Estrogen receptor antagonism uncovers gender-dimorphic suppression of whole body fat oxidation in humans: differential effects of tamoxifen on the GH and gonadal axes

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Abstract

Context: Tamoxifen, a selective estrogen receptor modulator, suppresses GH secretion in women but not in men. It increases testosterone levels in men. As GH and testosterone stimulate fat metabolism, the metabolic consequences of tamoxifen may be greater in women than in men.

Objective: To determine whether tamoxifen suppresses fat oxidation (Fox) to a greater degree in women than in men.

Design: An open-label study of ten healthy postmenopausal women and ten healthy men receiving 2-week treatment with tamoxifen (20 mg/day).

Endpoint measures: GH response to arginine stimulation, serum levels of IGF1, testosterone and LH (men only), sex hormone binding globulin (SHBG) and whole body basal and postprandial Fox.

Results: In women, tamoxifen significantly reduced the mean GH response to arginine stimulation (Δ -87%, P<0.05) and circulating IGF1 levels (Δ -23.5±5.4%, P<0.01). Tamoxifen reduced postprandial Fox in women (Δ -34.6±10.3%; P<0.05).

In men, tamoxifen did not affect the GH response to arginine stimulation but significantly reduced mean IGF1 levels (Δ -24.8±6.1%, P<0.01). Tamoxifen increased mean testosterone levels (Δ 52±14.2%; P<0.01). Fox was not significantly affected by tamoxifen in men.

Conclusion: Tamoxifen attenuated the GH response to stimulation and reduced postprandial Fox in women but not in men. We conclude that at a therapeutic dose, the suppressive effect of tamoxifen on fat metabolism is gender-dependent. Higher testosterone levels may mitigate the suppression of GH secretion and Fox during tamoxifen treatment in men.

Introduction

Estrogen plays a major role in the regulation of growth hormone (GH) secretion which is stimulated centrally by estradiol (E2) derived locally from aromatisation of testosterone in both men and women (1, 2). In men, estrogen not only regulates the GH–insulin-like growth factor (IGF) axis, but also the pituitary–gonadal axis, as the inhibition of luteinizing hormone (LH) secretion by testosterone requires prior aromatization to E2 (3). Thus, locally produced estrogen in the brain regulates the GH and gonadal system.

We recently reported that tamoxifen, a selective estrogen receptor modulator (SERM) that blocks central estrogen action, reduces GH secretion in women but not in men (4). Tamoxifen also enhanced LH secretion and increased testosterone levels in men (5). As testosterone stimulates GH secretion (1), it is conceivable that the
higher testosterone levels induced by tamoxifen in men mitigated the suppression of GH release. Thus, central estrogen blockade is expected to result in a lesser effect on the GH–IGF1 axis in men than women.

GH and testosterone both regulate fat mass. Fat mass is increased in GH-deficient and hypogonadal men and reversed by GH and testosterone replacements (6, 7, 8, 9, 10, 11). GH regulates fat mass via stimulation of lipolysis and fat oxidation (Fox) (12). Testosterone also stimulates Fox (13, 14, 15). Our group recently reported that the stimulatory effects of testosterone on whole body Fox occurs primarily acting in extra-hepatic tissues (16). Moreover, testosterone and GH stimulate whole body Fox when used alone and more so in combination (13, 17). Thus, GH and testosterone interact in the regulation of Fox and fat mass.

As both GH and testosterone regulate fat metabolism and central estrogen blockade are expected to result in gender-specific effects on the GH–IGF1 and gonadal axes, we postulated that the effect of tamoxifen on fatty acid oxidation is different between women and men. The present investigation tests the hypothesis that tamoxifen exerts a greater suppressive effect on Fox in women than in men.

