Aromatase inhibitor induced loss of grip strength is body mass index dependent suggesting an effect on the growth hormone - insulin-like growth factor-I axis.

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Abstract

Objective Preliminary results from a prospective magnetic resonance imaging (MRI) study showed that [illegible] decrease in grip strength [illegible] the aromatase inhibitor (AI) induced musculoskeletal syndrome (AIMSS). Here, we report the final results [illegible] the relationship between body mass index (BMI) and grip strength [illegible].

Patients and methods We conducted a prospective cohort study including 33 postmenopausal early breast cancer patients receiving either an AI (n=27) or tamoxifen (n=6). At baseline and after 6 months, patients received a rheumatologic examination and a MRI assessment of both hands and wrists. The primary endpoint was change from baseline in tenosynovial abnormalities. Secondary endpoints were changes from baseline in morning stiffness, intra-articular fluid and grip strength and its association with BMI.

Results After six months of anti-hormonal therapy, no AI user improved with respect to tenosynovial abnormalities, amount of intra-articular fluid and morning stiffness. On the contrary, 74% (95% CI, 51-89%), 56% (95% CI, 34-75%), and 22% (95% CI, 9-45%) of the patients worsened. Grip strength decreased 8% for the left hand (95% CI, 2-21%) and 11% for the right (95% CI, 4-17%). A regression analysis suggested that grip strength decreases more for subjects with high (around 30 kg/m^2) or with low BMI (around 20 kg/m^2).

Conclusion AIMSS is characterized by tenosynovial changes, intra-articular fluid and morning stiffness. We hypothesize that the quadratic association between BMI and loss of grip strength reflects AI induced changes on the endocrine control of the growth hormone insulin-like growth factor-I pathway.

Keywords Aromatase inhibitors, arthralgia, Magnetic Resonance Imaging, BMI, IGF-I, breast cancer

Introduction

The third generation aromatase inhibitors (AIs) anastrozole, letrozole and exemestane have become an established component of treatment for postmenopausal hormone-responsive breast cancer. There is superiority over tamoxifen in terms of both disease free survival and toxicity profile, with a lower incidence of thrombo-embolism and endometrial cancer [1-6]. The long term use of AIs in the metastatic, adjuvant and probably also preventive setting will increase worldwide [7-9].

AI induced musculoskeletal syndrome (AIMSS) was first reported in the metastatic setting [10]. Recent trials comparing AIs with tamoxifen or placebo recognized AIMSS as a problem, but incidence rates were underestimated [11-13]. Three features of AIMSS (arthritis, arthralgia, myalgia) were each significantly more frequent on letrozole than on placebo in tamoxifen pretreated patients in the MA 17 study [14]. In the Intergroup Exemestane Study (IES), the adjuvant switch trial with exemestane, arthralgia was worse and carpal tunnel syndrome (CTS) was 9 times more prevalent in patients who switched after 2 to 3 years from tamoxifen to exemestane compared to those remaining for the 5 years on tamoxifen [3]. Data regarding CTS are recently also available for patients in the ATAC trial, being 3.5 times more frequent in women receiving anastrozole than in women receiving tamoxifen [15]. AIMSS is now better defined and includes, in addition to arthralgia or joint pain, also musculoskeletal pain, CTS, joint stiffness and paresthesia. Therefore, in daily clinical practice, up to half of our patients experience AIMSS with some of whom report worsening of pre-existent symptoms. This hampers compliance and eventually, 1 out of 4 patients abandons treatment due to incapacitating symptoms which can severely impact daily functioning and quality of life [16-20].

