Original Study

Longer Times of Receipt of Adjuvant Endocrine Therapy Correspond to Improved Functional Capacity and Lower Adiposity in Women Receiving Adjuvant Therapy

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Abstract

This clinical research studied functional capacity level, length of time of receipt of therapy with aromatase inhibitors (AIs), and adiposity parameters. Women with breast cancer in the first years of the use of AIs showed greater functional disability and worse adiposity parameters, thus reinforcing the need for special attention during this time and emphasizing the importance of multiprofessional follow-up.

Purpose: To study the use of functional capacity (FC) level and duration of aromatase inhibitor (AI) therapy with adiposity parameters in women with breast cancer. **Patients and Methods:** FC was evaluated through the Health Assessment Questionnaire, which was assessed by classification and divided into 3 groups: G1 = mild to moderate difficulty, G2 = moderate to severe disability, and G3 = severe or very severe disability. Body mass, height, and waist circumference (WC) were measured, and body mass index (BMI) was calculated. Bioelectrical impedance analysis was used to calculate body fat (BF) and fat-free mass. The women were divided into 2 time groups (T1 and T2), which were determined by the median months of AI use (T1 $\leq$ 29.5 and T2 $>$ 29.5 months). **Results:** Impaired FC and adiposity parameters were significantly positively correlated. In addition, physical exercise was significantly lower in women assessed as G2 and G3 compared to those assessed as G1. The effect of FC on BMI, BF, and WC was also verified, as was the effect of the duration of AI receipt on BMI and BF. Women at T1 had significantly greater functional disability, BMI, and BF values. In addition, although not statistically significant, women in T1 who were assessed as G3 presented higher BMI, WC, and BF values than those in T2. **Conclusion:** Adiposity above the recommended parameters and impaired FC were associated with the shortest time of receipt of adjuvant endocrine therapy with AI.

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Introduction

Breast cancer (BC) is the second most common type of cancer in women worldwide and is the leading cause of cancer death in women.[1] Endocrine treatment with aromatase inhibitors (AI) has been recommended and widely used in postmenopausal women expressing estrogen and/or progesterone endocrine receptors,[2] thus substantially prolonging disease-free intervals and survival outcomes.[3]

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BC treatment involves adverse events, such as vasomotor symptoms, cognitive problems, and worsening quality of life.[4,5] Additionally, receipt of AI therapy results in adverse events, including musculoskeletal symptoms[4,6] such as arthralgia and myalgia.[7] These events interfere with the level of physical activity,[8] and inactivity may be a consequence of impaired functional capacity (FC),[9] eventually leading to limitations in the ability to execute simple daily activities.[10]

In addition to being an independent factor for developing distant metastases and death,[11] obesity may affect physical functions in BC survivors.[12] Because it is common for women to gain weight after being diagnosed with BC, especially after chemotherapy,[13,14] the impact of body composition on FC for different duration of AI receipts is of interest, given the importance of its adverse effects and adherence to long-term endocrine treatment.[3]

On this basis, we hypothesized that longer duration of AI receipts in women are positively correlated with adiposity parameters and impaired FC. Thus, this study aimed to associate the FC level and duration of AI receipt with adiposity parameters in women with BC.

Patients and Methods

Ethical Aspects

A cross-sectional study was conducted in the oncology division of the Hospital de Clínicas da Universidade Federal de Uberlândia, Minas Gerais, Brazil, with BC patients receiving AI endocrine therapy. The study was approved by the human research ethics committee of the Universidade Federal de Uberlândia (48367215.3.0000.5152/2015), and the entire study was conducted on the basis of the standards of the Helsinki Declaration and on the standards of Resolution CNS 466/12. All participants provided written informed consent.

Sample Calculation

The sample size required for this study was determined by G*Power 3.1.[15] The calculation of the sample size was based on a F test linear multiple regression with effect size of 0.15, an alpha level of 0.05, and test power of 80%. Given these specifications, a total of 84 women were required at final analysis.

Patients

Medical records of 256 patients with BC and receiving endocrine therapy with AI were analyzed in March 2015. Clinical data, such as cancer type, treatments received, duration of AI receipt, and presence of other comorbidities, were identified and recorded. A total of 107 patients did not meet the inclusion criteria (Figure 1).

The 149 women eligible for the study were contacted by telephone and invited to participate in the study. For those who agreed to participate, one meeting divided into 2 steps was scheduled at the hospital. Data were collected from January to August 2016, with a final sample of 93 patients. After the first meeting, 4 patients were excluded from the study, resulting in a final sample size of 89 patients (Figure 1).