Methods

Subjects

Ten healthy postmenopausal women (mean age 64±2 years; mean BMI 25±1 kg/m²) and ten healthy men (mean age 65±3 years; mean BMI 26±1 kg/m²) were recruited from the community through advertisements. Study participants were in good general health and had normal haematological tests, renal and hepatic function. Exclusion criteria included BMI ≥ 30 kg/m², hypothalamic or pituitary disorders, diabetes mellitus and chronic renal or hepatic illnesses. Subjects were not taking hormone replacement therapy or any medications known to interfere with endocrine systems. Throughout the study, subjects were instructed to follow their usual diet and physical activity. St Vincent’s Hospital Human Research Ethics Committee approved the study, which was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12607000586415).

Study design

This was an open labelled study of tamoxifen (Genox) administration. The dose of tamoxifen was 20 mg/day. All participants were asked to fast the night before each visit. On each visit assessment of GH status using the arginine stimulation test was performed, whole body basal and postprandial Fox was measured, as well as serum IGF1, LH, testosterone, and sex hormone binding globulin (SHBG) levels. Circulating LH levels were measured in five samples taken every 30 min over a 2-h period during the arginine stimulation test. Study bloods were collected and serum samples were obtained by centrifugation, and stored at −80°C until analysis. Data on neuroendocrine effects of tamoxifen in women and in men have been previously published (2, 5).

Arginine stimulation test

Subjects rested on a bed for at least 30 min before the baseline blood samples were taken. Thirty grams of L-arginine hydrochloride (Phebra Pty Ltd, Lane Cove West, NSW, Australia) was infused over a 30 min period. Blood samples for GH level measurements were taken at baseline and 30, 60, 90 and 120 min after commencement of arginine infusion. In healthy subjects, the arginine stimulation test has been shown to have good intra-individual reproducibility (18).

Substrate oxidation and resting energy expenditure assessment

Resting energy expenditure (REE) and substrate metabolism (Fox and carbohydrate oxidation (Cox)) were quantified after an overnight fast by indirect calorimetry using a metabolic monitor (ParvoMedics, Sandy, UT, USA), which was calibrated against standard gases before each study. Subjects were placed on a bed and allowed to rest for at least 30 min. A clear plastic hood was placed loosely over the subject’s head and shoulders for a 20 min period. O2 consumption and CO2 production were measured and REE, Fox and Cox were estimated using weight-based equations adjusted from Ferrannini (19). The measurement was repeated at 30 and 90 min after liquid standardized mixed meal containing 13 g protein, 11.4 g fat and 50.1 g carbohydrates (Ensure Plus, Abbott Laboratories). REE is expressed as kcal/day, Fox and Cox are expressed as mg/min. The mean intra-subject coefficients of variation (CV) for REE and Fox at our institution are 4.2 and 4% respectively (20).

Analytical methods

All samples for any individual were measured in the same assay run for each analyte. Serum GH was measured by
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ELISA calibrated against the WHO IS 80/505 (Biocline Australia Pty Ltd, Marrickville, NSW, Australia) with sensitivity of <0.1 mIU/l. The CV for GH were 4.4% at 6.5 mIU/l and 3.5% at 17.6 mIU/l. Serum IGF1 was measured by RIA after acid ethanol extraction as previously described (2). The CV for IGF1 were 5.1% at 5.15 IU/l and 8.1% at 17.4 mIU/l. Serum SHBG was measured using a commercial immunoassay (Immuliute 2000, Siemens Medical Solution Diagnostics, Los Angeles, CA, USA). The CV for SHBG at 5.3 and 86.2 nmol/l were 5.0 and 7.5% respectively. Normal range for testosterone in males 50–90 nmol/l. Serum testosterone was measured using a commercial immunoassay (Immuliute 2000, Siemens Medical Solution Diagnostics). The inter-assay CV for testosterone at 3.6 and 23 nmol/l were 9.3 and 9.0% respectively. Normal range for testosterone in males >50 years 8–32 nmol/l. Serum LH was measured by ELISA calibrated against the WHO 2nd IS 80/552 (Diagnostics Biochem Canada, Inc., Dorchester, ON, Canada). The CV for LH for women 5.1% at 5.15 IU/l and 8.1% at 17.4 mIU/l. Normal range for testosterone in females 20–110 nmol/l, males >50 years 20–90 nmol/l. Serum LH was measured using a commercial immunoassay (Immuliute 2000, Siemens Medical Solution Diagnostics). The inter-assay CV for LH were 5.1% at 5.15 IU/l and 8.1% at 17.4 mIU/l. Serum LH was measured by RIA after acid ethanol extraction as previously described (2). The CV for GH were 4.4% at 6.5 mIU/l and 3.5% at 17.6 mIU/l. Serum IGF1 was measured by RIA after acid ethanol extraction as previously described (2). The CV for IGF1 were 5.1% at 5.15 IU/l and 8.1% at 17.4 mIU/l. Serum SHBG was measured using a commercial immunoassay (Immuliute 2000, Siemens Medical Solution Diagnostics). The inter-assay CV for testosterone at 3.6 and 23 nmol/l were 9.3 and 9.0% respectively. Normal range for testosterone in males >50 years 8–32 nmol/l. Serum LH was measured by ELISA calibrated against the WHO IS 80/505 (Biocline Australia Pty Ltd, Marrickville, NSW, Australia). The CV for SHBG at 5.3 and 86.2 nmol/l were 5.0 and 7.5% respectively. Normal range for testosterone in males >50 years 8–32 nmol/l. Serum LH was measured by ELISA calibrated against the WHO IS 80/505 (Biocline Australia Pty Ltd, Marrickville, NSW, Australia).

