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Impact of body mass index on estradiol depletion by aromatase inhibitors in postmenopausal women with early breast cancer

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Background: Body mass index (BMI) has an impact on survival outcome in patients treated with aromatase inhibitors (AIs). Obesity is associated with an increased body aromatisation and may be a cause of insufficient estradiol depletion.

Methods: Sixty-eight postmenopausal oestrogen receptor-positive patients with early breast cancer were prospectively included in this study. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol were analysed immediately in the clinical routine lab and in a dedicated central lab before (T1) and 3 months after start with aromatase inhibitors (T2).

Results: A total of 40 patients were normal or overweight (non-obese: BMI 18.5–29.9 $kg\,m^{-2}$) and 28 were obese (BMI $\geqslant 30\,kg\,m^{-2}$). Aromatase inhibitors significantly suppressed estradiol serum levels (T1: 19.5 $pg\,ml^{-1}$, T2: 10.5 $pg\,ml^{-1}$, $P<0.01$) and increased FSH serum levels (T1: 70.2 $mIU\,ml^{-1}$, T2: 75.7 $mIU\,ml^{-1}$, $P<0.05$). However, after 3 months of AI treatment, estradiol levels of obese patients were nonsignificantly higher compared with non-obese patients (12.5 $pg\,ml^{-1}$ *vs* 9.0 $pg\,ml^{-1}$, $P=0.1$). This difference was reflected by significantly lower FSH serum levels in obese compared with non-obese patients (65.5 $mIU\,ml^{-1}$ *vs* 84.6 $mIU\,ml^{-1}$, $P<0.01$). The significant effects of BMI on FSH serum levels could be detected both in the routine as well as in the dedicated central lab.

Conclusion: Aromatase inhibitors are less efficient at suppressing estradiol serum levels in obese when compared with non-obese women.

BMI has an impact on breast cancer risk and prognosis (Renehan *et al*, 2008; Ewertz *et al*, 2011). Obese postmenopausal women have an increased risk of breast cancer and increased risk of disease recurrence and death when compared with normal weight women (De Azambuja *et al*, 2010; Protani *et al*, 2010; Ewertz *et al*, 2011;). This higher risk can be attributed, at least in part, to an increased total body aromatisation and consequently elevated oestrogen serum levels in obese postmenopausal women.

Aromatase inhibitors (AIs) – upfront or after 2–3 years of tamoxifen – are the gold standard of adjuvant endocrine therapy in hormone receptor-positive postmenopausal patients with breast cancer (Burstein *et al*, 2010). The aim of AIs is to block the

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aromatisation from androgens to estrogens and thereby deplete oestrogen serum levels in postmenopausal women. Recently it has been shown that BMI has an impact on the efficacy of AIs, mainly anastrozole, in patients with breast cancer (Sestak *et al*, 2010; Pfeiler *et al,* 2011). Obese patients treated with an AI have a worse outcome regarding disease recurrence and death compared with normal weight patients. Regarding current literature, it might be that BMI is not only a prognostic but also a predictive parameter in hormone receptor-positive breast cancer. This assumption could be strengthened by the reanalysis of the ABCSG6a trial, which compared an additional 3 years of anastrozole *vs* no further treatment after 5 years of endocrine therapy (Gant *et al,* submitted). The additional 3 years of anastrozole halved the relative risk of recurrence and significantly improved the overall survival in normal weight patients, whereas overweight/obese patients did not benefit from further endocrine treatment.

In summary, the insufficient ability of AIs to fully suppress oestrogen serum levels in obese women is a relevant hypothesis to explain the lower AI efficacy in this large group of patients.

Besides BMI, non-compliance is of major interest regarding endocrine therapy, as it can dramatically lower the outcome of patients assigned to AI treatment (Partridge *et al*, 2008; Hadji *et al,* 2013a). It has been shown repeatedly that up to 15% of the patients stop taking their AI after 1 year of adjuvant therapy and only 66% are still on therapy after 3 years. Though non-adherence is well recognised today, strategies to improve compliance are rare (Hadji, 2010; Hadji *et al,* 2013b). One reason for non-compliance may be the fact, that patients – as well as physicians – do not see or feel any (positive) effect of adjuvant endocrine therapy (other than unwanted side effects) and therefore receive little positive feedback and motivation to continue with treatment. A surrogate marker indicating successful medication may serve as such a positive feedback.

The aim of this study was to investigate whether BMI has an impact on the efficacy of AIs to lower oestrogen serum levels in adjuvant-treated postmenopausal patients with breast cancer. Furthermore, it was investigated whether follicle stimulating hormone (FSH) serum levels may be used as a surrogate parameter for estradiol serum levels in clinical routine. We show that obesity is directly related to lower depletion of estradiol serum levels under treatment with an AI and that FSH may be a surrogate marker for clinical routine to monitor successful medication.

