REVIEW ARTICLE
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Most prevalent side effects of aromatase inhibitors in the treatment of hormone-positive breast cancer: a scoping review

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ABSTRACT

Hormone-positive breast cancer is the most commonly diagnosed breast neoplasm among postmenopausal women and is strongly associated with the effects of estrogens on hormone receptors of breast cells. Aromatase inhibitors are especially prescribed for treatment, and are effective to reduce mortality rates and the development of a new contralateral breast tumor. However, even with the proven efficacy and safety in use of these medications, approximately 50% of the patients abandon treatment before the prescribed period due to their side effects. The study was carried out with the objective of mapping what national and international literature declare about the most prevalent side effects caused by aromatase inhibitors in the treatment of women with hormone-positive breast cancer. We used the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review to elaborate this review. The methodology of choice was a scoping review aiming at synthetizing relevant information in an objective and clear manner about this drug class that is so common in breast cancer therapy, mainly benefitting women who are users of such drugs. According to the literature, reduced bone mineral density, arthralgia, hot flushes and dryness of the vaginal mucosa are the most reported symptoms, directly related with the absence of estrogen action on the body. These effects have a direct repercussion on the quality of life and on the discontinuation of treatment, leading to reduced functionality and high mortality rates.

KEYWORDS: Aromatase inhibitors; breast neoplasm; estrogen receptor; side effects.

INTRODUCTION

Breast cancer is the most frequently diagnosed neoplasm in women around the world, and represents the second main cause of death among women. In the diagnosed cases, about 75% are hormone-positive[1-4], associated with the proliferative effects of estrogens on estrogen receptors (ER) of breast cells.

The main source of estrogens among menopausal women comes from the action of the aromatase enzyme, responsible for converting androgens into estrogen in peripheral tissues, such as breast tissue. Its inhibition reduces the amount of circulating estrogen, thus decreasing the proliferation and growth of tumor cells[1,5,6]. Therefore, the drugs that are mostly used to treat this type of neoplasm in post-menopausal women are those included in the aromatase inhibitor class[2].

Drugs in this class are divided in non-steroidal, anastrozole and letrozole, which inhibit the aromatase enzyme competitively; and steroidal, exemestane, which irreversibly bonds with the binding site[1,2,7]. Despite its proven efficacy and safety in cancer treatment, about 50% of the women using aromatase inhibitors abandon treatment before the five years stipulated as time of general treatment. The main reasons for abandonment are the side effects caused by the class, especially musculoskeletal syndrome, fatigue and insomnia[6].

The scoping review was the methodology of choice for synthetizing information in a simple and objective manner, allowing the identification of research gaps. The objective of this review is to gather information about aromatase inhibitor drugs, in order to inform and understand their effects on the everyday life of women affected by breast cancer. It is important that health professionals be aware of the most prevalent side effects of this class, so that they can control the course of therapy and reassure and harbor these patients, communicating with them.

Therefore, the question is: which are the most prevalent side effects caused by aromatase inhibitors in hormone-positive breast cancer therapy?

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METHODOS

A study was conducted with the objective of mapping what national and international literature shows about the most prevalent side effects caused by aromatase inhibitors in treatments for women with hormone-positive breast cancer. Therefore, we used the PCC mnemonics to create the research question.

So, P (participants) refers to adult, post-menopausal women, with hormone-positive breast cancer; C (concept) includes the adverse effects of aromatase inhibitors; C (context) has not been defined, so it can be either the hospital or the household context, as long as there is treatment with the established drug class and determined type of neoplasm.

Quantitative studies, integrative reviews, case studies and clinical trials were considered. We also included grey literature (unconventional or unpublished publications).

As recommended by the methodology from Instituto Joanna Briggs (JBI), the search was carried out in three stages using the following databases: PubMed, VHL regional portal, CAPES, Brazilian Digital Library of Theses and Dissertations, and Scientific Electronic Library Online. We used the descriptors "woman", "breast cancer", "aromatase inhibitors", "hormone receptor positive", and "side effects" according to the vocabulary from Medical Subject Headings for the PubMed base, in different combinations, using synonyms and Booleans AND and OR. We did not use filters for period and language of the studies.

