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Acupuncture and Vitamin D for the Management of Aromatase Inhibitor-Induced Arthralgia

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Abstract

Purpose of Review Aromatase inhibitor-induced arthralgia (AIA) is a very common syndrome which significantly affects breast cancer survivors' quality of life, and it often leads to non-compliance with aromatase inhibitor (AI) therapy. However, the treatment of AIA remains a clinical challenge. Here, we will review the current data for acupuncture and vitamin D in the management of AIA.

Recent Findings Acupuncture has been shown to improve AIA symptoms, but it has not consistently been proven to offer significantly more clinical benefit than sham acupuncture. Similarly, while some vitamin D trials have shown benefit, the studies have not consistently shown improvement in AIA symptoms.

Summary Neither acupuncture nor vitamin D can be touted as standard treatments for AIA. However, many patients do experience subjective improvement of their symptoms with these therapies. When other treatments, such as exercise and duloxetine, are not feasible or not effective, it is reasonable to offer a trial of acupuncture or vitamin D to patients who are suffering from AIA, as the potential harms are very few, and they do offer possible relief from AIA symptoms.

Keywords Acupuncture · Vitamin D · Aromatase inhibitor · Breast cancer · Arthralgia · Quality of life · Breast cancer survivors

Introduction

Aromatase inhibitors (AIs) are the most effective adjuvant therapy for post-menopausal women with hormone receptor-positive breast cancer [1], presumably because of AI's ability to reduce estradiol levels to almost zero via inhibition of peripheral conversion of androgens to estrogen [2]. However, this very effective estrogen suppression comes at the cost of significant joint pain for more than half of women on adjuvant AI therapy [3]. This syndrome of symmetric arthralgia, principally in the small joints, is termed aromatase inhibitor-induced arthralgia, or AIA. This common phenomenon can also include symptoms such as carpal tunnel syndrome, trigger finger, myalgia, and decreased grip strength. The defining major and minor criteria for AIA, as we have previously proposed them, are listed in Table 1 [4•]. Many risk factors have been described for development of AIA, including obesity, previous use of hormone replacement therapy, and prior use of chemotherapy before AI initiation [4•, 5•, 6•].

AIA not only detrimentally affects quality of life [7, 8], it also results in higher rates of non-adherence to AI therapy. By the 5th year of adjuvant endocrine therapy, 30–70% of women are no longer adherent to their AI medication [9]. While there are many reasons for non-adherence to AIs, up to 30% of patients discontinue therapy due to AIA [3, 10]. Clearly, this is a significant problem which must be systematically and comprehensively studied, in order to better understand the etiology and appropriate treatment for AIA. In this paper, we will review the data regarding acupuncture and vitamin D as potential treatments for AIA.

Acupuncture for AIA

Acupuncture is an ancient traditional Chinese medicine technique which dates back more than 3000 years, in which fine needles are inserted into selected body parts (acupuncture points) [11]. Acupuncture has steadily gained more acceptance

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Table 1 Proposed definition of AIA [4•]

AIA syndrome: must meet all major criteria, and at least three minor criteria	
Major criteria	Currently taking AI
	Joint pain that developed and worsened since starting AI
	Joint pain improves or resolves within 2 weeks of stopping AI
	Joint pain returns upon resuming AI
Minor criteria	Symmetrical joint pains
	Pain in hands and/or wrists
	Carpal tunnel
	Decreased grip strength
	Morning stiffness
	Improvement in joint discomfort on use or exercise

and popularity in the USA, with more than 6% of Americans having used acupuncture at some point [12]. Acupuncture has been proven to reduce pain due to joint aches and arthritis [13]. In the past decade, there has been considerable interest in using acupuncture as a non-medicinal tool to reduce AIA. The mechanism of acupuncture is incompletely understood, but some theories postulate that it may reduce pain by decreasing inflammation in key points of the body [14]. Other theories suggest that acupuncture may cause increased circulating opioid peptides [15] or improve blood flow [16].

