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The impact of an aromatase inhibitor on body composition and gonadal hormone levels in women with breast cancer

G. J. van Londen,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

S. Perera,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

K. Vujevich,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

P. Rastogi,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

B. Lembersky,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

A. Brufsky,

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

V. Vogel, and

Cancer Institute, Geisinger Medical Center, Danville, PA, USA

S. L. Greenspan

Medicine, University of Pittsburgh, 3471 Fifth Ave, Suite 500 Kaufmann Medical Bldg, Pittsburgh, PA 15213, USA

G. J. van Londen: vanLondenJ@upmc.edu

Abstract

Aromatase inhibitors (AIs) have become the standard adjuvant therapy of postmenopausal breast cancer survivors. AIs induce a reduction of bioavailable estrogens by inhibiting aromatase, which would be expected to induce alterations in body composition, more extensive than induced by menopause. The objectives are to examine the impact of AIs on (1) DXA-scan derived body composition and (2) gonadal hormone levels. This is a sub-analysis of a 2-year double-blind, placebo-controlled, randomized trial of 82 women with nonmetastatic breast cancer, newly menopausal following chemotherapy, who were randomized to risedronate (35 mg once weekly) versus placebo, and stratified for their usage of AI versus no AI. Outcomes included DXA-scan

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Correspondence to: G. J. van Londen, vanLondenJ@upmc.edu.

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derived body composition and gonadal hormone levels. As a group, total body mass increased in women over 24 months. Women on AIs gained a significant amount of lean body mass compared to baseline as well as to no-AI users ($P < 0.05$). Women not on an AI gained total body fat compared to baseline and AI users ($P < 0.05$). Free testosterone significantly increased and sex hormone binding globulin (SHBG) significantly decreased in women on AIs compared to no AIs at 24 months ($P < 0.01$) while total estradiol and testosterone levels remained stable. Independent of AI usage, chemotherapy-induced postmenopausal breast cancer patients demonstrated an increase of total body mass. AI users demonstrated maintenance of total body fat, an increase in lean body mass and free testosterone levels, and a decrease in SHBG levels compared to no-AI users. The mechanisms and implications of these changes need to be studied further.

Keywords

Breast cancer; Body composition; Gonadal hormones; Aromatase inhibitors

Background

There are over 100,000 new cases of hormone–receptor positive breast cancer per year in the US [1]. In order to reduce the risk of recurrence in postmenopausal women with hormone–receptor positive breast cancer, therapy with aromatase inhibitors [2] [AIs: anastrozole (Arimidex[®]), exemestane (Aromasin[®]), and letrozole (Femara[®])], is currently recommended for 5 years and has become the standard of care due to their superior reduction of breast cancer recurrence compared to estrogen–receptor–agonists–antagonists [ERAs, e.g., nolvadex (Tamoxifen[®])] [3]. When a long-term, adjuvant treatment is recommended for early stage breast cancer to decrease the risk for distant relapse or new second primary breast cancer, patterns of adverse effects weigh heavily into treatment planning and monitoring. In postmenopausal women, the main source of estrogen is peripheral conversion from androgens by aromatase [2]. Since AIs inhibit aromatase, postmenopausal women taking AIs experience a further reduction in circulating, bio-available estrogens as well as a theoretical increase in androgens [2]. A prolonged period of profound estrogen suppression and (relative) hyperandrogenemia could be expected to induce major alterations in body composition and cardiovascular risk, possibly more extensive than those induced by menopause [4]. The effects of AIs on non-cancer outcomes and other aspects of the hormonal milieu have been under-explored.

The Risedronate's Effect on Bone loss in Breast Cancer Study (REBBeca Study) demonstrated that administration of risedronate once weekly for 2 years in newly postmenopausal women with breast cancer, positively affected spine and hip BMD and bone turnover, independent of their concurrent use of an aromatase inhibitor (AI) [5]. The objectives of this secondary analysis were to examine the impact of AIs versus no AIs (i.e., ERAs and no hormonal therapy) on (1) body composition, using the whole body DXA-scan methodology (Hologic), and (2) gonadal hormone levels in these postmenopausal women.

