Decreased sensitivity to insulin during treatment with danazol in women with endometriosis

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Summary

The aim of this study was to verify to what extent danazol alters insulin sensitivity. To this end, insulin tests were performed before the application of danazol and during the last 15 days of a six-month treatment with this agent on nine women, from 21 to 37 years of age, who had endometriosis. The same test was also performed on nine healthy women, 21 to 35 years of age, in whom laparoscopy did not reveal endometriosis or other pelvic pathology. It was found that the total response of glucose to insulin was significantly lower in women with endometriosis during treatment with danazol than it was in the same women before the application of this agent or in normal women too. Our results support the view that danazol induces resistance to insulin.

Key words: Danazol; Endometriosis; Insulin resistance.

Introduction

It has been reported that during treatment with danazol in women with endometriosis, disturbance of glucose tolerance and hypersecretion of insulin are observed, as well as increase of insulin secretion after intravenous administration of tolbutamide [1]. These findings support the view that danazol induces resistance to insulin. The mechanism by which this drug causes insulin resistance is unknown [1, 2].

In terms of estimation of hypothalamic-pituitary axis in women with endometriosis, the patients were submitted to an insulin test before and during treatment with danazol. It was interesting that during such treatment the patients did not present severe symptomatic hypoglycemia. Therefore, the aim of this study was to verify to what extent danazol alters insulin sensitivity.

Material and Methods

Nine women, aged from 21 to 37 years (mean 27.6±5.3 years), who attended the Fertility Center of our Department, were studied. After their case histories were compiled, a clinical examination was made, and the husband's semen determined to be normal in all cases, there followed a detailed investigation of the women. This included checking of ovulation, evaluation of cervical mucus, and radiological examination of the fallopian tubes in all cases. All examinations showed normal results for all women.

Endometriosis was diagnosed for all nine women by laparoscopy. Evaluation of endometriosis stage [3] showed that five patients were at stage I, two at stage III, and two at stage IV. Danazol, an isoxazolic derivative of the synthetic steroid 5aethinyl-testosterone, was administered in a dosage of 200 mg every eight hours for six months to these patients.

All patients were studied twice. The first study was carried out before laparoscopy (Group II) and the second study was conducted during the last fortnight of the treatment (Group III). In nine healthy women, aged from 21 to 35 years (mean 26.6±4.2 years), who were also studied once, laparoscopy did not reveal endometriosis or other pelvic pathology (Group I).

Patients were on a standard diet containing approximately 15% protein, 35% lipid and 50% carbohydrate. The tests were performed after an overnight fast. A needle was inserted into a forearm vein at 8:30 A.M. and a slow infusion of physiologic saline begun. Three basal blood samples were drawn 15 minutes apart, and blood sampling was performed 15, 30, 45, 60, 75 and 90 minutes after insulin injection (0.1 U/kg body weight of regular crystalline insulin). Plasma glucose was measured using the glucose-oxidase method. Paired t-test was used for statistical analyses after the calculation of the total area under baseline levels (0 to 90 minutes).

Results

Fig. 1 presents the body weight of nine women with endometriosis before the application of danazol (Group II) and during the last 15 days of the six months treatment with the drug (Group III). As is shown by this Figure, body weight increased in all women by between 2 and 10 kilograms. The mean weight increased from 56.4 kilograms to 61.6 kilograms which is significant ($p<0.001$).

Hypoglycemia was achieved after insulin administration in all women, the control group (Group I), the endometriotic women before danazol therapy (Group II) and the endometriotic women during therapy (Group III). However, the glucose decrement (Fig. 2), as calculated by the area under baseline levels (0 to 90 minutes), was significantly lower in women with endometriosis during danazol treatment than before ($p<0.01$) and lower than those in normal controls ($p<0.001$).

Discussion

An interesting finding of our study was the increase of all patients' weight during the last 15 days of the six-