The initial analysis of the titles and abstracts was performed by two independent reviewers, and it was necessary to include a third reviewer when it was not possible to reach a consensus after discussion. Texts with potential were assessed in detail by each reviewer. For data selection, the identified studies had their information collected with the assistance of standardized Microsoft Excel® 2016 spreadsheets, and duplicates were removed.

This review was carried out according to JBI's methodology for scoping reviews, according to PRISMA-ScR guidelines. The previously elaborated research protocol was registered in the Open Science Framework platform, and its Digital Object Identifier was 10.17605/OSF.IO/J8UMV.

RESULTS

Among the five databases chosen for search, 238 studies were identified. After screening of titles and abstracts, 36 were selected for full reading and, from these, 22 met the inclusion criteria. Divergences between reviewers were solved by consensus.

The search results and selected studies are shown in a flowchart (Figure 1), as established by PRISMA-ScR.

The studies included different approaches of the several most prevalent adverse effects caused by aromatase inhibitors, and how these affect the lives of women undergoing breast cancer treatments. The general data are exposed in Table 1[1-22].

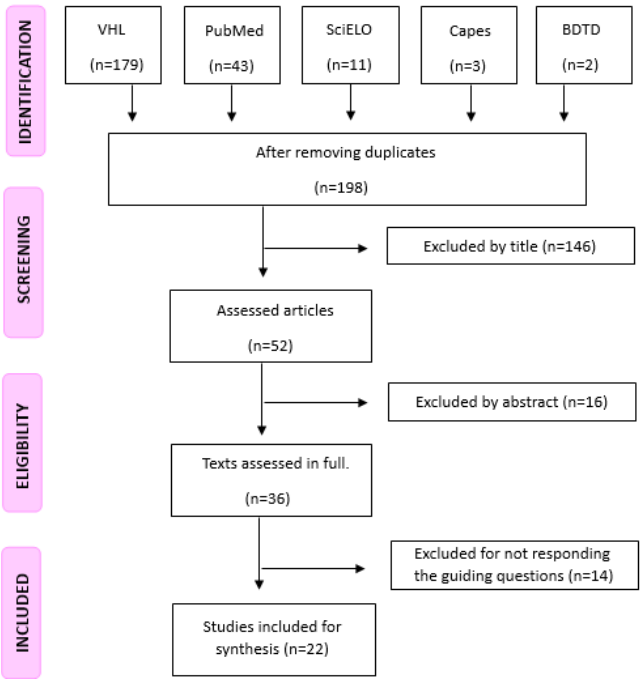


Figure 1. Study selection flowchart.

Of the 22 studies included in the synthesis, 15 mention musculoskeletal symptoms; 9, vasomotor symptoms; 8, gynecological/urogenital effects; 6, lipid profile; 6, cardiovascular effects; 3, ophthalmologic events; 3, effects on cognition; 3, mood swings; and 2, sleep and activities of daily living disorders. The selected productions are focused on the United Kingdom and the United States; 20 were published in English, 1 in French, 1 in Portuguese and 1 in Czech.

DISCUSSION

Breast cancer is the most common neoplasm among Brazilian women, and constitutes the second main cause of death by cancer in women[1-4]. The World Health Organization estimates there are more than one million new cases of breast cancer around the world per year[2] and, of these, more than 50% are hormone-positive, responding to hormone therapy with aromatase inhibitors[3].

The estrogen, chemical mediator produced by the ovaries from cholesterol, acts on different tissues during menacme due to the interaction with specific receptors to modulate essential functions in women's bodies[2]. Among the main functions of estrogen on women's bodies, we can mention the development of female characteristics, such as the increase of breasts and growth of pubic hair, and endometrial cell proliferation to allow the implantation of the embryo[6].

