Ovarian hyperandrogenism is a common disorder often presenting post menarche with anovulatory oligomenorrhea and signs of androgen excess. Associated hyperinsulinemic insulin resistance, dyslipidemia, and central fat excess herald long-term disease risk. Combined antiandrogen (flutamide 250 mg/d) and insulin-sensitizing (metformin) therapy has beneficial effects, in particular on dyslipidemia and androgen excess in young women. We studied the effects of low-dose flutamide-metformin combination on metabolic variables and body composition in adolescent girls with ovarian hyperandrogenism. Thirty teenage girls (age range, 13.6–18.6 yr) with hyperinsulinemic hyperandrogenism participated in a 12-month pilot study with a 3-month off-treatment phase and a 9-month treatment phase (randomized sequence) on combined flutamide (125 mg/d) and metformin (1275 mg/d). Body composition was assessed by dual-energy x-ray absorptiometry; endocrine–metabolic state and ovulation rate were screened every 3 months. Insulin sensitivity was assessed by homeostasis model assessment (HOMA). Overnight GH and LH profiles were obtained pretreatment and after 6 months on treatment (n = 8). Over the 3-month pretreatment control phase (n = 14) all study indices were unchanged. Flutamide-metformin treatment (n = 30) was followed within 3 months by marked decreases in hirsutism score and serum androgens, by a more than 50% increase in insulin sensitivity and by a less atherogenic lipid profile (all P < 0.0001). After 9 months on flutamide-metformin, body fat decreased by 10%, with a preferential 20% loss of abdominal fat; conversely, lean body mass increased, and total body weight remained unchanged; ovulation rate increased from 7–87% after 9 months. Baseline GH hypersecretion and elevated serum IGF-1 normalized after 6 months on flutamide-metformin. Within 3 months post-treatment (n = 16), a rebound was observed for all assessed indices. In conclusion, in teenage girls with ovarian hyperandrogenism, low-dose combined flutamide-metformin therapy attenuated a spectrum of abnormalities, including insulin resistance and hyperlipidemia. Improved insulin sensitivity and reduced androgen activity led to a marked redistribution of body fat and lean mass, resulting in a more feminine body shape. (J Clin Endocrinol Metab 88: 2600–2606, 2003)
prove following combined flutamide-metformin therapy but its effects on pituitary function have not been studied.

We now report a pilot study evaluating a low-dose combination of flutamide and metformin on body composition, endocrine-metabolic status, including GH and gonadotropin secretion, and ovulation rate in adolescents with hyperinsulinemic ovarian hyperandrogenism.

**Subjects and Methods**

We studied 30 teenage girls (age, 15.8 ± 0.3 yr; range, 13.6–18.6 yr), who were 3–8 yr beyond menarche and were either not at risk of pregnancy or using nonhormonal contraception. Inclusion criteria were: 1) hyperinsulinemia on a standard 2-h oral glucose tolerance testing, defined as peak serum insulin levels more than 150 U/ml (29) and/or mean serum insulin more than 84 mU/liter (29, 30); 2) ovarian hyperandrogenism as defined by a or oligo-menorrhea (duration of menstrual cycles >45 d) and/or hirsutism (Ferriman and Gallwey score >8; Ref. 31); elevated serum androstenedione, total testosterone, and/or free androgen index (testosterone × 100/SHBG) (32); and 17-hydroxyprogesterone hyperresponse (>160 ng/dl) to GnRH agonist (leuprolide acetate, Procrin, Abbott, Madrid, Spain; 500 g sc; Ref. 33).

Exclusion criteria were: body mass index (BMI) more than 25 kg/m²; thyroid dysfunction, Cushing’s syndrome, hyperprolactinemia; glucose intolerance (34); family or personal history of diabetes mellitus; late-onset congenital adrenal hyperplasia (35, 36); intake of medication that affect gonadal or adrenal function, or carbohydrate or lipid metabolism; abnormal blood count or serum electrolytes; and abnormal results in screening tests for liver and kidney function.