Although the anatomic correlate of AIMSS has been thoroughly evaluated with plain X-Rays [21], magnetic resonance imaging (MRI) [22], ultrasound [23, 24] and electromyography [23], the pathogenesis remains unknown. There is inconsistency regarding AI induced changes in inflammatory mediators previously associated with estrogen signaling, but pre-treatment cytokine levels may predict AIMSS [25, 26]. It is indeed important to identify patients at risk for AIMSS not only to clarify its pathogenesis, but also to suggest a proper treatment as this remains disappointing. Some approaches like vitamin D supplementation, acupuncture and diuretics look promising [27-30]. Reports on the effect of weight or body mass index (BMI) on AIMSS are conflicting but in the ATAC trial, obese women (BMI > 30kg/m^2) were more likely to report joint symptoms (37.2%) than women

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with a BMI of 25-30 kg/m^2 (31.3%) and women with a BMI lower than 25 kg/m^2 (31.0%) [31]. Szoeke et al. demonstrated a significant association between a high BMI and joint pain as well [32].

We prospectively assessed changes in rheumatologic symptoms (morning stiffness and grip strength) and in MRI findings (tenosynovial abnormalities and intra-articular fluid) in AI users. Interim results have previously been reported from a selection of patients [22]. In addition, we retrospectively assessed the association between BMI and changes in grip strength. A quadratic effect was hypothesized in that patients with either high or low pre-treatment BMI would show a greater grip strength decrease. Our findings generate a hypothesis to explain part of the AIMSS pathogenesis.

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Patients and methods

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Design, setting and participants

We conducted a prospective single-center cohort study in the University Hospitals Leuven (Leuven, Belgium). Consecutive postmenopausal women with early breast cancer scheduled to start first-line adjuvant endocrine therapy with any of the third generation AIs (anastrozole, letrozole, or exemestane) or tamoxifen were included in this study. The decision to start an AI or tamoxifen was based on our institution's in-house protocol for use of either therapy; there was no self-selection of patients based on age or underlying joint symptoms. Thirty-three patients were recruited between May 2006 and July 2008. Since this paper deals with AI induced problems and only a minority received tamoxifen, results for the tamoxifen patients are only reported briefly.

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Measurements and study variables

The methods were reported in the initial paper [22]. Briefly, patients completed demographic data and a rheumatologic history questionnaire. At baseline, weight and length were assessed to calculate pre-treatment BMI. A single blinded rheumatologist performed clinical examination of both hands, which included careful assessment of joint and tendon abnormalities and functional evaluation by a hand grip test. MRI of both hands and wrists was performed in each patient. All images were interpreted by the same blinded experienced musculoskeletal radiologist. Both clinical and radiologic follow-up investigations were repeated after 6 months of therapy or earlier when patients considered stopping treatment prematurely because of severe joint complaints.

MRI results are reported as number of images that showed the pathology over the total of images taken (there is one image for each hand and thus two images per patient). The repeat rheumatologic examination and MRI at 6 months took into account the baseline findings. The results of the rheumatologic examination after 6 months therapy are reported as either a new onset of symptoms or worsening of a pre-existing symptom from baseline for each patient. Scores for morning stiffness could be –1 (improvement of pre-existing findings or disappearance), 0 (no change) or 1 (worsening of pre-existing findings or new onset).Tenosynovial changes were defined as an increase in the amount of fluid in the tendon sheath or thickening and enhancement of the tendon sheaths. For tenosynovial abnormalities and intra-articular fluid, the scores for each hand were as per the rheumatological examination (-1, 0, 1). Also, a combined score was constructed by summing the scores of both hands. This score could equal –2 (improvement for both hands), –1 (improvement for one hand, no change for the other), 0 (no change for both hands, or improvement for one hand and worsening for the other), +1 (worsening for one hand, no change for the other), and +2 (worsening for both hands). Changes in grip strength were expressed as the percentage change versus baseline.

The study was conducted according to the guidelines for clinical studies described in the Declaration of Helsinki [33]. The protocol was approved by the Ethical Committee for Clinical Studies of the University Hospitals Leuven, Belgium, before commencement of the study and all participants provided written informed consent.

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Study endpoints

The primary endpoint was the change from baseline in tenosynovial abnormalities on MRI. Secondary endpoints were changes from baseline for morning stiffness, grip strength and intra-articular fluid on MRI. An additional retrospective endpoint was the relationship between BMI and changes in grip strength.