Besides, estrogen participates in the metabolism of calcium and the maintenance of bone mass, favors increasing fat deposition, promotes vaginal lubrication and increased libido[6]. Among premenopausal women, the main source of estrogen is the ovary.

Table 1. Year, type of study, authors, title, journal, country of publication and side effects.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
01	2001	Clinical trial	Elisaf et al.[18]	Effect of letrozole on the lipid profile in postmenopausal women with breast cancer	European Journal of Cancer	United Kingdom	Increased serum LDL, total cholesterol and ApoB levels; increased atherogenic risk factor rates; reduced HDL and ApoA1 levels.
02	2006	Narrative review	Mouridsen,[17]	Incidence and management of side effects associated with aromatase inhibitors is the adjuvant treatment of breast cancer in postmenopausal women	Current Medical Research and Opinion	United Kingdom	Heat waves; arthralgia; myalgia; anorexia; alopecia; nausea; visual disorders; endometrial cancer; metrorrhagia; vaginal dryness; reduced bone mineral density; coronary artery disease; angina; acute myocardial infarction; venous thromboembolism; hypercholesterolemia; nausea; diarrhea; increasing levels of LDL and total cholesterol; reduced HDL levels.
03	2008	Case report	Nemitz et al.[9]	Intensification of a diffuse chronic pain syndrome by the introduction of an aromatase inhibitor	Praxis (Bern)	France	Fibromyalgia; diffuse chronic pain; arthralgia; myalgia; hot flushes; reduced bone mineral density; rigidity.
04	2008	Narrative review	Cella and Fallowfield[12]	Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy	Breast Cancer Research and Treatment	United States	Wave heats; vaginal discharge; dyspareunia; arthralgia; bone loss; venous thromboembolic events; cerebral ischemia; endometrial cancer; heart failure; hypercholesterolemia; night sweats; ostealgia; metrorrhagia; nausea; headache; irritability; mood swings; insomnia; weight gain; diarrhea; vaginal pruritus; reduced libido; mastalgia; uterine atrophy.
05	2009	Narrative review	Kwan and Chlebowski[19]	Sexual dysfunction and aromatase inhibitor use in survivors of breast cancer	Clinical Breast Cancer	United States	Sexual dysfunction; vaginal dryness; vaginal pruritus; dyspareunia; reduced libido.
06	2009	Narrative review	Bundred[11]	Aromatase inhibitors and bone health	Current Opinion in Obstetrics and Gynecology	United Kingdom	Reduced bone mineral density.
07	2011	Prospective cohort study	Gallicchio et al.[15]	Androgens and musculoskeletal symptoms among breast cancer patients on aromatase inhibitor therapy	Breast Cancer Research and Treatment	United States	Arthralgia; bone loss; arthritis; increased risk of fractures.
08	2011	Field survey	Scarpa et al.[14]	Rheumatic complaints women taking aromatase inhibitors for treatment of hormone-dependent breast cancer	Journal of Clinical Rheumatology	Italy	Spondyloarthritis; oligoarthritis; arthralgia; myalgia; sacroiliitis; arthritis; wave heats; night sweats; vaginal dryness; osteopenia; osteoporosis.
09	2011	Narrative review	Phillips et al.[21]	Do aromatase inhibitors have adverse effects on cognitive function?	Breast Cancer Research	Australia	No cognitive adverse effect was proven according to the available studies.

Continue...

