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Exacerbation of diabetes related to exemestane treatment

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To the Editor

The high activity and low toxicity of exemestane, a third generation aromatase inhibitor, are well recognized [1,2]. Its adverse effects are relatively mild and mainly related to anti-estrogenic effect [1,2]. Compared to tamoxifen, only arthralgia and diarrhea occurred more frequently with exemestane [1]. Neither was an impact of exemestane on lipid metabolism demonstrated [3]. To our best knowledge, no cases of glucose tolerance deterioration or diabetes exacerbation associated with exemestane administration have been described. We apparently encountered such a situation in our patient treated with exemestane in a prospective clinical study.

A 62-year-old female with a history of right mastectomy for invasive breast cancer in 1983 presented in January 2001 with inoperable chest wall recurrence. Her significant medical history included type 2 diabetes, well controlled with oral hypoglycemic agents. On February 2, 2001, she commenced treatment with exemestane (25 mg daily) within the EORTC 10951 phase III study comparing exemestane and tamoxifen in advanced breast cancer. Upon that, exacerbation of diabetes was observed (glycemia up to >400 mg/dl). After modification of treatment, her fasting glycemia stabilized at <180 mg/dl (period 1, median 153 mg/dl) (Figure 1, 2). On July 17, 2001, exemestane administration was withdrawn for suspected progression. During the off-treatment period, her fasting glycemia did not exceed 160 mg/dl (period 2, median 139 mg/dl, $p=0.002$) (Figure 1, 2). There were no differences between postprandial glycemia "after breakfast" ($p=0.484$) and "after lunch" ($p=0.303$) in these two periods. Since additional examinations did not confirm disease progression, exemestane was reintroduced on August 23, 2001. Since then, glycemia began to rise steadily, eventually requiring the introduction of

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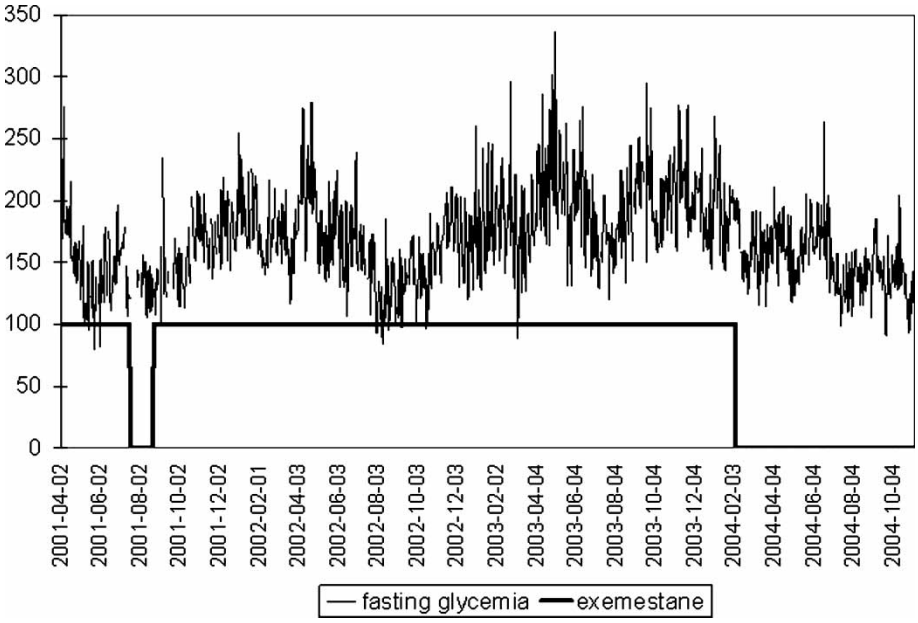

Figure 1. Consecutive fasting glycemia levels (mg/ml) for periods on and off exemestane treatment.

insulin. She continued on exemestane with almost complete tumor regression until February 4, 2004, with very unstable glycemia (period 3, median 176 mg/dl) (Figure 1, 2), when, due to the unavailability of exemestane in Poland, she was switched to a non-steroidal aromatase inhibitor, letrozole. With this medication, her fasting glycemia lowered significantly (period 4, median 150 mg/dl, $p < 0.001$) (Figure 1, 2). There was also a significant difference between these two periods for glycemia "after breakfast" ($p < 0.001$), "after lunch" ($p = 0.05$) and "before dinner" ($p < 0.001$). These changes were accompanied by a weight gain of 6 kg/6 weeks (most probably due to supraoptimal doses of insulin), requiring a decrease in hypoglycemic drugs. During the whole observation period no relevant changes in dietary plan, intake of calories or other recognized factors influencing the glycemia levels were present.