Randomized Controlled Trials Using Acupuncture for AIA

Crew et al. in 2010 conducted a single-institution randomized controlled trial (RCT) comparing true acupuncture against sham acupuncture in a cohort of stage I–III post-menopausal breast cancer patients taking aromatase inhibitors. In the study, 43 patients who identified themselves as having AIA were randomly assigned to receive true acupuncture vs. sham acupuncture twice weekly for 6 weeks. The primary endpoint of the study was the worst pain score on the Brief Pain Inventory-Short Form (BPI-SF) at 6 weeks. In the intervention group, acupuncture was given manually through standard acupuncture points, including an additional focus on the most painful joints. In the control arm, superficial needles were inserted in non-acupuncture points. Patients in the true acupuncture group reported lower BPI-SF score at 6 weeks (3 vs 5.5, $p < 0.001$). Additionally, other pain measures were also improved on the true acupuncture arm, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) pain scores. Physical well-being as measured by the FACT-G questionnaire was also significantly improved in the true acupuncture arm, as compared to the sham acupuncture arm [17].

Oh et al. from Australia performed a second RCT comparing true electro-acupuncture vs. sham electro-acupuncture (SEA). The study involved 32 patients on AI therapy who were randomized to receive either true or sham electro-acupuncture twice a week for 6 weeks. SEA was delivered using Streitberger needles which automatically retract on contact and do not penetrate the skin. The study did not show any difference between true and sham electro-acupuncture group in terms of joint pain on the WOMAC scale or overall pain on BPI-SF. Interestingly, there was no significant reduction in C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) levels in the true acupuncture arm either, suggesting that the acupuncture used in this trial may not have achieved reduction in systemic inflammation [18].

In a similar design, Bao et al. randomized 51 post-menopausal early-stage breast cancer patients with AIA to receive either true or sham acupuncture. In both arms, patients received acupuncture weekly for 8 weeks. Outcomes were measured using Health Assessment Questionnaire Disability Index (HAQ-DI) for functional ability, visual analog score (VAS) for pain, serum estradiol, serum beta-endorphin, and serum pro inflammatory cytokines. While both groups showed a significant reduction in HAQ-DI and VAS scores, there was no significant difference between the two groups, signifying that true acupuncture was not more effective than sham acupuncture. Inflammatory cytokines such as interferon-γ, IL-1, IL-6, IL-8, and IL-10 did not change with either true or sham acupuncture. However, the IL-17 level was significantly decreased from baseline in both groups [19], possibly indicating at least a partial reduction in inflammation in true and sham acupuncture.

In recognition of the fact that sham acupuncture could be imparting a placebo effect, the 2014 trial by Mao et al. randomized 67 patients to one of three arms: electro-acupuncture (EA), sham electro-acupuncture (SEA), or waitlist control. In the electro-acupuncture arm, group acupuncture was given twice weekly for 2 weeks followed by weekly for the next 6 weeks. The duration of treatment was the same in SEA arm using Streiberger needles on non-acupuncture points. The investigators and patients were blinded to the type of acupuncture that the patients were receiving; only the

acupuncturists knew whether each subject was receiving EA or SEA. Fifty-eight percent of patients in the EA arm believed they were getting EA, versus 28% in SEA group who believed they received EA. This difference was not statistically significant. The primary endpoint of this study was comparing Brief Pain Inventory (BPI) score between the electro-acupuncture and the waitlist group. Patients in the electro-acupuncture arm experienced significantly reduced pain as compared to the waitlist control group. Importantly, the difference in pain score was clinically significant (> 2 points difference), and it was sustained 4 weeks after the completion of acupuncture treatment. Interestingly, the SEA arm also experienced significantly improved pain compared to the waitlist group; however, the EA and SEA arms had no difference in pain improvement [20], similar to the Oh and Bao clinical trial results.