Methods

Materials and methods

Study design—This secondary analysis reports the body composition and gonadal hormone changes of 82 of the 87 women in the parent study for whom adjuvant cancer therapy data were available, who had been enrolled in a 2-year double-blinded trial based on their recent postmenopausal status (≤ 8 years) after having received polyadjuvant chemotherapy for nonmetastatic breast cancer and who had body composition data

available. Women had been randomized to active treatment with risedronate ($n = 43$, 35 mg po once weekly) or a matched placebo ($n = 44$), as previously described [5]. Briefly, women were not eligible if they had been diagnosed with a second primary cancer, abnormal bone, and mineral metabolism (due to medications or underlying disorders such as hyperthyroidism, malabsorption, renal failure, and hepatic failure), or current fracture.

The trial did not restrict concurrent use of adjuvant hormonal therapy as prescribed by their oncologist, allowing them to freely initiate or change a hormonal agent if medically necessary (e.g., AIs, ERAAs). Subjects were assigned to the AI group if they had been on anastrozole (Arimidex[®]), exemestane (Aromasin[®]), or letrozole (Femara[®]) for at least 3 months immediately preceding a follow-up assessment. Those who were not on adjuvant therapy or were on adjuvant hormonal therapy other than AIs [such as tamoxifen (Nolvadex[®]), toremifene (Fareston[®]), and fulvestrant (Faslodex[®])] were assigned to the no-AI group.

The University of Pittsburgh Institutional Review Board approved the protocol. Participants were advised about the nature of the study and they provided written informed consent before participation.

Outcome variables—Body composition (total body mass, body fat, and lean body mass) was measured at each visit (0, 6, 12, 18, and 24 months) using body composition software on a Hologic QDR-4500A bone densitometer (Hologic Inc., Bedford, MA). The coefficients of variation for total fat mass is 2.1%, total lean mass 1%, and total fat is 1% [6].

Gonadal hormones [testosterone (total and free), estradiol (total), and sex hormone binding globulin (SHBG)] were measured via Radioimmunoassay (RIA) methodology by the Clinical and Translational Research Center of Johns Hopkins's University. The corresponding inter- and intra-assay coefficients of variation are 5.39 and 4.73 for total testosterone, 5.67 and 5.00 for free testosterone, 6.97 and 3.72 for estradiol, and 6.54 and 6.54 for SHBG.

Statistical analysis—All data analysis was performed using SAS[®] version 9.2 (SAS Institute, Inc., Cary, North Carolina) with risedronate and placebo arms combined for greater statistical power in the absence of evidence that risedronate affects body composition and gonadal hormone levels. First, we compared the baseline characteristics of those on and not on an AI using independent samples *t*-tests. Next, for the analysis of body composition measures (collected every 6 months) analysis, we operationally defined a subject to have been an AI user at a given follow-up assessment if she had been on an AI for at least 3 of the 6 months since the previous assessment. In an initial model, we excluded from analysis any assessments of a subject after switching adjuvant cancer therapy from an AI to a no AI (or vice versa), and fit a linear mixed model with change from baseline in each body composition measure as the dependent variable; AI (yes/no), follow-up time (6, 12, 18, and 24 months) and their interaction as fixed effects of interest; and a subject random effect to obtain preliminary effects of AI on body composition. Next, these preliminary estimates were used to adjust body composition measures of those switching cancer therapy from a no AI to an AI in the middle of the study so that body compositions of those subjects could be analyzed as if they had been on AI from the start of the study. We used appropriately constructed contrasts to assess the AI effect at 6, 12, 18, and at 24 months. This process of estimation of effects and adjusting of outcomes was repeated a large number of times until the estimates stabilized and converged. This methodology has been successfully used elsewhere to address similar analyses [5]. For gonadal hormone analysis, we took a similar approach as above for the initial but did not perform the repetitive estimation process because data was collected only annually. Finally, we used Pearson product-moment

correlations to examine associations between changes in gonadal hormones and changes in body composition. Both raw and percent changes were considered in all analyses to ensure robustness of results.