Table 1. Continuation.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
10	2012	Case report	Rocha-Cadman, et al.[22]	Aromatase inhibitors and mood disturbances	Palliative and Supportive Care	United Kingdom	Mood swings; suicidal ideas; anxiety; sadness; anger; hot flushes; irritability; difficulty to concentrate.
11	2014	Narrative review	Van-Asten et al.[8]	Aromatase inhibitors in the breast cancer clinic: focus on exemestane	Endocrine Related Cancer	United Kingdom	Hot flushes; bone loss; increased bone remodeling rate; carpal tunnel syndrome; morning stiffness; arthralgia; worsen lipid profile; increased risk of having coronary disease; myocardial infarction; stroke; transient ischemic attacks; atrial fibrillation; vaginal dryness; metrorrhagia; dyspareunia.
12	2014	Narrative review	Abubakar et al.[6]	The influence of genetic polymorphisms on the efficacy and side effects of anastrozole in postmenopausal breast cancer patients	Pharmacogenetics and Genomics	United States	Reduced bone mineral density; arthralgia; joint stiffness; myalgia.
13	2015	Prospective cohort study	Rodríguez-Sanz et al.[13]	CYP11A1 expression in bone is associated with aromatase inhibitor-related bone loss	Journal of Molecular Endocrinology	United States	Myalgia; arthralgia; reduced bone mineral density.
14	2015	Systematic review and meta-analysis	Artigalás[2]	Estudo farmacogenético e farmacoeconômico em pacientes brasileiras portadoras de câncer de mama tratadas com inibidores da aromatase		Brazil	ANASTROZOLE: vaginal bleeding; hot flushes; endometrial cancer; ischemic stroke; deep vein thrombosis; pulmonary embolism. LETROZOLE: hot flushes; nausea; hair changes (rarefaction and fine hair); arthralgia; myopathy; and arthritis. EXEMESTANE: increased appetite; hot flushes; excessive sweating; peripheral edema; nausea; arthralgia; diarrhea; visual changes; fractures.
15	2017	Narrative review	Borrie and Kim[1]	Molecular basis of aromatase inhibitor associated arthralgia: known and potential candidate genes and associated biomarkers	Expert Opinion on Drug Metabolism & Toxicology	United Kingdom	Arthralgia; myalgia; reduced bone mineral density; vaginal dryness; metrorrhagia; reduced libido.
16	2016	Narrative review	Krásenská[16]	Treatment with aromatase inhibitors in postmenopausal women with breast cancer and the possibility of influencing side effect	Klinická Onkologie	Czech Republic	Vaginal atrophy; dyspareunia; wave heats; redness; sweats; bone loss; arthralgia; myalgia; vaginal dryness; worsen lipid profile; urogenital atrophy; vaginal pruritus; polyuria; carpal tunnel syndrome; reduced prehension strength; morning stiffness.
17	2018	Clinical trial	Bhave et al.[7]	Effect of aromatase inhibitor therapy on sleep and activity patterns in early-stage breast cancer	Clinical Breast Cancer	United States	Reduced daily activity; fatigue; insomnia; musculoskeletal symptoms.

Continue...

Table 1. Continuation.

Nº	Year	Type of study	Author	Title	Journal	Country	Side effects
18	2019	Cross-sectional study	Gonzaga et al.[4]	Changes in cardiac autonomic modulation in women with breast cancer using aromatase inhibitors and the relation with biochemical variables	Arquivos Brasileiros de Cardiologia	Brazil	Worsen lipid profile; increased triglycerides; reduced variability in heart rate; higher risk of cardiovascular diseases; weight gain.
19	2019	Longitudinal study	Underwood et al.[3]	Cognitive effects of adjuvant endocrine therapy in older women treated for early-stage breast cancer: a 1-year longitudinal study	Supportive Care in Cancer	Germany	Changes in verbal memory.
20	2020	Case study	Bicer et al.[20]	The effects of adjuvant hormonotherapy on tear functions in patients with breast cancer	International Ophthalmology	Netherlands	Retinal hemorrhages; hemiretinal artery occlusion; keratoconjunctivitis sicca; blurry vision; foreign body sensation; redness; photosensitivity; Sjögren's syndrome.
21	2020	Narrative review	Tenti et al.[10]	Aromatase inhibitors-induced musculoskeletal disorders: current knowledge on clinical and molecular aspects	International Journal of Molecular Sciences	Switzerland	Reduced bone mineral density; arthralgia; myalgia; morning stiffness; carpal tunnel syndrome; reduced prehension strength; rheumatoid arthritis; spondyloarthropathy; Sjögren's syndrome; systemic lupus erythematosus; scleroderma; antisynthetase syndrome; antiphospholipid syndrome; hot flushes; night sweats; sleeping disorders; fatigue; anxiety; mild depression; vulvovaginal and urogenital atrophy; vaginal dryness; dyspareunia; metrorrhagia; dysuria; hypertension; venous thrombosis; arrhythmia; heart failure; peripheral arterial disease; embolism; myocardial infarction; atrial fibrillation; difficulty to concentrate; verbal memory deficit; paresthesia in extremities.
22	2021	Narrative review	Hyder et al.[5]	Aromatase inhibitor-associated musculoskeletal syndrome: understanding mechanisms and management	Frontiers in Endocrinology	Switzerland	Musculoskeletal syndrome associated with aromatase inhibitors; reduced bone mineral density; arthralgia; myalgia; joint stiffness; tenosynovitis; carpal tunnel syndrome; trigger finger.