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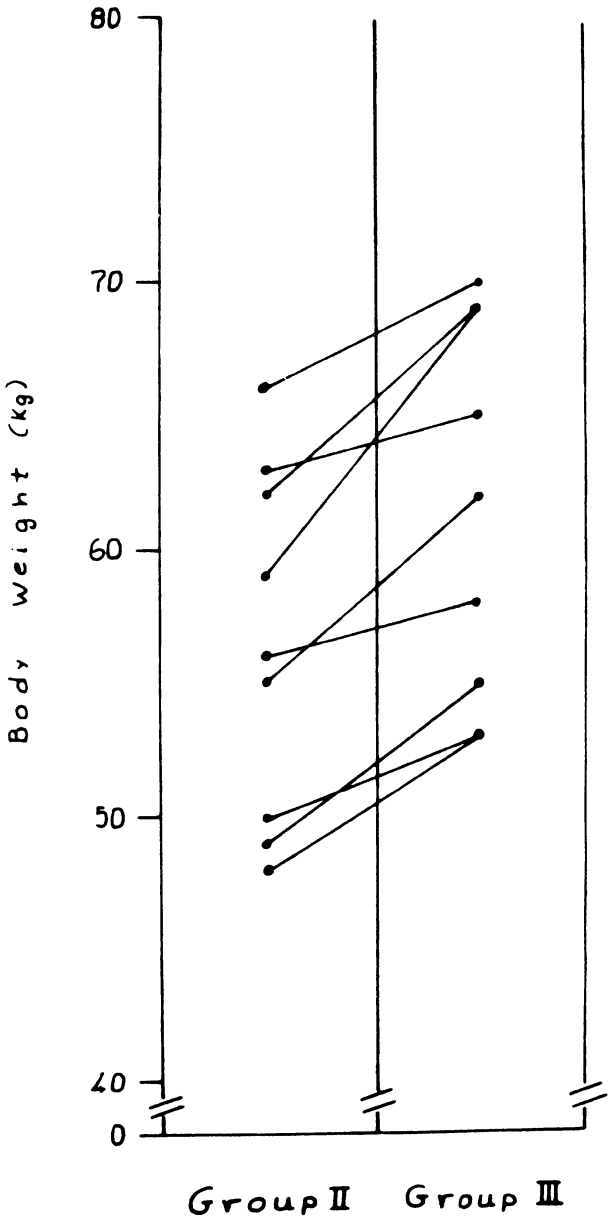

Fig. 1. — Body weight in nine women with endometriosis before (Group II) and during (Group III) treatment with danazol.

month treatment with danazol (Fig. 1). Therefore, the mean increase of patients' weight was from 56.4 kilograms to 61.6 kilograms, which was statistically significant ($p<0.001$). This increase in weight, which was induced by danazol, could be due to the effect of this drug on carbohydrate metabolism [1].

The significantly lower total response of glucose, which was seen in our patients during treatment with danazol (Fig. 2), shows that this drug induces resistance to insulin. This view was originally supported by Wynn [1], who submitted patients under treatment with danazol to the glucose tolerance and tolbutamide tests. The biochemical defect which induces resistance to insulin in

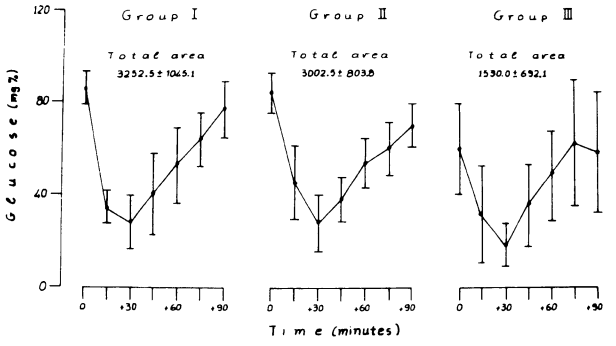

Fig. 2. — Glucose decrement after intravenous administration of 0.1 U/kg insulin in nine controls (Group I) and in nine women with endometriosis before (Group II) and during (Group III) treatment with danazol. Means ±SD are shown.

these patients in not clear. A decrease of the number of insulin receptors, a postreceptor defect [4], or an increase of glucagon secretion [2, 5] which is seen during treatment with danazol, could explain this phenomenon.

Since danazol induces resistance to insulin, patients with insulin sensitive diabetes who are submitted to treatment with danazol, need higher doses of insulin. Furthermore, patients who are submitted to treatment with danazol, are likely to present a lower response of growth hormone, of prolactin and cortisol to insulin induced hypoglycemia, not due to a defect of the hypothalamic-pituitary axis, but because of a lower total response of glucose to insulin. The same phenomenon is seen in patients with chronic hyperprolactinemia, which, as is known, causes resistance to insulin [6].

It is well known that in HAIR-AN syndrome hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN) are seen [4, 7], but whether the hyperinsulinemia causes the hyperandrogenemia or vice versa is not certain [4, 6, 8].

The insulin resistance, which was observed in our patients during treatment with danazol, a synthetic derivate of testosterone, supports the view that hyperandrogenism may induce insulin resistance. However, the increase in weight of our patients, which is known to be associated with a decreased number of insulin receptors and hyperinsulinemia [8-11], may have contributed to their insulin resistance irrespective of their androgen status.

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