Statistical analysis

Changes in tenosynovial abnormalities, intra-articular fluid and morning stiffness were analyzed using percentages, together with 95% confidence intervals (CI) for multinomial proportions [34], and using the sign test. Changes in grip strength were analyzed by the median percentage change versus baseline with a 95% CI based on the binomial distribution [35], and the sign test. For tamoxifen patients, the results were listed without constructing CIs or applying the sign test. The effect of BMI on the percentage change in grip strength for AI users was analyzed using fixed-effects repeated measurements regression analysis. The repeated measurements represent the presence of two grip strength results per patient, one from each hand. We therefore have twice as much data points as patients. Predictors used in the model were hand (to account for the repeated measurements), BMI, age, changes in tenosynovial abnormalities per hand (-1, 0, or 1) and changes in intra-articular fluid per hand (-1, 0, or 1). Special attention was given to the hypothesized quadratic effect of BMI, and for age and BMI possible nonlinearities were explored using local regression (loess). To investigate model assumptions and the influence of data point on the model fit, influence diagnostics were examined, such as studentized residuals, Cook's D, the covariance ratio and the normal quantile plot [36].

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Results

Baseline demographic and medical characteristics

Thirty three patients completed all the planned investigations and were included in this report. Of these patients, 27 were treated with an AI (letrozole, n = 8, exemestane, n = 12, anastrozole, n= 7) and 6 with tamoxifen. Baseline demographic and medical characteristics are described in Table 1. Median age was 64 years (range, 51 to 74 years) and median BMI was 24 kg/m^2 (range, 18 to 45 kg/m^2) for AI treated patients. Tamoxifen users had a median age of 61 years (range, 54 to 68 years) and a median BMI of 23 kg/m^2 (range, 21 to 26 kg/m^2). Two patients in the AI group and two in the tamoxifen group received adjuvant chemotherapy prior to endocrine therapy.

Over half of the postmenopausal breast cancer patients scheduled to receive adjuvant endocrine therapy had some form of pre-existing musculoskeletal disorder. On baseline MRI, there was fluid accumulation seen in the joints of nine AI users and in two of the tamoxifen patients. Tenosynovial abnormalities were seen in seven of the AI users and in two of the tamoxifen patients.

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Table 1 Baseline demographic and medical characteristics

	AI	Tam
Number of patients	27	6
Age, years; median (range)	64 (51-74)	61 (54-68)
BMI, kg/m^2; median (range)	24 (18-45)	23 (21-26)
Years past menopause, median (range)	13 (0-39)	11 (1-28)
Previous intake of HRT, n (%)	14 (52%)	3 (50%)
Clinical tumor size, n (%)		
<2cm	11 (41%)	2 (33%)
≥2 to 5cm	16 (59%)	3 (50%)
>5cm	0 (0%)	1 (17%)
Pathologic nodal status, n(%)		
Node negative	15 (56%)	2 (33%)
Node positive	12 (44%)	4 (67%)
Adjuvant chemotherapy, n (%)		
FEC regimen	0 (0%)	1 (17%)
Sequential taxane and FEC	2 (7%)	1 (17%)
Rheumatologic findings, n (%)		
Osteoarthritis	18 (67%)	5 (83%)
Morning stiffness	9 (33%)	1 (17%)
Grip strength, kPa; median (range)		

Left hand	41.6 (23.3-71.3)	39.0 (30.3-49.0)
Right hand	48.6 (27-65.3)	43.3 (31.6-51.0)
MRI findings, n (%)		
Intra-articular fluid	9 (33%)	2 (33%)
Tenosynovial abnormalities	7 (26%)	2 (33%)

AI: aromatase inhibitor, Tam: tamoxifen, HRT: hormonal replacement therapy

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MRI changes after 6 months of anti-hormonal therapy

