Current Oncology Reports (2023) 25:825–831
https://doi.org/10.1007/s11912-023-01413-5

Aromatase Inhibitor Musculoskeletal Syndrome and Bone Loss: a Review of the Current Literature

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Accepted: 20 March 2023 / Published online: 13 April 2023

Abstract

Purpose of Review The study aims to review the literature regarding musculoskeletal complications of aromatase inhibitors and treatment options for these complications.

Recent Findings Aromatase inhibitors are common medications to treat hormone receptor-positive breast cancer in postmenopausal women and have been shown to improve survival and prevent disease recurrence. However, 20–60% patients stop treatment prematurely due to side effects. Side effects include joint stiffness and pain, tendonitis, tendon tears, muscle pain, and carpal tunnel syndrome known as aromatase inhibitor musculoskeletal syndrome (AIMSS) as well as bone loss. Proposed mechanisms of AIMSS include decreased estrogen levels, inflammation, and genetic factors. Switching aromatase inhibitors, exercise, non-steroidal anti-inflammatory medications, duloxetine, acupuncture, prednisone, and bisphosphonates are some treatment options for this syndrome and will be discussed in more detail in this review.

Summary Aromatase inhibitors are important in the treatment of hormone receptor-positive breast cancer in postmenopausal women. As we study the incidence of side effects of these medications including bone loss and AIMSS and determine the mechanisms of these symptoms and possible treatment options, we will decrease the incidence of patients discontinuing treatment prematurely and improve symptoms, quality of life, and survival in this patient population.

Keywords Aromatase inhibitor · Musculoskeletal complications · Cancer rehabilitation · Cancer treatment side effects

Introduction

According to the American Cancer Society, an estimated 287,850 new cases of breast cancer will be diagnosed in 2022, and about 43,250 women will die from breast cancer.

Treatment for breast cancer includes surgery, radiation, and medications. Aromatase inhibitors (AIs) are common medications used to treat hormone receptor-positive breast cancer in postmenopausal women. Aromatase is a cytochrome p450 enzyme that converts androgens to estrogen. Aromatase facilitated production of estrogens occurs mainly in the ovaries of premenopausal women and adipose tissue in postmenopausal women. Aromatase is also found in the central nervous system, bone, muscle, testis, skin, prostate, and adrenals. Aromatase inhibitors suppress estrogen levels throughout the body by inhibiting the enzyme aromatase. Because estrogen correlates with the growth of neoplastic breast cancer tissue in hormone receptor-positive breast cancers, aromatase inhibitors are ideal targets to treat this type of breast cancer due to their ability to reduce estrogen levels.

Studies have consistently shown that aromatase inhibitors reduce breast cancer recurrence and decrease breast cancer mortality versus tamoxifen in postmenopausal women with hormone receptor-positive breast cancer [1]. Aromatase inhibitors also have a lower incidence of life-threatening adverse events including thromboembolic events and endometrial cancer compared with tamoxifen [2]. Despite the benefit of aromatase inhibitors, patients may discontinue use prematurely due to side effects. In one study, 20% of patients discontinued AI therapy at 24 months and 32% at 4 years [3]. Other studies have shown that the incidence of discontinuing the medication can range up to 60% [4, 5].

This article is part of the Topical Collection on *Cancer Rehabilitation*

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Aromatase Inhibitor Musculoskeletal Syndrome

The most common reason for discontinuation of aromatase inhibitor therapy is musculoskeletal side effects. The constellation of symptoms that result is known as aromatase inhibitor musculoskeletal syndrome (AIMSS) and consists of arthralgias, myalgias, joint stiffness, tenosynovitis, tendonopathy, tendon tears, and carpal tunnel syndrome. Patients describe symmetric joint pain and stiffness, bone pain, tendon symptoms, and numbness (in the case of carpal tunnel syndrome). Symptoms most commonly affect the hands, wrists, knees, ankles, and shoulders, but can affect the spine and pelvis. Patients may also describe decreased grip strength [6•, 7•]. Most symptoms begin within 2 months of starting the aromatase inhibitor, but there have been reports of symptoms starting as late as 10 months after beginning therapy [6•].