Statistical analysis

As the GH response to arginine displays large inter-subject variation and is not normally distributed, data were logarithmically transformed for parametric analysis. The GH response to arginine and changes in circulating LH levels were analysed by repeated measures ANOVA. Peak GH levels were calculated as maximum increment over pre-stimulated GH concentration. Calculated free testosterone (CFT) levels were derived from total testosterone and SHBG levels using the Ly and Handelsman method (21). Treatment effects were assessed using paired t-tests with Bonferroni’s correction and comparison between treatments analysed by factorial ANOVA where appropriate. Results were expressed as mean with S.E.M. and a P value of <0.05 was considered to be significant. Statistical analysis was undertaken using the Statistical Software Package SPSS (IBM SPSS Statistics 21) and GraphPad Software Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

Table 1 Endpoint measures at baseline (nil) and during the treatment with tamoxifen (20 mg/day). Data are expressed as means ± s.e.m. Conversion factor for GH: 1 mIU/l = 0.33 µg/l.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Women</th>
<th>Tamoxifen</th>
<th>Men</th>
<th>Tamoxifen</th>
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<tr>
<td>Weight (kg)</td>
<td>66.9±3.3</td>
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<td>Peak GH (mIU/l)</td>
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<td>GH AUC (mIU/l per 120 min)</td>
<td>745.8±290</td>
<td>51.3±161*</td>
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<td>IGF1 (nM/l)</td>
<td>16±1.6</td>
<td>12.3±1.5*</td>
<td>18.9±1.6</td>
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<tr>
<td>SHBG (nM/l)</td>
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<td>REE (kcal/day)</td>
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<td>1305±38.3</td>
<td>1551±45.8*</td>
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<td>Basal Fox (mg/min)</td>
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<td>Postprandial Fox</td>
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<td></td>
<td>Basal Cox (mg/min)</td>
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<td></td>
<td>At 30 min (mg/min)</td>
<td>96.4±13.3%</td>
<td>166.9±15.1*</td>
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<td>Testosterone (nM/l)</td>
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<td>Calculated free testosterone (pmol/l)</td>
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<td>231±18.8</td>
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</table>

*P<0.05 compared to baseline; †P<0.01 compared to baseline; #P<0.05 difference in baseline value in men compared to that in women; §P<0.05 difference in tamoxifen-induced change between men and women.
Hormones

Median baseline GH concentrations were 2.1 and 0.7 mIU/l for women and men respectively. In women, when compared to the baseline study, the GH response to arginine stimulation was significantly attenuated by 20 mg of tamoxifen (median reduction in area under the curve (AUC) by 87% over 120 min; \( P < 0.05 \); Table 1; Fig. 1A). Tamoxifen also significantly reduced the peak GH response to stimulation (\( P < 0.05 \); Table 1). In men, the GH response to arginine was not significantly reduced by tamoxifen, although a trend was evident (Fig. 1B). Thus, tamoxifen significantly attenuated GH response to stimulation in women but not in men.

