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CLINICAL TRIAL

A prospective assessment of musculoskeletal toxicity and loss of grip strength in breast cancer patients receiving adjuvant aromatase inhibitors and tamoxifen, and relation with BMI

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Abstract Aromatase inhibitor (AI) therapy for estrogen receptor-positive breast cancer is known to induce or enhance musculoskeletal problems. We have previously reported that loss of grip strength is more pronounced in AI-users with extremes in BMI. We here report results from a larger prospective study. Postmenopausal early breast cancer patients scheduled to start AI or tamoxifen therapy were recruited. A functional assessment grip strength test was performed at baseline, 3, 6, and 12 months of therapy. BMI was assessed, and a rheumatologic questionnaire was completed at each visit. 188 patients on an AI and 104 patients on tamoxifen were enrolled. 74 % of AI-users reported new/worsened musculoskeletal complaints compared with 37 % in the tamoxifen group. This was translated in a larger grip strength decrease in patients experiencing AI-induced pain opposed to patients without new/worsened complaints ($p = 0.0002$). 15 % of AI-users discontinued therapy due to musculoskeletal symptoms, who were characterized by a larger grip strength reduction versus adherent patients ($p = 0.0107$). Young age ($p = 0.0135$), taxane-based chemotherapy ($p = 0.0223$), and baseline VAS score >4 ($p = 0.0155$) were predictors for AI-related musculoskeletal pain. In addition, a quadratic trend of BMI with grip strength change ($p = 0.0090$) and probability of discontinuation was observed ($p = 0.0424$). Musculoskeletal events were a substantial problem in AI-treated patients and an important reason for treatment discontinuation. The decrease in grip strength was larger in AI- than in tamoxifen-users, with a more pronounced change in symptomatic patients. The inverse relationship between BMI extremes and grip strength change was confirmed in this large group of AI-patients.

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Introduction

Numerous large clinical trials have shown an improved disease free survival when including an aromatase inhibitor (AI) in the adjuvant endocrine therapy regimen of breast cancer patients as compared to tamoxifen alone [1]. As breast cancer recurrence decreases, ensuring an adequate quality of life when taking this long-term daily oral therapy becomes increasingly important. However, AI-use has been associated with multiple adverse effects, thereby threatening therapy adherence and effectiveness [2]. Particularly, the negative impact on the musculoskeletal system represents an important issue with more than half of patients experiencing these troublesome symptoms [3–5].

Most frequently encountered complaints include arthralgia, myalgia, carpal tunnel syndrome (CTS), stiffness, and paresthesia which are enclosed in the AI-induced musculoskeletal syndrome (AIMSS).

We did previously show that the subjective symptoms of AIMSS are associated with physiologic changes to the joint and functional impairments like loss of grip strength [6]. These abnormalities were more important in AI- than in tamoxifen-users. Importantly, the hand grip test was well correlated with the tenosynovial changes seen on magnetic resonance imaging (MRI). Furthermore, in this small group of AI-treated patients, musculoskeletal changes were more pronounced in women with very low and very high baseline BMI [7].

In the current cohort study, we prospectively evaluated these findings in a larger population, together with other putative predictive factors of AI-related musculoskeletal pain. The change in grip strength and incidence of endocrine therapy-related adverse events were assessed in early breast cancer patients treated with an AI or tamoxifen.

Patients and methods

Study design

Consecutive postmenopausal women with an early hormone receptor-positive breast cancer scheduled to start adjuvant hormonal therapy with any of the third generation AI (letrozole, anastrozole or exemestane) or tamoxifen were recruited at University Hospitals Leuven between February 2009 and June 2012. The decision to treat with an AI or tamoxifen was based on our institution's in-house protocol for the use of either therapy [8]; there was no self-selection of patients based on age or pre-existing joint symptoms. Women with severe rheumatologic disorders or concomitant intake of sex hormone-containing drugs such as hormone replacement therapy were excluded. All other treatments, including analgesics, were permitted and their use was monitored. Demographic data, including BMI and waist-to-hip ratio (WHR), and a rheumatologic questionnaire were collected at baseline. Functional assessment test of grip strength was performed by squeezing the balloon of a modified sphygmomanometer (Martin Vigorimeter Measuring Instrument, Albert Waeschle Ltd, Dorset, UK) three times with the maximal force being recorded. Re-evaluations were done at 3, 6, and 12 months after endocrine therapy start. In cases wherein discontinuation of the drug was warranted (as determined by the attending physician), a repeat evaluation was performed 3 months after termination of the initial endocrine treatment.

