Modification of Abdominal Fat Distribution After Aromatase Inhibitor Therapy in Breast Cancer Patients Visualized Using 3-D Computed Tomography Volumetry

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Abstract

The pattern of abdominal fat distribution is hormone linked and it can affect or be predictive of various diseases, in particular metabolic syndrome is associated with an increase amount of visceral adipose tissue. After system therapy with aromatase inhibitor in breast cancer patients, we found a relative increase of visceral adipose tissue regardless of whether they gained or lost weight after therapy.

Introduction/Background: The purpose of this study was to describe modification of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) distributions in breast cancer patients after aromatase inhibitor (AI) therapy using computed tomography (CT) volumetric measurement of abdominal body fat distribution. **Patients and Methods:** Sixty-four consecutive patients who were receiving adjuvant AI therapy were included in this study. Patients were evaluated using CT before and after at least 6 months of AI therapy with imaging follow-up of 4.3 ± 2.2 years. Abdominal fat distribution was automatically calculated using a workstation that obtained total abdominal adipose tissue (TAAT) area (mm^3). SAT was manually segmented and VAT was determined as TAAT − SAT. Percentages were calculated for change of TAAT, VAT, and SAT. VAT/SAT ratio was calculated. **Results:** Percentage of TAAT after AI therapy was increased by a mean of 9.1% from baseline (16,280.3 ± 6953.3 mm^3) to (17,763.6 ± 6850.8 mm^3). Two groups of patients were observed; those with an increase in TAAT and those with a decrease. Modification of VAT/SAT ratio was observed (from 1.38 to 1.69) in all subjects, reflecting a relative increased volume of VAT (mean, 18%) and slight mean reduction of SAT (mean 1.9%). **Conclusion:** In our study, therapy with AI in breast cancer patients was accompanied with a change in fat distribution to relatively greater VAT/SAT ratio in patients, regardless of whether they gained or lost weight after therapy. Because this pattern of fat distribution is associated with metabolic disorders, attention must be paid to these clinical manifestations in patients during their follow-up management.

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Introduction

Breast cancer is the most common malignancy in women, represents 18% of all female cancers, and there are > 100,000 new cases of hormone receptor-positive breast cancers per year in the United States.[1] To reduce the risk of recurrence in postmenopausal women with hormone receptor-positive breast cancer, aromatase inhibitor (AI) therapy is currently recommended for 5 years and has become the standard of care because of their superior reduction of breast cancer recurrence compared with estrogen receptor agonists and antagonists.[2] It is well known that estrogen plays an important role in initiating and promoting breast cancer.[3] Because of this recognition, hormone therapy plays an important role in the treatment of breast cancer, in fact, AIs are drugs that inhibit the aromatase-mediated synthesis of estrogens in peripheral tissues, with the effect of decreasing body estrogen level. The AIs may be