The study was conducted in Barcelona, with approval by the hospital’s Institutional Review Board, informed consent from parents and/or girls, and assent from minors.

**Study design**

In an open-labeled 12-month study, each subject underwent a 9-month treatment phase and a 3-month off-treatment phase (Fig. 1). At start of study, timing of the off-treatment phase in each subject was randomized to: pretreatment (group 1; n = 14) or posttreatment (group 2; n = 16). During the 9-month treatment phase, all girls received daily flutamide (125 mg/d) and metformin (1275 mg/d).

**Endocrine-metabolic assessment**

Fasting glucose, insulin, LH, FSH, SHBG, dehydroepiandrosterone-sulfate (DHEAS), estradiol, testosterone, androstenedione and lipid profile were measured at baseline and at 3-month intervals until the 12th month. Insulin secretion and sensitivity were calculated from fasting glucose and insulin levels using the homeostasis model assessment (HOMA, Refs. 37 and 38). Blood count and liver and kidney function test were also performed after 1, 3, and 6 months on treatment, as additional safety variables. Ferriman-Gallwey scores were performed by a single investigator every 3 months.

A subgroup of eight girls consented to additional measurement of serum IGF-I and IGF binding protein (IGFBP)-1 concentrations, and LH, FSH, and GH levels during an overnight profile (20-min sampling from a peripheral vein, from 2100 h until 0900 h) on two occasions (before treatment, and after 6 months on treatment). Hormonal assessments were performed either in the follicular phase (d 3–7) of the menstrual cycle or after 2 months of amenorrhea.

Baseline hormone levels were compared with published reference data of age- and pubertal stage-matched population (39, 40). Healthy age- and BMI-matched postmenarcheal siblings of type 1 diabetic children (age, 15.5 yr; BMI, 19.9 kg/m²; height sd score, 0.26) provided control data for overnight GH, LH, and FSH. All had normal HbAlc levels and were islet cell antibody negative.

**Ovulation assessment**

Ovulation was assessed by measuring serum progesterone concentration, weekly for a consecutive 4 wk, before treatment, after 6 and 9 months on treatment and, in group 2, after 3 months off treatment. Ovulation was post factum identified by serum progesterone concentration more than 8 ng/ml in a sample obtained 5–8 d before menses (9).

**Waist to hip ratio**

Waist circumference was measured by tape measure at the level of the umbilicus during end-expiration to the nearest 0.5 cm. Hip circumference was measured at the level of maximal antero-posterior excursion. Each was measured three times, and the medians were used to calculate waist to hip ratio.

**Body composition**

Body composition was assessed by dual-energy x-ray absorptiometry with a Prodigy Lunar Corp. (Madison, WI) coupled to Lunar Corp. software (version 3.4/3.5; Ref. 41). Absolute (kg) and relative (%) whole body fat and lean mass were assessed, as well as fat content in the abdominal region, which was defined as the area encompassed between the dome of the diaphragm (cephalad limit) and the top of the greater throcater (caudal limit) (42). The total radiation dose for each examination was 0.1 mSV per meter. The coefficients of variation (CV) for scanning precision, calculated from 30 consecutive scans of an external phantom (Holologic, Inc., Waltham, MA), were 2.0% and 2.6% for fat and lean body mass, respectively (43). The intra-individual CV for abdominal fat mass was 0.07%.

**Hormone assays**

Serum glucose was measured by the glucose oxidase method. Immunoreactive insulin was assayed by immunoassay microparticles X (Abbott Diagnostics, Santa Clara, CA). Intraassay and interassay CV were 4.7% and 7.2%, respectively. LH, FSH, and progesterone were measured by immunoneuromeniculinumencine (IMMULITE 2000, Diagnostic Products Corp., Los Angeles, CA); CV were 3.5% and 5.0% for LH, 4.6% and 6.3% for FSH, and 7.8% and 8.5% for progesterone. Serum testosterone, 17-hydroxyprogesterone, androstenedione, estradiol, SHBG, and DHEAS levels were assayed as described (11). IGF-I concentrations were measured in ethanolic extracts by ELISA (Diagnostic Systems Laboratories, Inc., Tooting, London, UK); assay sensitivity was 0.03 ng/ml; intraassay and interassay CV were 4.5% and 6.5%, and 8.8% and 4.8%, at 48.4 and 170 ng/ml. Plasma IGFBP-1 levels were measured by ELISA (Diagnostic Systems Laboratories, Inc.); assay sensitivity was 0.25 ng/ml. Intraassay and interassay CV were 6.1% and 5.3%, and 10.4% and 5.1%, at 7.0 and 48.4 ng/ml.