After six months we observed that tenosynovial abnormalities and amount of intra-articular fluid had worsened relative to baseline (Table 2). On MRI follow-up, 20 AI patients (74%, 95% CI = 51 – 89%) had worsening of pre-existing changes or new onset of any pathology in joints or tendons, thirteen of them in both hands. Of the tamoxifen patients with valid MRI data, three had no changes and two worsened for both hands. Regarding intra-articular fluid, 56% (95% CI = 34 – 75%) of the AI-users had an increase in intra-articular fluid. In the tamoxifen treated patients, two patients showed an increase in intra-articular fluid in one hand, whereas one patient worsened for both hands. For both tenosynovial abnormalities and intra-articular fluid, no one improved relative to baseline. The p-value of the sign test to test for a change from baseline was <0.001 for both MRI measurements.

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Table 2 Changes from baseline for MRI measurements

	Tenosynovial abnormalities		Intra-articular fluid	
	AI	Tam[a]	AI	Tam[a]
	N	*N*	*N*	*N*
Score	*% (95% CI)*		*% (95% CI)*	
-2	0	0	0	0
	0% (0-20%)		0% (0-20%)	
-1	0	0	0	0
	0% (0-20%)		0% (0-20%)	
0	7	3	12	2
	26% (11-51%)		44% (23-68%)	
1	7	0	11	2
	26% (11-51%)		41% (21-64%)	
2	13	2	4	1
	48% (26-71%)		15% (5-39%)	

p-value for sign test to test whether there is a significant difference from 0 in the change in tenosynovial thickening for AI users: <0.001 and in intra-articular fluid for AI users: <0.001

score: -2 (improvement for both hands), -1 (improvement for one hand, no change for the other), 0 (n change for both hands, or improvement for one hand and worsening for the other), +1 (worsening for one hand, no change for the other) and +2 (worsening for both hands)

AI: aromatase inhibitor, Tam: tamoxifen, CI: confidence interval

[a] one patient was excluded due to invalid MRI data

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Change in grip strength and morning stiffness from baseline to 6 months anti-hormonal therapy

Changes in morning stiffness are presented in Table 3. Six AI patients (22%, 95% CI = 9 – 45%) experienced increased morning stiffness from baseline whereas no one improved. The p-value of the sign test was 0.031. It is noteworthy that none of the tamoxifen patients experienced increased or new onset morning stiffness.

Grip strength in the left and right hands decreased after 6 months of anti-hormonal therapy (Table 4). There is a tendency to have more strength in the right hand (which is more often the dominant hand; Table 1), and to have a stronger decrease in strength for this hand. The left hand in AI patients experienced a median decrease of 8% relative to baseline (range, -20.5; -2), whilst for the right hand a median reduction of 11.4% relative to baseline (range, -16.8; -4.2) was observed. For both hands, the p-value of the sign test was 0.009. For the tamoxifen users, grip strength decreased with median 4.20 (range, -32.3, -10.6) in the right hand and with median 0.2 (range, -14.1; -5.6) in the left hand.

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Table 3 Changes from baseline for morning stiffness

	AI	Tam
	N	*N*
Score	*% (95% CI)*	
Improvement	0	0
(-1)	0% (0-17%)	
No change	21	6
(0)	78% (55-91%)	
Worsening	6	0
(1)	22% (9-45%)	

p-value for sign test to test for a statistically significant change from baseline: 0.031.
AI: aromatase inhibitor, Tam: tamoxifen, CI: confidence interval

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Table 4 Percent change from baseline for grip strength by hand

Therapy / Hand	Median % change (95% CI)[a]	p[b]	Range
AI			
Left	-8.0 (-20.5, -2.0)	0.009	-82.7 – 51.5
Right	-11.4 (-16.8, -4.2)	0.009	-77.5 – 36.4
Tam			
Left	-0.2		-14.1 – 5.6
Right	-4.2		-32.3 – 10.6

[a] confidence interval is based on binomial distribution (Conover, 1980)
[b] sign test
AI: aromatase inhibitor, Tam: tamoxifen, CI: confidence interval

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Relationship between BMI and grip strength for AI users