The study was approved by the Ethical Committee for Clinical Studies of University Hospitals Leuven, Belgium before commencement of the study (s51575).

Questionnaire

The questionnaire addressed musculoskeletal symptoms that the patient experiences, if they were novel or worsened during the last 3 months of endocrine therapy, the methods and treatments tried for symptom management, and the benefit obtained from each management method used. Subjects rated symptoms they experienced the previous week on a 5-point Likert scale (NSABP symptom checklist) ranging from "not at all" to "extremely". Included in that module was a 10 point visual analog scale (VAS) on which the participant was asked to mark her average pain severity for musculoskeletal pain of the previous 24 h.

Subjects were also asked about menopausal complaints and to state how likely symptoms were related to the AI or tamoxifen medication using a 5-point Likert scale (from "definitely not due to medication" to "definitely due to medication" or "I don't know"). To assess adherence to therapy, the Medication Adherence Report Scale (MARS 5) questionnaire was used, which has shown effectiveness in endocrine treatment before [9]. This scale gives an indication of the extent to which non-adherent behaviors occur, including how often patients have consciously not taken their drugs or forgotten to take them [10].

AI-induced musculoskeletal pain was defined as an increase in arthralgia or myalgia relative to baseline; AIMSS presence was defined as the presence of $\geq$3 out of five features (arthralgia, myalgia, joint stiffness, tingling, CTS).

Table 1 Baseline demographic and medical characteristics

	AI	Tamoxifen
Number of patients	188	104
Age, years; mean (range)	63 (47–88)	64 (46–88)
BMI, kg/m^2; mean (range)	26 (17–41)	27 (19–40)
Years past menopause; mean (range)	13 (0–40)	15 (0–38)
WHR, mean (range)	0.9 (0.7–1.2)	0.9 (0.7–1)
Age at menarche, years; mean (range)	13 (10–21)	13 (10–17)
Grip strength, kPa; mean (range)		
Left hand	50.2 (20–86)	49.9 (2–90)
Right hand	52.6 (21–100)	52.4 (19–105)
Tumor grade; *n* (%)		
1	12 (7)	32 (31)
2	105 (57)	63 (60)
3	67 (36)	9 (9)
Pathologic nodal status; *n* (%)		
Node negative	58 (36)	87 (89)
Node positive	105 (64)	11 (11)
Adjuvant chemotherapy; *n* (%)	70 (37)	2 (2)
Taxane regimen; *n* (%)	60 (32)	2 (2)
Adjuvant radiotherapy; *n* (%)	21 (89)	81 (78)
Pain VAS; mean (range)	2.6 (0-10)	1.6 (0-7)
Musculoskeletal pain; *n* (%)	107 (66)	49 (50)

AI aromatase inhibitor; *BMI* body mass index; *WHR* waist-to-hip ratio; *VAS* visual analog scale

Statistics

The primary endpoint was to assess the effect of BMI on loss of grip strength in AI-treated postmenopausal breast cancer patients. The sample size was calculated based on data from our preliminary study to predict the percent change in grip strength after 6 months using 33 patients [6]. In these data, we observed a quadratic effect of BMI on change in grip strength using a very small sample. Regarding sample size for the present study, we aimed to detect an increase in adjusted R^2 of 0.2 when adding BMI information to the "age only" model. 100 patients allowed a 90 % power at an alpha level of 0.05, however a sample size of 300 patients was chosen regarding the longitudinal nature of the present study and to ensure sufficient power and precision of the estimated effects. Secondary objectives of this study were the effect of AI and tamoxifen on grip strength, the frequence of musculoskeletal and other menopausal symptoms, and predictive factors of AI-induced musculoskeletal toxicity.

