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Resistance Training as a Candidate Intervention for Aromatase Inhibitor Adherence in Postmenopausal Breast Cancer Survivors: A Narrative Review of Musculoskeletal Outcomes and Adherence Pathway

Katarzyna Aleksandrowicz

Medical University of Lodz: Lodz, Łódź Voivodeship, PL

ORCID: https://orcid.org/0009-0008-5935-8265

E-mail: katarzyna.aleksandrowicz@stud.umed.lodz.pl

Aleksandra Woźniak

Norbert Barlicki University Clinical Hospital No. 1 in Łódź, Stefan Kopcinski 22 Street, 90-153: Łódź, Poland

ORCID: https://orcid.org/0009-0003-5382-1451

E-mail: aleksandra.wozniak465@gmail.com

Matylda Król

Copernicus Memorial Hospital, Pabianicka ST. 62, 93-513 Lodz, Poland

ORCID: https://orcid.org/0009-0000-7759-4933

E-mail: matylda.krol@gmail.com

Mateusz Meszka

Central Teaching Hospital of Medical University of Lodz, Pomorska 251, 92-213 Łódź

ORCID: https://orcid.org/0009-0001-6147-7000

E-mail: mateusz.meszka@stud.umed.lodz.pl

Anna Mamach

Norbert Barlicki University Clinical Hospital No. 1 in Łódź, Stefan Kopciński 22 Street, 90-153: Łódź, Poland

ORCID: https://orcid.org/0009-0004-5934-8674

E-mail: annamamach@gmail.com

Aleksandra Straszewska

Central Teaching Hospital of Medical University of Lodz, Pomorska 251, 92-213 Łódź, Poland

ORCID: https://orcid.org/0009-0003-6293-9689

E-mail: o.straszewska10@gmail.com

Patrycja Sobantka

Central Teaching Hospital of Medical University of Lodz, Poland

ORCID: https://orcid.org/0009-0004-3128-5181

E-mail: patsob84@gmail.com

Oliwia Grygorczuk

Military Institute of Medicine - National Research Institute, Szaserów 128, 04-141, Warsaw, Poland

ORCID: https://orcid.org/0000-0003-3089-4546

E-mail: oliwia.grygorczuk@outlook.com

Zofia Grodzka

Independent Public Health Care Complex named after Marshal Józef Piłsudski in Płońsk (SPZZOZ): Płońsk, PL

ORCID: https://orcid.org/0009-0002-0904-810X

E-mail: zosiagrodzka99@gmail.com

Szymon Mokrzecki

Norbert Barlicki University Clinical Hospital No. 1 in Łódź, Stefan Kopcinski 22 Street, 90-153: Łódź, Poland

ORCID: https://orcid.org/0009-0005-8228-2711

E-mail: szymon.mokrzecki@gmail.com

Karolina Brzezińska

Medical University of Lodz: Lodz, Łódź Voivodeship, PL

ORCID: https://orcid.org/0009-0008-4403-6060

E-mail: karola.brzezinska@gmail.com

Corresponding Author

Katarzyna Aleksandrowicz, katarzyna.aleksandrowicz@stud.umed.lodz.pl

Abstract

The use of adjuvant aromatase inhibitor (AI) therapy decreases recurrence in postmenopausal hormone receptor-positive breast cancer. Survival benefit depends on patients' compliance to the prescribed course. Up to 85.9% of women report AI-induced musculoskeletal symptoms (AIMSS). In the CANTO cohort AIMSS independently predicted noncompliance (aOR 2.35, 95% CI 1.51–3.64). This narrative review analysed evidence on resistance training (RT) in postmenopausal AI-treated survivors putting an emphasis on the patients' compliance to proposed treatment.Two cohorts meeting strict inclusion criteria - the HOPE trial and the de Paulo group - together with two boundary cohorts, converge directionally. RT alleviate AIMSS severity, improves body composition, improves quality of life, and is safe to apply to everyday life. In HOPE resistance training combined with aerobic training reduced the worst experienced pain by a 1.8 point (95% CI 0.9–2.6; $p<0.001$), exceeding the minimal difference which is

important clinically. Cochrane GRADE rates the overall evidence as very low. Proposed mechanisms remain biologically plausible but untested in AI-treated survivors.No completed trial has used AI compliance as a primary outcome. The REJOIN trial is yet to be pending. We propose a hypothesis-generating operational prescription - three sessions per week with progressive loading at 55-75% one-repetition maximum, impact components, supervised delivery, minimum nine months - as a target for confirmatory trials with adherence as the primary endpoint.

Keywords: aromatase inhibitors; resistance training; breast cancer survivors; musculoskeletal pain; medication adherence; bone density; quality of life

1. Introduction

1.1 Breast cancer epidemiology and adjuvant aromatase inhibitor therapy

Breast cancer is one of the most frequently diagnosed malignancy in women. Moreover it is one of the leading causes of mortality related to cancer in European women. Over 75% cases present the expression of estrogen receptors (ER) and/or progesterone receptors (PR). That means that the dominant clinical phenotype is the hormone receptor-positive breast cancer Aromatase inhibitors such as anastrozole, letrozole and exemestane are the standard adjuvant treatment for postmenopausal women in the early stage of the hormone receptor-positive disease.Large randomised trials including ATAC and BIG 1-98 showed that five years of adjuvant AI therapy reduce the risk of the recurrence and breast cancer related mortality compared with the use of tamoxifen in postmenopausal patients. The current guidelines recommend extending the AI treatment up to 10 years in patients with higher risk of recurrence. The survival benefit depends on the sustained exposure to the prescribed treatment.The

difference between prescribed and received therapy has direct consequences for the stated outcome - a distinction that becomes clinically critical when treatment tolerance is poor.