Aromatase inhibitor arthralgia is one specific manifestation of AIMSS and includes joint pain and stiffness. There are no widely accepted criteria for the diagnosis of aromatase inhibitor-induced arthralgia; however, there are proposed criteria [8]. It is proposed that patients meet all of the major and 3 of the minor criteria. Major criteria include currently taking AI therapy, joint pain which has developed or worsened since starting AI therapy, joint pain improves or resolves within 2 weeks of stopping AI therapy, and joint pain returns upon resuming therapy. Minor criteria include symmetrical joint pains, pain in hands and/or wrists, carpal tunnel syndrome, decreased grip strength, morning stiffness, and improvement in joint discomfort with use or exercise (Table 1).

Table 1 Proposed criteria for the diagnosis of aromatase inhibitor arthralgia syndrome

Major criteria
Currently taking AI therapy
Joint pain which has developed or worsened since starting AI therapy
Joint pain improves or resolves within 2 weeks of stopping AI therapy
Joint pain returns upon resuming AI
Minor criteria
Symmetrical joint pains
Pain in hands and/or wrists
Carpal tunnel syndrome
Decreased grip strength
Morning stiffness
Improvement in joint discomfort with use or exercise

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Proposed Mechanisms

At this time, the mechanism of AIMSS is not known. Some theories are related to decrease in estrogen levels. Declining levels of estrogen result in increased production of proinflammatory cytokines in articular chondrocytes resulting in joint pain and swelling. Estrogen also has antinociceptive properties, and lower levels of estrogens from AIs can result in higher pain levels. In animal models, mice with removed ovaries have higher cartilage turnover which could contribute to joint pain [9]. There is also some radiographic evidence demonstrating the inflammatory nature of aromatase-induced arthralgia. A small study showed all 12 patients who were taking aromatase inhibitors had MRI findings of inflammation and thickening of tendons [10].

Some literature shows the association between aromatase inhibitors and autoimmune rheumatic diseases. There are case reports of patients developing rheumatoid arthritis after starting aromatase inhibitors. These patients had erosions noted on radiographs and positive serologic tests for rheumatoid arthritis. They had improvement of symptoms and clinical markers after stopping the aromatase inhibitors [11–13]. There was also a cohort study out of Italy that examined the risk of developing rheumatoid arthritis related to tamoxifen, anastrozole, exemestane, or letrozole. They found an increased risk of rheumatoid arthritis in the aromatase inhibitor group (adjusted HR 1.62 (95% 1.03–2.56), even when adjusting for age and severity of neoplasm (adjusted HR 1.75 (95%1.07–2.86) [14]. However, this literature is from 2014 to 2017. Following 2017, there is a paucity of literature around this association.

Risk Factors

Studies looking at risk factors for AIMSS have shown inconsistent findings. Some studies have shown an association between being overweight (BMI > 30 and weight > 80 kg) and increased joint symptoms [15, 16]; however, others did not find this association. Patients in perimenopause may be at greater risk for the development of musculoskeletal symptoms due to relatively higher drop in estrogen levels with aromatase inhibitor treatment [17]. There has not been a clear association with taxane use and AIMSS [17]. There is also some evidence that genetic factors, including single-nucleotide polymorphisms in certain genes, may play a role in aromatase inhibitor bone loss [6•].

