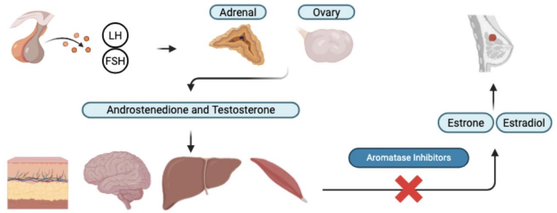
Scoping Review of Biologic and Imaging Markers Associated with Aromatase Inhibitor-Related Musculoskeletal Symptoms

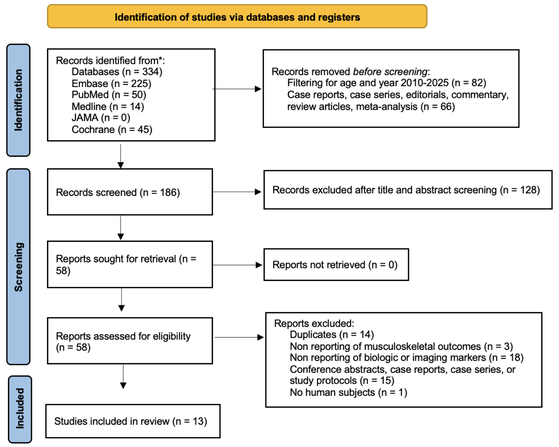
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INTRODUCTION

- Joint pain from aromatase inhibitors is frequently cited as the leading cause of premature discontinuation
- Approximately 50% of patients will report new onset or worsening joint pain 1 year after therapy initiation
- Approximately 30% of patients discontinue therapy after 1 year
- Only 50%–68% of patients remain fully compliant with therapy after 3 years



METHODS



RESULTS

The following Medical Subject Heading terms were used: 'breast cancer' and 'aromatase inhibitor' and 'arthralgia' and ('biomarker' or 'biological marker' or 'inflammatory marker' or 'imaging' or 'radiology'). Articles published between January 1, 2010, and January 1, 2025, were considered.

Study/Year	Country	Patients (n)	Age	Biomarker	Type
Martinez 2023	US	30	66	Biologic	Proteomic Lipidomic
Taheri 2025	US	20	59	Biologic	Proteomic Lipidomic
Jing 2025	China	60	49	Biologic	Proteomic Lipidomic
Bauml 2015	US	203	60	Biologic	Inflammatory Markers
Laroche 2014	France	135	61	Biologic	Inflammatory Markers Genetic
Lintermans 2016	Belgium	254	63	Biologic	Genetic
Romero 2020	US	1049	63	Biologic	Genetic
Borrie 2020	Canada	196	65	Biologic	Genetic
Robidoux 2011	US	30	67	Biologic Imaging	Inflammatory Markers Genetic Ultrasound
Shanmugam 2012	US	48	61	Biologic Imaging	Inflammatory Markers Radiograph Ultrasound
Henry 2010	US	29	61	Imaging	Ultrasound
Martinez 2022	US	16	64	Imaging	Ultrasound
Lintermans 2011	Belgium	33	64	Imaging	MRI

Table 1 showing thirteen included studies in scoping review with year, country, number of patients, age, biomarker category, and type

RESULTS

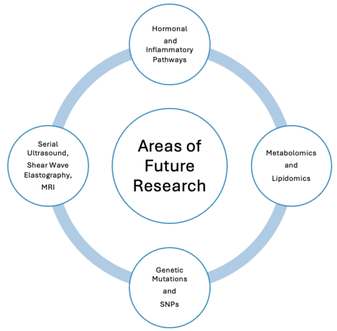
All studies focused on postmenopausal women receiving aromatase inhibitors for early-stage hormone receptor-positive breast cancer. Across studies, participants were female, with most aged between 50 and 67 years. The categories of markers studied included biologic (n=8), genetic (n=6), and imaging-based (n=5), with some studies focusing on multiple modalities.

Biomarker Categories	Findings Associated with Worse AIMSS	Findings Associated with Better AIMSS
Laboratory and Inflammatory Markers	- Elevated IGF1 - Elevated CRP, eotaxin, VDBP, and MCP 1 associated with moderate to severe arthralgia - Vitamin D higher in pain-increase group - High BMI associated with development of arthralgia	- Elevated BMI associated with lower risk of early treatment discontinuation. Low and high BMI was a predictor for AI-induced loss of grip strength - High dose Vitamin D associated with decrease in AIMSS - CRP <5 associated with remaining free of pain - Type 1 collagen higher in no pain exacerbation group
Proteomic Lipidomic	- Impaired hepatic OATP1B transporters (which regulate concentrations of AI in plasma) - Lower estradiol - Lower sex-binding protein associated with pain development	- Higher levels of CYP450 metabolites of DHA (epoxydocasapentaenoic acids) negatively correlated with arm pain
Genetic Polymorphisms	- SNP HSD17B2 associated with higher odds of AIMSS (gene in estrogen pathway) - 8-HETE, which is an activator of PPARa, which regulates aromatase expression - rs2073618 in OPG associated with worsening of AIMSS - SNP CYP19A1 associated with discontinuation due to arthralgia - ESR1 (codes estrogen receptor alpha)	None of the studies found genetic polymorphisms associated with improved AIMSS symptoms
Imaging	- Increased shear wave velocity and stiffness at baseline - Tenosynovium thickening and increased intra-articular fluid on MRI	- Patients with absence of tendon sheath abnormalities prior to starting AI, were less likely to develop AIMSS

Table 2 showing biomarker categories and examples of each category, including key findings from scoping review within each category

CONCLUSION

- This scoping review evaluated **thirteen studies** involving biologic and imaging markers associated with aromatase inhibitor-related musculoskeletal symptoms (AIMSS) in women with early-stage breast cancer
- The most promising signals include **biologic** markers like 8-HETE, novel **genetic** variants such as HSD17B2, and **imaging** modalities like shear wave elastography, which may allow for early identification of patients at risk.
- Many used **subjective or inconsistent criteria** to define musculoskeletal symptoms, and several were small, single-center studies with limited power, especially in genetic analyses with low allele frequencies.
- Most studies either **lacked racial and ethnic diversity, or did not report on it,** despite biologic and genetic factors likely varying across populations.
- The **timing** of biomarker and imaging assessments was inconsistent, with some studies evaluating patients long after symptom onset, potentially missing early changes.
- Future research should focus on **forming standard definitions** of AIMSS, incorporating **diverse** populations, and **long-term** study designs to validate and integrate these possible biomarkers.



ACKNOWLEDGEMENTS

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References

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