1.2 AIMSS — pathophysiology and prevalence

The main problem with complying with AI therapy is inhibitor–induced musculoskeletal syndrome (AIMSS). AIMSS includes arthralgia, morning joint stiffness, myalgia - in minority of the cases carpal tunnel syndrome has been reported. Its pathophysiology results directly from the mechanism of AI treatment. Estrogen deficiency escalates pro-inflammatory signalling - in particular IL-6 and TNF-α - in synovial tissue what drives the chondrocyte inflammation. That accelerates the loss of skeletal muscle by withdrawing anabolic support from the IGF-1/mTOR axis. The molecular consequences of this phenomenon are examined in Section 5.2. Symptoms typically show between two to six months after the start of the AI therapy. Estimated frequency of the symptom appearance is about 50%, though they may vary depending on the study design: Beckwée et al. (2017), in a systematic review of 21 studies enrolling 13,177 women, reported this figure [1], with Gupta et al. (2020) confirming it in a management-focused overview [2]; Hyder et al. (2021) provide the mechanistic account of the inflammatory and musculoskeletal pathways through which estrogen deficiency generates the syndrome [3]. Symptoms range from manageable to sufficiently severe to determine whether therapy continues - a threshold will be examined in the next section.

1.3 AIMSS as a barrier to the patients ’compliance and clinical cost

The clinical importance of AIMSS goes beyond the severity of symptoms. It leads to the question whether prescribed treatment is properly completed. Hershman et al. (2010), in a cohort of 8,769 women with stage I–III ER-positive breast cancer, found that 32% of patients discontinued the AI therapy by 4.5 years. They reported that only 49% completed the full prescribed treatment with a medication possession ratio ≥80%. The women who stopped the treatment stated the adverse event (musculoskeletal symptoms) were the main reason of their decision. These numbers predate the systematic collection of outcomes reported by patients that prospective registry cohorts now permit. The CANTO cohort, enrolling 4,854 postmenopausal AI-treated survivors across 26 French centres, found that up to 85.9% of patients reported AIMSS at least once over six years of longitudinal follow-up- a higher proportion than in earlier cross-sectional estimates, what is caused by continuous symptom reporting rather than a single

point measurement. Among women with AIMSS, non-adherence reached 18.1% versus 6.8% in asymptomatic women (adjusted odds ratio 2.35, 95% CI 1.51–3.64), and permanent discontinuation was recorded in 14.1% versus 3.4% [5]. Physical therapy -the most utilized structured non-pharmacological intervention - was used by 42.2% of affected women at year four, far exceeding the 1.4% who received pharmacological analgesia - indicating that non-pharmacological management is the preferred clinical response even when the evidence base for it remains limited. Observational associations between AI adherence and overall survival carry a recognised confound - women who adhere to medication tend to adopt other health-protective behaviours - and the relationship between adherence and outcome is partially attributable to unmeasured factors, discussed in Section 5.6. Nonetheless, the mechanistic rationale for ensuring adequate AI exposure is established by randomised trial data. AIMSS is the primary modifiable barrier to that exposure. Interventions that reduce AIMSS may therefore support adherence, and the search for such interventions defines the question that is adressed by this review.

1.4 Exercise as a non-pharmacological countermeasure: state of the evidence

Clinical guidelines from ACSM, ASCO, NCCN, and ESMO recommend resistance training for breast cancer patients due to cardiovascular, metabolic and functional benefits. None of these guidelines consider the type of the hormonal therapy prescribed. The Roberts et al. (2020) Cochrane review of exercise interventions for joint pain in AI treated patients showed that given evidence is not sufficient, driven by substantial heterogeneity and GRADE very low certainty; as examined in Section 5.1, this diverges from the directional signal recoverable in AI-specific enrollments.

A small number of independent study programs enrolling AI-treated postmenopausal women have reported consistent effects of resistance-inclusive training on pain and musculoskeletal outcomes, constituting a hypothesis-generating body of evidence rather than a definitive one. Henry et al. (2021), in a systematic review of predictors of pain reduction across AIMSS interventions, suggest that physical exercise may be a potential factor for the pain reduction which could modify the effect of treatment [6]. There is no published review yet that would give the explanation on the biological level of resistance-specific effect in a framework that maps exercise-induced adaptations onto AI-induced pathophysiology, or connects the

musculoskeletal outcomes those programs report to the compliance problem those symptoms underlie.

1.5 The gap and aim of this review

There are three specific absences that motivate this synthesis. First - there is no already existing review integrating molecular pathways through which resistance training may alleviate musculoskeletal disruptions caused by AI therapy - this issue is analysed further in Section 5.2. Secondly there is lack of a review that would directly connect resistance training with the discontinuation of treatment by the patients whose decision was conditioned on the pain that was experienced - the analysis is provided in Section 5.3. Third, no clinical guidance offers an AI-tailored resistance training prescription differentiated by endocrine therapy subtype for the symptom phenotype and bone-risk profile of these survivors, the practical question addressed in Sections 5.4 and 5.5. The REJOIN trial, the only registered randomised controlled trial directly testing resistance training as a potential support for AI adherence, has not yet published outcomes [7], establishing that this gap remains active and clinically relevant.

This narrative review concludes the available evidence for the resistance training in postmenopausal women treated with AI. It encapsulates biological mechanisms that connect the resistance training effect with the use of AI and suggests practical guidelines as a hypothesis-generating foundation for future trials.

2. Methods

2.1 Search strategy and study identification

We searched PubMed (NCBI Entrez) on 16–18 May 2026 using four Boolean queries combining MeSH-aligned synonyms with free-text terms, ranging from a broad Population × Intervention filter to narrower configurations restricted by outcome domain, publication type, and adherence-specific terms. We additionally screened reference lists of two landmark sources—the HOPE trial (Irwin et al., 2015) and the Cochrane review (Roberts et al., 2020)-for additional eligible studies. The search was limited to English-language publications. Embase, CINAHL, and SPORTDiscus were not searched, reflecting the narrative rather than systematic scope of this review; this is acknowledged as a limitation. No protocol was registered with PROSPERO.