Among post-menopausal women, it is especially produced in the fat tissue, breasts, brain, liver and muscles through the conversion of androgens by the aromatase enzyme (CYP19A1)[1-4].

The molecular action of estrogen begins in the cytoplasm, after bonding with estrogen receptors, represented by two subtypes, ERα (ESR1) and ERβ (ESR2)[6]. Most breast tumors express both receptor subtypes[6]. ERα is the main regulator of the estrogen proliferative action in the breast tissue, whereas ERβ has contrary effects by promoting antiproliferative and apoptotic functions[6].

Since hormone-positive breast cancer cells are modulated by the interaction between estrogen and its receptors, the most used therapy for this type of neoplasm include aromatase inhibitors. These drugs act by bonding, reversibly and irreversibly, to the heme group of the aromatase enzyme, thus preventing the aromatization of androgens, resulting in a state of estrogen deprivation (Figure 2)[1,2].

Aromatase inhibitors are classified as first, second or third generation, and these have been the most used ones recently[2,8]. The third generation is represented by anastrozole and letrozole, nonsteroidal competitive inhibitors, and exemestane, a steroidal non-competitive inhibitor that is irreversibly bonded with aromatase.

Anastrozole is administered in a 1 mg dose per day, being capable of reducing body aromatization in 97%. Letrozole reduces the biosynthesis of estrogens in 99% with a 25 mg daily dose, and exemestane reduces it in 98% with a 25 mg daily dose[9]. The three drugs are related with a range of side effects that affect the quality of life of patients, often leading to therapy discontinuation.

Most frequent side effects

Musculoskeletal effects

As presented in Table 1, most articles mention musculoskeletal effects as the most prevalent ones, present in about one third to half of the patients. Due to the repercussion of these symptoms on their quality of life, they are the main cause of treatment discontinuation[5,10] and medication change to estrogen receptor selective modulators, especially tamoxifen. Low adherence to treatment is associated with higher mortality rates related to breast cancer and higher recurrence rates[5].

Among these effects, reduced bone mineral density, which has a direct relation with increased risk of fractures due to fragility, mortality and loss of functionality, arthralgia and development of rheumatic autoimmune diseases are emphasized in 12 articles[10]. Effects on bones, especially the trabecular bone, begin in the first six months of use, mainly affecting lumbar vertebrae and the hip[11]. Ostealgia and myalgia can be associated with loss

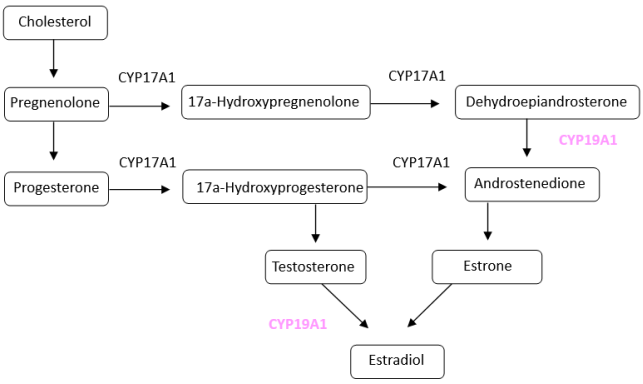


Figure 2. Estrogen metabolism[23].

in nociceptive estrogen modulation in the central nervous system and the increased process of bone resorption[12].