Evaluation

At the first meeting, the patients completed a questionnaire that addressed issues related to sociodemographics, clinical profile, and physical exercise; the latter questions determined whether the women engaged in physical exercise, the type of exercise, the weekly frequency, the duration (in minutes), and the duration of practice (in months). The patients' FC was evaluated using the Health Assessment Questionnaire, which was assessed on the basis of classification. Patients were divided into 3 groups—G1, mild to moderate difficulty; G2, moderate to severe disability; and G3, severe or very severe disability—per the cutoff points adopted (0-1, 1-2, and 2-3, respectively).[16,17] The cutoff for duration of AI receipt was determined by the median number of months and was divided into 2 time groups according to duration of receipt of AI: T1 $\leq$ 29.5 months and T2 $>$ 29.5 months. Afterward, the patients were anthropometrically evaluated. A mechanical scale was used to measure weight, with 100 g sensitivity. For height, a vertical stadiometer with a 1 mm precision scale was used, and for waist circumference (WC) a flexible and inelastic tape was used, following the World Health Organization's recommended protocol.[18] To classify obesity, the body mass index (BMI) was calculated. BMI $\geq$ 25 kg/m^2 was considered overweight for adult women,[18] and BMI $>$ 27 kg/m^2 was considered overweight for elderly women[19] (those over 60 years of age).[20] WC $\geq$ 88 cm was considered to indicate a very high risk for metabolic complications.[18]

At the second meeting, the women were subjected to bioelectrical impedance analysis (BIA 450; Biodynamics, Shoreline, WA), which was performed according to the analysis protocol.[21] From the obtained values, body fat (BF) and fat-free mass (FFM) in kilograms were calculated using the predictive equations proposed by Segal et al,[22] which consider age, BMI, height, resistance measured by bioelectrical impedance analysis, and body weight. Eleven patients had water retention (total body water $>$ 75%), and these women were excluded from the BF and FFM analyses.