METHODS

Sixty-nine hormone receptor-positive patients with breast cancer who were scheduled for adjuvant endocrine therapy with an AI (anastrozole or letrozole) were prospectively included in this study. Patients were not allowed to have any endocrine treatment in their patient history. Neoadjuvant or adjuvant chemotherapy was not an exclusion criteria. One patient was excluded due to premenopausal status. After informed consent, blood was taken before starting with endocrine treatment as well as 3 months thereafter. Blood was analysed in two ways: one sample was directly sent to the clinical routine lab, which measured serum estradiol, FSH, luteinizing hormone, glucose, insulin and SHBG; a second sample was centrifuged immediately after donation. Serum was then aliquoted and stored at $-20\,^{\circ}C$. The entire batch was sent and analysed in a dedicated central laboratory.

Estradiol levels were measured by the sensitive electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics GmbH, Mannheim, Germany). Measurements of FSH, were also performed by ECLIA (Roche Diagnostics GmbH). The assay was performed with a conventional sensitivity limit of $5\,pg\,ml^{-1}$ and an intra-assay variance of 1.4–3.3% and an inter-assay variance of 2.2–4.9%.

At the central lab, estradiol, FSH and luteinizing hormone levels were measured with kits for electrochemiluminescence immunoassays purchased from Roche Diagnostics on a 'Modular-170 <EEE>' auto-analyzer. The detection limit for estradiol was $15\,pg\,ml^{-1}$ at the central lab.

Patients filled in a questionnaire regarding typical endocrine symptoms before starting endocrine therapy with an AI as well as after 3 months of treatment. The questionnaire contained six questions on vegetative, four questions on gastrointestinal, three questions on gynaecological, six questions on psychological, six questions on musculoskeletal, three questions on respiratory side effects and four questions on others. Answers were classified into five categories ranging from no side effect at all (10 points) to severe and frequent (50 points). Additionally, patients were questioned about their therapy compliance and their trust concerning an anticancer effect of the AI. Weight and height were taken before and 3 months after therapy with an AI. Patients were grouped as non-obese with a BMI $< 30\,kg\,m^{-2}$ and as obese with a BMI of $30\,kg\,m^{-2}$ or more according to the WHO (World Health Organization).

This prospective study was carried out according to the ethical principles of the Helsinki Declaration with approval of the local ethic committee (EK Nr: 1114/2009).

Statistical analyses. To compare means of serum levels before and after AI treatment as well as between obese and non-obese patients the Student's *t*-test was used. The Spearman rank correlation was used for investigation of the relationship between BMI and estradiol as well as FSH serum levels. To compare the demographics and tumour characteristics between obese and non-obese patients a Student's *t*-test was used for means and χ^2-test or Fisher's exact test were used, where appropriate, for frequencies.

All statistical calculations were performed using the SPSS 17.0 statistical software (IBM, Chicago, IL, USA). For all analyses, *P*-values were two-sided and considered to be statistically significant if *P*-values were < 0.05.

RESULTS

Data of 68 patients with a mean BMI of $29.3\,kg\,m^{-2}$ and a mean age of 66 years were analysed. A total of 60 patients received anastrozole and 8 patients received letrozole as adjuvant endocrine treatment. Forty patients were non-obese and 28 patients were obese according to pre-specified criteria. Demographics and tumour characteristics are shown in Table 1.

A very strong correlation between FSH serum levels measured by the clinical routine laboratory and FSH serum levels measured by the dedicated central laboratory could be observed at baseline ($r = 0.988$, $P < 0.01$) as well as after 3 months of treatment with an AI ($r = 0.964$, $P < 0.01$).

Regarding all 68 patients, mean baseline estradiol serum level was $19.5\,pg\,ml^{-1}$ (s.e.m. = 2.0) and could be reduced to $10.5\,pg\,ml^{-1}$ (s.e.m. = 1.1) after 3 months of treatment with an AI ($P < 0.01$). Consequently, inverse changes could be observed regarding FSH serum levels. The mean baseline FSH serum level was $70.2\,mIU\,ml^{-1}$ (s.e.m. = 4.5) and increased to $75.7\,mIU\,ml^{-1}$ (s.e.m. = 3.6) after 3 months of treatment with an AI ($P < 0.05$).