Bone Loss

Aromatase inhibitors are known to result in loss of bone density [18, 19]. Low estrogen levels cause accelerated trabecular bone loss and disruption in the balance of osteoblast and osteoclast activity. The rate of bone loss has been reported to be up to 2 times higher among those who are taking aromatase inhibitors compared to healthy postmenopausal controls [6•]. The altered bone architecture and bone loss result in increased fracture risk. Risk factors that increase fracture risk in postmenopausal women with breast cancer identified by the European Society of Medical Oncology are the following: age > 65 years, *T* score < − 1.5, smoking, BMI < 24, family history of hip fractures, personal history of fragility fracture over age 50, and oral glucocorticoid use for > 6 months [20]. However, it appears that patients with obesity have bone loss as well, likely related to a more significant drop in estrogen levels [21]. Patients taking aromatase inhibitors should be screened for osteoporosis and fracture risk through history and bone mineral density examination. Treatment should consist of a diet with appropriate amount of calcium, vitamin D supplementation if needed, weight-bearing exercise program, smoking cessation, and limiting alcohol consumption. Antiresorptive therapy should be considered when *T* score is less than − 2 with 2 or more of the above mentioned risk factors. Bone mineral density should be monitored every 1–2 years in this population [20, 21].

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) has been reported in patients taking aromatase inhibitors. Risk factors for aromatase inhibitor-induced carpal tunnel syndrome or stenosing tenosynovitis include hormone replacement therapy before cancer treatment, history of musculoskeletal symptoms, age younger than 60 years, prior chemotherapy, and body mass index greater than 25 kg/m^2. A study by Chung et al. noted that the incidence of carpal tunnel syndrome among those taking aromatase inhibitors can be increased up to 10 times compared to tamoxifen. Patient discontinuation of aromatase inhibitor treatment because of carpal tunnel syndrome and stenosing tenosynovitis was reported in this study. Non-surgical management led to complete resolution of carpal tunnel syndrome symptoms in up to 67% of cases [22•]. A large population study showed a higher rate of carpal tunnel syndrome in patients taking aromatase inhibitors than those without hormone therapy (1.3% vs 0.4%) and tenosynovitis occurred at a higher rate in the aromatase inhibitor group (2.3% vs 1/1%). In this study, aromatase inhibitor (AI) users frequently needed oral medication for CTS and developed severe CTS which frequently required surgery. More than half of the CTS and tenosynovitis occurred within 12 months after hormone commencement [23]. Another study showed a worsening of 2 point discrimination testing in the hand 3 months after starting aromatase inhibitor therapy [24].

Tendonopathy, Tendon, and Muscle Tear

There have been case reports of tendon tear and muscle tendon rupture. Mitsimponas et al. described three cases of tendon or muscle tear following treatment with letrozole [25]. Each patient had no injury, no overuse of the tendon, had no evidence of systemic disease or cancer recurrence, took no other medications, and had no other explanation for the tendon or muscle tear. One case was a 74 years old with stage IIB breast cancer treated with mastectomy followed by chemotherapy and radiation and then letrozole therapy. One year after starting letrozole, she developed persistent pain in her left shoulder. MRI of the shoulder demonstrated partial tendon tear of the supraspinatus, and she was referred for surgical repair. A second case was a 62 years old with stage 1 breast cancer treated with lumpectomy, chemotherapy, and radiation followed by letrozole. She also developed shoulder pain 11 months after starting the letrozole, and MRI showed severe tendonopathy of the supraspinatus tendon. Her symptoms resolved 1 month after changing her aromatase inhibitor. A third case had stage IIA breast cancer treated with lumpectomy and radiation. Eighteen months after starting letrozole, she developed shoulder pain. MRI showed a complete rupture of the supraspinatus tendon and subscapularis muscle and partial tear of the infraspinatus tendon. She was referred for surgical treatment, and the letrozole was discontinued.

The cause of tendonopathy or tendon tear associated with aromatase inhibitor use is also not known. One proposed mechanism is apoptosis of tenocytes and tenoblasts. This leads to abnormal extracellular matrix maintenance and repair as well as disrupted intercellular signaling and structural disintegration. There is likely a combination of increased expression of lytic enzymes, lessened cholesterol content in cell membranes, and neoangiogenesis within highly ordered tendon tissue. Intrinsic factors such as age and joint laxity and extrinsic factors such as occupation and activities are likely risk factors. Other possible causes include inherited disorders, endocrine and metabolic disorders, and rheumatologic diseases [26].