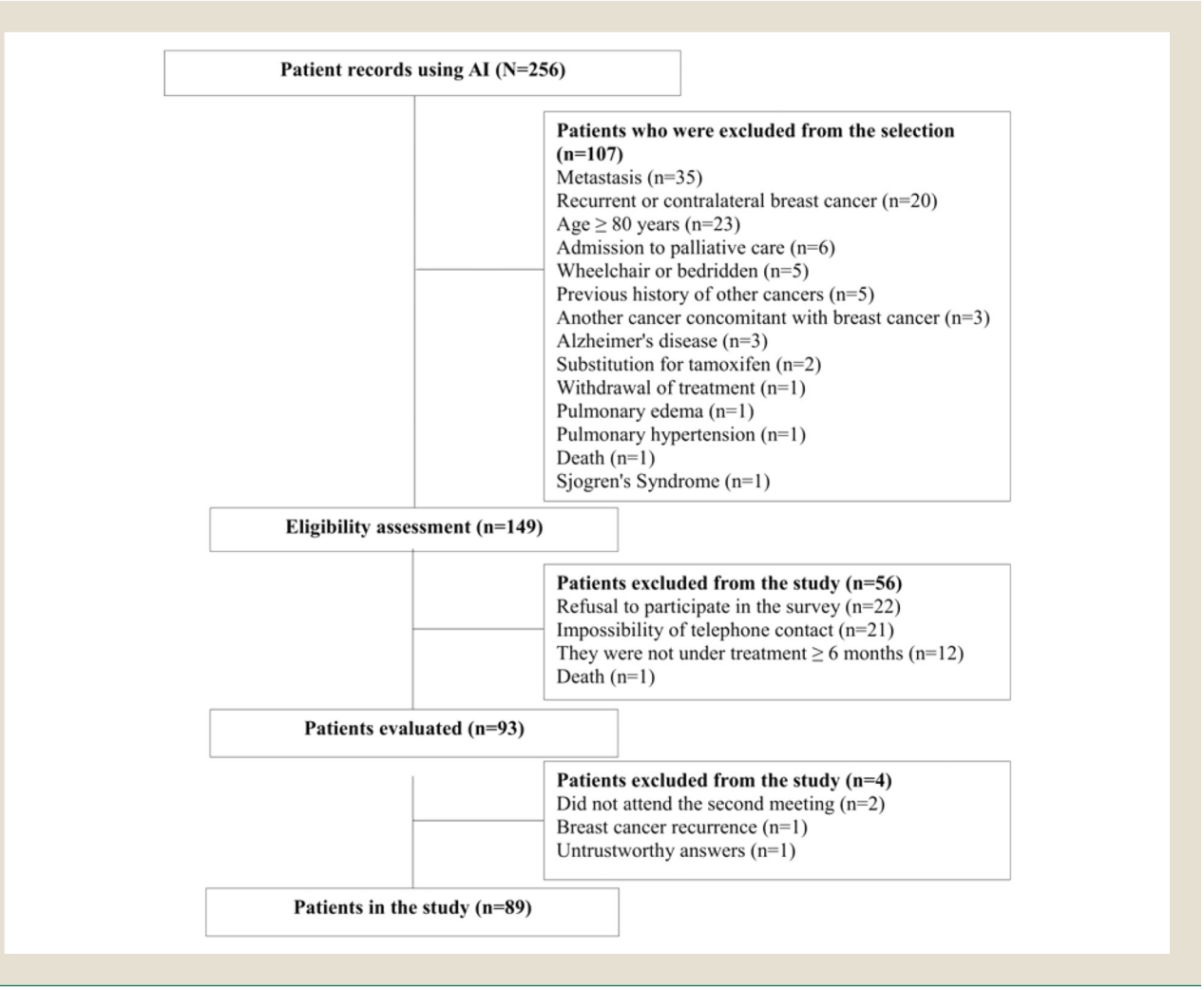
Statistical Analysis

A descriptive analysis of the data by frequency was performed for qualitative variables, and measures of central tendency (mean and median) and dispersion (standard deviation and percentiles) were used for the quantitative variables. Numerical variables were analyzed for normality by the Kolmogorov-Smirnov test. The Mann-Whitney test was used to compare the variables. The association between FC and the variables BMI, FFM, age, and physical exercise was analyzed by Spearman correlation. Generalized estimating equations (GEE) were used to examine the association between groups for FC, duration of AI receipt, and adiposity parameters, adjusting for chemotherapy, age, smoking, alcohol consumption, and physical exercise. The GEE model accounted for associations among the within-subject outcome variables BMI, WC, BF, and FFM and provided consistent estimates of the standard error parameters using robust estimators. The adjustment method for multiple comparisons was sequential Sidak. All statistical analyses were performed by SPSS 21 (IBM, Armonk, NY), and values of $P < .05$ were considered significant.

Results

Supplemental Table 1 shows the sociodemographic and clinical characteristics of the 89 women with BC receiving AI therapy. The sample consisted mostly of women with low educational level (60.6%) and low income (48.3%). More than one comorbidity was reported by patients and confirmed in the medical records; 56.2%

Figure 1 Diagram Reporting Number of Women Screened and Recruited (N = 89)



Abbreviation: AI = aromatase inhibitor.

(n = 50) had systemic hypertension, 22.5% (n = 20) had musculoskeletal symptoms (arthritis, osteoarthrosis, and/or osteoporosis), 21.3% (n = 19) had type 2 diabetes, 11.2% (n = 10) had hypothyroidism, 5.6% (n = 5) had hyperthyroidism, 3.3% (n = 3), had depression or emotional disorders, and 37.1% (n = 33) presented with other comorbidities, mainly diseases related to the lipid profile. Regarding lifestyle, 89.9% (n = 80) of the patients did not smoke, 22.5% (n = 18) were former smokers, 74.2% (n = 66) did not consume alcohol, and 17.9% (n = 12) were formerly alcoholic.

Regarding previous treatments, 84.3% of the women (n = 75) underwent radiotherapy, 76.5% (n = 68) underwent chemotherapy, and all woman underwent surgery; none was statistically significantly different according to duration of AI receipt ($P = .075$; $P = .709$; $P = .073$, respectively). Some patients received only one treatment: radiotherapy, chemotherapy, or surgery followed by AI receipt (respectively, 22.5%, n = 18; 12.3%, n = 11; 3.3%, n = 3). A history of receipt of tamoxifen before AI use was found in 44.9% (n = 40), with a median duration of 10 months (3.0-22.7 months). The most common AI was anastrozole (77.5%, n = 69), followed by letrozole (15.7%, n = 14), which differed significantly between treatment duration ($P = .047$). No significant differences were found between T1 and T2 regarding age or other parameters (Supplemental Table 1).

Of the participants, 60.7% (n = 54) had excess weight and 66.3% (n = 59) showed a very high risk for metabolic complications. Excluding those with water retention (n = 11), the women presented a median BF and FFM of 28.4 and 42.8 kg, respectively.

As shown in Supplemental Table 2, women in T1 had higher medians for weight, BMI, WC, and BF compared to those in T2; this was statistically significant for BMI and BF (29.4 vs. 26.8 kg/m^2, $P = .045$; 31.5 vs. 22.3 kg, $P = .033$, respectively). For FC, we observed higher median scores for women in T1 than for those in T2 (1.1 vs. 0.8, $P = .017$, respectively), as well as a higher percentage of women who were classified as G3 (13.3 vs. 6.8%, $P = .014$, respectively).

A significant positive correlation was observed between functional disability and BMI ($\rho = 0.305$), WC ($\rho = 0.297$), and BF ($\rho = 0.335$), with $P < .01$ for all. FFM and age showed no significant correlation with FC.

In the GEE analyses, we verified an effect of FC on the obesity parameters BMI, BF, and WC ($P = .018$, $P = .013$, and $P = .019$, respectively). In addition, we verified an effect of duration of AI receipt on BMI and BF ($P = .019$ and $P = .041$, respectively). We found no significant interaction effects between duration of AI receipt and FC relative to anthropometric and body composition variables (Supplemental Table 3).