At baseline, a weak non-statistical significant correlation between BMI and estradiol serum level could be observed ($r = 0.2$, $P = 0.24$). After 3 months of treatment with an AI, a moderate, barely significant correlation between BMI and estradiol serum level could be detected ($r = 0.35$, $P = 0.05$).

Regarding FSH, an inverse correlation between BMI and FSH serum levels could be observed at baseline ($r = -0.55$, $P < 0.01$) as well as after 3 months of endocrine treatment with an AI ($r = -0.34$, $P = 0.06$). Regarding FSH and estradiol serum levels, a

Table 1. Demographics and tumour characteristics of the 68 patients with early breast cancer undergoing therapy with aromatase inhibitors

Variable	Non-obese patients $n = 40$ (58.8%)	Obese patients $n = 28$ (41.2%)	*P*-value
BMI[a] (mean)	25.5 kg m^{-2}	34.9 kg m^{-2}	<0.01
Age (mean)	66 years (48–90 years)	66 years (51–79 years)	0.932
Anastrozole	35 (88%)	25 (89%)	
Letrozole	5 (12%)	3 (11%)	
Pathologic tumour size, cm			
<1	13 (32%)	8 (29%)	
1–2	17 (43%)	11 (39%)	
>2	10 (25%)	9 (32%)	0.550
Tumour grade			
G1	10 (25%)	5 (18%)	
G2	25 (63%)	19 (68%)	
G3	5 (12%)	4 (14%)	0.544
Lymph nodes			
Negative	35 (88%)	21 (75%)	
Positive	5 (12%)	7 (25%)	0.224
Oestrogen receptor			
Negative (−)	0 (0%)	0 (0%)	
Low expression (+)	1 (2%)	0 (0%)	
Medium expression (++)	3 (8%)	1 (4%)	
High expression (+++)	36 (90%)	27 (96%)	0.281
Progesteron receptor			
Negative (−)	4 (10%)	6 (21%)	
Low expression (+)	3 (7%)	0 (0%)	
Medium expression (++)	17 (43%)	6 (21%)	
High expression (+++)	16 (40%)	16 (58%)	0.954
Her2/neu receptor			
Negative	37 (93%)	27 (96%)	
Positive	3 (7%)	1 (4%)	0.505

[a]BMI = body mass index.

weak nonsignificant negative correlation could be observed before as well as after 3 months of AI treatment ($r = -0.25$ and $r = -0.12$, respectively).

Non-obese *vs* obese patients. At baseline, a slightly higher mean estradiol serum level of 1.3 pg ml^{-1} was detected in obese compared with non-obese patients (20.2 pg ml^{-1} *vs* 18.9 pg ml^{-1}, $P = 0.76$). Three months of treatment with an AI significantly reduced the mean estradiol serum level in non-obese patients as well as obese patients (18.9 pg ml^{-1}, s.e.m. = 3.3 to 9.0 pg ml^{-1}, s.e.m. = 1.2, $P < 0.05$ and 20.2 pg ml^{-1}, s.e.m. = 2.6 to 12.5 pg ml^{-1}, s.e.m. = 1.7, $P < 0.01$, respectively) (Figure 1).

However, after 3 months of treatment, estradiol serum levels were numerically lower in non-obese patients when compared with obese patients (9.0 pg ml^{-1} *vs* 12.5 pg ml^{-1}, $P = 0.10$).

These nonsignificant differences in estradiol serum levels between obese and non-obese patients could be underlined in the FSH analyses.

Obese patients had significantly lower FSH serum level at baseline when compared with non-obese patients (57.2 mIU ml^{-1} *vs* 79.1 mIU ml^{-1}, $P < 0.01$). Three months of AI treatment increased FSH serum levels in non-obese patients as well as

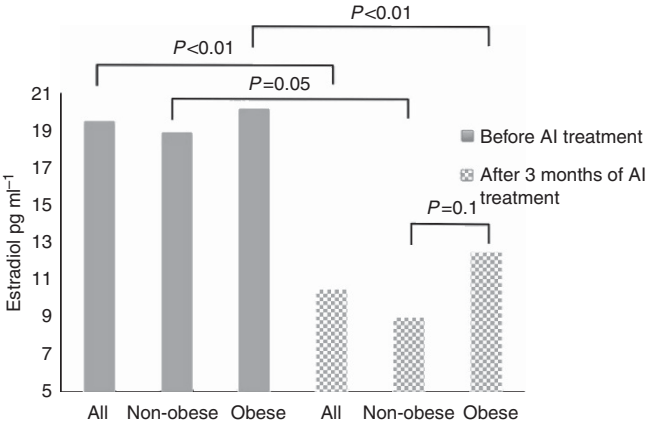

Figure 1. Change of estradiol serum levels of the 68 patients with early breast cancer before and after 3 months of AI treatment.

obese patients (79.1 mIU ml^{-1}, s.e.m. = 5.5 to 86.2 mIU ml^{-1}, s.e.m. = 4.6, $P = 0.14$ and 57.2 mIU ml^{-1}, s.e.m. = 4.6 to 62.5 mIU ml^{-1}, s.e.m. = 4.4, $P < 0.05$, respectively) (Figure 2).