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nonsteroidal, such as the triazole derivatives, anastrozole and letrozole, or steroidal, such as exemestane.[4] In postmenopausal women the dominant source of estrogens is the peripheral conversion from androgens, which is catalyzed by aromatase, an enzyme of the cytochrome P450 subfamily, mediated by the *CYP19A1* gene. Aromatase enzymes in premenopausal women are highly expressed in placenta and in granulose cells of ovarian follicles.[5] Additionally, aromatases are present, at lower levels, in several nonglandular tissues including subcutaneous fat, liver, muscle, brain, normal breast, and breast cancer tissue.[6] Estrogen production after menopause is solely from nonglandular sources, in particular from subcutaneous fat.[7] Recent studies have observed that that treatment with AIs might be associated with an increase of cardiovascular diseases.[8,9] Amir et al[8] reported in their metaanalysis that longer duration of AI use was associated with an increased odds ratio of cardiovascular disease. During menopause, androstenedione produced in the adrenal glands, and, to a lesser extent, testosterone produced in the ovaries, are released into the circulation, and then sequestered to nonglandular tissues such as liver and breast, where they are converted to estrone and estradiol, respectively, by aromatase enzymes located in nonglandular tissues, especially subcutaneous fat.[6] Body fat mass and its distribution in men and women is determined by both sex steroids, androgens and estrogens, which play important roles, and their effect results in different patterns of total abdominal adipose tissue (TAAT) distribution. The male pattern of fat distribution is termed "android," which is characterized by a high amount of visceral adipose tissue (VAT), and the female pattern is termed "gynoid," which is characterized by peripheral or gluteofemoral fat distribution with a greater amount of subcutaneous adipose tissue (SAT). SAT of the abdomen is defined as the fat tissue located between the skin and abdominal musculature, and VAT is the fat tissue present within the abdominal cavity. VAT tissue contains adipocytes that are more metabolically active, and are linked to a series of disease processes involving the cardiovascular systems[10] and also carcinogenesis.[11] Different fat compartments are thereby associated with differential metabolic risks.[12] Previous studies on the risk of developing metabolic diseases have shown that the VAT compartment might possess unique pathogenic properties[13] that can influence the risk of developing metabolic diseases.[14] Visceral adipose obesity is well known be associated with adverse metabolic effects and increased cardiovascular risk, and a prominent aspect of this tissue is a predominance of androgen action over that of estrogen.[15,16] In fact, circulating androgen levels are greater in women with central obesity compared with nonobese women.[17] Previous reports indicate that aromatase deficiency in humans[18] and in mice[19] results in a predominance of androgens over estrogens, abdominal obesity, and insulin resistance.[20] A prolonged period of estrogen suppression, such as occurs during AI therapy, results in relative hyperandrogenemia,[21] that might induce major alterations in body composition that might be more extensive than those induced by menopause.[22] Quantification of abdominal adipose tissue can be performed using several methods. In clinical practice, measurement of body mass index (BMI) is commonly performed, however, this approach does not evaluate an increase in visceral fat,[23] and similarly limited are surface measurements such as the circumference of the hip, the waist to hip circumference ratio, or abdominal sagittal diameter, which also do not separate VAT from SAT with any reliability.[24] The most accurate and reproducible methods are computed tomography (CT)- or magnetic resonance images, which allow visualization of the body compartments.[25] In the current medical literature, there are many studies that describe the measurement of abdominal fat tissue using imaging with the intent to understand the relationship between VAT and the metabolic syndrome.[26] To the best of our knowledge, no previous study has used objective quantification of VAT and SAT with cross-sectional imaging to evaluate the potential modification of fat compartment distribution in women taking AIs for the treatment of breast cancer. The purpose of our study was to determined the presence of anthropometric modification using CT volumetry of abdominal body fat distribution in patients with previous breast cancer who are taking AI therapy.

Patients and Methods

Patients

This study was approved by our institutional ethics committee with written informed consent. This retrospective study included 64 consecutive Caucasian female patients (mean age, 55.8 ± 11.7 years; age range, 36-77 years), who underwent CT scanning between September 2005 and December 2012. Selection criteria were: histologically confirmed breast cancer after radical mastectomy, postmenopausal status, AI adjuvant therapy for at least 6 months before CT restaging, no recurrence of breast cancer, and no other substantial disease over the follow-up period (average, 4.3 ± 2.2 years). Clinical characteristics of the subjects are summarized in Table 1.

Table 1 Clinical Characteristics of the Study Sample (n = 64 Patients)

Characteristic	Value
Age, Years	55.9 ± 11.7
Aromatase Inhibitor	
Anastrozolo	n = 33/64
Letrozolo	n = 31/64
Stage, %	
Ia	4
Ib	4
IIa	21
IIb	23
IIIa	6
IIIb	1
IIIc	5
Anthracycline-Based Adjuvant Chemotherapy, %	
No	9
Yes	55
Histology, n	
ER status (positive)	63/64
PR status (positive)	60/64
c-erb-B2 status (triple positive)	6/64
Grading, %	
1	7
2	32
3	25