Supplemental Table 4 shows the post hoc comparison of the interaction between FC and duration of AI receipt. Although not statistically significant, we observed that women in G3 (with severe or very severe disability) and in T1 presented higher values for BMI (33.90 ± 4.31 vs. 28.17 ± 4.45 kg/m^2), WC (103.00 ± 9.96 vs. 93.60 ± 7.12 cm), and BF (36.38 ± 8.68 vs. 26.90 ± 9.74 kg) than those in G1 and G2. In addition, in comparing the duration of AI receipt, women in T1 and G3 also had higher values. We found no significant differences when comparing the 3 FC groups at T1 or T2 for all variables.

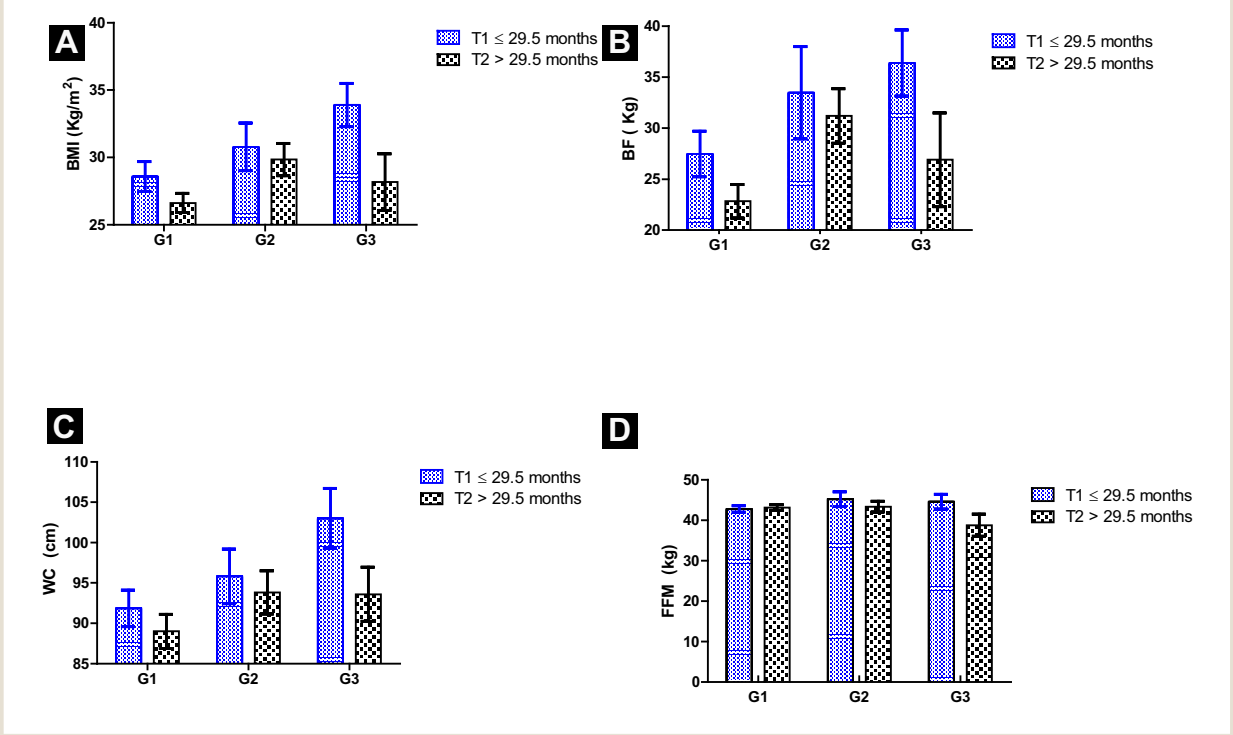
Figure 2 shows the post hoc comparison of obesity parameters between the interaction of FC and duration of AI receipt. Supplemental Table 5 shows the variables related to exercising and FC. A significant difference was observed between FC and engaging in physical exercise ($P = .018$). In addition, physical exercise and functional disability were weakly negatively correlated (G1 vs. G2 and G3) ($\rho = -0.256$, $P = .015$).

Discussion

An effect of FC was verified for obesity parameters and between duration of AI receipt on the BMI and BF in that impaired FC was found in women with higher anthropometric and body composition measurements. Additionally, we found that adiposity above the recommended parameters and greater functional disability were associated with the shortest adjuvant endocrine therapy duration time of receipt of AI. Thus, because of the long period of recommended AI use,[23] the negative aspects of obesity and the interaction of functional disability and obesity suggest that multiprofessional monitoring is needed to improve or maintain adequate nutritional status and FC in women after endocrine therapy.