After 3 months of treatment with an AI, the FSH serum levels were significantly lower in obese patients compared with non-obese patients (62.5 mIU ml^{-1} *vs* 86.2 mIU ml^{-1}, $P<0.01$, respectively).

Side effects and compliance. Complete questionnaires at baseline and 3 months thereafter could be obtained from 36 patients.

Comparing side effects of obese *vs* non-obese patients no difference in frequency or strength could be observed at baseline as well as after 3 months of AI treatment (Table 2). No correlation between FSH or estradiol serum levels and side effects could be detected (data not shown).

All patients were asked if they had forgotten to take the AI within the 3 months of treatment. Three (10.7%) obese patients and five (12.5%) non-obese patients declared that they had forgotten to intake the AI at least once within the 3 months of endocrine therapy.

DISCUSSION

We prospectively investigated endocrine metabolites before and during AI treatment in postmenopausal breast cancer patients. We found slightly elevated estradiol serum levels in obese patients before starting the AI treatment. Three months of AI treatment significantly lowered estradiol serum levels in obese as well as in non-obese patients. However, after 3 months of AI treatment, obese patients had higher estradiol levels compared with non-obese patients.

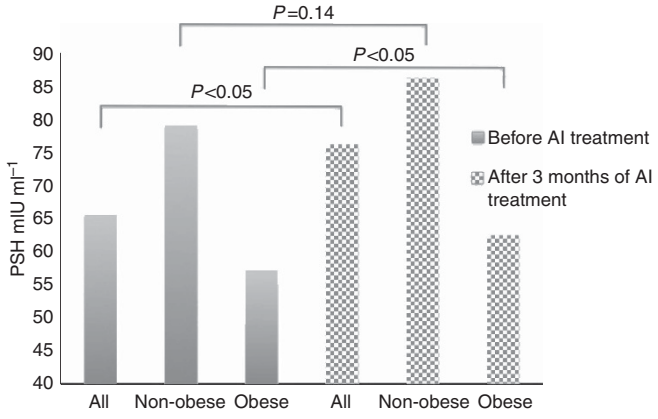

Figure 2. Change of FSH serum levels of the 68 patients with early breast cancer before and after 3 months of AI treatment.

Analyses of FSH serum levels underlined these results. At baseline, obese patients had significantly lower FSH levels, mainly due to the negative feedback via estradiol. Aromatase inhibitor treatment leads to a distinct increase in FSH levels in obese as well as in non-obese patients. However, after 3 months of AI treatment obese patients remained at significantly lower FSH serum levels compared with non-obese patients – possibly due to higher estradiol levels. As FSH serum levels can be easily measured in clinical routine labs, FSH may be a good surrogate marker for an AI treatment effect.

We observed no impact of BMI or serum hormone levels on side effects. However, this must be stated with caution due to the limited number of patients who reported on side effects in our trial.

The observation concerning a difference in depleted estradiol levels according to BMI was subtle and did not reach statistical significance due to a limited sample of patients and statistical power. However, the finding was associated with a clear increase in FSH levels in the obese subgroup, indicating a differential hormonal environment captured by two snapshots at AI baseline and after 3 months of therapy.

Furthermore, our prospective data are in line with the retrospective analysis by Folkerd *et al*, 2012. who demonstrated that estradiol levels during AI treatment are related to BMI (Folkered *et al*, 2012). In this study, as in ours, the higher estradiol serum levels in obese compared with non-obese patients were observed – even though those differences are numerically small.

The concept of estradiol depletion using an AI has improved disease outcome in postmenopausal patients with hormone receptor-positive breast cancer when compared with the former gold standard tamoxifen. Dose finding studies showed that low dosages of anastrozole (1 mg) and letrozole (2.5 mg) were able to nearly fully block the aromatase and thereby lower estradiol serum levels to a minimum (Plourde *et al*, 1994; Dowsett *et al*, 1995; Yates *et al*, 1996). However, these studies included small number of patients (e.g., 10–20 patients) and did not factor in possible confounders like insulin resistance, age or BMI.