In both women and men, the mean IGF1 level significantly fell during the treatment with 20 mg tamoxifen by 23.5 \( \pm \) 5.4 and 24.8 \( \pm \) 6.1% respectively (\( P < 0.01 \); Fig. 2A and B). The effect of tamoxifen on circulating IGF1 levels was not significantly different between men and women.

SHBG rose significantly during treatment with tamoxifen in both women and men (\( P < 0.01 \) and \( P < 0.05 \) respectively; Table 1). The increase in SHBG was greater in women than in men (29.5 \( \pm \) 6.4 vs 20.2 \( \pm \) 6.9%; \( P = 0.05 \)).

In men, circulating LH levels rose significantly during tamoxifen treatment by nearly twofold (\( P < 0.001 \); Fig. 3A). Testosterone levels increased during tamoxifen treatment by 52 \( \pm \) 14.2% (\( P < 0.01 \); Fig. 3B). CFT also significantly increased (\( \Delta \) 63.6 \( \pm \) 14.8%; \( P < 0.001 \); Table 1).

Substrate oxidation and REE

Tamoxifen did not significantly affect REE, nor the rates of basal Fox or Cox in women and in men (Table 1).

Ingestion of the liquid standardized mixed meal acutely suppressed Fox. In women, Fox fell to a greater degree with tamoxifen treatment during the 2 h postprandial period compared to the control study (\( P < 0.05 \); Table 1; Fig. 4A). At 30 min, the rate of Fox was 34.6 \( \pm \) 10.3% lower during tamoxifen treatment (Table 1) and over the period of 2 h the area under the curve was lowered by 29.9%. In men, there was no significant difference in postprandial Fox between tamoxifen and control studies. Tamoxifen significantly enhanced the postprandial rise in Cox in women but not men (\( P < 0.01 \); Table 1).

Thus, only in women tamoxifen significantly reduced postprandial fatty acid oxidation rates and increased Cox.

**Figure 1**
GH response to arginine stimulation at baseline (nil) and during tamoxifen treatment in healthy women (A) and men (B). Data are presented as mean increment in serum GH after arginine infusion over pre-stimulation GH levels. \( *P < 0.05 \) compared to nil. Conversion factor: 1 mIU/l = 0.33 mg/l.

**Figure 2**
Percent changes in serum IGF1 levels in women and men during 20 mg tamoxifen treatment. Data are expressed as means \( \pm \) S.E.M.
Other endpoints

In women, tamoxifen did not significantly change serum levels of total cholesterol, HDL cholesterol, TGs and glucose (Table 1). In men, tamoxifen did not significantly change total cholesterol, HDL cholesterol and glucose, whereas there was a small but significant ($P<0.05$) reduction in TG levels (Table 1).

Discussion

Tamoxifen significantly attenuated GH response to stimulation in women but not in men. In both women and men, tamoxifen significantly increased SHBG levels, a response that was greater in women. Tamoxifen significantly reduced IGF1 levels in men and women by a similar degree. In men, it increased circulating levels of LH and testosterone. Tamoxifen significantly reduced postprandial Fox and increased Cox in women but not in men. Thus, tamoxifen exerted gender-related effects on GH secretion, substrate oxidation and SHBG but not on IGF1.

Central stimulation of GH secretion in both men and women by testosterone require aromatization to estrogen (1, 2). Studies in rodents also provide evidence that local estrogen production drives GH secretion via aromatisation, from the observation that pituitaries in aromatase knockout (ArKO) mice are hypoplastic and GH levels low (22). In men with aromatase deficiency, the GH response to stimulation is markedly blunted and is not restored by systemic $E_2$ replacement (23). These observations indicate that local estrogen production is required for the central stimulation of GH secretion. The present study shows that tamoxifen predictably reduced GH secretion through a central estrogen antagonistic effect.