The role of excessive BF as a potential risk and prognostic factor for BC is well known and accepted.[11] The results of a TEAM trial suggested that obese patients are less likely to benefit from estrogen receptor antagonists.[24] Specifically, studies have suggested that AI treatment efficacy can be modified by BMI,[24-27] can result in a greater risk of local or distant relapse, and may result in shorter disease-free and overall survival.[25,27] In this regard, evidence suggests that estrone sulfate and estradiol suppression by AI may be less effective in overweight women.[28] Serum levels of these 2 hormones have been reported to be significantly associated with BMI in postmenopausal women.[29]

Figure 2 Post Hoc Comparison of Anthropometric Measures and Body Composition Between Interaction of FC and Duration of Receipt of AI. (A) Difference in BMI Values Between FC Groups and Duration of Receipt of AI. (B) Difference in WC Values Between FC Groups and Duration of Receipt of AI. (C) Difference in BF Values Between FC Groups and Duration of Receipt of AI. (D) Difference in FFM Mass Values Between FC Groups and Duration of Receipt of AI. Statistically Significant by ANOVA. Post Hoc Comparison (Sidak sequential method)



Abbreviations: BF = body fat; BMI = body mass index; FC = functional capacity; FFM = fat-free mass; G1 = mild to moderate difficulty; G2 = moderate to severe disability; G3 = severe or very severe disability; T1 = ≤ 29.5 months of receipt of aromatase inhibitors; T2 = > 29.5 months of receipt of aromatase inhibitor; WC = waist circumference.

In our study, adiposity parameters were positively correlated with greater functional disability. Obesity is associated with functional decline,[30] altered spatiotemporal gait parameters,[31] and a significantly higher metabolic cost of walking compared to people of eutrophic body weight.[32] Specifically, obese women have slower gait speeds with correspondingly shorter stride lengths, relatively weaker lower limbs (they needed more time to perform 5 sit-to-stand movements), and poorer endurance than normal-weight subjects.[31] However, the correlations between obesity and FC are multifaceted and complex.

BC survivors are significantly more likely to report difficulty performing heavy housework, walking half a mile, and walking up and down stairs compared to their cancer-free peers.[33] The significant weight gain observed during BC treatment[13,34] may be one of the influencing factors. Furthermore, Brazilian public health sources suggest that women with BC often deviate (temporarily or permanently) from their work activities after being diagnosed with neoplasia, which probably decreases energy expenditure and facilitates weight gain. Young et al,[12] in a cohort of 1841 early-stage BC survivors, found that women with BMI $\geq$ 30 kg/m^2 had significantly higher functional decline compared to those with BMI $<$ 25 kg/m^2 (2.06 vs. 0.96 for moderate/severe limitations; 3.92 vs. 3.27 for mild limitations; 1.31 vs. 0.47 for lower-body limitations; and 0.76 vs. 0.49 for all other limitations; $P < .001$).

Patients receiving AIs have a higher incidence (35-50%) of musculoskeletal symptoms, particularly arthralgia,[7] in addition to joint pain and stiffness.[35] These musculoskeletal symptoms may be related in part to estrogen deprivation,[36] but autoimmune conditions (rheumatoid arthritis or Sjögren syndrome) may also occur in patients treated with AI.[37,38] The toxic effects and significant musculoskeletal discomfort may lead to suboptimal treatment adherence[35] because of the long period of recommended endocrine therapy.[3] Up to one third of patients affected may experience musculoskeletal pain so severe that it requires therapy interruption.[39] Given this and the importance of treatment on mortality,[40] it is important to understand the influence of time in this context.

Our data did not support the original hypothesis. The shortest adjuvant endocrine therapy time with AIs was associated with greater functional disability in addition to adiposity parameters above those recommended. Reports of time to onset of musculoskeletal symptoms have a broad range, from 6 weeks to 6 months.[6,41] In addition, the T1 and T2 groups were homogeneous for antineoplastic treatment types before endocrine therapy with AI. The effects of other BC therapies before endocrine therapy, such as chemotherapy and tamoxifen, may also play a role in developing AI-related musculoskeletal symptoms.[42] In addition, higher BMI, WC, and BF values in the first years of endocrine therapy for BC can be influenced by previous treatments such as chemotherapy.[43] Therefore, the greater functional disability in the first years could have arisen from the prolonged effects of previous treatments before endocrine therapy, such as chemotherapy or the concomitant steroids provided to patients with this treatment, rather than AI use. Similarly, in a recent study published by our group, we found a significant effect of the interaction of chemotherapy with a shorter duration of tamoxifen use relative to adiposity parameters.[43] In addition, psychological factors such as anxiety and depression are common in the first years of endocrine therapy[44] and may interfere with changes in body composition. To our knowledge, ours is the first study to compare groups at different duration of AI therapy with body composition and FC. More research is needed to pursue alternative causes.