2.2 Eligibility criteria

We included randomised controlled trials (RCTs), systematic reviews (SRs), meta-analyses (MAs), and network meta-analyses (NMAs). Eligible populations represented postmenopausal women with early-stage (stage I–III) hormone receptor-positive breast cancer receiving adjuvant aromatase inhibitor therapy (anastrozole, letrozole, or exemestane) after completion of chemotherapy and/or radiotherapy. Resistance training (RT) was defined according to ACSM Roundtable criteria (Campbell et al., 2019): ≥2 sessions per week, ≥60% one-repetition maximum or equivalent intensity, ≥8 weeks duration. Programs in which RT was the dominant component of a combined (RT plus aerobic) intervention were also eligible.All studies meeting these criteria lasted over 36 weeks in practice.

Two studies fell at the boundary of these criteria and are reported separately: Garcia-Unciti et al. (2023) delivered one dedicated RT session per week with one impact-aerobic session [8], below the ≥2 RT sessions per week threshold; and Winters-Stone et al. (2011) enrolled a mixed-hormone-therapy cohort with a planned moderator analysis of AI use [9]. These boundary cohorts contribute to body composition and bone outcomes respectively, but are not counted among the strict-criteria evidence base.

We excluded programs based solely on stretching or yoga without progressive overload, premenopausal women, mixed hormonal therapy cohorts without a distinct aromatase inhibitor subgroup analysis, and studies conducted during active chemotherapy or radiotherapy.

2.3 Synthesis framework

Studies were individually weighted according to hierarchy of evidence based on three levels: systematic reviews, meta-analyses, and network meta-analyses including Cochrane reviews (tier S); randomized controlled trials with n > 100 (tier A); randomized controlled trials with n ≤ 100 (tier B); observational studies and narrative reviews (tier C). We organised the evidence in accordance with adherence pathway model, in which resistance training reduces aromatase inhibitor-induced musculoskeletal syndrome (AIMSS) and thereby supports medication adherence. We did not perform formal mediation analysis. The reduction of AIMSS is treated as proposed mechanism rather than a statistically verified mediator. We present this adherence-pathway framework as a hypothesis-generating model to guide future trials.

3. Results: Resistance Training and Aromatase Inhibitor-Induced Musculoskeletal Symptoms

3.1 Evidence from the HOPE trial (landmark RCT)

The Health Outcomes and Physical Exercise (HOPE) trial is the largest RCT that evaluates the effect of physical exercise on experiencing pain in women especially with AIMSS [10]. The trial enrolled 121 postmenopausal BC survivors receiving AI therapy for at least six months with clinically relevant joint pain (BPI worst pain ≥3) and randomized them to 52 weeks of combined training -150 min/week of aerobic exercise plus twice-weekly supervised progressive resistance - or usual care.

The intensity of the worst pain experienced assessed with the use of the Brief Pain Inventory (BPI) was decreased by 1.6 points (29%) in the exercise arm versus an increase of 0.2 points (3%) in controls, what gave a between-group treatment effect of 1.8 points (95% CI 0.9–2.6, $p<0.001$) [10] - the value that exceeds the conventional minimal clinically significant difference of 1 point for BPI worst pain experienced. Secondary musculoskeletal measures were following the same direction: WOMAC total improved by 9.9 points (95% CI 2.8–16.9, $p<0.001$) and upper-extremity function (DASH) by 8.0 points (95% CI 3.1–12.9, $p=0.002$). No exercise-related adverse events occurred. Four women - two per arm - discontinued AI therapy, and 12-month AI adherence rates were similar (80% vs. 76%).

A secondary analysis conducted by Arem et al. (2016) found that attendance at supervised sessions were a significant prediction of the magnitude of pain reduction, what confirms the significance of dose-response matters when applying the protocol to clinical settings [11].

3.2 Systematic reviews and meta-analyses

Two independent meta-analysis reached divergent conclusions regarding combined effect of physical exercise on AIMSS. This divergence is methodologically informative.

Lu et al. (2020) researched 9 RCTs (n=743) selected specifically for AI-induced musculoskeletal symptoms [12]. Exercise was associated with significant reductions in pain (SMD -0.46, 95% CI -0.79 to -0.13, $p=0.006$; $I^2=63\%$) and stiffness (SMD -0.40, 95% CI -0.71 to -0.08, $p=0.01$; $I^2=0\%$), and an increase in grip strength (SMD +0.43, 95% CI 0.16 to 0.71, $p=0.002$; $I^2=0\%$). The pain SMD falls in the medium-effect range by conventional thresholds.

Heterogeneity among the studies was significant for the pain, however it was absent for stiffness and grip strength.

The Cochrane review by Roberts et al. (2020) applied broader criteria: 7 RCTs (n=400) with mixed exercise modalities and populations not uniformly selected for baseline AIMSS [13]. In the analysis which pooled four pain-reporting studies (n=284) the effect on pain levels was slighter and statistically insignificant (SMD -0.23, 95% CI -0.78 to 0.32; GRADE: very low certainty). The smaller effect reflects heterogeneity of applied exercises or lach of population selection, what diminishes the signal that Lu's AI-specific design preserved. Both reviews reported no adverse events.

3.3 Network meta-analytic positioning

Bae et al. (2023) conducted the only network meta-analysis comparing pharmacological and non-pharmacological interventions for AIMSS, synthesizing 17 RCTs (n=1,516) across 10 distinct interventions [14]. Exercise ranked 4th among 10 for pain reduction — behind acupuncture (1st), sham acupuncture (2nd), and multicomponent herbal medicine (3rd), but ahead of duloxetine, vitamin D, and omega-3 fatty acids. Certain herbal substances performed worse below the control groups. Raptopoulos & Constantinou (2020), reviewing 10 overlapping studies narratively, reach the same practical conclusion: exercise is feasible, safe, and consistently associated with AIMSS reduction [15]. Taken together, the NMA data position exercise as a competitive non-pharmacological option - most appropriately as part of multimodal management, not a replacement for established pharmacotherapies.