Linear models were used for analyses with change of grip strength as response variable. Clustering of observations due to the presence of repeated measurements was accounted for by introducing a fully unstructured residual covariance matrix. Proportional odds models were used for analyses with a 3-level ordinal musculoskeletal pain (absent, present, new/worsened). Logistic regression models were used for the analyses of discontinuation. All tests are 2-sided and p values <0.05 were considered significant. All analyses have been performed using SAS software, version 9.2 of the SAS system for Windows.

Table 2 Sites of reported joint pain by patients on endocrine agents

	AI	Tamoxifen
Hands/fingers, *n* (%)	101 (62)	27 (27)
Shoulders, *n* (%)	100 (61)	14 (18)
Back, *n* (%)	96 (59)	32 (33)
Hips, *n* (%)	76 (48)	19 (19)
Knees, *n* (%)	105 (64)	32 (33)
Feet/toes, *n* (%)	63 (38)	16 (16)
Tingling hands/fingers, *n* (%)	77 (47)	32 (32)
Tingling feet/toes, *n* (%)	41 (25)	3 (3)

AI aromatase inhibitor

Results

Baseline demographic and medical characteristics

A total of 292 early breast cancer patients were enrolled; 104 patients started tamoxifen and 188 AI therapy. Letrozole was most frequently prescribed ($n = 147$, 78 %), followed by anastrozole ($n = 39$, 21 %). Only 2 patients (1 %) were treated with exemestane. Baseline patients characteristics are displayed in Table 1. 70 patients (37 %) had received prior adjuvant chemotherapy in the AI group relative to 2 patients (2 %) of the tamoxifen-treated group.

Musculoskeletal symptoms and grip strength

Musculoskeletal pain was frequently encountered prior to endocrine therapy start (Table 1). These complaints increased over the study period; 65 % of tamoxifen and 89 % of AI-treated patients reported musculoskeletal pain during at least one of the follow-up visits with 37 and 74 % having new or worsened pain, respectively.

AIMSS (≥3 features: arthralgia, myalgia, joint stiffness, tingling, CTS) was experienced by 18 % of the tamoxifen group and by 60 % of AI-users.

Hands, knees, shoulders, and back were among the most frequently affected sites, as reported by the patient (Table 2). In addition, tingling in fingers was commonly encountered in both groups.

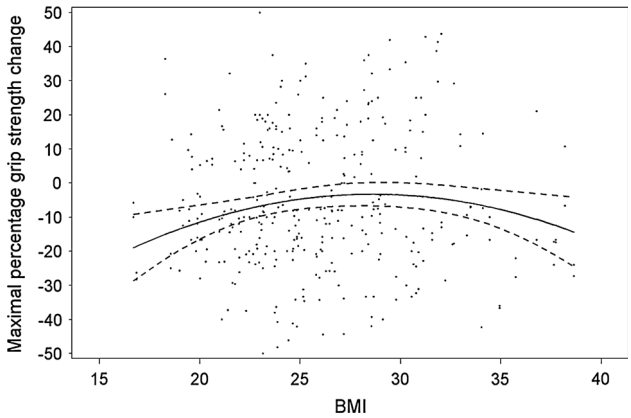

Fig. 1 Observed and model-predicted maximal percentage grip strength change (+95 % CI) during the 1-year follow-up by BMI for AI-users. *BMI* body mass index; *CI* confidence interval; *AI* aromatase inhibitor