In physiological situations, estrogens modulate the balance between the activity of osteoblasts and osteoclasts, increasing the production of osteoprotegerin (OPG) and inhibiting the production of receptor activator of nuclear factor kappa B (RANKL) and of the macrophage colony-stimulating factor-1. Besides, estrogen inhibits the synthesis of pro-inflammatory cytokines by Th1 cells and monocytes, such as interleukin-1B, interleukin-6, interleukin-12, interferon gamma (IFN-y) and tumor necrosis factor alpha (TNF-a)[5], inducing the production of anti-inflammatory cytokines by Th2 cells, such as interleukin-2, interleukin-10, interleukin-4 and transforming growth factor beta (TGF-b)[10].

OPG prevents RANKL from bonding with the receptor of nuclear factor kappa B (RANK), resulting in the non-differentiation and activation of osteoclasts. This reduces bone resorption. Resorptive cytokines modulate the expression of these receptors, increasing their activity. Therefore, under the effect of estrogen deprivation caused by the use of aromatase inhibitors, the synthesis of these substances increases, as well as the dysregulation of Treg cell activity, and the production of anti-inflammatory cytokines and OPG decreases, with consequent increase of osteoclast activity[5,10].

The increased activity of osteoclasts causes higher bone resorption, leading to reduced bone mineral density and the development of osteopenia, osteoporosis and, consequently, fractures due to fragility. As brought up by 13.64% of the studies, increased bone resorption in some women may be associated with the existence of single nucleotide polymorphisms (SNPs), found in the genes that coordinate balance between the activity of osteoblasts and osteoclasts, as well as in estrogen receptors, vitamin-D receptor (VDR), RANK and OPG[10,13].

Three SNPs associated with higher risk of fractures were found in patients on aromatase inhibitors, in six genes regulated by estrogen action, CTSZ, SLMO2, ATP5E, TRAM2, TRAM14A, MAP4K4[5,10]. With the depletion of hormone levels, the genes are no longer inhibited and reduced bone mineral density is favored[5].

Arthralgia

Arthralgia affects about 74% of the patients and can range from mild to moderate, causing loss of functionality and impacting the patients' quality of life. Symptoms appear in the first six weeks of treatment, reaching is maximum at six months[5]. The most common ones are arthralgia, arthritis, morning stiffness, spondyloarthritis, sacroiliitis, carpal tunnel syndrome, trigger finger, tenosynovitis and reduced prehension strength. Figure 3 shows the main affected joints[1,12,14].

Risk factors for the development of arthralgia include hormone replacement therapy, chemotherapy with taxanes, obesity, vitamin D deficiency, arthralgia or previous osteoarthrosis,

perimenopause, joint and synovial fluid inflammation and previous use of tamoxifen[5,10]. For the diagnosis of arthralgia induced by aromatase inhibitors, it is necessary for patients to meet all of the major criteria, or at least three of the minor criteria[5], presented in Table 2.

Joint inflammation is related to the aromatase enzyme expression in synovial cells and chondrocytes of articular cartilage. Estrogen seems to have a chondroprotective effect, therefore, its deficiency has been reported with higher production of TNF-a, interleukin-6 and interleukin-1 in synovial fluid, causing pain and joint edema, besides causing damage to articular cartilage and degeneration of the subchondral bone[5,10].