3.4 Additional RCT evidence (Winters-Stone 2011)

Winters-Stone et al. (2011) randomized 106 postmenopausal BC survivors (≥50 years) to 52 weeks of combined resistance and impact training (POWIR) or flexibility training (FLEX) [9]. The studied sample was not AI specific. 43-43% of women were prescribed AI and 13-17% were using Selective Estrogen Receptor Modulators (SERMs), the rest of the women were not using hormonal therapy. AIMSS was not a primary outcome. Group assigned to exercise consisting of resistance and impact training produced greater lean mass gain in women treated by AI in comparison to non-AI POWIR participants (hormone therapy × group × time interaction p=0.01). The positive effect of POWIR on spine bone mineral density (BMD) was noted comparing to FLEX group (+0.41% vs. -2.27% in FLEX, p<0.01) - a signal

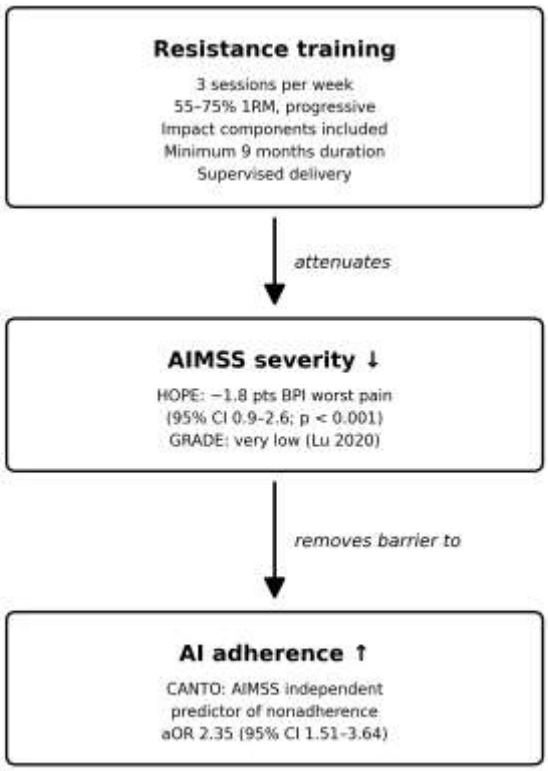

Figure 1. Hypothesised adherence pathway linking resistance training to aromatase inhibitor adherence in postmenopausal breast cancer survivors. Solid arrows indicate directional associations supported by the cited studies. GRADE certainty for the resistance training → AIMSS link is rated very low (Lu 2020). Sustained AI adherence is associated with improved breast cancer outcomes in the broader adherence literature; the pathway-level link from resistance training to recurrence reduction has not been tested with adherence as a primary outcome, and the REJOIN trial is designed to address this gap.

discussed further in Section 4.4. Both findings come from post-hoc subgroup results in a trial in which women were prescribed different hormonal treatments. That leads us to consider these findings as hypothesis-generating rather than AI-specific evidence.

4. Results: Secondary outcomes

4.1 Quality of life

The secondary analysis of QoL in HOPE trial was conducted by Baglia et al. (2019) and it goes beyond the pain findings of Section 3.1 and includes the endocrine symptoms and fatigue [16]. On the FACT-B endocrine subscale (FACT-B-ES) the results were improved by 15.6 point in an exercise group compared to 3.7 point in a control group (between-group difference 11.9,

95% CI 5.3–18.5, p<0.001). The fatigue assessed with the use of FACIT-Fatigue scale was reduced by 5.7 point in the in the intervention group, whereas the reduction in control group was by 0.5 point (between-group difference 5.2, 95% CI 2.5–8.0, p<0.001). Similar direction was noted when assessing SF-36 subscores of physical functioning and pain with SF-36 questionnaire, what is consistent with BPI data in Section 3.1. The concordance across four instruments - BPI, FACT-B-ES, FACIT-Fatigue, SF-36 - argues against a scale-specific artefact and speaks for a consistent multi-domain effect. The QoL improvement tracks the magnitude and timeline of pain reduction. It rather speaks for symptom relief than an independent exercise effect on mood or energy metabolism.

Paulo et al. (2019) followed 36 postmenopausal AI-treated BC survivors through nine months of combined resistance and aerobic training and assessed QoL with SF-36 and EORTC QLQ-C30 [17]. Significant time-by-group interactions emerged for SF-36 bodily pain (Cohen's d 2.76, p<0.001), physical functioning (d 1.32, p=0.008), and vitality (d 1.52, p<0.001), and for EORTC pain (d 1.47, p=0.001) and fatigue (d 1.96, p<0.001). Emotional and mental health domains did not reach group-by-time significance.The effect-size profile - weighted toward physical and pain outcomes rather than emotional functioning - is consistent with HOPE and suggests that the QoL benefit is anchored in musculoskeletal symptom relief.

The alignment between pain reduction (Section 3.1) and multi-domain QoL improvement across both trials points to a symptom-linked pattern: when AIMSS diminishes, quality of life improves.

4.2 Body composition

Hypoestrogenism induced by the AI treatment accelerates lean mass loss and promotes visceral fat redistribution. This metabolic shift tends to aggravate AIMSS severity, impairs functional capacity and elevates cardiometabolic risk. Body composition is therefore a clinically meaningful secondary outcome with implications beyond symptom management.

Body composition was analysed by Thomas et al. (2017) in the HOPE trial. The between-group difference in lean mass at 52 weeks was significant (p=0.03): exercise arm +0.32 kg (95% CI -0.43 to 1.07), control -0.88 kg (95% CI -1.7 to -0.07). The exercise-arm CI includes zero - the within-group gain was not individually significant, but the contrast against the control-arm loss was. Body fat percentage fell by 1.4 percentage points in exercisers (95% CI -2.5 to -0.25)

versus an increase of 0.48 percentage points in controls (95% CI -0.74 to 1.71; between-group p=0.03) [18]. In a population where the use of AI therapy tends to lead to muscle mass loss, holding lean mass stable is clinically significant - the kilogram values understate the clinical context.

