Association of sarcopenia with endocrine therapy toxicity in patients with early breast cancer

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Abstract

Background

Endocrine therapy reduces recurrence risk and improves survival in women with hormone receptor-positive breast cancer; however, side effects can decrease quality of life, leading to reduced treatment adherence. Sarcopenia is the loss of skeletal muscle mass that happens with age; it is associated with reduced chemotherapy adherence in patients with breast cancer. The impact of sarcopenia on endocrine therapy tolerance has not been investigated. The current study evaluates the association of sarcopenia with endocrine therapy toxicity and treatment tolerance.

Methods

Skeletal muscle mass (SMM) was measured by bioelectrical impedance spectrometry. Skeletal Muscle Index (SMI) was calculated to assess for sarcopenia: SMI= (SMM kg)/ (patient height, m2). Patients with SMI ≤ 6.75 kg/m2 were considered sarcopenic. A chart review was performed to obtain patient characteristics, endocrine therapy toxicity, and early treatment change or termination. Fisher's exact test was performed to associate patient characteristics and outcomes with sarcopenia status.

Results

Four hundred eighty-two patients with stage I-III breast cancer were prescribed endocrine therapy and had undergone sarcopenia evaluation. The median age was 61 years (29 to 88 years). Sarcopenia was identified in 35% of patients. On multivariable logistic analysis, sarcopenia was independently associated with increased odds of experiencing endocrine-related side effects (p=0.01). In addition, patients with sarcopenia stopped or changed their medication due to side effects more often than those without sarcopenia (p=0.05).

Conclusion:

The presence of sarcopenia in patients with EBC represents a potentially modifiable risk factor for more significant endocrine therapy side effects and reduced treatment tolerance.

Introduction

Most patients with breast cancer present with hormone receptor (HR)-positive disease [1, 2]. The use of adjuvant endocrine therapy for 5 to 10 years after surgery reduces recurrence risk and improves survival for women with estrogen receptor and/or progesterone receptor-positive breast cancer [3]. Common side effects of endocrine therapy include musculoskeletal pain (arthralgias), hot flashes, and fatigue; in addition, endocrine treatments have been associated with bone density loss and cardiovascular events [4, 5]. Experiencing treatment-related side effects can decrease quality of life and reduce therapy adherence. Identification of patients at increased risk for experiencing these side effects may provide an opportunity for interventions to mitigate these effects.

Associations between body composition and breast cancer have been well documented, though findings have been conflicting. While obesity has been associated with an overall increase in breast cancer risk, obesity appears to have a protective effect in premenopausal women, reducing the risk of breast cancer (8). Among patients with breast cancer, those who are obese have higher rates of larger tumors, faster disease progression, and greater hormonal therapy resistance [6–8]. Studies have consistently shown that patients with breast cancer who were classified as grade 2 or 3 obese (BMI > 35) have worse survival compared to patients classified as normal weight [9]. On the other hand, research findings have been inconsistent regarding survival rates in breast cancer patients who were classified as overweight or obese (BMI > 25) [9, 10]. Similar discordance exists in the literature regarding the impact of obesity on outcomes with endocrine therapy for breast cancer [11]. Given inconsistent associations of BMI with clinical outcomes in patients with breast cancer, assessment of body composition by body compartments (i.e., muscle, fat, water) separately has evolved as a potentially more informative approach.

Sarcopenia is the decline in lean body mass or muscle mass, which happens over years of life [12] and has been associated with an increased risk of death and reduced quality of life [13]. It has also been associated with a worse prognosis in multiple cancer types (15). Sarcopenia can be detected by a variety of methods, including computed tomography (CT) scans and bioelectrical impedance spectrometry (BIS) [14]. BIS and CT scan images estimate muscle mass, which is then divided by the squared height of the patient in meters to obtain skeletal muscle index (SMI). Patients with low SMI (< 6.75 kg/m^2 if using BIS or < 40 cm^2/m^2 if using CT scans) are characterized as sarcopenic.

In patients with breast cancer, sarcopenia predicts worse survival and reduced chemotherapy completion rates in both early-stage breast cancer (EBC) and metastatic breast cancer (MBC) [15–17]. The impact of sarcopenia on endocrine therapy tolerance has not been well studied. This retrospective study assesses the association between sarcopenia and severe side effects of endocrine therapy in a cohort of women with EBC.

Methods

Following institutional review board approval, data were collected via chart review and from stored BIS measurements on a cohort of patients with EBC who had undergone BIS analysis (Sozo machine, ImpediMed) as a part of their routine cancer care at our institution from 2015 until June 2021 and were subsequently prescribed endocrine therapy a minimum of 6 months prior to data collection Baseline characteristics included age at diagnosis, race, comorbidities (hypertension, diabetes, heart failure, cirrhosis, chronic kidney disease stage III, COPD, hypothyroidism on treatment, previous breast cancer, previous cancer, severe osteoarthritis, rheumatoid arthritis, coronary artery disease, peripheral vascular disease, osteoporosis, and previous stroke), breast cancer stage., height, weight (at time of BIS analysis). Receipt of radiation therapy, chemotherapy treatment, and type of endocrine treatment prescribed were recorded.