Findings

Clinical characteristics at baseline—Information about screening, randomization and follow-up are published in detail elsewhere [5]. At baseline, 11 women reported to consume an AI, 21 no hormonal therapy, while the remaining 50 women were on alternate hormonal therapy [of whom 47 nolvadex (Tamoxifen®)]. There were no statistically significant differences between the two groups at baseline as reported in Table 1.

Changes in body composition (Fig. 1)—The total body mass increased 1.79 ± 0.74 kg ($P < 0.05$) from baseline over 24 months for women who were on AIs, as well as those who were not (1.76 ± 0.66 kg), without any significant difference between these groups (Fig. 1). Total body fat increased $1.2 \pm 0.4\%$ ($P < 0.05$) for women not on AIs while it remained stable in AI users resulting in a significant difference ($P < 0.05$) between the AI and no-AI users over 24 months. The opposite was observed for the lean body mass changes over 24 months: AI users displayed a 1.16 ± 0.28 kg increase in lean body mass compared to both baseline and no-AI users ($P < 0.05$).

Changes in gonadal hormone levels—There were no significant changes between the AI users and no-AI users for total testosterone and estradiol values at 24 months (Fig. 2). However, the free testosterone levels were significantly higher and the SHBG levels were significantly lower compared to no-AI users at 24 months ($P < 0.01$).

Interpretation

This secondary analysis of the REBBeca study demonstrated that chemotherapy-induced, newly postmenopausal women with breast cancer increased their total body mass significantly over 24 months. Those who used AIs demonstrated stable total body fat mass, increased lean body mass as well as free testosterone levels, and decreased SHBG levels, compared to no-AI users.

The effect of ERAAs or AIs on body composition has been relatively underexplored. Raloxifene, an ERAA, has revealed mixed results on body composition. Two randomized clinical trials demonstrated that it exerts estrogenic agonistic effects on body composition as early as after 8 weeks of drug therapy (i.e., shifts body composition from android to gynoid distribution) [7, 8]. However, a third randomized trial did not detect an effect of raloxifene on body composition over 12 months, but the baseline values of body composition differed between controls and women on raloxifene [9]. A large, 24 month, randomized clinical trial is underway [10]. The effect of tamoxifen, another ERAA, on body composition has also been inconsistent. A cross-sectional study revealed that post-menopausal tamoxifen users, compared to postmenopausal controls, had higher values for CT-scan derived liver density and visceral fat areas [11]. However, a randomized clinical trial did not demonstrate an effect of tamoxifen on body weight or body fat distribution [12]. The effect of an aromatase inhibitor on body composition was examined in a trial, which randomized postmenopausal women, who had received at least 2 years of treatment with tamoxifen, to either continuation treatment with tamoxifen versus a switch to an AI (exemestane) [13]. This trial revealed that the women who were randomized to continuation treatment with tamoxifen did not demonstrate a change in fat mass and ratio of “fat free mass over fat mass” over 1 year. However, the women who were randomized to exemestane revealed a decrease in fat mass and an increase in ratio of “fat free mass/fat mass”. The author did not provide an explanation for the finding that AIs do not decrease muscle mass, as was expected based on

the relationship between estrogens and muscle mass [14], but increase muscle mass. Although we did find a statistically significant alteration in body composition, the clinical relevance of an increase of 1.16 kg in lean mass for women on AIs, or an increase of 1.16% of body fat for women not on AIs, is not known.

To the best of our knowledge, there are no additional publications available reporting the effect of AIs on body composition. We hypothesized that the increase in lean body mass in women on AIs is related to a relative increase in male gonadal hormones. AIs inhibit aromatase, an enzyme which is responsible for the majority of estrogen production in postmenopausal women by converting male gonadal hormones peripherally [2]. As a result, inhibition of aromatase leads to lower estrogen levels, but can also theoretically contribute to accumulation of male gonadal hormones, as we have shown (Fig. 2). The effect of AIs on male gonadal hormones in postmenopausal women was assessed by Dowsett et al. Both these investigations reported no changes of male gonadal hormone levels in women on anastrozole [15] (but duration of treatment was only up to 14 days) and letrozole [16] (duration of treatment was 12 months). A positive interaction between androgens and muscle mass has been established in men and is only beginning to be explored in women [17, 18].

