Clinical, endocrine and metabolic effects of acarbose, an α-glucosidase inhibitor, in PCOS patients with increased insulin response and normal glucose tolerance

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BACKGROUND: The aim of this study was to evaluate whether treatment with acarbose, an α-glucosidase inhibitor, improved hyperandrogenic symptoms, insulin and androgen serum concentrations in hyperinsulinaemic patients with polycystic ovary syndrome (PCOS). METHODS: 30 hyperinsulinaemic women with PCOS and 15 controls were evaluated. Patients were randomized, using a computer-generated randomization list, into two groups of 15 each and treated with placebo or 300 mg/day of acarbose for three months. Hirsutism and acne/seborrhoea scores, hormonal and sex hormone binding globulin serum concentrations, glycaemia and insulin responses to a standard oral glucose load (75g) were measured in all patients before and after three months of treatment. RESULTS: A significant reduction of the acne/seborrhoea score was observed in patients treated with acarbose and eight of them resumed a regular menstrual rhythm. These clinical improvements were associated with a significant reduction of the insulin response to glucose load, a significant decrease of LH, total testosterone and androstenedione and with a significant increase of sex hormone binding globulin serum concentrations. The serum concentrations of FSH, dehydroepiandrosterone sulphate, prolactin and 17α-hydroxyprogesterone did not change significantly. No clinical, metabolic and hormonal modifications were observed in PCOS patients treated with placebo. CONCLUSIONS: This is the first report showing a reduction of the acne/seborrhoea score in hyperinsulinaemic patients with PCOS treated with acarbose. This improvement was associated with a significant decrease of the insulin response to oral glucose load and of LH and androgen serum concentrations and with a significant rise of sex hormone binding globulin concentration.

Key words: acarbose/hyperinsulinaemia/hypoglycaemizing drugs/polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine pathology characterized by menstrual abnormalities, hirsutism, acne, seborrhoea, ovaries with multiple small follicles, chronic anovulation, elevated plasma LH concentrations, or an increased LH to FSH ratio, and hypersecretion of androgens (Franks, 1995). Hyperinsulinaemia is another well-known feature. Up to 20% of women with PCOS, screened by means of an oral glucose tolerance test (OGTT) showed an impaired glucose tolerance (Dunaif et al., 1987), suggesting that this subgroup of patients is at risk for developing type 2 diabetes mellitus. Hyperinsulinaemia may be due to an increased insulin secretion (Holte et al., 1994), a defect of insulin action (Dunaif et al., 1989), a decreased hepatic clearance of insulin (Ciampelli et al., 1997) or to an interaction among all these metabolic alterations. A still unresolved question remains as to whether body mass and body fat distribution contribute to the onset of the insulin resistance in these patients (Ovesen et al., 1983; Dunaif et al., 1987; Holte et al., 1994).

Several mechanisms have been postulated to explain the observed correlation between hyperinsulinaemia and hyperandrogenism in PCOS patients. Insulin may act at the pituitary, the ovarian, and/or the hepatic level increasing androgen synthesis and/or decreasing androgen metabolism. In-vitro studies have shown that insulin stimulates androgen synthesis from stromal and thecal ovarian tissue (Ehrman et al., 1992). Increased ovarian P450c17α activity, a key enzyme in the biosynthesis of androgens, has been reported in obese and non-obese hyperinsulinaemic women with PCOS, and P450c17α activity appears to be stimulated by insulin in PCOS (Nestler and Jakubowicz, 1997). Moreover, insulin was found able to enhance both basal and gonadotrophin releasing hormone (GnRH)-stimulated LH release (Prelevic et al., 1990a; Fulghesu...
et al., 1995) and to inhibit sex hormone-binding globulin (SHBG) synthesis at the hepatic level (Nestler et al., 1991), enhancing consequently the level of circulating free testosterone concentrations. Insulin may also inhibit the hepatic synthesis of insulin-like growth factor-1 (IGF-1) binding protein, leading to an increased availability of this hormone to the ovary (Leroith et al., 1995). These observations suggest that insulin plays a pathogenetic role in the onset of hyperandrogenism in some patients with PCOS.