Garcia-Unciti et al. (2023) used Magnetic Resonance Imaging (MRI) to analyse body composition - method more sensitive than DXA for visceral and subcutaneous fat differentiation - and reported a significant reduction in visceral adipose tissue (−7.9 vs +7.8 cm^2, p=0.036) and in body weight (−1.2 vs +0.7 kg, p=0.033) over a 52-week program in postmenopausal BC survivors. Subcutaneous adipose tissue did not reach between-group significance (p=0.188) [8]. A crucial caveat is the program combined the resistance training with impact-aerobic component, therefore we cannot unequivocally state whether RT was a dominant contributor to the body composition changes.

Despite of the different imaging modalities, different program structures, and different follow-up lengths in HOPE and Garcia-Unciti both research are compatible with the direction of their findings. RT decreases unfavourable body composition changes induced by AI use. The magnitude of effects in HOPE - the difference of 1.2 kilograms of lean mass difference and 1.9 percentage point fat difference are moderate yet consistent with expected anabolic and lypolitic effect of progressive resistance training.

4.3 Muscular function

The results concerning muscle function in this literature are scattered across studies and instruments. It prevent us from pooled quantification, however the direction of the outcomes regarding lower-limb functional measures, upper-body strength trajectories, and combined-program data is consistent

Grip strength is considered as a validated marker of general muscular function in oncological patients. It significantly improved in exercise group in HOPE trial after 6 month (between-group difference -0.7 psi, 95% CI -1.4 to -0.1, p=0.03), however the effect diminished to being considered as non-significant after 12 months (-0.3 psi, 95% CI -1.1 to 0.5, p=0.47) [10]. Regarding the combined character of aerobic-resistance HOPE protocol we cannot state whether the improvement was linked to RT alone. Nevertheless upper-extremity loading in RT protocol is the most probable factor affecting the results. Gradual reduction of the effect

between 6 and 12 months may suggest dose-response or adherence-related fading worth examining in future trials.

De Paulo et al. examined adaptation course of RT in BC survivors in comparison to healthy postmenopausal women sample. They found that meaningful upper-body strength gains in the BC group emerged only at nine months - three months later than in healthy controls [19]. Baseline upper-body strength was 22% lower in BC survivors than in healthy controls (19.5 kg vs 25.0 kg), what may be a result from combined effect of previous chemotherapy treatment, AI related musculoskeletal toxicity and physical deconditioning that BC survivors must overcome before training response materialises.Trials using 8–12-week primary endpoints may therefore systematically underestimate strength benefit if upper-body function is the target outcome.

In the Garcia-Unciti cohort, body composition changes occurred despite of the lack of significant between-group difference in thigh muscle mass (p=0.121) [8]. Combined character of the protocol and the absence of individual strength outcomes make it unfeasible to certainly determine an influence of a specific intervention.

No adequately significant trial has been conducted yet to state whether an improvement of strength and functional capacity in women treated with AI reduce fall rates or fracture incidents. Given the cumulative skeletal and neuromuscular risks in this population, this gap is clinically relevant.

4.4 Bone mineral density - tertiary context

AI therapy decrease the oestrogen levels to the concentrations that are near to be undetectable. It eliminates the prime factor which takes part in remaining the osteoblast-osteoclast balance. It leads to bone loss rates of 1–3% per year in the early treatment years. In the HOPE trial, Thomas et al. (2017) demonstrated no significant difference between the groups in terms of total body BMD at 52 weeks (p=0.37) [18]. The trial did not measure the lumbar spine BMD specifically. The result is consistent with the physiological mechanisms: progressive resistance training without ground-reaction impact loading components (jumping, skipping) may have not been sufficient to stimulate osteogenesis in cortical and trabecular bone.

Winters-Stone et al. (2011) randomized BC survivors to 52 weeks of resistance plus impact training versus flexibility training and found spine BMD maintained in the impact arm versus significant loss in controls (+0.41% vs. -2.27%, $p<0.01$) [9]. The sample was not specific regarding to hormonal therapy prescribed (42–43% AI, 13–17% SERM). The BMD effect did not significantly differ from the treatment used, what means that the finding can be generalised to the cohort yet it is not specific to AI itself. Comparing with the HOPE result, raises the question whether impact loading is the possible mechanistic differentiator between programs that preserve bone and programs that do not.

The question of the greatest clinical significance - whether long term programs combining RT with impact loading components prevent fragility fractures in AI treated BC survivors remains unexamined. These constraints inform the prescription rationale in Sections 5.4 and 5.5.

5. Discussion

5.1 Synthesis of evidence: resistance training is effective and safe

The analysed evidence follow a consistent direction despite of substantial variety of used protocols. Two study programs meeting strict inclusion criteria - the HOPE trial [10, 11, 16, 18] and the de Paulo group [17, 19] -found resistance-inclusive exercise associated with reductions in AIMSS severity, improvements in body composition (lean mass preservation in HOPE and de Paulo), and improvements in health-related quality of life. A third cohort, Garcia-Unciti et al. [8], falls at the lower boundary of inclusion criteria (one RT session per week paired with one impact-aerobic session) but adds directionally consistent body composition data, including visceral fat loss. In the HOPE trial, the largest and most methodologically rigorous of these programs (n=121, 52 weeks, AI-specific enrollment), worst pain in the exercise arm fell by 1.6 BPI points whereas the usual-care arm worsened by 0.2 points, yielding a 1.8-point between-group treatment effect (95% CI 0.9–2.6, $p<0.001$) [10] that exceeds the conventional minimal clinically important difference of 1 point. No exercise-related adverse events occurred in any of the reviewed trials. The de Paulo group found no withdrawals attributable to the training protocol over nine months - all dropouts (17% in the BC arm) were attributed to personal reasons [19]; program adherence reached 83% in BC survivors versus 96% in healthy controls, a gap consistent with treatment-related barriers rather than exercise intolerance.