Patient Education

Because of the relatively high prevalence of AIMSS in patients receiving aromatase inhibitors, it is important to educate patients about the possible symptoms prior to starting medication. Patients who develop symptoms should be

assessed for specific musculoskeletal conditions as each may require different treatments. X-rays can evaluate for degenerative changes and can exclude inflammatory arthritis, erosions, and fractures. Ultrasound or MRI can be useful to evaluate for tendonopathy, tendon tears, and inflammation. Electrodiagnostic evaluation can assist in the diagnosis of carpal tunnel syndrome or other peripheral nerve compression. Laboratory evaluation can screen for inflammatory arthropathies and exclude other causes of musculoskeletal pain such as vitamin D deficiency or thyroid abnormalities.

Treatment Options for Aromatase Inhibitor Musculoskeletal Syndrome

Switch Aromatase Inhibitors

In some patients, certain aromatase inhibitors are better tolerated than others, and there is evidence that switching aromatase inhibitors can be helpful in reducing musculoskeletal symptoms. Typically the aromatase inhibitor is discontinued for a period of 2–8 weeks before a different inhibitor is trialed. In the ATOLL trial, 179 patients who discontinued anastrozole due to musculoskeletal symptoms were given letrozole. At 6 months, 72% continued with letrozole, the remainder discontinued letrozole due to severe joint pain. However, of those that continued on letrozole, 74% continued to experience arthralgias, myalgias, arthritis, and tendonitis [27]. Another study showed that almost 40% of patients were able to tolerate a different AI [5]. The phase III SOLE trial looked at postmenopausal women who had completed 4–6 years of adjuvant endocrine therapy were randomized to continuous or intermittent letrozole [28]. While the primary outcome measure was disease-free survival, those receiving intermittent letrozole reported better quality of life scores and better musculoskeletal pain scores. These patients had already tolerated 4–6 years on endocrine therapy, and may not have experienced significant AIMSS leading to discontinuation of therapy, so the significance of these results is unknown.

Exercise

In the HOPE trial, 121 postmenopausal women with AI-associated arthralgias were randomly assigned to an exercise regimen or usual care [29]. The exercise regimen consisted of twice-weekly supervised resistance and strength training plus moderate aerobic exercise for 150 min per week. Patients undergoing the exercise regimen had reduction in their worst pain score (20 versus 1% average score reduction, respectively) and pain severity (21 versus 0% reduction) compared with usual care. They also experienced more weight loss and improvement in their exercise capacity. In addition, a dose–response relationship between exercise and symptom severity was identified. Compared with women who attended fewer than 80% of the exercise sessions, those who attended 80% or more experienced a greater reduction in their worst pain score (25 versus 14%, respectively). Another study showed improvement in cardiovascular fitness and pain in patients participating in aerobic exercise and strength training [30•]. Other studies have shown benefits in pain and quality of life measures in patients participating in a combination of aerobic and strengthening exercise, aquatic exercise, and yoga [31, 32••].

Occupational therapy and physical therapy can be prescribed to address specific musculoskeletal related issues. Exercise studies included various forms of therapy and showed overall benefit of exercise as noted above; however, there are no studies looking solely at the effects of physical and occupational therapy in this population [33•]. Based on our knowledge of the treatment of musculoskeletal conditions from other etiologies, stretching, strengthening, joint protection, and braces can be beneficial.