Many available pharmacological agents are able to decrease insulin secretion and/or to increase insulin sensitivity, such as sulphonylureas, biguanides, thiazolidinediones, somatostatin analogues and α-glucosidase inhibitors (Nestler et al., 1989; Prelevic et al., 1990b; Velazquez et al., 1994; Dunaif et al., 1996; Geisthovel et al., 1996). The α-glucosidase inhibitors act by slowing the absorption of carbohydrates from the intestines, so minimizing the post-prandial rise of blood glucose concentration (Coniff et al., 1995). Gastrointestinal side-effects require gradual dosage increments over weeks or months after therapy is initiated. Serious adverse reactions are rare and weight gain may be minimized with this therapy. Acarbose, the only drug of this class used in clinical practice, reversibly prevents α-glucosidase activity in the brush-border of the intestinal mucosa, decreasing disaccharide digestion, and so, consequently, reducing enteral monosaccharide absorption (Toeller, 1991). Acarbose has been shown able to flatten the post-prandial glucose and insulin increase and to decrease the serum androgen concentrations in hyperinsulinaemia pre-menopausal women with hyperandrogenaemia (Geisthovel et al., 1996). Since this drug is well tolerated and has few side-effects, it may be used for the treatment of hyperandrogenic women with hyperinsulinaemia. Hence, the purpose of this study was to evaluate whether treatment with acarbose had any effect on clinical symptoms, hormone serum concentrations and insulin response to OGTT in PCOS patients with hyperinsulinaemia.

Materials and methods

Patient selection

30 normal weight PCOS patients were referred to the Reproductive Endocrinology Unit, University Hospital of Catania, and participated in this study. 15 healthy normal weight women with normal menstrual cycles (27–34 days) and normal ovarian appearance (assessed by trans-vaginal ultrasound) were selected as the control group. All women (patients and controls) were in good health and none had taken any medication known to affect carbohydrate metabolism or gonadal function for at least 6 months before the study. Spontaneous onset of puberty and normal sexual development were reported in both patients and controls. Since puberty, all PCOS patients had been affected by hirsutism, acne/seborrhoea, oligomenorrhoea or secondary amenorrhoea, whereas no abnormal hair growth and/or body distribution, absence of acneic/seborrhoeic manifestations and regular menses were reported in the control subjects.

The following inclusion criteria were established for PCOS patients: (i) menstrual abnormalities (<6 menstrual periods in the last year); (ii) clinical manifestations of hyperandrogenism, such as hirsutism and raised acne/seborrhoea scores; (iii) elevated serum concentrations of total testosterone (>80 ng/dl) and/or androstenedione (>190 ng/dl); (iv) normal serum prolactin (PRL) and a normal thyroid function test; (v) regular basal concentrations and/or normal response of 17α-hydroxyprogesterone (17α-OHP) to the adrenocorticotropic hormone (ACTH)-stimulation test; (vi) body mass index (BMI) within normal range; (vii) normal glucose tolerance; and (viii) elevated insulin response to OGTT.

By trans-vaginal ultrasonography, all PCOS patients showed subcapsular follicles of 3–8 mm diameter in one plane in one ovary, increased stroma and ovarian volume.

Study design and procedures

The study was approved by the Ethical Committee of our Department and written informed consent was obtained from each woman. All PCOS patients and controls underwent clinical examination, evaluation of the hirsutism score according to Ferriman and Gallwey (Ferriman and Gallwey, 1961) and evaluation of the acne/seborrhoea score according to Cook et al. (Cook et al., 1979). For each woman, the body mass index (BMI) was calculated using the following formula: BMI = weight (kg)/height (m)². In all patients and controls, basal serum concentrations of LH, FSH, testosterone, androstenedione, dehydroepiandrosterone-sulphate (DHEAS), PRL, 17α-OHP and SHBG were determined during the follicular phase (cycle days 2–7) of a spontaneous or progestin-induced cycle. Two months before the study, an ACTH stimulation test (Synacthen 250 mg i.v., Ciba-Geigy, Varese, Italy) was given to PCOS patients during the early follicular phase of a spontaneous or progestin-induced cycle (days: 2–5) and the serum concentrations of 17α-OHP were measured before and 60 min after the injection of ACTH. Ultrasound ovarian volume was calculated during the follicular phase, according to the formula (D1/2)×(D2/2)×(D3/2) where D1 is the length, D2 the width and D3 the depth of the ovary.