Change in grip strength was predicted using tenosynovial changes, fluid changes, age and BMI. There was one patient with BMI 45 kg/m^2 whose data had an enormous influence on the model fit. This case had a highly deviant BMI (second largest BMI was 32.9 kg/m^2), and we decided to omit this patient from the analysis. As showed in Table 5, the quadratic effect of BMI was a predictor of grip strength change (parameter estimate -0.68, SE 0.21, p=0.003). The BMI values of the patients included in the analysis range between 18 and 33 kg/m^2. This effect is visualized in Figure 1 for a random hand of 'average' patients (i.e. 64 years, worsened tenosynovial abormalities, unchanged intra-articular fluid). When BMI increases from 18 to 25, the expected percentage decrease in grip strength becomes smaller. When BMI increases from 25 to 33, the expected decrease becomes larger again. A nonparametric regression analysis using local regression (loess) that included the highly influential case supported the quadratic effect of BMI between 18 and 33 kg/m^2.

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Table 5 Parameter estimates from the repeated measures regression analysis to predict the percentage change from baseline in grip strength

Effect	Parameter Estimate	SE	p
Intercept	2.09	7.24	
Hand			
Left	1.24	5.18	0.812
Right (reference)	0	-	-
BMI[a]	0.42	0.91	0.650
BMI square[a]	-0.68	0.21	0.003
Age[a]	0.50	0.58	0.396
Tenosynovial changes	-7.21	6.92	0.304
Fluid changes	-0.17	5.75	0.976

[a] BMI and age values were centered in the regression model by subtracting their respective median (25 kg/m^2 and 64 years)
SE: standard error

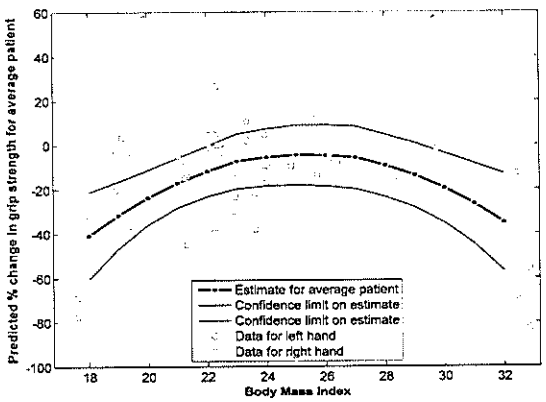


Figure 1. Visualization of the estimated relationship between BMI and percentage change in grip strength in AI users after controlling for hand, age, tenosynovial and fluid changes from baseline. The relationship shown is the estimated percentage change in grip strength by BMI for average patients (64 years old, worsened tenosynovial abnormalities, unchanged intra-articular fluid). The pointwise 95% confidence limits are shown.

Discussion

Results of this study for all patients are in line with our previously reported preliminary results [22]. Serial assessment, rheumatologic examination and MRI of hand and wrist after 6 months therapy showed a marked worsening of all parameters compared to baseline. The tenosynovium thickened substantially in AI users, whereas the amount of intra-articular fluid increased. Our finding regarding a high BMI as a predictor for AI induced loss of grip strength is consistent with findings reported by Crew et al. and Sestak et al. [20, 29]. A high BMI has previously been associated with aches and stiff joints in a population-based prospective study of perimenopausal Australian-born women, menstruating at baseline and interviewed annually over 8 years to test the effect of decreasing estrogens on arthralgia [32]. However, we also found an association between AI induced loss of grip strength and a low BMI. Although Crew et al. only reported high BMI as a risk factor for AIMSS in a cross-sectional survey of consecutive postmenopausal women receiving adjuvant AI therapy for early-stage hormone-sensitive breast cancer, joint pain and stiffness were also more frequent in women with a low BMI as compared to women with a normal BMI; this increase was significant for joint pain, but not for stiffness [20]. This is in line with our findings of a functional loss in women with extremes in BMI.