$E_2$ derived from aromatisation also mediates the negative feedback of testosterone on LH secretion (3, 24). Thus, by blocking central estrogen action, tamoxifen removes testosterone feedback inhibition, enhancing LH secretion and increasing testosterone production in men (5). Tamoxifen suppressed the GH axis to a lesser degree in men than in women. This may be explained by higher testosterone levels in men increasing substrate availability for aromatization to $E_2$, mitigating suppression of GH secretion in men.

An interesting observation in the present study is that the greater inhibition of GH secretion by tamoxifen was not accompanied by a greater reduction in IGF1 levels in women compared to men. In addition to its central effect, tamoxifen also acts directly on the liver inhibiting IGF1 production via an estrogen agonist effect (25). The observation that IGF1 did not fall to a greater degree in women suggests that tamoxifen may be exerting a greater hepatic effect in men than in women. This could arise from a gender difference in hepatocyte response to tamoxifen or in drug metabolism of tamoxifen.

Figure 3

Percent changes in serum LH and testosterone levels in men during 20 mg tamoxifen treatment. Data are expressed as means ± S.E.M.

Figure 4

Fat oxidation rates in a fasting state (Basal) and postprandially at 30–60 min and 90–120 min after the mixed meal in women (A) and men (B). Data are expressed as means ± S.E.M.
SHBG, an estrogen-responsive hepatic protein, may be used to compare the hepatic responsiveness of tamoxifen between the sexes. The observation that SHBG increased less in men suggests a lesser, rather than a greater estrogenic effect in men. However SHBG is also an androgen-responsive hepatic protein, which is reduced by testosterone, evident from men having a lower baseline mean SHBG concentration. The compensatory rise of testosterone could blunt the direct SHBG enhancing estrogen-like effect of the drug. Therefore SHBG changes cannot be used as a reliable hepatic marker of tamoxifen action in this study.

Can a secondary increase in testosterone induced by tamoxifen influence the IGF1 response in men? We have previously reported that testosterone does not increase circulating IGF1 in hypopituitary men with GH deficiency (GHD) (13). When replaced with GH, addition of testosterone in hypopituitary men has minimal effect on circulating IGF1 (26). Thus, the evidence indicates that testosterone increases circulating IGF1 by stimulating GH secretion with little contribution from direct hepatic action. Therefore, the increase in testosterone levels by tamoxifen is unlikely to influence its inhibitory effect on hepatic IGF1 production. Another possible explanation may be a gender difference in tamoxifen metabolism. In rodents, hepatic expression of cytochrome P4503A, an enzyme that metabolizes tamoxifen, is lower in males than in females (27). If this is true in humans, higher blood concentrations of tamoxifen could explain its more potent hepatic estrogen-like effect in men. The collective evidence indicates that tamoxifen exerts a greater inhibitory hepatic IGF1 effect in men than in women, but the mechanisms involved are unclear.

Tamoxifen suppressed Fox in women but not men, which can be explained in part by the greater suppression in women of GH secretion which stimulates Fox. We cannot exclude additional mechanisms including a direct inhibitory effect of tamoxifen on hepatic fatty acid metabolism. Several in-vitro studies have reported that tamoxifen induces hepatocyte steatosis, up-regulates SREBP-1c and its downstream target genes, increases fatty acid synthesis, impairs mitochondrial β-oxidation and respiration, and reduces hepatic TG secretion (28, 29). Some studies report no direct effect of tamoxifen on hepatocyte fatty acid oxidation, whereas systemic treatment of tamoxifen in mice substantially increases hepatic TG content and activates fatty acid synthesis (30). However, no gender difference in the direct effect of tamoxifen has been reported. Therefore, in our study, the reduction in fatty acid oxidation in women may not reflect counteracts the inhibitory effect of tamoxifen on GH secretion, resulting in a no net effect on GH secretion, contrary to that in women. As both testosterone and GH increase fat oxidation, the stimulation of gonadal axis and small inhibitory effect on GH–IGF1 axis results in a no net effect on fat oxidation in men.