All subjects underwent OGTT (glucose 75 g, Dextro O.G.–T.Saft; Boehringer Mannheim, Mannheim, Germany) at 08.00, after 3 day standard diet (300 g carbohydrate) followed by an overnight fasting, to evaluate glucose tolerance and the pancreatic β-cell response to glucose load. Venous blood samples for glucose and serum insulin concentrations were drawn at 0, 30, 60, 90, 120, 150 and 180 min after glucose ingestion. Glucose tolerance was defined according to the criteria of the National Diabetes Data Group (National Diabetes Data Group, 1979). Normal glucose tolerance was defined when plasma glucose at 0 min was <115 mg/dl, peak value <=200 and <140 at 120 min; impaired glucose tolerance when plasma glucose at 0 min was 115–140, peak value >200 and 140–199 at 120 min; and diabetes mellitus when plasma glucose at 0 min was >140, peak value >200 and >200 at 120 min. A normal insulinaemic response to OGTT was considered as a maximum insulin peak of 100 mU/ml in one or more serum samples. This cut-off value was obtained from a control population of 67 normal weight (BMI: 22.2 ± 0.5 kg/m²), young (age range: 22–35 years) eumenorrhoic women with a normal endocrine profile, studied during the early follicular phase of their cycles (Ciotta et al., 1999). Early phase insulin secretion (insulinogenic index) was calculated as the ratio between serum insulin and blood glucose concentrations 30 min after the glucose load (Wareham et al., 1995). This index has been shown previously to correlate strongly with the first phase of insulin response following an intravenous glucose tolerance test (Kosaka et al., 1996).

PCOS patients were randomly divided into two groups. Randomization was achieved by a computer generated list. The final random set of numbers was assigned to the treatment with placebo whereas the second set was assigned to the treatment with acarbose, 300 mg/day (Glucobay; Bayer, Milan, Italy), for 3 months. Each woman was instructed to take the drug 3 times/day before eating and the study was conducted in a double-blinded fashion. At the end of

Acarbose treatment in PCOS patients with increased insulin response
the treatment, each patient underwent the same clinical, endocrine and OGTT evaluations as before the treatment.

In the amenorrhoeic patients, the control endocrine testing was effected after uterine bleeding obtained after administration of medroxyprogesterone.

Hormone measurements

Blood samples were withdrawn through an indwelling catheter placed in the antecubital vein, after an overnight fast. The blood samples were centrifuged, and the sera were collected and stored at -20°C, until insulin, LH, FSH, testosterone, androstenedione, DHEAS, PRL, 17α-OHP and SHBG serum concentrations were measured. Serum glucose concentrations were determined immediately by the glucose oxidase method. Insulin was measured by a commercially available radioimmunoassay kit (Technogenetics, Milan, Italy), for which the intra and inter assay coefficients of variation (CVs) were 4.8 and 8.2% respectively. LH, FSH, testosterone, androstenedione, DHEAS and PRL were measured using commercially available immunoradiometric kits (Technogenetics). Measurements of serum 17α-OHP (Pantex, Santa Monica, CA, USA) and SHBG (Interech, Strasen, Luxemburg) were performed by the double-antibody radioimmunoassay method. All samples were assayed in duplicate. The intra-assay CVs of LH and FSH were 4.2 and 6.9% respectively, and the inter-assay CVs were 9.9 and 10.8% respectively. The intra-assay and inter-assay CVs for each steroid were 7.9 and 10.1% for testosterone, 8.0 and 10.8% for androstenedione and 5.3 and 9.8% for DHEAS respectively. The intra-assay and inter-assay CVs for PRL were 6.2 and 4.9% respectively. The intra-assay and inter-assay CVs for 17α-OHP and SHBG were 5.6 and 5.9%, and 4.2 and 4.9% respectively.