Another estrogen action is to increase the activity of 1-α-hydroxylase enzyme, responsible for the hydroxylation of 5-hydroxy-cholecalciferol (calcidiol) to its active form, 1.25-dihydroxy-cholecalciferol (calcitriol). Therefore, according to Borrie and Kim, patients on aromatase inhibitors with musculoskeletal symptoms are more likely to have deficient baseline levels of vitamin D when compared to asymptomatic patients. Vitamin D levels are related to the intensity of arthralgia[1].

The activity of 1-α-hydroxylase enzyme, codified by CYP27B1, may be altered and result in reduced catalyzation of calcidiol to calcitriol due to the presence of two SNPs (rs4646536 and rs10877012) in the CYP27B1 gene[1]. Besides, the action of vitamin D on the body may be reduced by another SNP (rs1156882) found in the VDR gene, which codifies the calcitriol receptor, affecting its transcriptional activity and levels of gene expression[1].

Other SNPs were found in ESR1 (rs2234693 and rs9340799), in OPG (rs2073618), in VRD receptor, in CYP17A, in CYP19A1 and in gene HSD17B2, which codifies the enzyme that oxidizes oestradiol to estrone, which are associated with the onset of arthralgia 12 months after the beginning of treatment[10].

Main articulations affected by the use of aromatase inhibitors

- Sacroiliac;
- Talocrural;
- Radioulnar;
- Radiocarpal;
- Metacarpophalangeal;
- Distal interphalangeal;
- Proximal interphalangeal;
- Sternoclavicular joints;
- Metatarsophalangeal.

Figure 3. Main articulations affected by the use of aromatase inhibitors.[1,12,14]

Autoimmune rheumatic diseases

The main autoimmune diseases reported in three articles are rheumatoid arthritis, which is the most common, Sjögren's syndrome, systemic lupus erythematosus, fibromyalgia, antisynthetase syndrome and antiphospholipid syndrome[5,10]. These diseases are mostly related to the use of anastrozole and letrozole, and may manifest symptoms within three to six months. In the case of Sjögren's syndrome, observed by Tenti et al., there was reduction in arthralgia after exchanging letrozole for exemestane[10] after five years of treatment.

Nowadays, there are few studies about the pathogenesis of autoimmune diseases related to the use of aromatase inhibitors, but there is strong evidence that it is related with the effects of anastrozole in Th1/Th2 cellular balance, favoring the Th1 population (increase in interleukin-12 and IFN-y). Besides, the imbalance in the production of pro and anti-inflammatory cytokines and the inhibited differentiation of T *naive* to Treg cells[5,10], influenced by the low levels of estrogen, can also help to understand how these diseases are developed[15].

Vasomotor

Vasomotor effects, such as heat, redness and night sweats, are very common, reported in 36.4% of the included studies. They can be caused due to the activation of noradrenergic and serotonergic pathways in the central nervous system, resulting from the decreasing levels of estrogen[17]. This can cause anxiety, agitation, tachycardia, increased body temperature, sweating and chills[16]. Estrogen also modulates the thermoregulation center in the hypothalamus, which can change its activity when deficient[12].

Cardiovascular and lipid profile

According to Gonzaga et al., and Mouridsen, estrogen represents the main cardioprotective factor for women, responsible for increasing the synthesis of vasodilator enzymes and improving lipid profile. With the decrease of this hormone, there is an increase in serum levels of triglycerides, low-density lipoproteins (LDL), total cholesterol and apolipoprotein B (ApoB)[4,17,18].

Corroborating with a worsen lipid profile, there is reduction of high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1)[4,17,18]. Estrogen deficiency is also associated with increased sympathetic activity and reduced parasympathetic activity, which, added to a worse lipid profile, increases cardiovascular

Table 2. Definition of arthralgia induced by aromatase inhibitors according to Tenti et al.,[10].