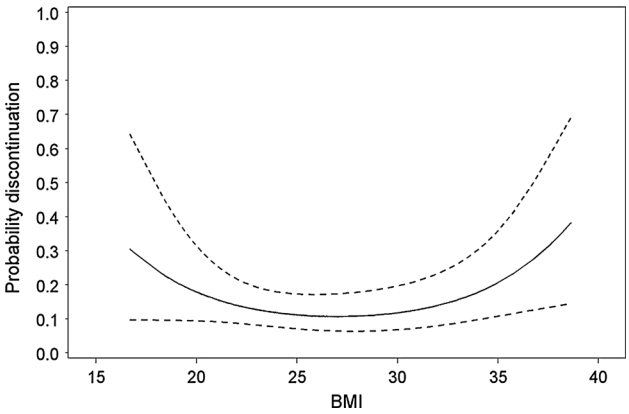

Fig. 2 Model-predicted probability of discontinuation (+95 % CI) during the 1-year follow-up by BMI for AI-users. *BMI* body mass index; *CI* confidence interval; *AI* aromatase inhibitor

AI-related musculoskeletal toxicity was shown to be strongly associated with decrease in grip strength ($p = 0.0011$). In that regard, a significant decrease of grip strength over time was seen in AI-users (−4 kPa; $p < 0.0001$), after correction for age and baseline grip strength. No change could be demonstrated for tamoxifen-treated patients (−0.7 kPa; $p = 0.5327$).

A 2.5 kPa larger decrease in grip strength was seen for patients experiencing AI-induced pain compared to AI-treated patients without new or worsened pain ($p = 0.0002$). Furthermore, this reduction was more distinct in patients urged to stop AI therapy secondary to musculoskeletal complaints (−10 kPa) versus adherent patients (−4 kPa) ($p = 0.0107$).

A minor mean increase in grip strength was observed in patients who switched to tamoxifen ($n = 13$), however this change was not statistically significant ($p = 0.6181$).

Pain intensity, as measured with VAS, increased with a median of 1 unit in tamoxifen-users and 2 units in AI patients on a 0–10 scale over the 12 months period.

Predictors of musculoskeletal toxicity in AI-users

Taxane-based chemotherapy was a risk factor for worsened or new AI-related musculoskeletal pain ($p = 0.0223$). In addition, a higher baseline VAS score and young age (≤55 years) were associated with both musculoskeletal toxicity ($p = 0.0155$ and $p = 0.0135$, respectively) and early AI discontinuation ($p = 0.0128$ and $p = 0.0125$, respectively). A trend toward decreasing musculoskeletal toxicity with increasing time after menopause ($p = 0.0767$) was observed, nevertheless this trend disappeared after correction for age ($p = 0.2037$).

Age 55 years or less ($p = 0.0168$), late menarche ($p = 0.0347$), and high baseline VAS score ($p = 0.0509$) were all associated with a larger decrease in grip strength.

No effect of number of positive lymph nodes, Her-2 status or WHR could be demonstrated.

In AI-users, a quadratic trend of baseline BMI with maximal % grip strength change was observed, with a larger decrease in grip strength in patients with extremes in BMI ($p = 0.0090$; Fig. 1). Furthermore, a similar quadratic association for BMI with probability of early AI therapy discontinuation could be demonstrated ($p = 0.0424$; Fig. 2). The latter was also seen for baseline WHR ($p = 0.0325$).

Methods for pain relief

Musculoskeletal pain was predominantly managed with over-the-counter pain relievers. 41 % of AI-users reported the use of narcotic analgesics and non-steroidal anti-inflammatory drug (NSAID) compared to 24 % of tamoxifen-treated patients (Table 3). In the majority of the patients, these agents seemed to be effective (87 and 91 %, respectively). Physical therapy and exercise were the most commonly applied interventions, as reported by the patient. However, it should be noted that a large number of patients did not report any management approach for their pain.

