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The Role of the Gut Microbiome in Aromatase Inhibitor-Associated Musculoskeletal Symptoms: Diet as a Potential Moderator

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Introduction

- Aromatase inhibitors (AIs) are the gold standard treatment for breast cancer survivors (BCS), reducing cancer recurrence risk.
- Nearly half of women prescribed AIs have difficulty tolerating side effects, particularly AI-associated musculoskeletal symptoms (AIMSS) that manifest as joint pain, stiffness, myalgia, and bone pain.
- The mechanisms underlying AIMSS remain unclear, and no reliable treatments are available to reduce pain and improve daily functioning.
- This study aims to examine key gut microbiome patterns associated with AIMSS and identify lifestyle differences (e.g., physical activity and diet) between BCS with low and high pain levels.

Methods

- In this cross-sectional, observational study design, BCS who had been on AIs for at least three months were recruited through the UConn Health Cancer Center and social media (e.g., Facebook) between June 2022 and July 2024.
- Data on musculoskeletal symptoms and lifestyle were collected using reliable self-reported questionnaires. Gut microbiome (GM) was characterized through fecal 16S rRNA sequencing.
- Participants were dichotomized based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score using K-means clustering and the 3rd quartile.
- α- and β-diversity indices measured GM diversity, and Emu model was used to profile taxa associated with AIMSS, adjusting for age.

This study was supported by the UConn SoN faculty seed grant and the InCHIP faculty seed grant.

Results

Table 1. ***Demographic and Clinical Characteristics of the Sample***

Variable	Overall (n = 50)	Low Pain Group (n = 38)	High Pain Group (n = 12)	*p*-value
Age	61.78 (9.66)	63.29 (9.34)	57.00 (9.47)	.042
Race				.277
Black/AA	3 (6%)	1 (2.63%)	2 (16.7%)	
White	47 (94%)	37 (97.4%)	10 (83.3%)	
Education				.396
High School or below	4 (8%)	2 (5%)	2 (17%)	
Bachelor's degree	11 (22%)	8 (21%)	3 (25%)	
Advanced degree	35 (70%)	28 (74%)	7 (58%)	
Income				.603
< $50,000	8 (16%)	6 (16%)	2(17%)	
$50,000 - $100,000	17 (34%)	13 (34%)	4 (33%)	
> $100,000	23 (46%)	18 (47%)	5 (42%)	
Unknown	2 (4%)	1 (3%)	1 (8%)	
AI type				.666
Anastrozole	35 (70%)	25 (66%)	10 (83.3%)	
Exemestane	6 (12%)	5 (13%)	1 (8.33%)	
Letrozole	7 (14%)	6 (16%)	1 (8.33%)	
Unknown	2 (4%)	2 (5%)	0 (0%)	
Tumor stage				.921
DCIS (stage 0)	1 (2%)	1 (3%)	0 (0%)	
Stage I	25 (50%)	18 (47%)	7 (58%)	
Stage II	18 (36%)	14 (37%)	4 (33%)	
Stage III	5 (10%)	4 (10%)	1 (9%)	
Unknown	1 (2%)	1 (3%)	0 (0%)	
Treatment period (month)	27.96 (22.13)	29.46 (24.29)	23.33 (13.28)	.762

Table 2. ***Pain and Lifestyle Profiles of the Sample***

Variable	Overall (n = 50)	Low Pain Group (n = 38)	High Pain Group (n = 12)	*p*-value
Pain (WOMAC total score)	21.3 (17.4)	13.5 (8.8)	45.9 (14.6)	< .001
Perceived stress (PSS)	13.3 (7.5)	11.1 (5.9)	20.3 (7.9)	< .001
Health-promoting Lifestyle (HPLPII)	3.0 (0.5)	3.1 (0.5)	2.7 (0.5)	. 022
Physical activity METs (GPAQ)	3090.7 (3572.9)	3274.1 (3822.7)	2510.0 (2688.4)	.570
Healthy Eating Index (HEI) total score (DHQII)	70.0 (8.3)	72.0 (7.5)	63.7 (7.7)	< .001
Seafood and plant protein	4.75 (0.7)	4.89 (0.32)	4.30 (1.24)	.030
Fatty acids limit	5.9 (3.2)	6.6 (3.1)	3.7 (2.9)	< .001
Healthy unsaturated fats	5.9 (2.9)	6.5 (2.6)	3.9 (2.4)	.01

Figure 1. Gut Bacterial Richness, Dissimilarity and Abundance

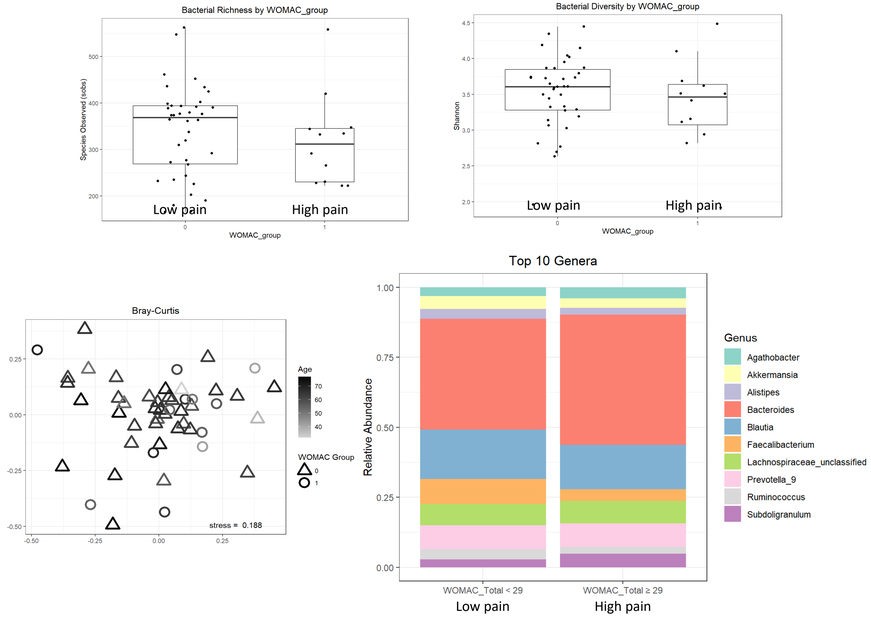

Table 3. Gut Microbial Taxa Significantly Associated with WOMAC scores

Genus	Estimate	Std. Error	Size	*p*-value
Christensenellaceae_R-7_group	-1.37327	0.657648	5084	0.014
Hungatella	1.847447	0.396039	3074	0.022
Clostridia_UCG-014_ge	-4.66678	0.40024	1933	0.027
Faecalibacterium	-2.61736	0.770205	7892	0.028
Lachnospiraceae_ND3007_group	-0.98148	0.504885	11960	0.030
Gastranaerophilales_ge	4.64504	0.424115	1660	0.034

Discussion

- GM composition is linked to AIMSS and may serve as a potential biomarker, and the symptom could be targeted through dietary manipulation. Larger prospective studies are needed to assess how AIs impact GM over time and its relationship with AIMSS.