Body composition

The Sozo BIS was used to measure patient Skeletal Muscle Mass (SMM) and weight. Height was measured during the clinic visit on the day of the BIS body composition evaluation. Skeletal Muscle Index (SMI) was calculated to assess for sarcopenia: SMI= (SMM, kg)/ (patient height, m2). Patients were divided into non-sarcopenic (SMI > 6.75 kg/m2) and sarcopenic (SMI ≤ 6.75 kg/m2)[18].

Endocrine treatment side effects

Endocrine therapy toxicities were obtained through medical record review and assessed common and severe endocrine treatment-related side effects [19]. These included arthralgia, fatigue, hot flashes, nausea/vomiting, bone fracture, and cardiovascular incidents (acute coronary syndrome, stroke, myocardial infarct, and pulmonary embolism).

Toxicities described in the medical record were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) [20] to characterize grade 3 or 4 endocrine therapy toxicity. In addition, information on early treatment termination or changes in the therapy due to severe side effects was also collected. The follow-up period was a minimum of six months after starting the treatment with endocrine therapy.

Statistical analysis

Fisher's exact test was performed to associate the patients' characteristics, endocrine therapy toxicity, and early therapy change or discontinuation with sarcopenia status. In addition, multivariate logistic regression models were used to evaluate these associations adjusting for age comorbidities and BMI. Odds ratio (OR) was reported as the measure of association estimated from these models. All analyses were done using R (R Core Team) statistical software and a 0.05 significance level.

Results

Table 1 summarizes patients' characteristics. Four hundred eighty-two patients were identified with stage I-III breast cancer who were prescribed endocrine therapy and had undergone BIS. The median age was 61 years (range: 29 to 88 years); all patients were female, 90% were white, 74% had one or more comorbidities, and 63% had stage 1 disease. Endocrine therapy included tamoxifen (n = 103), aromatase inhibitor therapy (n = 419), and ovarian ablation (n = 23; either with bilateral salpingo-oophorectomy or with a gonadotropin-releasing hormone agonist); some patients received multiple treatments. Baseline sarcopenia was identified in 35% of patients.

Table 1
patients characteristics

Variable	482
Age at BC diagnosis	61 (29–88)
Mean (min-max)	292 (61)
< 65 years old	190 (39)
> 65 years old	
Race: white	432 (90%)
Body Mass Index	6 (1%)
Underweight (< 18.5 kg/m^2)	134 (28%)
Normal (18.5 to < 25 kg/m^2)	189 (39%)
Overweight (25 to < 30 kg/m^2)	153 (32%)
Obese (> 30 kg/m^2)	
Breast cancer stage	308 (64%)
Stage 1	125 (26%)
Stage 2	49 (10%)
Stage 3	
Radiation therapy	360 (75%)
Chemotherapy received	197 (41%)

Variable	482
Comorbidities ≥ 1	360 (74%)
Hypertension	232 (48%)
Diabetes	70 (15%)
Severe Heart failure	9 (2%)
Cirrhosis	5 (1%)
Chronic kidney disease stage III	31 (7%)
COPD	30 (6%)
Hypothyroidism	80 (17%)
Previous breast cancer	27 (6%)
Previous cancer	28 (6%)
Severe osteoarthritis	89 (18%)
Rheumatoid arthritis	13 (3%)
Coronary artery disease	14 (3%)
Peripheral vascular disease	5 (1%)
Osteoporosis	115 (24%)
Stroke	9 (2%)
Type of treatment (patients may have received 2 or more)	23 (5%)
Ovarian ablation	419 (87%)
Aromatase inhibitor	103 (21%)
Tamoxifen	
Skeletal Muscle Index (SMI) Kg/m^2	7.14 (4.84–12.61)
Median (min-max)	169 (35%)
Sarcopenia < 6.75	
Early treatment change or termination	61 (13%)
Endocrine toxicity	58 (12%)

Sarcopenia and endocrine therapy toxicity

Overall, 12% of patients experienced CTCAE grade 3 or 4 endocrine-related toxicities (arthralgia 8%, bone fracture 0%, cardiovascular incidents 0.8%, fatigue 1%, hot flashes 3%, nausea/vomiting 0%). On

multivariable logistic analysis, the presence of sarcopenia was independently associated with a significant increase in the odds of experiencing endocrine-related side effects compared to those without sarcopenia (OR 2.31 95% CI 1.19–4.50, p = 0.01). Early treatment change or discontinuation due to side effects was observed in 13% of the cohort. Patients with sarcopenia stopped or changed their medication due to side effects more often than those without sarcopenia (OR 1.94 95% CI 1.003–3.76 p = 0.05) (Table 2).