In overnight profile serum samples, LH and FSH were measured by RIA, using standards first IRP 68/40 and first IRP 78/549, respectively. For both assays, the lower limit of sensitivity was 0.8 U/liter, and interassay CV less than 10%. For LH, the intraassay CV was 8.3% and 10% at 2.4 and 15.0 U/liter; and for FSH, 10.3% and 7.3% at 2.8 and 14.9 IU/liter. GH was measured by immunoradiometric assay (44). Samples were kept frozen at −20 C until assay.

**Calculations and statistics**

Pulsatility of overnight hormone secretion was assessed by Pulsar. This program detects puls as deviations based on height and duration...
TABLE 1. Clinical, hormonal, and dual-energy x-ray absorptiometry variables in the two study groups that were randomized for either a pretreatment control phase (group 1; n = 14; mean age, 15.3 yr) or a posttreatment control phase (group 2; n = 16; mean age, 15.9 yr) of 3 months without therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 14)</th>
<th>Group 2 (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference*</td>
<td>−3 months</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>21.4 ± 0.3</td>
<td>21.8 ± 0.4</td>
</tr>
<tr>
<td><strong>Ferriman-Gallwey score</strong></td>
<td>&lt; 8</td>
<td>15.4 ± 1.1</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>67.3 ± 0.9</td>
<td>73.0 ± 1.2</td>
</tr>
<tr>
<td><strong>Waist/hip ratio</strong></td>
<td>0.717 ± 0.008</td>
<td>0.780 ± 0.011</td>
</tr>
<tr>
<td><strong>Ovulatory/anovulatory</strong></td>
<td>23:1</td>
<td>1:13</td>
</tr>
<tr>
<td><strong>HOMA S (%)</strong></td>
<td>78 ± 5</td>
<td>64 ± 5</td>
</tr>
<tr>
<td><strong>SHBG (µg/dl)</strong></td>
<td>1.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td><strong>Testosterone (ng/dl)</strong></td>
<td>31 ± 3</td>
<td>116 ± 12</td>
</tr>
<tr>
<td><strong>Androstenedione (ng/dl)</strong></td>
<td>126 ± 14</td>
<td>264 ± 21</td>
</tr>
<tr>
<td><strong>DHEAS (µg/dl)</strong></td>
<td>133 ± 15</td>
<td>238 ± 20</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mg/dl)</strong></td>
<td>70 ± 5</td>
<td>111 ± 5</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mg/dl)</strong></td>
<td>62 ± 5</td>
<td>52 ± 3</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dl)</strong></td>
<td>61 ± 4</td>
<td>70 ± 5</td>
</tr>
<tr>
<td><strong>BMD (g/cm²)</strong></td>
<td>1.08 ± 0.02</td>
<td>1.10 ± 0.03</td>
</tr>
<tr>
<td><strong>Total fat mass (kg)</strong></td>
<td>13.3 ± 1.3</td>
<td>18.6 ± 1.6</td>
</tr>
<tr>
<td><strong>Abdominal fat mass (kg)</strong></td>
<td>2.3 ± 0.3</td>
<td>5.3 ± 0.7</td>
</tr>
<tr>
<td><strong>Lean body mass (kg)</strong></td>
<td>37.4 ± 1.2</td>
<td>35.7 ± 1.0</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. BMD, Bone mineral density; HDL, high-density lipoprotein; LDL, low-density lipoprotein. * Healthy volunteers matched for height and weight (n = 24 for endocrine-metabolic variables; n = 22 for body composition; age, 16.2 ± 0.2 yr); b healthy volunteers assessed over 3 months (n = 24; age, 15.6 ± 0.2; Ref. 58); c P ≤ NS for all variables vs. −3 months; d P < 0.01; e P ≤ 0.0001 vs. 0 months; f P < 0.0001 vs. pretreatment, by χ²; g P < 0.01; h P < 0.001 vs. 9 months on. i P < 0.001 by χ².
from a smoothed detrended baseline, using the assay sd as a scale factor. The following parameters were calculated: baseline, mean, maximum and mean peak amplitude, number of pulses per 12 h, as previously described (44).