Major criteria	Minor criteria
1. Using aromatase inhibitors; 2. Joint pain at the beginning or worsening since the beginning of therapy; 3. Improvement or resolution of joint pain two months after treatment discontinuation; 4. Joint pain reappears after returning to therapy.	1. Symmetrical joint pain; 2. Pain in fist and/or interphalangeal joints; 3. Carpal tunnel syndrome; 4. Reduced prehension strength; 5. Morning stiffness; 6. Improvement in joint discomfort with exercises.

risk. Therefore, there is increased risk of developing cardiovascular diseases, such as coronary disease, atrial fibrillation and systemic arterial hypertension[4].

Among aromatase inhibitors, exemestane was the only one without reports of effects on lipid profile; however, it was related to atrial fibrillation[10]. Meanwhile, anastrozole and letrozole were associated with venous thrombotic events, cerebral ischemia, heart failure, acute myocardial infarction and peripheral obstructive vascular disease[4,18].

Gynecological/urogenital

The gynecological effects related to the use of aromatase inhibitors work as an exacerbation of menopausal symptoms and repercuss on the relations with partners and female self-image[19]. Since estrogen acts by increasing lubrication in the vaginal canal and controls sexual behavior, especially in the follicular phase of the menstrual cycle, it is expected that its reduction leads to changes in desire and sexual performance[16,19].

Therefore, the main gynecological effects found in 41% of the articles include vaginal dryness, reduced libido, dyspareunia, vaginal pruritus, urogenital and vulvovaginal atrophy, metrorrhagia and mastalgia. Besides, reduced levels of estrogen increases the exposure to urinary tract infections (UTI), dysuria and polyuria[10,16,19].

Increased frequency of UTI happens because there is loss in the hormone protective action, which maintains a slightly acid pH in the vaginal canal. The bacteria that usually causes cystitis go up to the urethra of the periurethral region, vaginal introitus and perianal region[19].

Other side effects

Other side effects related with estrogen deficiency include retinal hemorrhage, hemiretinal artery occlusion, keratoconjunctivitis sicca, blurry vision, foreign body sensation, red eye, and photosensitivity. These effects are associated with the presence of estrogen receptors in the cornea, iris, crystalline, ciliary body, conjunctive, lacrimal and Meibomian glands[17,20].

The dry eye syndrome, or keratoconjunctivitis sicca, is the most common ophthalmologic effect and is prevalent among older women, resulting from the regulatory action of estrogens on lacrimal glands. When serum levels are low, they culminate in xerophthalmia with aqueous deficiency, rupture, apoptosis and necrosis of acinar cells[20]. Bicer et al. suggest that estrogen deprivation caused by the use of aromatase inhibitors can lead to the development of Sjögren's syndrome[20].

Due to the presence of estrogen receptors in areas of the central nervous system related to cognition, such as hippocampus, prefrontal cortex, amygdala and basal ganglia, the signs of difficulties in concentration and poor verbal memory can be explained by the reduced estrogen activity in these receptors. Estrogens also work in the promotion of neuroplasticity and regulation of learning and memory pathways, especially by the decreased synthesis of the n-methyl-d-aspartate receptor protein, involved in the glutamatergic activation of the hippocampus[3,9,21].

The evidence for mood swings are unusual. Patients may present with irritability, mild depression, suicidal ideas, anxiety, sadness and anger[22]. Users of these drugs can also have insomnia, fatigue, reduced daily activity, nausea, headache, weight gain, scleroderma, anorexia or more appetite, even though these effects are less frequent.

CONCLUSIONS

It was observed that decreased bone mineral density and arthralgia are the most reported effects by patients, followed by vasomotor and gynecological symptoms. Musculoskeletal effects are not only the most prevalent ones, but are also the main cause of treatment discontinuation, leading to the need to investigate its development during the years of therapy. The importance of handling the symptoms of these patients reflects on breast cancer mortality and recurrence rates, besides the relief and improvement in quality of life.

AUTHORS' CONTRIBUTION

GRZ: Conceptualization, Investigation, Methodology, Writing – review & editing. KAR: Conceptualization, Investigation, Methodology, Writing – review & editing. HC: Investigation, Methodology, Writing – review & editing. AISC: Conceptualization, Writing – review & editing.

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