Table 2
Summary of multivariate logistic regression model for any endocrine therapy

Factor	Comparison	Odds Ratio	95% LCL*	95% UCL**	P-value
Age	>=65 vs. <65	1.404	0.759	2.603	0.28
BMI	Overweight vs. Normal Weight	1.639	0.753	3.663	0.22
	Obese vs. Normal Weight	2.245	0.997	5.249	0.06
SMI	**< 6.75 vs. >=6.75**	**2.314**	**1.195**	**4.501**	**0.01**
Number of Comorbidities	>=1 vs. 0	1.257	0.693	2.296	0.45
*LCL – lower confidence limit ** UCL – Upper confidence limit					

Table 3
Summary of multivariate logistic regression model for early endocrine therapy change or discontinuation

Factor	Comparison	Odds Ratio	95% LCL*	95% UCL**	P-value
Age	>=65 vs. <65	1.322	0.725	2.418	0.36
BMI	Overweight vs. Normal Weight	1.952	0.876	4.549	0.11
	Obese vs. Normal Weight	**2.813**	**1.225**	**6.824**	**0.02**
SMI	**< 6.75 vs. >=6.75**	**1.941**	**1.003**	**3.755**	**0.05**
Number of Comorbidities	>=1 vs. 0	1.794	0.988	3.258	0.055
*LCL – lower confidence limit ** UCL – Upper confidence limit					

Supplement 1 summarizes the univariate logistic regression of sarcopenia and any endocrine toxicity. Older patients (p = 0.02) and patients with sarcopenia (p = 0.03) had worse endocrine therapy toxicity, while no association was observed for BMI or any comorbidity.

Discussion

To our knowledge, this is the first report of the impact of sarcopenia on endocrine therapy toxicity and endocrine treatment adherence in patients with EBC. Our findings suggest an opportunity to identify patients at higher risk for severe endocrine therapy side effects and early treatment discontinuation.

Current guidelines recommend that adjuvant endocrine therapy be continued for 5 to 10 years. However, prolonged treatment duration combined with prevalent side effects [21–23] may lead to a decrease in adherence; up to 50% of patients report not taking these medications as often as prescribed, and up to 20% discontinue endocrine therapy in the first year due to side effects [24, 25]. We have identified sarcopenia as an important risk factor for endocrine therapy toxicity and intolerance. We did not find medical comorbidity or BMI to be risk factors for endocrine therapy toxicity.

A recent review demonstrated that exercise could improve or reverse sarcopenia among cancer survivors [26]. Physical exercise is often recommended to reduce arthralgias and other side effects of endocrine therapy [27–29]. It has been shown that exercise decreases sarcopenia and improves bone density and quality of life in patients on endocrine therapy [30, 31]. It would be of interest to study whether targeting patients with sarcopenia for a supervised exercise program could mitigate endocrine treatment toxicity and improve therapy adherence.

Possible etiologies for the association between sarcopenia and worse endocrine therapy tolerance are that patients with sarcopenia have greater frailty and metabolic dysfunction [32, 33]. Patients with sarcopenia have higher levels of pro-inflammatory factors, including fibrinogen, TNF alfa, IL-6, C-reactive protein, which may impact the metabolism of drugs, promote further sarcopenia and impair cancer therapy due to side effects [34–36]

Limitations of our study include the retrospective observational design and the homogeneous population (90% white), which may influence the external validity of the results. Also, the timing of the collection of body composition data was not standardized with respect to the initiation of endocrine therapy or receipt of additional treatment, including chemotherapy and surgery, which may influence body composition and affect results. Strengths of our study include the size of the cohort, and the use of BIS rather than CT scans to screen for sarcopenia. BIS is a reliable, inexpensive, easy-to-use, radiation-free technique and provides the skeletal muscle mass immediately with potential for real-time use in clinical decision making.

In patients with EBC, sarcopenia was associated with worse endocrine therapy side effects independent of BMI and other medical comorbidities. Future prospective studies may determine optimal interventions to mitigate toxicity for this at-risk group.

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Author contribution

GFPA–conceptualization, data curation, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft and writing review and editing

SAV–conceptualization, investigation, methodology, project administration, software, supervision, validation, visualization, writing to review and editing

WW–formal analysis and writing review and editing

HCFM- conceptualization, data curation, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing the original draft and writing review and editing

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to confidentiality reasons but are available from the corresponding author on reasonable request

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Cleveland Clinic

Consent to participate

Informed consent was not needed due to observational characteristic of the study

Prior presentations

Not applicable

Disclaimers

Not applicable

Acknowledge

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