Statistical evaluation

Results are expressed as mean ± SEM throughout the study. The effects of acarbose on glycaemia and insulin responses to OGTT were analysed by one-way and two-way analyses of variance (ANOVA), followed by Duncan’s multiple range test. All other clinical and hormonal parameters were analysed by one-way ANOVA, followed by Duncan’s test or unpaired Student’s t-test, as appropriate. Significance was accepted where P < 0.05.

Results

Pre-treatment values

PCOS patients had an age range and a BMI similar to that of controls, whereas their hirsutism and acne/seborrhoea scores were significantly higher (P < 0.001; Table I). From the endocrine point of view, PCOS patients had significantly higher concentrations of LH, testosterone, androstenedione and 17αOH-P (P < 0.001), significantly lower serum concentrations of SHBG (P < 0.001) and similar concentrations of FSH, DHEAS and PRL with respect to controls (Table I). PCOS patients and controls showed normal fasting glycaemic and insulinemic concentrations. The glycaemic response to OGTT was similar to that found in controls, suggesting a regular glucose tolerance, whereas insulin response was significantly higher in patients with PCOS (P < 0.05, Figure 1). The insulinogenic index was also significantly higher (P < 0.05) in PCOS patients with respect to controls (Table I).

Effects of acarbose treatment

All patients treated with acarbose reported abdominal distension and diarrhoea, whereas 5 patients treated with placebo reported headache and gastric pyrosis. Hepatic and renal functions, as well as haemochrom, lipoprotein and electrolyte profiles were normal during treatment. The BMI did not vary significantly during treatment. On the other hand, there was a significant reduction of the acne/seborrhoea score in patients treated with acarbose (P < 0.05) in comparison with the pre-treatment value, whereas it did not change in PCOS patients treated with placebo (Table II). The hirsutism score did not change significantly, although a slight decrease of hair growth was reported by 6 patients (40%) after 3 months of treatment with acarbose. A return to a regular menstrual rhythm was reported by 9 patients treated with acarbose (60%), whereas patients treated with placebo did not report any modification.

These clinical changes were associated with a significant decrease of LH, testosterone and androstenedione serum concentrations in patients treated with acarbose (Table II) with respect to the pre-treatment values (P < 0.05). In the same patients, there was a significant increase of serum SHBG (P < 0.05) versus the pre-treatment value, and no changes in FSH, DHEAS, PRL and 17αOH-P. The PCOS patients treated with placebo did not show any significant change in any of these hormones nor SHBG (Table II).

Blood glucose concentrations following OGTT did not change significantly during treatment with acarbose, whereas the insulin response to OGTT showed a significant decrease (P < 0.05, Figure 2). No significant changes in glycaemia and insulin responses to OGTT were observed in the group of patients treated with placebo compared with the pre-treatment values (Figure 2). The insulinogenic index decreased after treatment with acarbose (P < 0.05), whereas it did not change in patients treated with placebo (Table II).

Discussion

An association between PCOS and hyperinsulinaemia was described for the first time in 1976 by Kahn et al. (Kahn et al., 1976). Hyperinsulinaemia in PCOS is currently considered the result of marked insulin resistance as well as decreased insulin clearance (Chang et al., 1989). Recently, several studies have investigated the cellular mechanisms underlying insulin resistance in PCOS employing a classical insulin target tissue (isolated adipocytes) and a reduction of insulin-stimulated glucose transport in the presence of normal insulin binding has been demonstrated (Ciardili et al., 1992; Marsden et al., 1994). The insulin resistance of many PCOS patients appears to be secondary to a defect in insulin signalling resulting from excessive serine phosphorylation of the insulin receptor, which inhibits the proximal intracellular insulin signalling cascade, leading to impaired glucose oxidation and non-oxidation. It has been postulated that a factor extrinsic to the insulin receptor, a serine/threonine kinase, could cause this abnormality (Dunaif et al., 1996).