The largest randomized trial of acupuncture for AIA to date was conducted by Hershman et al. as a multicenter randomized control study involving 226 patients. Patients were randomized to one of three arms: true acupuncture, sham acupuncture, and waitlist group by 2:1:1 randomization. True acupuncture was delivered manually by a trained acupuncturist through standard acupuncture points plus most painful joint-specific points, while sham acupuncture was given using minimally invasive shallow needles using non-acupuncture points plus joint-specific and auricular points. Acupuncture in both the true and sham arms was delivered for a total of 12 weeks—twice weekly for 6 weeks, followed by once a week for 6 weeks. In the waitlist arm, no treatment was given for 24 weeks. The primary end-point of this study was change in BPI-WP (Brief Pain Inventory-Worst pain) score at the end of 6 weeks. From baseline, there was a decrease in pain in all three groups at 6 weeks; however, the decrease in the pain score was statistically significantly greater in the true acupuncture group as compared to each of the control groups. Although the results were statistically significant, they did not merit clinical significance. The pre-specified threshold for clinically meaningful reduction in pain was 2 points on the BPI-WP scale. However, at 6 weeks, the sham acupuncture group and the waitlist control had each reduced worst pain by roughly 1 point less than the true acupuncture. Furthermore, at 12 weeks, when comparing the true and sham acupuncture groups, there was no significant difference in pain interference or pain severity scores. Thus, true acupuncture was not proven to be clinically more beneficial than sham acupuncture or the wait list control group [21••]. Table 2 briefly summarizes the clinical trials examining acupuncture for the treatment of AIA.

Conclusion

There have been multiple randomized controlled studies investigating the benefit of acupuncture for AIA. Interpretation of these studies remains difficult due to small sample size, different scales used to measure outcomes, non-consistent results, and placebo effect. All of the trials, except for Crew et al. [17], showed that true acupuncture was not more effective than sham acupuncture. However, both true and sham acupuncture do result in clinically significant reduction in pain from AIA, indicating that there likely is a placebo and/or therapeutic effect from the act of needling. These confusing results, in combination with the unclear physiology behind acupuncture, indicate that there is value in acupuncture, but it may not be due to physiologic changes in the body. Rather, it could be due entirely to placebo effect.

This is not new information within the acupuncture field. Other trials have shown 25–55% placebo effect with SA [22–24]. In fact, many argue that sham acupuncture should not be used as a control group comparison because there may be some therapeutic effect from the tactile stimulation entailed in sham acupuncture. Regardless, one may argue that even if the AIA symptoms improve due to placebo effect, this is still clinically significant and meaningful for patients. The newer trials thus include a waitlist control group, which helps us to isolate the true combined effect of acupuncture, including both the potential placebo and therapeutic effects.

Furthermore, there are many practical barriers to the real-life utilization of acupuncture. Firstly, the durability of acupuncture benefit is an important issue. Many trials have not done extended follow-up to determine the longevity of response from a finite acupuncture treatment. In practice, we know that symptoms often recur many weeks after acupuncture is completed, frequently prompting additional "booster" treatments. Secondly, insurance does not typically cover the cost of acupuncture. Thus, in many locations, it may be difficult to find affordable acupuncture provided by reputed and licensed practitioners. Finally, it may be inconvenient or impractical for some patients to attend twice weekly acupuncture sessions for several weeks.

Vitamin D for AIA

Although the exact mechanism of AIA is unknown, several theories postulate that estrogen depletion, low levels of vitamin D, and increase in inflammatory cytokines may play an important role in the pathogenesis of AIA [4•]. It has been noted that AIA is very similar to the phenomenon of "arthritis of menopause," presumably because estradiol levels are very low in both states. Estradiol increases 1-alpha hydroxylase activity, which catalyzes conversion of 25(OH)D to its active form, $1,25(OH)_2D$ [25]. Estrogen also increases the activation of the vitamin D receptor [25]. Therefore, a low estrogen state could potentially decrease the amount of active vitamin D available, supported by the fact that 75–90% of women on AI therapy are vitamin D insufficient [26, 27]. Vitamin D