The finding of an increase in testosterone may have clinical relevance. If a relative increase of testosterone can induce a 1.16 kg increase in lean body mass, it warrants our attention to also explore its effects on cardiovascular risk factors and disease. The pro-atherogenic role of androgens, relative to estrogens, in female cardiovascular disease is being increasingly recognized [19–21]. Similarly, we are only starting to understand that SHBG per se can play an active role as well: decreased levels of SHBG increase risk of diabetes mellitus II and vice versa [22, 23]. Therefore, the observation that women on AIs have a triple insult is potentially worrisome (higher levels of androgens, lower levels of SHBG and estrogens). Currently, the effects of AIs on lipid profile and cardiovascular risk remain inconclusive [24–27] and require further exploration especially in light of a recent publication which reported higher mortality in non-relapsed breast cancer patients on AIs [28].

There are several limitations to this study. A relatively small proportion of women in this study were on AIs. Since this represents a secondary analysis we were unable to control for many factors such as lifestyle habits and the exact timing of initiation/modification/discontinuation of hormonal therapy. Body composition had been assessed via DXA methodology which is an acceptable method but we could not assess compartmental information, which may possibly underlie our observation that total body fat did not change significantly over 24 months in women on AIs [29]. Similarly, DXA methodology does not allow us to differentiate between muscle and water within lean body mass. This knowledge may be essential, since hormonal therapy has been shown to be able to affect water content [30]. Therefore, the effect of AIs on lean body mass cannot be assumed to be related to a change in muscle mass only, without also taking into account water content. Gonadal hormone levels were measured using RIA methodology. Time-fluctuation may have interfered with these assessments. In addition, lower levels of estrogen are near the detection limit of RIA methodology, which may explain why we observed a trend toward lower estrogens in AI-users, which did not reach statistical significance. In addition, systemic gonadal hormone levels alone may not provide sufficient information, since the microenvironment needs to be taken into account as well [31]. Finally, similar to Francini et al. [13], our data do not provide an insight into the “chicken and egg” phenomenon, i.e., whether changes in body composition precede gonadal hormone level changes, or vice versa, or a combinational vicious cycle.

The strengths of this study include that this is the first study revealing the effect of AIs on body composition (and gonadal hormone profile). The study was performed at a single center resulting in the usage of one DXA machine and a limited number of technologists, allowing us to obtain a better estimate of true treatment effect. The duration of follow-up was 2 years, which provides a good insight into the long-term effects of AIs on body composition.

We conclude that chemotherapy-induced postmenopausal breast cancer patients over 24 months demonstrate an increase of total body mass, independent of AI usage. The use of AIs is associated with a maintenance of total body fat, an increase in lean body mass and free testosterone, and a decrease in SHBG levels compared to no-AI users at 24 months. These observations provide an important insight into non-cancer effects of AIs, which may have long-term consequences. The mechanisms and implications of these changes require further exploration.

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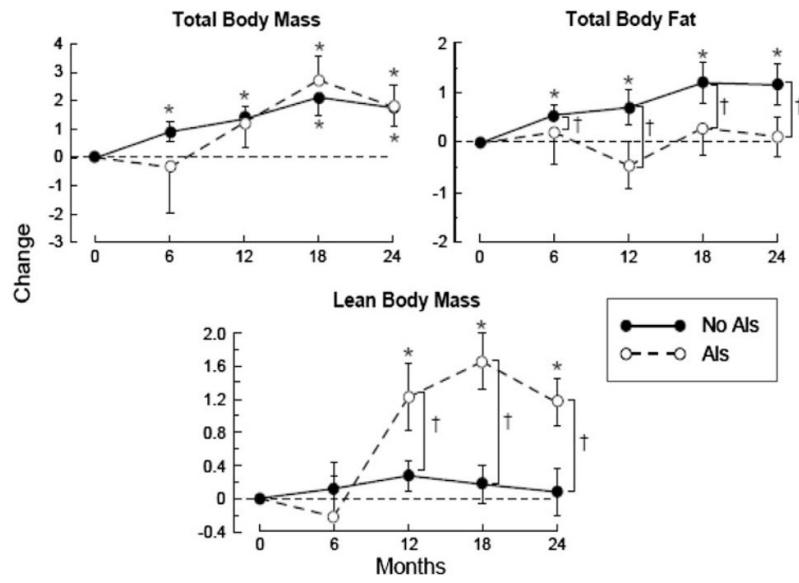