The network meta-analytic evidence of Bae et al. (2023) ranks exercise fourth among ten competing interventions for AIMSS [14], what is coherent with clinically relevant yet not dominant effect. Winters-Stone et al. (2011) add a hypothesis-generating signal of greater training-induced lean mass gain in AI users compared with non-AI users in the resistance+impact arm (interaction p=0.01) [9], though the mixed-HT sample limits direct extrapolation.

Against this directional consistency, the Cochrane review by Roberts et al. (2020) returned a pooled pain effect that was smaller (SMD −0.23, 95% CI −0.78 to 0.32) and non-significant, with GRADE very low certainty [13]. This divergence from the AI-specific meta-analysis of Lu et al. (SMD −0.46, p=0.006) [12] reflects methodological differences rather than factual contradiction: Roberts pooled trials with heterogeneous exercise types and populations not selected for baseline AIMSS, attenuating the signal that AI-specific enrollment criteria preserve. The uncertainty quantified by the Cochrane review is genuine and should inform future trial design; it does not negate the convergent direction observed across the AI-specific evidence reviewed here.

5.2 Mechanistic pathways linking resistance training to AIMSS attenuation

Aromatase inhibitors decrease estrogen levels to nearly undetectable, engaging four pathways which are responsible for clinical syndrome of AIMSS [3]. Estrogen normally suppresses osteoclastogenesis in bone by reducing RANKL expression and upregulating its decoy receptor OPG. Its deficiency tilts the balance towards resorption and it accelerates the bone mineral density loss. In joints, the decrease of estrogen disinhibits production of IL-6 and IL-1 in articular chondrocytes what promotes arthralgia in AIMSS. In skeletal muscle estrogen promote anabolic signalling through the use of IGF-1 and further mTOR activation. Its suppression contributes to accelerated muscle loss in women treated by AI.

Resistance training exert an effect that is counteracting along each axis. Despite the evidence coming from experimental models and general exercise physiology - in AI treated women these pathways remain biologically plausible, yet they have not been directly confirmed. Mechanical loading activates osteocyte mechanostat signaling that favors OPG over RANKL, what directly opposes the molecular ratio that AI treatment disrupts - though this pathway is documented mostly in preclinical models and healthy postmenopausal women rather than AI-treated BC

survivors specifically. At the molecular level RT activates IGF-1 and the mTOR pathway, what provides anabolic stimulus against the low estrogen concentration. The HOPE trial body composition data (lean mass +0.32 vs −0.88 kg, between-group p=0.03; exercise-arm 95% CI -0.43 to 1.07) [18] and de Paulo findings (+0.4 kg at nine months) [19] are coherent with discussed mechanism. Chronic RT may also reduce the general systemic inflammation intensity. It may lower TNF-α and shift the cytokine profile toward anti-inflammatory, what could partially reduce arthritis despite the direct evidence in AI-treated cohorts being absent.

Hyder et al. (2021) describe the pathophysiology of AIMSS and note, separately, that exercise is beneficial to musculoskeletal system [3]. That review does not offer mechanistic integration: the molecular overlap between AI-induced pathway disruption and RT-induced pathway recovery. That integration is what the present synthesis provides, and its translational implication - that resistance training may address AIMSS through pathways pharmacological analgesia does not - is developed further in Section 5.3.

5.3 Resistance training as a candidate intervention within an adherence framework

In a 2010 analysis of 8,769 women, Hershman et al. found that approximately one-third of AI-treated postmenopausal women decided to discontinue treatment by 4.5 years. Among the patients who remained, 28% were considered non-compliant to the prescription (medication possession ratio <80%) and only 49% completed full five years with adequate adherence [4]. Among the women who discontinued the treatment, 84% of them pointed the adverse effects as the major reason for their decision - the musculoskeletal symptoms were the dominant complaint [4]. Incomplete drug exposure reduces the survival benefit.

The CANTO cohort quantifies this link prospectively. Across 26 French centres, 4,854 postmenopausal AI-treated survivors were followed for six years. 85.9% of them reported AIMSS at some point [5] - a higher proportion than cross-sectional estimates, likely reflecting active longitudinal ascertainment. Non-adherence reached 18.1% in women with AIMSS versus 6.8% in those without (aOR 2.35, 95% CI 1.51–3.64); permanent discontinuation was 14.1% versus 3.4% [5]. The severity gradient is steep. G3 AIMSS carried 6.36-fold adjusted odds of non-adherence (95% CI 3.48–11.65), against 3.28-fold for G1–2 [5]. Physical therapy uptake (42.2% at year four) - the most utilized structured non-pharmacological intervention -

far exceeded pharmacological analgesia (1.4%), indicating a clinical preference for non-pharmacological management that the evidence base has not yet matched [5].

If AIMSS is considered as the dominant factor affecting the compliance of AI use, interventions which are likely to reduce the symptoms may become candidates for supporting adherence.The level of pain reduction described in Section 5.1 - from the two strict-criteria cohorts, meeting the minimal clinically important threshold - suggests a biologically plausible chain (Figure 1): RT reduces AIMSS; AIMSS is a quantified driver of AI discontinuation; RT may therefore support continued treatment [10]. This chain constitutes a mechanistic hypothesis, not a statistical mediation. Two qualifications bound it. Whether a 1.8-point between-group BPI treatment effect crosses the threshold required to modify a treatment discontinuation decision - a higher bar than the symptomatic minimal clinically important difference - remains untested. Even complete AIMSS resolution would not ensure adherence, as practical, socioeconomic, and psychological barriers contribute independently. No published trial has enrolled RT with AI adherence as the primary outcome.

The HOPE trial itself measured AI adherence as a secondary outcome and reported similar 12-month adherence rates (80% versus 76%) [10]. This null finding does not refute the proposed chain. Adherence was not a primary endpoint and the trial was not powered to detect adherence effects; with only four discontinuations across both arms - two per group - the event count precluded meaningful inference. Twelve months is also a short window relative to the trajectory of AI discontinuation, which peaks between years two and four. The HOPE adherence result is therefore best read as uninformative for the central hypothesis rather than as evidence against it; only a trial designed and powered for adherence - such as REJOIN - can deliver a falsifiable test.