Table 2 Summary of randomized controlled trials using acupuncture for AIA

Year	Investigators	Intervention	# Patients	Treatment length	Outcome measure	Effective?
2010	Crew et al. [17]	True vs. sham acupuncture	43	Twice weekly for 6 weeks	BPI-SF, WOMAC, M-SACRAH, FACT-G	Yes
2012	Oh et al. [18]	Electroacupuncture (EA) vs. sham EA	32	Twice weekly for 6 weeks	WOMAC, BPI-SF, CRP	No
2013	Bao et al. [19]	True vs. sham acupuncture	51	Weekly for 8 weeks	HAQ-DI, VAS	No
2014	Mao et al. [20]	EA vs. sham EA vs. waitlist control	67	Twice weekly for 2 weeks, then weekly for 6 weeks	BPI, WOMAC, DASH, PPT	Yes, but SEA was equally effective as EA
2018	Hershman et al. [21••]	Acupuncture vs. sham acupuncture vs. waitlist control	226	Twice weekly for 6 weeks, then weekly for 6 weeks	BPI, WOMAC, M-SACRAH, PROMIS PI-SF, FACT-ES	Not clinically significant. All 3 arms resulted in pain reduction

deficiency, in turn, is known to cause a syndrome of muscle and joint aches which is very similar to AIA [28]. Furthermore, vitamin D is known to inhibit release of inflammatory cytokines IL-1, IL-6, and TNF-α from macrophages [29, 30]. Therefore, many researchers postulate that AIs cause extremely low estrogen levels, which lead to lower vitamin D and, thus, cause dis-inhibition of inflammatory cytokines, ultimately resulting in AIA.

Vitamin D deficiency is linked to non-specific musculoskeletal symptoms including pain, stiffness, and impaired muscle strength [31, 32]. This syndrome is very similar to the joint symptoms seen in aromatase inhibitor-induced arthralgia. Interestingly, the IBIS-II trial did confirm that 87% of post-menopausal women were vitamin D deficient (serum level < 30 ng/ml) at baseline. However, this low baseline vitamin D level did not predict for later development of AIA [33]. Thus, several randomized clinical trials have been conducted to clarify the question of whether vitamin D treatment may treat or prevent AIA.

Studies Exploring the Role of Vitamin D Supplementation for AIA

Khan et al. showed in a single-center study of 60 patients that vitamin D supplementation can decrease joint pain due to AIA. In the study, all women on adjuvant AI therapy were initially given 1200 mg/day of calcium and 600 IU/day of vitamin D supplementation. After 4 weeks, those patients with vitamin D < 40 ng/ml received 50,000 IU vitamin D3 supplementation each week for 12 weeks. Pain, as measured by the HAQ-II (Health Assessment Questionnaire-II), was found to be significantly improved in the patients who achieved a 25 hydroxy Vit D level > 66 ng/ml vs those with levels < 66 ng/ml ($p = 0.02$) [34]. Another prospective study involving 290 patients showed that vitamin D supplementation was not effective in preventing AIA, but those women who attained vitamin D level > 40 ng/ml had less joint pain than those women whose levels remained < 40 ng/ml at 3 months [35]. A double-blind RCT involving 60 patients investigating the role of high-dose vitamin D2 supplementation on AIA also showed some transient benefit. In this trial, patients with baseline vitamin D2 < 30 ng/ml were randomized into two treatment groups: vitamin D2 50,000 IU weekly, or placebo weekly, for 8–16 weeks (8 weeks if baseline 25 hydroxy vitamin D was 20–29 ng/ml, and 16 weeks if baseline 25 hydroxy vitamin D level was < 19 ng/ml), then monthly for 4 months. BPI-WP scores were lower in vitamin D2 supplementation arm as compared to placebo arm at 2 months ($p = 0.0045$), although these initial benefits were not maintained at 4 months and 6 months [36].