Importantly, women with higher adiposity parameters may present earlier recurrence; therefore, in our study, a sample of women without metastasis would be underrepresented in adiposity parameters at later times. However, analyzing the dynamics of BC patients' recurrences suggests a multiple peak pattern, whereas estrogen receptor–positive tumors are less likely than negative tumors to recur in the first years of follow-up.[45,46] In addition, obesity was associated with increased risk of late recurrence and distant metastases, occurring 5 years after the initial diagnosis.[11,47] Therefore, we believe that the sampling and methodologic characterization did not interfere with the results.

Physical inactivity, in turn, has the main clinical manifestations of decreased muscle strength and impaired balance and fatigue, which directly affect the patient's self-care and social activities during the disease. Therefore, physical inactivity due to functional disability may become a vicious cycle of generalized weakness and impaired quality of life.[9] In our study, we found a significant difference between greater functional disability and less physical exercise. In addition, a weak negative correlation was found between exercise and functional disability. Knowing that impaired FC directly interferes with physical inactivity,[9] studies suggest that physical inactivity contributes to worsening health in BC survivors.[8] In addition, musculoskeletal effects may result in discontinued AI treatment in more than 10% of patients,[8] which may compromise endocrine therapy adherence and which may be a risk for recurrence.

Possible limitations of this study should be considered. The cross-sectional evaluation makes it impossible to establish causal relationships involving changes in body composition during AI use. Future studies should focus on cohorts with varied medical and social demographics to correctly ascertain the natural history of being overweight and of obesity on functional disabilities at different moments of AI use. Because of prescribing patterns, most participants were being treated with anastrozole, and no conclusions can be drawn about other third-generation AIs. In addition, assessing the serum levels of sex hormones such as estrone and estradiol would be important to verify the relationship between obesity and the duration of AI receipt.

Conclusion

The effects of cancer and its treatment on functional limitations may be worrisome because other age-related conditions can become susceptible to obesity and declining physical function. Our data did not support the original hypothesis because adiposity above the recommended parameters and impaired FC were associated with the shortest time of receipt of adjuvant endocrine therapy with AI. During the first years of endocrine therapy with AI, women still

experienced the residual effects of chemotherapy. This study suggests the importance of prior treatment and multiprofessional effort at the beginning of endocrine therapy to improve or maintain adequate nutritional status and FC. These strategies may help improve medication efficacy, help improve adherence to endocrine treatment, and consequently help reduce the risks of disease relapse. It is necessary to carry out prospective studies to confirm the results of this study.

Clinical Practice Points

- Continuous receipt of AI may cause adverse events related to musculoskeletal symptoms, which may be a consequence of functional disability. In turn, this functional disability is associated with adiposity parameters and lower levels of physical exercise.
- Considering that is common for women to gain weight after a BC diagnosis, especially after chemotherapy, the impact of body composition on FC for different durations of AI receipt in patients with BC is of interest.
- Given the importance of adherence to long-term treatment, this study adds that women in the first years of AI use showed greater functional disability and worse adiposity parameters.
- This reinforces the importance of multiprofessional follow-up to improve adequate nutritional status, particularly in the early years of AI use, considering the importance of the prolonged effects of previous treatments such as chemotherapy.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.09.003.

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Supplemental Data

Supplemental Table 1 Sociodemographic and Clinical Characteristics of Women With Breast Cancer Receiving Endocrine Therapy with AIs and Divided Into 2 Time Groups of AI Receipt

Characteristic	All Patients (N = 89)	T1 (N = 45)	T2 (N = 44)	*P*
Age (years)	65 (58.5-69.5)	65 (58.5-70.0)	65.5 (58.2-69.0)	.831
Education				
Illiterate	2 (2.2)	2 (4.4)	0 (0.0)	.602
Elementary school incomplete/complete	52 (58.4)	26 (57.7)	26 (59.1)	
High school incomplete/complete	21 (23.6)	10 (22.3)	10 (22.7)	
Technical vocational course	1 (1.1)	1 (2.2)	0 (0.0)	
Graduate degree/postgraduate	13 (14.6)	5 (11.1)	8 (18.1)	
Income (R$)[a]				
440-1.760	43 (48.3)	22 (48.9)	21 (47.8)	.948
1.761-3.520	31 (34.8)	17 (37.7)	14 (31.8)	
> 3.520	15 (16.9)	6 (13.3)	9 (20.5)	
Race				
White	43 (48.3)	21 (46.7)	22 (50.0)	.851
Latin American	39 (43.8)	18 (40.0)	21 (47.7)	
Black	6 (6.7)	5 (11.1)	1 (2.3)	
Asian	1 (1.1)	1 (2.2)	0 (0.0)	
Comorbidities				
No	13 (14.6)	7 (15.6)	6 (13.6)	.799
Yes	76 (85.4)	38 (84.4)	38 (86.4)	
Family history of BC or ovary cancer	33 (37.0)	17 (37.7)	16 (36.4)	.770
Sugary				
Quadrantectomy	51 (57.3)	30 (66.7)	21 (47.7)	.073
Mastectomy	38 (42.7)	15 (33.3)	23 (52.3)	
Radiotherapy	75 (84.3)	41 (91.1)	34 (77.3)	.075
Chemotherapy				
Adjuvant	53 (59.6)	23 (51.1)	30 (68.2)	.709
Neoadjuvant	15 (16.9)	9 (20.0)	6 (13.6)	
No chemotherapy	21 (23.6)	13 (28.9)	8 (18.2)	
AI				
Anastrozole and letrozole	6 (6.7)	4 (8.9)	2 (4.5)	.047
Letrozole	14 (15.7)	10 (22.2)	4 (9.1)	
Anastrozole	69 (77.5)	31 (68.9)	38 (86.4)	
Prior tamoxifen	40 (44.9)	17 (37.8)	23 (52.3)	.172
Tumor Subtype				
Ductal invasive	86 (96.6)	44 (97.8)	42 (95.5)	.546
Lobular invasive	3 (3.4)	1 (2.2)	2 (4.5)	
Clinical Stage				
I	26 (29.2)	15 (33.3)	11 (25.0)	.415
II	48 (53.9)	23 (51.1)	25 (56.8)	
III	13 (14.6)	6 (3.3)	7 (15.9)	
NR	2 (2.2)	1 (2.2)	1 (2.3)	