Anthropometric data and hormonal results are expressed as mean ± SEM. Paired two-sided t tests were used for comparisons; P values <0.01 were considered significant.

Results

Table 1 displays clinical characteristics, endocrine-metabolic variables, ovulatory state, and body composition data of the two study subgroups at the start and end of their treatment and control phases. Over the 3-month pretreatment control phase (n = 14), all study indices were stable.

At start of treatment (0 months), all study variables were comparable in the two randomized subgroups; accordingly, they were pooled in Figs. 2 and 3.

Flutamide-metformin treatment was followed by swift and persisting decreases in hirsutism score, fasting insulin, and serum androgens, and by a less atherogenic lipid profile (all P < 0.0001 within 3 months; Fig. 2). Before treatment, the fraction of ovulatory girls was 7%; this increased to 67% after 6 months, and to 87% within 9 months on flutamide-metformin (Fig. 3).

There was no change in body weight or BMI on treatment, but waist circumference and waist-hip ratio decreased; on dual-energy x-ray absorptiometry we detected a 10% decrease in total body fat, including a preferential 20% loss of abdominal fat; unexpectedly, a consistent increase in lean mass was observed, so that the initial 2 kg deficit in lean mass was recovered after 9 months on treatment (all P < 0.0001; Fig. 2). Interestingly, these indices of body composition were
TABLE 2. GH and gonadotropin pulsatility data from eight adolescents, together with selected endocrine-metabolic data, before and after 6 months on flutamide + metformin treatment

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Pretreatment</th>
<th>On treatment</th>
<th>Difference (mean and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HomA S (%)</td>
<td>78 ± 5</td>
<td>60 ± 7e</td>
<td>119 ± 14d</td>
<td>59 (21–97)e</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>31 ± 3</td>
<td>118 ± 14d</td>
<td>70 ± 9</td>
<td>48 (23–77)d</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>70 ± 5</td>
<td>113 ± 7d</td>
<td>79 ± 6</td>
<td>29 (22–36)d</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>62 ± 5</td>
<td>52 ± 3</td>
<td>61 ± 4</td>
<td>9 (–13–29)d</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>61 ± 4</td>
<td>75 ± 2d</td>
<td>49 ± 5</td>
<td>26 (6–11)d</td>
</tr>
<tr>
<td>GH (mcg/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.9 ± 2.0</td>
<td>15.7 ± 1.9e</td>
<td>9.9 ± 1.4</td>
<td>6.7 (1.9–11.5)e</td>
</tr>
<tr>
<td>Maximum</td>
<td>46.1 ± 8.4</td>
<td>71.8 ± 7.7d</td>
<td>51.7 ± 9.4</td>
<td>18.3 (–14.5–31.1)</td>
</tr>
<tr>
<td>Amplitude</td>
<td>19.2 ± 4.2</td>
<td>30.8 ± 3.4d</td>
<td>20.1 ± 4.0</td>
<td>6.1 (–7.5–19.8)</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.9 ± 0.4</td>
<td>6.4 ± 2.1b</td>
<td>2.2 ± 0.3</td>
<td>4.2 (–0.3–8.8)</td>
</tr>
<tr>
<td>Pulse frequency</td>
<td>4.6 ± 0.3</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.3</td>
<td>0 (–0.7–0.7)</td>
</tr>
<tr>
<td>IGF-I (µg/liter)</td>
<td>392 ± 28</td>
<td>643 ± 52c</td>
<td>362 ± 34</td>
<td>281 (186–376)c</td>
</tr>
<tr>
<td>IGFBP-1 (mcg/liter)</td>
<td>11.9 ± 3.1</td>
<td>8.8 ± 1.1</td>
<td>14.9 ± 2.2</td>
<td>6.0 (–3.2–19.8)</td>
</tr>
<tr>
<td>LH mean (IU/liter)</td>
<td>6.9 ± 1.6</td>
<td>4.2 ± 1.1</td>
<td>6.0 ± 1.5</td>
<td>1.8 (–4.6–10)</td>
</tr>
<tr>
<td>FSH mean (IU/liter)</td>
<td>3.6 ± 0.3</td>
<td>3.0 ± 0.5</td>
<td>3.7 ± 0.5</td>
<td>0.8 (–1.7–0.3)</td>
</tr>
</tbody>
</table>