However, other prospective trials failed to show a benefit of vitamin D for AIA. For example, Shapiro et al. conducted a single-center phase III RCT comparing two different doses of vitamin D3 replacement (4000 IU/daily vs 600 IU/daily) for 6 months. In this trial, 113 patients were randomized onto one of these two arms for 6 months. They found no difference between the two groups in terms of AIA incidence, as measured by the BCPT-MS (breast cancer prevention trial symptom scale-musculoskeletal) [37].

The VITAL trial also sought to clarify the potential role of vitamin D in treating AIA. One hundred sixty patients with vitamin D level < 40 ng/ml starting letrozole were randomized to one of two arms: 30,000 IU/week vitamin D3 vs placebo. All patients received daily 1200 mg calcium and 600 IU vitamin D3 supplementation, as per IOM guidelines. The primary endpoint was aromatase inhibitor-associated musculoskeletal symptom (AIMSS) event, defined as worsening of joint pain using a categorical pain intensity scale (CPIS), disability from joint pain using HAQ-II questionnaire, or discontinuation of letrozole due to musculoskeletal symptoms. At 24 weeks, 51% of women on the placebo arm experienced an AIMSS event, as compared to 37% of those on the high-dose vitamin D arm. While this difference was not statistically significant, the authors do point out that there was a statistically significant

Table 3 Summary of randomized trials using vitamin D for AIA

Year	Investigators	Intervention	# Patients	Treatment length	Outcome measure	Effective?
2010	Khan et al. [34]	After initial daily 600 IU vitamin D for 4 weeks, patients with Vitamin D < 40 ng/ml were given vitamin D3 50,000 IU/weekly	60	16 weeks	HAQ-II	Yes, pain improved in patients with vitamin D level > 66 ng/ml
2011	Prieto-Alhambra et al. [35]	Vitamin D3 16,000 IU every other week and D3 800 IU/day	290	12 weeks	VAS	No
2011	Rastelli et al. [36]	50,000 IU Vitamin D2 weekly × 8–16 weeks, then monthly for 4 months	60	6 months	BPI-WP	Yes, but only effective at 2 months. No benefit at 4 and 6 months
2016	Shapiro et al. [37]	Vitamin D3 4000 IU/day vs 600 IU/day	113	6 months	BCPT-MS	No
2017	Khan et al. [38••]	Vitamin D3 30,000 IU/week vs placebo	160	24 weeks	CPIS, HAQ-II, or AI discontinuation	No. Post hoc analysis using BPI scale favored intervention arm
2018	Niravath et al. [39]	50,000 IU Vitamin D3 weekly × 12 weeks ➔ 2000 IU daily × 40 weeks vs. 800 IU daily	93	52 weeks	HAQ-II	No

improvement in the secondary endpoint of BPI score, in favor of the high-dose vitamin D arm [38••].

Another prospective trial of high-dose vitamin D3 (50,000 IU weekly for 12 weeks, followed by 2000 IU daily for 4 weeks) versus standard dose vitamin D3 (800 IU daily for 52 weeks) also showed no difference in development of AIA while on adjuvant AI therapy, despite a significant increase in vitamin D level on the high-dose arm. The trial was terminated early due to a planned futility analysis which showed no benefit of high-dose vitamin D supplementation, as evidenced by lack of difference in HAQ-II scores after enrollment of 93 patients [39]. A summary of the trials examining vitamin D for the treatment of AIA is presented in Table 3.

A retrospective analysis of the MA.27 study examined the roles of baseline vitamin D level, inflammatory cytokines, and vitamin D receptor polymorphism on risk of AIA. In MA.27, women were randomized to adjuvant exemastane versus anastrozole. Among the 7576 women enrolled on the trial, 72 patients with AIA were compared with 144 patients who did not develop AIA. Analysis revealed that neither elevated inflammatory cytokines nor low levels of vitamin D were associated with increased risk of AIA. However, women with the vitamin D receptor (VDR) Fok-1 variant genotype were more likely to have lower IL-1 beta levels and less likely to develop AIA (both statistically significant) [40]. This finding may help explain why some clinical trials have shown benefit from vitamin D and others have not. Host factors may have significant effects on metabolism and activity of vitamin D.