Figure 5

In women, tamoxifen attenuates estrogen-stimulated GH secretion, by blocking central estrogen receptors. In the liver, it exerts estrogen-like effects that inhibit GH receptor signalling, by reducing IGF1 production and fat oxidation. In men, tamoxifen treatment stimulates LH, which is followed by an increase in testosterone levels. The increase in testosterone

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gender specific direct hepatic effect of tamoxifen on fat metabolism but rather an effect secondary to reduced GH secretion.

Is the transient post-prandial suppression of Fox clinically significant? The reduction in postprandial Fox from our study was on average 13 mg/min over 2 h. If extrapolated to three meals per day, this may equate to an accumulation of fat of about 5 g/day approximating 1.8 kg per year. Some studies in women with breast cancer have observed that tamoxifen causes weight gain. In a cohort of more than 500 newly diagnosed women with breast cancer, tamoxifen increased weight by 1.0 kg over 1 year (31). However, another long-term study in breast cancer patients showed no difference in weight gain between tamoxifen users and non-users (32). However weight is not a reliable indicator of adiposity. We had previously reported the metabolic impact of oral estrogen treatment to postmenopausal women who gained 1.2 kg body fat over 6 months, which occurred without a change in body weight because of a concurrent loss of lean body mass (LBM) (20). These body compositional changes occurred in parallel with the post-prandial suppression of Fox of 8 mg/min and sustained fall in IGF1. Thus, the biochemical changes induced by oral estrogens are similar to those observed with tamoxifen in the present study. Based on these findings, we predict that long-term treatment with tamoxifen is likely to induce similar detrimental changes in body composition.

Tamoxifen is used for treatment of breast cancer in both sexes, for infertility and male gynecomastia. Based on our findings we can predict a gender difference in tamoxifen-related side-effects. In women, the dual reduction of GH and IGF1 production by tamoxifen induces a state of GHD. GHD is characterized by a reduction in Fox, an increase in fat mass and the development of hepatic steatosis (33, 34). Hepatic steatosis is a frequent complication of tamoxifen in women treated for breast cancer (35). As GH stimulates hepatic Fox and TG export (36), the evidence supports a metabolic significant and detrimental impact of tamoxifen on liver function via suppression of the GH–IGF axis (37, 38). In men, the activation of the gonadal axis ameliorates the suppression of the GH/IGF axis evident in women. Therefore, men are less at risk of the detrimental metabolic consequences of tamoxifen.

A weakness of this study is that it was not placebo-controlled. However, the outcome measures are objective. We did not measure IGF1 binding proteins, but it is known that SERMs increase circulating IGFBP-3 levels (37, 39), which in the face of reduced IGF1 may result in significant reduction in IGF1 bioavailability and a loss of anabolism. We did not assess other aspects of lipid metabolism, such as lipolysis, TG synthesis or hepatic export. Because GH positively regulates VLDL synthesis (36), we predict that tamoxifen may inhibit hepatic TG export as a consequence of its suppression of the GH axis. This effect may explain the development of steatosis with tamoxifen therapy (35).

In summary, this study demonstrates that tamoxifen suppresses the GH–IGF system with the effects greater in women than in men. We propose that the attenuated effect in men can be explained by co-activation of the pituitary gonadal system as illustrated in Fig. 5. In women, tamoxifen reduces GH secretion and GH action inhibiting hepatic IGF1 production and Fox in the liver. In men, concurrent central stimulation of the gonadal axis increases circulating testosterone concentration which neutralises the central inhibition of GH secretion by tamoxifen. The additional stimulatory effect of testosterone on Fox abrogates the suppression of hepatic Fox observed in women (Fig. 5).

We conclude that tamoxifen suppresses the secretion and metabolic action of GH, effects that are greater in women than in men. Men are less at risk of the metabolic consequences of SERMs, such as development of obesity and hepatic steatosis.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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