Menopausal symptoms

Patients were asked about the experience of various menopausal symptoms (Table 4). Approximately, 80 % of patients complained of hot flashes. Leg cramps, feeling blue, and weight gain were also frequently reported by both groups. In addition, half of patients were affected by memory loss and concentration problems. However, twice

Table 3 Methods tried to relieve musculoskeletal symptoms during the 1-year follow-up and effectiveness, as scored by the patient

	AI		Tamoxifen	
	Patients who tried method, *n* (%)	Effectiveness, *n* (%)	Patients who tried method, *n* (%)	Effectiveness, *n* (%)
Medication	74 (45)	64 (87)	24 (24)	21 (88)
Physical therapy	34 (21)	18 (76)	6 (6)	6 (100)
Acupuncture	3 (2)	2 (67)	5 (5)	5 (100)
Massage	9 (6)	5 (75)	4 (4)	3 (75)
Increase exercise	31 (19)	16 (77)	8 (8)	6 (75)
Yoga	3 (2)	2 (100)	2 (2)	NR
Lose weight	2 (1)	1 (0)	4 (4)	NR
Surgery	4 (3)	2 (100)	0 (0)	0 (0)

AI aromatase inhibitor; *NR* not reported

Table 4 Presence of menopausal symptoms during the 1-year follow-up and proportion attributable to therapy, as reported by the patient

	AI		Tamoxifen	
	Patients who experience symptom, *n* (%)	Attributable to therapy, *n* (%)	Patients who experience symptom, *n* (%)	Attributable to therapy, *n* (%)
Hot flashes	132 (81)	114 (86)	74 (74)	63 (85)
Leg cramps	100 (61)	37 (37)	67 (67)	26 (39)
Blue	68 (42)	22 (32)	35 (35)	4 (11)
Memory loss	92 (56)	33 (36)	50 (50)	10 (20)
Concentration problems	64 (39)	29 (45)	40 (40)	9 (23)
Loss sex drive	85 (64)	44 (52)	31 (36)	10 (32)
Pain during intercourse	43 (34)	30 (70)	14 (18)	4 (18)
Vaginal dryness	71 (47)	51 (72)	23 (27)	8 (35)
Weight gain	83 (52)	35 (42)	43 (43)	19 (44)
Weight loss	39 (24)	4 (10)	18 (18)	0 (0)
Anxious	50 (31)	11 (22)	27 (27)	4 (15)

AI aromatase inhibitor

as much of AI-treated patients (20 %) specifically attributed these adverse events to their therapy as compared to tamoxifen-users (10 %). Furthermore, gynecologic symptoms, like loss of sex drive, pain during intercourse, and vaginal dryness were much more common in AI-users.

Adherence

Adherence to treatment was evaluated by asking the patients about their endocrine therapy intake by means of the MARS5 questionnaire. 84 % of tamoxifen-users reported to be fully adherent to their medication, relative to 73 % in the AI group. Forgetfulness was the most frequent reason mentioned among women reporting seldom-sometimes not taking their medication. Intentional non-adherence was predominantly caused by the occurrence of adverse events, resulting in early AI therapy discontinuation in 28 patients (15 %). 20 patients (71 %) switched to tamoxifen, 4 patients (14 %) to another AI therapy; three to anastrozole, one to exemestane. The remaining 4 patients (14 %) ended all endocrine therapy. Discontinuation was most observed within the first 3 months (37 %) and between 6 and 12 months (48 %) after AI start.

In the tamoxifen group, 2 patients developed musculoskeletal symptoms, 1 patient vaginal loss, and 1 patient a deep vein thrombolic event and consequently discontinued tamoxifen therapy (4 %). 3 out of the 4 patients switched to AI medication.

Discussion

In the present cohort study, we were able to prospectively confirm the quadratic relationship between BMI and change in grip strength, which we previously demonstrated in a small group of patients [7]. Women with a low or very

high baseline BMI were more likely to experience a decrease in grip strength over the 12-month study period. In addition, this finding was strengthened by a similar relationship between BMI and risk of early AI therapy discontinuation.

Our results endorse the importance and adverse impact of musculoskeletal events on daily quality of life and adherence in breast cancer patients treated with an AI. This was established both by patient-reported musculoskeletal pain and a decrease in grip strength, which was more pronounced in symptomatic patients.