The REJOIN trial is designed to test this hypothesis directly [7]. Pending those results, the existing literature on non-pharmacological adherence interventions in this population is limited. A 36-month randomized trial of twice-weekly text-message reminders did not improve AI adherence (3-year adherence failure 81.9% vs 85.6%; HR 0.89, 95% CI 0.76–1.05, p=0.18) [20]; the trial authors concluded that improving long-term adherence will likely require more personalized and sustained behavioral interventions. Separately, a randomized trial of acupuncture targeting AI-related joint pain reported a 1.08-point reduction in BPI worst-pain at 52 weeks versus sham (p=0.01) [21], showing that the symptomatic driver of non-adherence is

itself modifiable by non-pharmacological means - though this trial did not measure AI adherence as an outcome. Taken together, these results suggest that the candidate intervention space for supporting AI adherence may be more profitably directed at strategies that act on AIMSS directly - the rationale for examining RT in this role. RT is not the only candidate - acupuncture ranked first in the Bae et al. (2023) NMA [14] - but uniquely combines AIMSS management with lean mass preservation and bone protection, addressing the broader AI-induced pathophysiology. Interpretation of observational adherence–OS associations is further constrained by healthy adherer bias, addressed in Section 5.6.

5.4 Comparison with existing guidelines

Four independent guidelines address exercise in cancer survivorship, and each endorses resistance training at comparable intensity. ACSM (Campbell et al., 2019) [22] recommends 2–3 sessions per week at 60–75% 1RM for cancer survivors, identifying arthralgia and fatigue as exercise-sensitive outcomes. ASCO (Ligibel et al., 2022) [23] extends this endorsement to patients on active oncological treatment, without differentiating endocrine therapy as a subgroup warranting modified prescription. NCCN (Sanft et al., 2025) [24] maintains the 2–3×/week recommendation and acknowledges AIMSS as a recognized treatment toxicity, yet specifies no modified protocol for AI-treated women. ESMO (Coleman et al., 2020) [25] addresses AI-induced bone loss and mentions exercise as a preventive component, but assigns primary management to bisphosphonates and denosumab and provides no resistance training dose. The prescription language across all four derives from general cancer survivorship evidence, not from AI-specific trials.

None of the four documents differentiates resistance training prescription by adjuvant endocrine therapy subtype. The general survivorship parameters they encode were not derived from AI-specific populations and do not address the AIMSS symptom profile, the accelerated bone loss AI use superimposes on postmenopausal decline, or the upper-extremity trainability trajectory identified in the evidence reviewed in Sections 5.1–5.2. This structural absence mirrors the evidence-level divergence described in Sections 5.1–5.3: the contrast between the Roberts et al. (2020) Cochrane estimate [13] and the AI-specific meta-analytic signal has not propagated into guideline text, which by design draws on the most cautious interpretation of heterogeneous pooled data.

The result is a practical gap. Clinicians treating postmenopausal AI-treated survivors can consult four authoritative sources and find resistance training endorsed in general terms, but none provides an operationally distinct protocol for the symptom phenotype and bone risk profile of this population — the question addressed in Section 5.5.

5.5 Proposed operational prescription for AI-treated postmenopausal survivors

CANTO data reveal a steep severity gradient (univariate, unadjusted): women with G3 AIMSS adhered to physical activity recommendations only 42.9% of the time, versus 61.2% for G1 [5]. Generic exercise advice falls shortest for those who suffer most. In real-world practice, clinicians most often switch the AI (19.7%) or refer to physical therapy (42.2%); pharmacological options remain largely unused (duloxetine 1.4%) [5]. Pending confirmatory evidence, a supervised, AI-specific resistance protocol could fill the space between generic activity guidance and unstructured physical therapy referral - the guideline gap identified in Section 5.4 has practical consequences.

Synthesizing controlled evidence from the strict-criteria cohorts, with corroborating signals from the boundary studies, we propose the following empirically supported starting point, subject to individualization and direct validation. Frequency of three sessions per week is derived from the de Paulo protocols [17, 19]; cumulative resistance load across months - not individual session intensity - drove the pain and quality-of-life response observed at nine months [17]. The HOPE trial achieved comparable AIMSS reduction with twice-weekly supervised resistance combined with three weekly aerobic sessions [10], so the parameter should be interpreted as a minimum cumulative dose rather than a strict session count. The Garcia-Unciti trial, which delivered only one RT session per week, observed body composition changes without significant muscle mass gain; the authors themselves concluded that at least two RT sessions per week are required to elicit muscle mass improvements [8], a lower bound consistent with the prescription proposed here. Intensity progresses from 55% to 75% of one-repetition maximum, the systematic ramp the de Paulo group applied across nine months [19] and the tested loading trajectory for this population. Each session incorporates impact loading alongside resistance work when bone outcomes are targeted; the Winters-Stone POWIR program preserved spine BMD with combined resistance and impact training [9], whereas the HOPE program of resistance plus aerobic exercise without ground-reaction impact produced no BMD effect [18] - implicating impact loading as the active component for bone. Minimum

program duration is nine to twelve months for AIMSS outcomes - the interval across which the HOPE (52 weeks) and de Paulo (nine months) programs demonstrated consistent benefit - and twelve months when bone endpoints are included.

Supervised delivery appears preferable on compliance grounds, though the supporting evidence is indirect. Westphal et al. (2018) enrolled fifty AI-treated survivors in a trial whose primary outcome was aerobic power output, not AIMSS or resistance-specific measures, which limits direct application [26]; the compliance differential is nonetheless informative: supervised participants accumulated 28.5 versus 18.3 metabolic-equivalent-hours per week ($p=0.043$), a gap that persisted into the subsequent autonomous phase.

