve visual, olfactory and/or auditory effects.

Tension-type headache is one of the most common pain complaints in the world. Tension-type headaches are about 1.5 times more common in women than in men [11]. Migraine headaches are 2–3 times more common in women than in men and the duration of headaches is longer in women than in men [10]. The prevalence of migraine headache peaks in women during the fertile years and decreases after menopause, whereas in men it is relatively stable throughout lifespan. Many women migraine headache sufferers report the association of headache occurrence with their menstrual cycle, in particular with menstruation [12].

3. The role of sex hormones

The association of pain symptoms of these musculoskeletal pain conditions with the reproductive cycle of women is strongly suggestive of a role of the estrogens and/or progesterones, the main female sex hormones, in sex-related differences in pain. Nevertheless, an alternative suggestion that testosterone, the major male