HDL, High-density lipoprotein; LDL, low-density lipoprotein; CI, confidence interval. a Healthy volunteers matched for height and weight (n = 25 for endocrine-metabolic variables; age, 16.3 ± 0.2 yr; n = 7 for overnight GH, LH, and FSH profiles; age, 15.5 ± 1.0 yr). b P < 0.05 and c P < 0.001 vs. controls. d P < 0.01, e P < 0.001, and f P < 0.05 vs. pretreatment values.

still improving after 9 months, although all endocrine-metabolic parameters had already reached their improved steady state level after 3–6 months on treatment.

By 3 months post treatment (Table 1, group 2), most indices significantly rebounded toward pretreatment values, confirming that changes were treatment related but also indicating the persistence of an underlying endocrine skew (Figs. 2 and 3).

GH-gonadotropin pulsatility data before and after 6-month treatment in eight subjects are shown in Table 2. Compared with controls, study girls had higher mean, maximum, and baseline overnight GH levels, increased GH pulse amplitude, elevated serum IGF-I levels, and a trend toward lower IGFBP-1. These abnormalities were no longer apparent after 6 months on treatment.

Discussion

In girls with hyperinsulinemic hyperandrogenism, combined low-dose androgen-receptor blockade and insulin-sensitization therapy strikingly improved not only the endocrine-metabolic state but also their body shape and body composition. This occurred without altering total body weight, and the broad spectrum of changes was reversed within 3 months of discontinuing treatment.

The improvements in endocrine-metabolic abnormalities in these teenage girls were similar in magnitude to those recently reported in young women using the same combination, but on a higher flutamide dose (16). Low-dose flutamide therapy is less likely to be associated with hepatotoxicity and can maintain the improvements in hirsutism score and serum androgen levels that have been induced by a higher flutamide dose; however, neither dose on its own consistently changes menstrual cyclicity or ovulation rate (16, 45). Our current results suggest that flutamide 125 mg/d is an effective and safe starting dose to treat hyperinsulinemic hyperandrogenism, provided it is combined with insulin-sensitization therapy. Combined treatment has a stronger pathophysiological basis, and is also more cost effective than high-dose flutamide in monotherapy.

As previously described (16), combination therapy im-pressively increased ovulation rates, which rapidly reversed off flutamide-metformin. The major effect has been attributed to metformin (16), used either in monotherapy or adjuvant to gonadotropins and clomiphene citrate in older PCOS women with subfertility (9, 10, 46, 47). Effectiveness is thought to result mainly from improvement in insulin sensitivity, leading to decreased ovarian androgen production and enhanced follicular development (9, 46). In addition, metformin might directly inhibit theca-cell androgen production (48).