Fig. 1. Changes (mean and standard error) in total body mass (kg), total body fat (%), and lean body mass (kg) over 24 months (* $P \leq 0.05$ change from baseline, † $P \leq 0.05$ between-group comparison). AI aromatase inhibitor

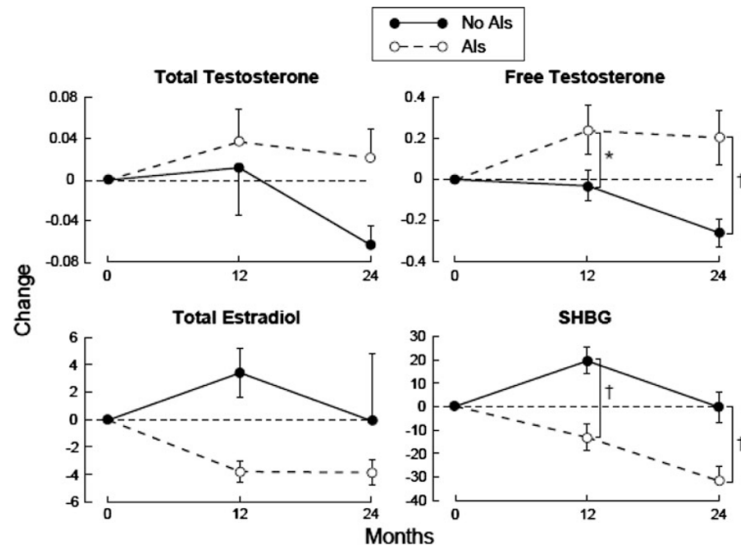


Fig. 2. Changes (mean and standard error) in total testosterone (ng/ml), free testosterone (pg/ml), total estradiol (pg/ml), and SHBG (nmol/l) over 24 months (between-group comparisons: * $P \leq 0.05$, † $P \leq 0.01$). *AI* Aromatase inhibitor, *SHBG* sex hormone binding globulin

Table 1

Baseline relevant clinical characteristics, body composition, and gonadal hormone levels between AI and no-AI users (no statistically significant differences)

Parameters	No AIs mean \pm SE (median) (n = 71)	AIs mean \pm SE (median) (n = 11)
Age (yr)	49.78 \pm 0.61	51.18 \pm 2.14
Years postmenopausal	3.15 \pm 0.22	3.39 \pm 0.61
ERAA	50	NA
No adjuvant hormonal therapy	21	NA
Body composition		
Total body mass (kg)	74.9 \pm 2.0	76.4 \pm 4.1
Lean body mass (kg)	44 \pm 0.8	45.6 \pm 1.9
Total body fat (%)	37.70 \pm 0.78	36.99 \pm 1.21
Gonadal hormones		
Testosterone total (ng/ml)	0.28 \pm 0.02	0.30 \pm 0.03
Testosterone free (pg/ml)	1.27 \pm 0.07	1.49 \pm 0.16
SHBG (nmol/l)	157.27 \pm 10.46	97.35 \pm 15.21
Estradiol total (pg/ml)	27.68 \pm 5.68	17.34 \pm 8.55

For additional baseline characteristics, please refer to a prior publication [5]

SE Standard error, *SHBG* sex hormone binding globulin, *AI* aromatase inhibitor