We have previously demonstrated a strong correlation between decrease in grip strength and tenosynovial changes, as seen on MRI in symptomatic AI-users [6]. The grip strength test has high inter-rater reliability and takes a minimal amount of time to administer. Furthermore, it is an objective, easy to reproduce, and inexpensive test. This has implications both in terms of patient monitoring, as well as for clinical trial designs, and for future promising interventions to alleviate this important treatment-related adverse effect. It should be noted that two other studies were not able to establish an association between change in grip strength and AI-induced musculoskeletal symptoms, however patient number was lower and a less sensitive dynamometer was used [11, 12].

On the other hand, adverse events were also collected by patient-reported outcomes, capturing the actual condition of the patient with their subjective perception and not merely the clinician's impressions, as the majority of previous toxicity evaluations are based on [13].

The high numbers of patients affected by AI-related musculoskeletal toxicity and early AI discontinuation stress the need for proper interventions. Like the present study demonstrates, most patients look for relief with over-the-counter analgesics, merely a symptomatic management option as the etiology remains still unclear. Exercise should be encouraged in these patients as shown by the recent hormones and physical exercise (HOPE) study, which demonstrated significant improvements in AI-related musculoskeletal pain in AI-users randomized to moderate exercise during 1 year versus patients assigned to usual care [14].

Numerous investigational interventions have been suggested to relieve the above discussed complaints [15–19]. However, none of these have resulted in level III evidence so far. We recently hypothesized a role for the growth hormone (GH)/insulin-like growth factor I (IGF-I) axis, with larger changes in symptomatic patients [7].

In this prospective analysis, young age and high baseline VAS score were predictive factors for both musculoskeletal pain and premature AI therapy discontinuation. These findings are consistent with several previously published studies [20, 12, 21–23].

Similarly, patients who received taxane-based chemotherapy were more likely to experience musculoskeletal toxicities, confirming the results of multiple studies including those of the ATAC trial [20, 24, 25].

More contradictory results exist regarding the effect of prior tamoxifen on musculoskeletal toxicity, with both protective [3, 26] and triggering effects reported [22, 23]. In the present study, all patients were treated upfront with an AI and consequently none of them received prior tamoxifen, so we were not able to evaluate this factor.

A trend toward a decreased likelihood of musculoskeletal toxicity with increasing time after menopause was observed. Nevertheless, this trend disappeared after correction for age, as opposed to several other published studies [25, 27, 28].

Future studies should also address baseline psychological factors, like anxiety, which have recently been shown to play a major role in pain development [29].

Adherence was high for both patient groups, 84 and 73 % of our tamoxifen and AI-treated patients, respectively, stated to be fully adherent to their endocrine therapy, which was assessed by asking the patient about her adherence behavior. However, self-reporting is known to largely overestimate actual adherence, which is a limitation of the current study. Other studies report only half of women successfully completes 5 years of endocrine therapy [30], thereby threatening breast cancer outcome.

As reported by several other groups, musculoskeletal symptoms were already frequently experienced by the participants at baseline, prior to AI start. This might be due to previous chemotherapy, concomitant medication, or comorbid conditions. Nonetheless, our results and those of others clearly underline the additional adverse effect of AI use on these complaints.

Strengths of the current study include the large study population and the prospective longitudinal design with baseline data and multiple assessments in which the patient serves as its own control. Furthermore, we included a comparable tamoxifen-treated group and collected patient-reported complaints to reflect the total clinical setting.

In summary, our results confirm that musculoskeletal events are a substantial problem in patients treated with an AI and an important reason for early treatment discontinuation. The decrease in grip strength over time was larger in AI- than in tamoxifen-treated patients, with a more pronounced change in symptomatic patients and patients urged to stop AI treatment. The adverse effect of extremes in baseline BMI on grip strength was confirmed in this large group of AI patients. In addition, we identified young age, taxane chemotherapy, and pre-existing pain as clinical predictors of musculoskeletal pain under AI treatment.

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Conflict of interest The authors have declared no conflicts of interest.

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