Upper-body progression may be delayed relative to healthy comparators; the de Paulo cohort found statistically significant upper-extremity strength gains only from month nine, and initial loads in this region should reflect that trajectory [19]. Monitoring should cover AIMSS severity, functional trajectory, and bone mineral density at twelve months, with cardiovascular risk screening and post-surgical upper-limb assessment as prerequisites. This prescription constitutes an empirically supported starting point that requires direct testing with AI adherence as a primary outcome.

5.6 Limitations of evidence and review

Several limitations qualify the conclusions drawn above. The evidence base for resistance training in AI-treated survivors comprises two independent study programs meeting strict inclusion criteria [10, 19] and two boundary cohorts: Garcia-Unciti et al. [8], delivering one dedicated RT session per week alongside one impact-aerobic session (below the ≥2 RT/week threshold), and Winters-Stone et al. [9], enrolling a mixed-hormone-therapy cohort with a planned moderator analysis of AI use. Protocol heterogeneity across these programs is substantial enough that the Cochrane pooling returned very low GRADE certainty [13], and the bone signal in particular is weak for resistance training alone - the HOPE trial found no significant change in total body BMD ($p=0.37$) [18] and did not assess lumbar spine BMD, and Winters-Stone et al. showed that impact loading appears necessary for skeletal benefit [9]. No reviewed trial followed participants beyond twelve months, leaving fracture prevention untested. The de Paulo cohort enrolled women without active musculoskeletal symptoms in some analyses [19], so trainability and safety estimates may not represent survivors with the full AIMSS phenotype.

The causal chain linking resistance training to AI adherence is indirect at every link. No published trial has enrolled RT with AI adherence as its primary outcome; REJOIN [7] is designed to fill this gap but remains pending. The mechanistic pathways described in Section 5.2 are biologically plausible in experimental models, but no study has tested them directly in BC survivors receiving AI therapy. The observational associations between adherence and overall survival carry a structural confound: women who adhere to AI therapy tend also to adhere to other health-protective behaviors, and the adherence–survival relationship is therefore partially confounded by unmeasured behavioral and socioeconomic factors. A parallel selection effect operates at the intervention level: women who enrol in and complete supervised RT programs are likely more functional at baseline, more adherent to other health behaviours, and more motivated - the HOPE 80% versus 76% AI adherence difference may partly reflect this rather than the exercise effect itself. Lapidari's grade-stratified analysis was unadjusted (cell size precluded multivariable modelling); the severity gradient cited in Section 5.5 should therefore be interpreted as descriptive rather than confirmatory.

This synthesis carries the methodological limits of a narrative review. We restricted the literature search to PubMed, excluding Embase, CINAHL, and SPORTDiscus, with attendant risk of publication and language bias. The reviewed trials are geographically concentrated in the United States, Brazil, and Spain [8, 9, 10, 19], limiting generalizability to Central and Eastern European populations relevant to the Quality in Sport readership. We completed no PROSPERO registration and applied no formal risk-of-bias assessment.

6. Conclusion

Two cohorts meeting strict inclusion criteria - the HOPE trial and the de Paulo group - together with two boundary cohorts (Garcia-Unciti et al., delivering one RT session per week below the ≥2/week threshold; Winters-Stone et al., a mixed-hormone-therapy cohort) consistently point in the same direction: structured resistance training reduces AIMSS severity, improves body composition, and improves disease-specific quality of life in postmenopausal breast cancer survivors receiving aromatase inhibitors. This convergence across heterogeneous programmes and populations is a signal worth acting on. Cochrane-rated very low certainty of evidence, however, precludes definitive conclusions.

On the basis of this convergent signal, we synthesise a candidate operational prescription: a minimum of three resistance-training sessions per week, progressing from 55% to 75% of one-repetition maximum, sustained for at least nine months to address AIMSS and at least twelve months to confer meaningful skeletal protection, with impact loading added for bone benefit and supervised delivery preferred where feasible. We further propose that the RT→reduced AIMSS→preserved AI adherence chain constitutes a biologically plausible and clinically tractable hypothesis - not a demonstrated causal pathway. Until randomised evidence with adherence as an outcome exists, RT is a candidate intervention, not a guideline-ready adherence strategy.

Direct testing requires a multicentre randomised controlled trial enrolling AI-treated survivors with AIMSS at baseline, with AI adherence at 24 or 36 months as a co-primary outcome alongside AIMSS severity. The REJOIN trial, currently pending, is designed to address part of this gap; larger trials with adherence as a co-primary outcome are still needed. Translation into Central and Eastern European oncological practice - of direct relevance to the Quality in Sport readership - additionally requires adapted clinical guidelines specifying AI-concordant exercise protocols and physiotherapy infrastructure capable of supervised delivery.

Disclosure

Author's Contributions

Conceptualization: Katarzyna Aleksandrowicz, Oliwia Grygorczuk, Matylda Król

Check: Aleksandra Woźniak, Matylda Król, Aleksandra Straszewska, Karolina Brzezińska

Methodology: Aleksandra Woźniak, Patrycja Sobantka, Zofia Grodzka, Karolina Brzezińska

Formal Analysis: Katarzyna Aleksandrowicz, Patrycja Sobantka, Zofia Grodzka, Szymon Mokrzycki

Investigation: Szymon Mokrzecki, Mateusz Meszka, Anna Mamach

Resources: Aleksandra Straszewska, Mateusz Meszka, Anna Mamach

Data curation: Patrycja Sobantka, Aleksandra Straszewska, Anna Mamach

Writing - original draft preparation: Katarzyna Aleksandrowicz, Matylda Król, Mateusz Meszka

Writing - review and editing: Aleksandra Woźniak, Oliwia Grygorczuk, Szymon Mokrzecki, Karolina Brzezińska

Supervision: Katarzyna Aleksandrowicz, Oliwia Grygorczuk, Zofia Grodzka

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The author declares no conflicts of interest.

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In preparing this work, the authors used Claude (Anthropic) for the purpose of research workflow organisation, systematic search support, English-language editing, text formatting, verification of cited values. After using this tool the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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