Increased fat tissue leads to elevated estradiol serum levels via increased aromatisation in postmenopausal women (Longcope *et al*, 1986; Key *et al*, 2003). Thus, BMI potentially has an impact on the efficacy of AIs to lower estradiol serum levels. Indeed, retrospective analysis of phase III clinical trials demonstrated that overweight and obese patients have a worse disease outcome when treated with anastrozole compared with normal weight patients (Sestak *et al*, 2010; Pfeiler *et al*, 2011; Gnant *et al*, 2013). As this

Table 2. Side effects observed in the 68 patients with early breast cancer before and after 3 months of AI treatment (0 points = no appearance, 50 points = severe appearance)

	Before AI treatment			Three months of AI treatment		
Side effects	**Non-obese[a] *vs* obese[a]**		***P*-value**	**Non-obese[a] *vs* obese[a]**		***P*-value**
Gastrointestinal SE	13.8	13.4	0.85	14.2	14.7	0.83
Musculoskeletal SE	17.0	22.7	0.07	21.1	21.0	0.97
Gynaecological SE	15.7	14.0	0.45	14.7	14.4	0.88
Psychological SE	17.3	17.4	0.96	17.0	18.1	0.63
Vegetative SE	20.8	21.1	0.42	22.7	24.8	0.85
Respiratory SE	15.3	17.2	0.24	16.9	17.4	0.75
Other SE	15.7	18.8	0.89	17.2	18.0	0.48

Abbreviations: AI = aromatase inhibitor; SE = side effects.
[a]Means are shown.

could not be shown for tamoxifen in these trials, BMI might be a predictive parameter regarding endocrine therapy.

However, the recently published reanalysis of the BIG-1-98 trial did not show a predictive effect regarding letrozole and tamoxifen, respectively (Ewertz *et al*, 2012). As previously shown, letrozole is more potent in lowering estradiol levels and thereby possibly overcoming the increased aromatisation in obese patients (Geisler *et al*, 2002). As only eight patients received letrozole in our trial, we were not able to compare the efficacy of anastrozole and letrozole in obese and non-obese patients. Nonetheless, this is a question of major interest and should be answered in upcoming studies.

Other factors like inflammation in fat tissue of obese patients as well as insulin resistance could contribute to the clinical impact of BMI on (endocrine responsive) breast cancer. Inflammation in fat tissue, leading to the immigration of macrophages, to neovascularisation and, in the long run, to insulin resistance may not only be a factor in breast cancer development but also progression (van Kruijsdijk *et al*, 2009). Insulin resistance may counteract AI treatment through direct activation of the oestrogen receptor by insulin. Thus, it is without doubt that aromatase and oestrogen serum levels are not the only mechanisms that drive breast cancer development and prognosis, but of course they are important ones.

The second major finding in this study is that we were able to demonstrate opposed effects on FSH serum levels compared with estradiol serum levels during AI treatment. As FSH can be easily measured in routine clinical labs, FSH may be used as a surrogate parameter for the efficacy of an AI. We demonstrated significant increases in FSH serum levels during AI treatment. Furthermore, lower FSH serum levels in obese patients before as well as after 3 months of treatment with an AI could be shown. An intact feedback loop on the hypophysis has previously been described in postmenopausal women (Shaw *et al*, 2010). Higher estradiol serum levels lower FSH serum levels via this negative feedback loop even in postmenopausal women. Serum FSH levels are much higher and thereby easier to measure with a higher sensitivity compared with estradiol serum levels in postmenopausal women. We demonstrated a very strong, significant correlation between FSH serum levels measured in the clinical routine laboratory and FSH levels measured in the dedicated central laboratory. As we demonstrated a weak correlation between FSH and estradiol serum levels, FSH serum levels may be used for therapy surveillance and therapy compliance.

Although this data is clearly in need of further clinical validation, there is a potential to establish FSH as a compliance tool. Elevated FSH levels could indeed be a valuable surrogate marker to establish a notion of effective endocrine treatment. In our small prospective trial we investigated patient trust in the antitumoural effect of the AI treatment. Before AI treatment, all patients believed in a positive effect of the AI. After 3 months of treatment, 7.4% of the patients stated that they doubt the effect of the AI treatment. This loss of conviction in the efficacy of AI is certainly a factor contributing to the complex issue of malcompliance shown in several studies. Such a marker has a potential of increasing concordance to therapy.

The impact of BMI can be demonstrated – even in a clinical routine laboratory – by using FSH levels as a surrogate parameter for estradiol levels. This study established BMI as a predictive clinical factor concerning oestrogen depletion under aromatase inhibitor treatment. This study adds to the evidence that important survival disadvantages under AI therapy might be due to, at least in part, incomplete inadequate oestrogen depletion in obese women.

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