We previously discussed the scoring system we adapted for reporting changes in morning stiffness, MRI images and hand grip strength [22]. Tenosynovial and articular changes as seen on MRI identify the anatomic substrate for the hand pain and disability which characterize AIMSS and the increased incidence of CTS. The strength of our prospective study is that each patient served as her own control. Therefore, our results may be considered as unbiased since we report changes induced by treatment rather than mere prevalence of symptoms or radiologic findings, likely to be biased by the high background of nonspecific muscle and joint aches in women affected by breast cancer. There is an association with prior chemotherapy, especially taxanes [37] and younger postmenopausal age [12].

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A potential weakness in our study design was MRI reproducibility as we lack data on inter- and intraobserver variability in image interpretation. However, all images were assessed by the same musculoskeletal radiologist who was blinded to the treatment patients were receiving and to the other clinical data.

It has been hypothesized that AIMSS is caused by profound estrogen deprivation induced by the potent third generation AIs. There are numerous reports exploring a possible link between estrogen deprivation, joint disorders and pain. Because estrogen can exert a direct antinociceptive effect on the central nervous system [38-41], one may hypothesize that estrogen deprivation could lead to enhanced pain sensation at a peripheral level. The absence of circulating estrogens at the level of estrogen receptors in joint tissue may also induce as yet unknown biochemical and pathophysiological changes at peripheral sites, leading to debilitating joint pain. It is clear that other mechanisms play an important role in AIMSS.

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Numerous studies have documented a reversed U-shaped association between BMI and health related issues [42-45]. Our finding of a non-linear effect of BMI and AI induced loss of grip strength suggests an underlying biological effect. We hypothesize this effect is mediated by the effect of AIs on the growth hormone Insuline like growth factor I (GH-IGF-I) pathway for several reasons. First of all, there is a U-shaped association between BMI and circulating IGF-I levels. Individuals with a BMI of 26-27 kg/m^2 have a higher IGF-I concentration compared to those with either a lower or a higher BMI [46-50]. Secondly, studies of GH administration for prevention or treatment of effects of aging have been prematurely stopped as they worsen or induce arthralgia and CTS [51]. The increased incidence of arthralgias, edema and CTS in women treated with GH was directly correlated with changes in IGF-I levels. Thirdly, endocrine therapies for breast cancer affect serum IGF-I concentrations [52]. Whereas IGF-I levels are lowered by tamoxifen as a result of its estrogenic activity on different target systems in a dose-dependent way [53, 54], various studies have demonstrated an increase in circulating IGF-I in postmenopausal women receiving AI treatment for breast cancer [55-58]. In a randomized controlled trial comparing tamoxifen with the AI vorozole, IGF-1 levels fell significantly in the tamoxifen group, whereas vorozole patients showed a non-significant increase. The difference between groups was significant [59]. This may explain the high rate of symptomatic CTS in those who switch from tamoxifen to an oral AI reported in IES due to the significant rise in IGF-I levels. This phenomenon of painful joints by lowering circulating estrogens was also seen in postmenopausal women who changed from oral to transdermal estrogens, which led to upregulation of IGF-1 [60]. We therefore hypothesize that an AI induced increase in IGF-I would preferentially affect those with low IGF-I levels. Since lean and obese women have lower levels of IGF-I than women with a normal BMI, we would therefore expect a higher frequency of AIMSS in the women with high or low BMI. We are currently investigating this hypothesis in a prospective study of AI induced changes in grip strength and serum levels of IGF-I and its binding proteins. If our hypothesis is confirmed, this could potentially lead to additional options for therapy. For example, Lombardi et al. have recently shown that somatostatin is useful to treat symptomatic patients with elevated IGF-I levels including those with arthralgia [61]. Ongoing clinical studies with AIs and blockers of IGF may reveal whether blocking IGF together with an AI leads to lower likelihood of AIMSS than in those on the AI alone, although since these studies are primarily being conducted in subjects with metastatic breast cancer the symptoms may be difficult to assess.

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Our results are hypothesis generating. The excellent correlation between clinical and MRI findings provides an objective substrate for the subjective complaints of AIMSS.