Supplemental Table 1 Continued

Characteristic	All Patients (N = 89)	T1 (N = 45)	T2 (N = 44)	*P*
Tumor Grade[b]				
1	14 (15.7)	7 (15.6)	7 (15.9)	.502
2	66 (74.2)	32 (71.1)	34 (77.3)	
3	5 (5.6)	4 (8.9)	1 (2.3)	
NR	4 (4.5)	2 (4.4)	2 (4.5)	
Molecular Subtypes				
Luminal A	30 (33.7)	16 (35.6)	14 (31.8)	.898
Luminal B	54 (60.7)	28 (62.2)	26 (59.1)	
NR	5 (5.6)	1 (2.2)	4 (9.1)	

Data are presented as n (%) or as median (25th–75th percentile). Statistical significance is Mann-Whitney test.
Abbreviations: AI = aromatase inhibitor; BC = breast cancer; NR = not reported; T1 = ≤ 29.5 months of receipt of AI; T2 = > 29.5 months of receipt of AI.
[a]Minimum wage per month is R$880.
[b]Tumor grades are as follows: 1, well-differentiated (low grade); 2, moderately differentiated (intermediate grade); 3, poorly differentiated (high grade).

Supplemental Table 2 Functional Capacity, Anthropometric, and Body Composition Characteristics in Relation to Length of Time Receiving AI Endocrine Therapy in Women With Breast Cancer

	All Patients		T1		T2		
Characteristic	N	Median (25th–75th Percentile)	N	Median (25th–75th Percentile)	N	Median (25th–75th Percentile)	*P*
Weight (kg)	89	68.2 (60.2-76.2)	45	69.8 (62.6-77.3)	44	67.8 (58.9-75.5)	.131
BMI (kg/m^2)	89	28.3 (25.4-31.4)	45	29.4 (25.8-32.7)	44	26.8 (25.3-30.5)	.045
WC (cm)	89	92.5 (85.7-100.8)	45	94.0 (86.3-101.0)	44	90.1 (83.2-97.9)	.153
BF (kg)	78	28.4 (17.8-35.1)	37	31.5 (19.3-36.9)	41	22.3 (17.3-33.4)	.033
FFM (kg)	78	42.8 (40.6-46.5)	37	42.8 (40.9-46.2)	41	42.5 (40.2-46.5)	.635
HAQ score	89	0.9 (0.4-1.4)	45	1.1 (0.6-1.6)	44	0.8 (0.3-1.2)	.017
HAQ classification (%)							
G1	48	53.9	18	40.0	30	68.2	
G2	32	36.0	21	46.7	11	25.0	.014
G3	9	10.1	6	13.3	3	6.8	

Statistical significance by Mann-Whitney test.
Abbreviations: AI = aromatase inhibitor; BF = body fat; BMI = body mass index; FFM = fat-free mass; G1 = mild to moderate difficulty; G2 = moderate to severe disability; G3 = severe or very severe disability; HAQ = Health Assessment Questionnaire; T1 = ≤ 29.5 months of receipt of AI; T2 = > 29.5 months of receipt of AI; WC = waist circumference.