Studies on the hypothalamic-pituitary function of nonobese adolescents with ovarian hyperandrogenism are scarce. Disorderly amplified LH pulsatility and orderly augmented GH secretion have been reported (27, 28, 49). Compared with controls, the adolescents we studied had elevated pulsatile GH levels, which normalized on treatment. The GH hypersecrecion could relate to increased estrogen, aromatizable androgen, or insulin availability (28) and appear to be functionally relevant as IGFBP-1 levels were also raised. This apparent increase in the setpoint of the somatotropic axis may reflect earlier programing by fetal growth restraint followed by postnatal catch-up growth, a sequence that is sometimes part of the ontogeny of ovarian hyperandrogenism (50, 51).

The results of this pilot study indicate that excess central fat in women with hyperinsulinemic hyperandrogenism is a consequence, rather than a cause, of their endocrine condition. Thus, body shape seems to reflect the endocrine-metabolic state, as does bone mineral density (41), but there may be a time-lag of several months. Previous data show that central adiposity may in turn augment hyperinsulinemic hyperandrogenism, possibly by increasing circulating free fatty acids (FFA; Refs. 52 and 53). Therefore, our findings suggest a feedback-loop whereby these endocrine-metabolic changes and excess central fat may aggravate and perpetuate each other. Our observations open perspectives for early intervention to correct central adiposity and dyslipidemia, using flutamide-metformin or other therapies. Candidates for early intervention could include adolescents at high risk for PCOS, such as girls who experienced the sequence of low birth weight and precocious pubarche (51, 54).
In our study, loss of central fat was compensated by an increase in fat-free mass. Intriguingly, this redistribution in body composition occurred despite reductions in circulating levels of the anabolic hormones insulin, GH, IGF-I, and androgens. Muscle insulin resistance is associated with reduced muscle bulk, reduced glucose uptake, and increased dependency on circulating FFA. In women with hyperinsulinemic hyperandrogenism, the central fat depot is a likely major source of FFA, and one could speculate that elevated GH levels during fasting could increase FFA mobilization. The increase in muscle bulk could follow the reduction in central fat and increased muscle insulin sensitivity, but this requires confirmation by further dynamic studies.

The effects of flutamide-metformin on body shape were obtained without implementing any changes in diet, exercise, or lifestyle, and without changing total body weight. These findings indicate for the first time that the regulation of body weight is essentially independent of abdominal fat mass and its hormonal correlates, or that any substantial dependency on such factors does not occur within a time-lag of several months. Thus, the addition of lifestyle changes to reduce weight in obese subjects with PCOS, would be expected to amplify the effects of flutamide-metformin on body composition and could further reduce risks for longer-term adulthood disease (55).

The body shape of nonobese women is normally characterized by a low waist to hip ratio that typically appears after mid-puberty (56), without substantial change in body fat mass (57). Such a low waist to hip ratio may henceforth be regarded as a clinical marker of insulin sensitivity, and an index of a lack of excess androgen activity. The normal onset of ovulatory function has been proposed to concur with the late-pubertal increase in insulin sensitivity, partly due to the waning of pubertal GH hypersecretion (11). It remains to be verified whether the normal onset of ovulatory cycling does indeed coincide with the late-pubertal reduction in waist to hip ratio.

A combination treatment containing an androgen receptor blocker increased lean body mass, and this increment (in kg) consistently matched the loss in total fat mass. A similar but lesser effect has been observed with metformin monotherapy in anovulatory adolescent girls with mild hyperinsulinemic hyperandrogenism secondary to prenatal growth restraint (58), a condition that is associated with reduced lean body mass in infancy and early childhood (59), and with central adiposity from late childhood onwards (60). It remains to be studied whether a longstanding deficit in lean body mass may govern the accumulation of excess central fat in girls and women with hyperinsulinemic hyperandrogenism. If so, then the focus for treatment of hyperinsulinemic hyperandrogenism may shift to a much younger age because human myogenisis occurs mainly before birth (61).

In conclusion, in teenagers with ovarian hyperandrogenism, low-dose flutamide-metformin therapy attenuated a wide spectrum of abnormalities, including excess fat mass and reduced lean mass. A low waist to hip ratio is a feminine marker for insulin sensitivity and for a lack of hyperandrogenism and hypomatsotropism.

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