Clinically, we have noted that some patients have a clear and dramatic improvement in AIA symptoms with vitamin D supplementation. For example, in my own practice, I have a handful of patients who are exceptional responders, with disappearance of AIA symptoms after a 12-week course of high-dose vitamin D. After several months when vitamin D levels begin to drop again, many of them again respond to another course of vitamin D. Yet, other patients notice no change in their AIA symptoms with vitamin D replacement. These differences may be due to host factors such as vitamin D receptor genetic polymorphisms.

Conclusion

Vitamin D deficiency is common among breast cancer survivors. However, evidence from RCTs do not consistently favor high-dose vitamin D supplementation for prevention or treatment of AIA. Standard dose vitamin D supplementation should be continued in every postmenopausal breast cancer patient to maintain calcium homeostasis, as patients on AI are already at high risk for osteoporosis and fractures [41, 42]. However, while there may be a subset of women who are more susceptible to vitamin D treatment, vitamin D cannot be routinely recommended as treatment for AIA at this point.

Discussion

Randomized controlled trials using acupuncture and vitamin D have been somewhat conflicting in their results. Trials in both of these arenas have been limited by varying trial designs, lack of universal method for quantifying AIA pain, and small numbers. Future clinical studies for AIA are needed to study impact of host factors on personalized risk of AIA.

While the evidence for acupuncture and vitamin D are not yet definitive, there is strong evidence for the benefits of aerobic exercise and duloxetine in treating AIA. In the HOPE study, 121 breast cancer patients with AIA were assigned to exercise (150 min per week of aerobic exercise and supervised strength training twice a week) or usual care. At 12 months, patients assigned to the aerobic exercise group reported 1.6 points decrease in worst pain on BPI scale compared to 0.2 point increase in usual care group [43]. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, was found to be superior to placebo in decreasing AIA pain in a randomized controlled trial. Within 2 weeks of starting duloxetine, more than half of patients reported a significant improvement in joint pain and stiffness, and over two thirds of the patients enjoyed this improvement after 6 weeks of duloxetine. However, it should be noted that the improvement over placebo was rather modest, with the duloxetine-treated patients having an average of only 0.86 point improvement on the BPI scale [44].

Switching from one AI to another is also another strategy. In a multicenter study of patients who had discontinued anastrozole due to musculoskeletal symptoms, letrozole was started after a 1-month washout period. At the end of 6 months, 70% of the patients remained on AI therapy; additionally, there was 19% lower mean BPI pain scores compared to baseline when patients were on the new AI [45].

Our approach to AIA in clinical practice incorporates all of this data. For mild arthralgia, we recommend exercise and weight loss. We also often switch AIs as an early attempt at AIA treatment. Additionally, vitamin D should be replaced if the patient is deficient, and regular exercise should be strongly encouraged for all patients. For patients who are refractory to these methods, we often recommend a trial of acupuncture. For more severe AIA in patients who are willing to take an additional medication, we may start duloxetine. For moderate-severe arthralgia, we sometimes use a brief course of NSAIDs or short duration corticosteroids. Finally, if the patient is still having significant arthralgia despite these treatments, we may switch to Tamoxifen.

The study of aromatase inhibitor-induced arthralgia is complicated by many factors, including lack of an accepted measurement tool to quantify AIA, and significant placebo effect seen with many interventions. As illustrated above, most of the acupuncture trials showed a significant placebo effect with sham acupuncture. Similarly, trials with omega-3 fatty acid [46] and duloxetine [44] have also shown significant placebo effect. As the field continues to grow, we advocate for more rational analyses, aimed at understanding the etiology of AIA. Currently, we have several trials which compare one intervention to another, with very little understanding of the true target. Also, we encourage clinical validation of a single tool for the accurate measurement of AIA, which can be used across clinical trials for more reliable quantitation of this somewhat nebulous syndrome.

Compliance with Ethical Standards

Conflict of Interest Kartik Anand and Polly Niravath declare they have no conflict of interest.

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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- •• Of major importance

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