Supplemental Table 3 Model Effect Tests of AI Receipt Duration, Functional Capacity Groups, and Anthropometric and Body Composition Variables in Women With Breast Cancer Receiving Endocrine Therapy With AIs

Characteristic	Effect	*df*	Wald χ^2	*P*
BMI (n = 89)	Duration of AI receipt	1	5.519	.019
	FC	2	8.018	.018
	Duration of AI receipt × FC	2	1.948	.378
WC (n = 89)	Duration of AI receipt	1	3.788	.052
	FC	2	7.903	.019
	Duration of AI receipt × FC	2	1.420	.492
BF (n = 78)	Duration of AI receipt	1	4.167	.041
	FC	2	8.745	.013
	Duration of AI receipt × FC	2	0.868	.648
FFM (n = 78)	Duration of AI receipt	1	3.064	.080
	FC	2	1.995	.376
	Duration of AI receipt × FC	2	3.480	.176

Data adjusted for chemotherapy, age, smoking, alcohol consumption, and physical exercise. Statistical significance by ANOVA.
Abbreviations: AI = aromatase inhibitor; BF = body fat; BMI = body mass index; df = degree of freedom; FC = functional capacity; FFM = fat-free mass; WC = waist circumference.

Supplemental Table 4 Post hoc Comparison of Interaction Between Functional Capacity and Endocrine Therapy With AI Duration of Receipt on Anthropometric and Body Composition Variables in Women With Breast Cancer

Characteristic	HAQ Classification	Mean ± SD		*P*	95% Wald Confidence Interval			
					T1		T2	
		T1	T2		Lower	Upper	Lower	Upper
BMI (kg/m^2) (n = 89)	G1	28.58 ± 4.85	26.62 ± 3.97	.739	26.48	30.84	25.26	28.06
	G2	30.79 ± 8.30	29.85 ± 4.18	.944	27.51	34.45	27.58	32.29
	G3	33.90 ± 4.31	28.17 ± 4.45	.297	30.89	37.19	24.34	32.59
WC (cm) (n = 89)	G1	91.86 ± 9.87	89.00 ± 11.80	.938	87.53	96.39	84.95	93.25
	G2	95.83 ± 15.85	93.83 ± 9.30	.986	89.44	102.68	88.73	99.22
	G3	103.00 ± 9.96	93.60 ± 7.12	.526	95.98	110.54	87.25	100.41
BF (kg) (n = 78)	G1	27.46 ± 9.53	22.83 ± 8.80	.651	23.39	32.23	19.85	26.27
	G2	33.47 ± 17.56	31.19 ± 8.95	.936	25.69	43.62	26.35	36.92
	G3	36.38 ± 8.68	26.90 ± 9.74	.651	30.56	43.31	19.25	37.59
FFM (kg) (n = 78)	G1	42.82 ± 3.45	43.19 ± 3.87	.919	41.26	44.44	41.80	44.61
	G2	45.26 ± 7.07	43.39 ± 4.47	.975	41.82	48.97	40.84	46.09
	G3	44.63 ± 4.87	38.83 ± 5.76	.669	41.22	48.33	33.86	44.54

General estimated equations were used for analysis. Data were adjusted for chemotherapy, age, smoking, alcohol consumption, and physical exercise. Statistical significance by ANOVA and post hoc comparison (Sidak sequential method).
Abbreviations: AI = aromatase inhibitor; BF = body fat; BMI = body mass index; FFM = fat-free mass; G1 = mild to moderate difficulty; G2 = moderate to severe disability; G3 = severe or very severe disability; HAQ = Health Assessment Questionnaire; T1 = ≤ 29.5 months of receipt of AI; T2 = > 29.5 months of receipt of AI; WC = waist circumference.

Supplemental Table 5 Characteristics of Physical Exercise Practice Relative to Functional Capacity of Women With Breast Cancer Receiving Endocrine Therapy With AIs (N = 89)

Characteristic	All Patients	G1	G2 and G3	*P*
Physical Exercise				
Yes	36 (40.4)	25 (69.4)	11 (30.6)	.018
No	53 (59.6)	23 (43.4)	30 (56.6)	
Type of Physical Exercise				
Aerobic	28 (77.5)	19 (67.9)	9 (32.1)	.995
Anaerobic	3 (8.3)	3 (100)	0 (0.0)	
Aerobic and anaerobic	5 (13.9)	3 (60.0)	2 (40.0)	
Frequency (Weekly)				
1-2×	10 (27.8)	8 (80.0)	2 (20.0)	.985
3-4×	13 (36.1)	7 (53.8)	6 (46.2)	
5-7×	13 (36.1)	10 (76.9)	3 (23.1)	
Time spent (minutes), median (25th-75th percentile)	55 (40-60)	60 (41.3-60)	50 (40-60)	.429
Practice time (months) median (25th-75th percentile)	18 (4.3-36.0)	15 (2.5-36)	18 (7.5-33)	.882

Data are presented as n (%) unless otherwise indicated. Statistical significance by Mann-Whitney test.
Abbreviations: AI = aromatase inhibitor; G1 = mild to moderate difficulty; G2 = moderate to severe disability; G3 = severe or very severe disability.