Non-Steroidal Anti-Inflammatory Medications and Prednisone

Initial recommendations for the treatment of AIMSS included non-steroidal anti-inflammatories (NSAIDs) for joint-related symptoms [7•]. This can be considered for a short course in patients who do not have contraindications. However, patients may experience gastrointestinal side effects. Renal and cardiovascular effects need to be considered as well. As an alternative to NSAIDs, one study looked at 5 mg of prednisone for 1 week. Sixty-seven percent of patients reported decreased pain scores after 1 week, and 50% reported continued decreased pain levels at 2 months. Further studies are needed to determine the long-term benefit of prednisone [34].

Duloxetine

In the SWOG S1202 trial, patients with stage 1 to 3 breast cancer who developed aromatase inhibitor MSK syndrome, who were randomized to duloxetine 30 mg daily for 1 week, 60 mg daily for 11 weeks, and 30 mg daily for 1 week, had improved symptoms compared with placebo. There was also functional improvement as noted by Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) and Functional Assessment of Cancer Therapy-Endocrine Scale Trial Outcome Index. After stopping treatment, symptoms were similar. Side effects of duloxetine included fatigue, xerostomia, nausea, and headache [35].

Acupuncture

Several studies have shown decreased pain scores with acupuncture. In two studies, there was a small decrease in symptoms with acupuncture vs sham (1 point in 1–10 scale of symptoms) [36, 37]. Roberts conducted a systematic review of treatment options for AIMSS and found that 4 of 6 studies examining the effects of acupuncture showed improvement in symptoms [32••].

Vitamin D

Vitamin D has not shown consistent improvement in symptoms, but a trial can be considered when other treatments are ineffective [37].

Omega 3 Fatty Acid

Omega 3 fatty acids have also been studied in treating AIMSS. A study by Shen et al. failed to show benefit of Omega 3 fatty acids compared to placebo in 249 patients. However, the authors did find an improvement in joint pain and stiffness and WOMAC scores among obese patients [38]. Another pilot study showed good tolerability of Omega 3 fatty acids and benefit on quality of life [39], suggesting that Omega 3 fatty acids can be considered for treatment of joint pain in patients treated with aromatase inhibitors.

Bisphosphonates

Bisphonates have the potential to decrease symptoms related to aromatase inhibitor arthralgia (AIA) due to their effects on improved bone density. A prospective phase II, single arm trial was aimed at evaluating the treatment with zoledronic acid in reducing the incidence of AIA. Fifty-nine postmenopausal women with breast cancer received zoledronic acid (4 mg i.v.) 1–2 weeks before letrozole and then after 6 months. A significantly lower incidence of AIA at a 1-year follow-up was shown in patients receiving zoledronic acid, compared with controls. [40].

Conclusion

Aromatase inhibitors are common treatments for estrogen receptor-positive breast cancers and can reduce the risk of breast cancer recurrence and improve survival. However, side effects may lead to premature discontinuation of therapy, placing patients at risk for increased morbidity and mortality related to their cancer. Common side effects of aromatase inhibitors include bone loss and musculoskeletal symptoms, known as aromatase inhibitor musculoskeletal syndrome (AIMSS). This syndrome consists of joint pain and stiffness, myalgia, tendonopathy, bone loss, carpal tunnel syndrome, and rarely tendon or muscle tears. Due to the relatively high prevalence of this syndrome (20–60%), patients should be educated about the possible symptoms prior to starting aromatase inhibitors. At this time, mechanisms of this syndrome are unknown. Proposed etiologies include estrogen deficiency, inflammation, and genetic factors. Effective treatments include switching aromatase inhibitors, exercise, acupuncture, and duloxetine. There is less evidence to support the use of bisphosphonates, prednisone, NSAIDS, OMEGA 3 fatty acids, and vitamin D, but they can be considered in appropriate populations. Bone density should also be assessed in patients receiving aromatase inhibitors through history and bone density examination. As we study the incidence of side effects of these medications including bone loss and AIMSS and determine the mechanisms and treatment options, we will decrease the incidence of patients who stop treatment prematurely. Patients can then complete their full treatment course with improved symptoms, quality of life, and survival.

Declarations

Conflict of Interest The author declares no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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