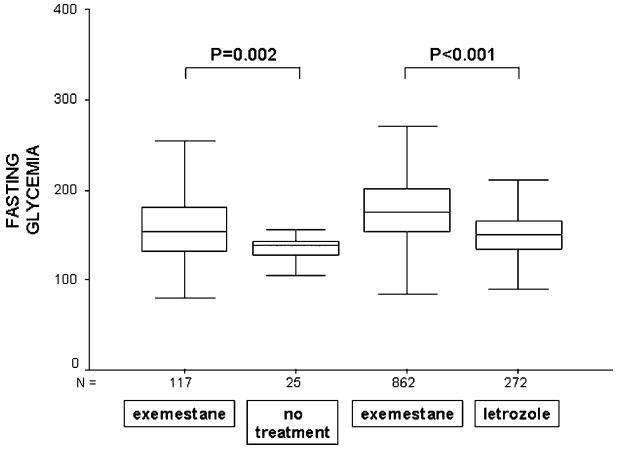

Figure 2. Median fasting glycemia levels (mg/ml) for periods on and off exemestane treatment (median values are indicated by middle lines, boxes represent internal quartiles, whiskers represent range).

Our results showed deterioration of diabetes related to exemestane. The relationship between increased androgen levels (secondary to low aromatase activity) and type 2 diabetes was described as early as in 1920s ("diabetes in woman with a beard") [4]. Recent studies elucidated its molecular mechanisms, linking single nucleotide polymorphisms (SNP) of genes involved in sex hormone metabolism (including CYP 19 gene, encoding for aromatase) with insulin sensitivity and risk of diabetes [5]. Interestingly, a separate mechanism relating risk of diabetes to sex hormone levels has also been found in animal studies: estrogens were demonstrated to protect pancreatic ß-cells from apoptosis induced by oxidative stress, thus maintaining insulin production and preventing diabetes in mice [6].

Importantly however, the phenomenon observed in our case was most probably unrelated to sex hormone levels, as opposite effects were observed during exemestane and letrozole treatments (otherwise producing similar hormone changes). Literature data on the effects of exemestane and non-steroidal aromatase inhibitors on lipid and bone metabolism suggest that despite their similarly potent estradiol lowering activities, these two groups have distinct features regarding their impact on at least some of estrogen dependent physiologic effects [3].

It may be hypothesized that also insulin sensitivity is influenced by these two classes of aromatase inhibitors in a different way: exemestane is asso-

ciated with diminished insulin sensitivity, whereas letrozole either has no effect or may even increase insulin sensitivity. This difference might be attributed to the steroidal vs the non-steroidal structure of each compound, respectively. Possibly, the androgenic structure of exemestane [7] may be directly responsible for the diabetes-promoting action (independent from its effect on aromatase and estrogen levels), as demonstrated for other androgens. The elucidation of this phenomenon warrants further research.

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Selective internal radiation therapy in patients with carcinoid liver metastases

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To the Editor

Most midgut carcinoids are malignant with metastases, most frequently to the regional lymph nodes and the liver. Metastatic midgut carcinoids may, due to secretion of serotonin, give rise to the carcinoid syndrome. Amelioration of the carcinoid syndrome can be achieved by medical treatment with alpha-interferon and somatostatin analogs or by debulking of liver metastases. Methods for such debulking include surgery, hepatic arterial embolization using occluding particles with or without cytotoxic drugs, and radiofrequency ablation. A new method for reduction of liver metastases, not accessible to surgery, is Selective Internal Radiation Therapy (SIRT), which means hepatic arterial embolization with ^{90}Yttrium-labelled microspheres either made of resin (SIR-Spheres™) or glass (Theraspheres™) [1].

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