A positive correlation between insulin and androgen serum concentrations has been clearly shown in patients affected by PCOS (Burghen et al., 1980; Shoupe et al., 1983). Hyperand-
feature of this syndrome. Furthermore, studies in which the hyperandrogenaemia of PCOS was corrected did not show any improvement in metabolic sensitivity to insulin (Dale et al., 1992; Dunai et al., 1995).

Insulin may act at the pituitary level, the ovarian and/or the hepatic level to increase androgen synthesis and/or free testosterone serum concentrations. Previous in-vitro studies showed that insulin is also able to stimulate androgen secretion from stromal and thecal ovarian cells (Barbieri et al., 1986). In addition, an increased ovarian P450c17α activity is reported in obese and non-obese hyperinsulinemic women with PCOS (Ehrman et al., 1992; Nestler and Jakubowicz, 1997) and P450c17α activity appears to be stimulated by insulin in PCOS. Since insulin receptor phosphorylation appears to modulate the activity of cytochrome P450c17α, it has also been hypothesized that a unique defect produces both insulin resistance and the hyperandrogenism in some PCOS patients (Dunaif et al., 1995). In fact, in both non-obese and obese women with PCOS, an increase in ovarian P450c17α activity has been reported (Ehrman et al., 1992; White et al., 1995).

On the basis of these findings, hyperandrogenism in PCOS women with hyperinsulinemia may result from a direct and indirect LH-mediated stimulatory effect on ovarian androgen secretion. This action is amplified by the ability of insulin to suppress SHBG synthesis at the hepatic level (Nestler et al., 1991) which enhances the level of circulating free testosterone. In addition, insulin may further increase serum androgen concentrations by acting at the adrenal gland level. Indeed, the selective catheterization of the adrenal vein in hyperinsulinaemic hyperandrogenic patients revealed a strong positive correlation between serum insulin and adrenal androgen concentrations (Martikainen et al., 1996), and many studies have shown hypersecretion of adrenal hormones in PCOS subjects compared with healthy women. Consequently, it may be postulated that hyperinsulinemia increases cytochrome P450c17α activity in the adrenal gland of these patients (Moghetti et al., 1996). Insulin can also influence adrenal

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**Figure 1.** Glycaemia (upper panel) and insulin (lower panel) in response to an oral glucose load (75 g) in patients with PCOS (n = 30) and normal women (controls) (n = 15).

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**Table I.** Clinical features and endocrine profiles of PCOS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PCOS</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>20.9 ± 0.7 (16–26)</td>
<td>20.5 ± 0.6 (16–26)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.15 ± 0.48 (19.33–25.89)</td>
<td>22.77 ± 0.34 (19.92–25.81)</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>6 ± 0.3 (4–8)</td>
<td>20 ± 0.6 (14.8–26)</td>
</tr>
<tr>
<td>Acne/seborrhoea score</td>
<td>0.07 ± 0.04 (0–0.5)</td>
<td>1.95 ± 0.1 (1–3)</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>5.1 ± 0.4 (3.2–8.5)</td>
<td>9.6 ± 0.5 (3.7–13.6)</td>
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<tr>
<td>FSH (IU/l)</td>
<td>5.7 ± 0.3 (3.6–9.2)</td>
<td>6.3 ± 0.4 (3.2–10.2)</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>1.60 ± 0.14 (0.76–2.43)</td>
<td>3.26 ± 0.07 (2.67–4.16)</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>6.11 ± 0.21 (4.89–7.68)</td>
<td>8.70 ± 0.31 (5.93–11.52)</td>
</tr>
<tr>
<td>DHEAS (µmol/dl)</td>
<td>6.57 ± 0.42 (3.96–8.67)</td>
<td>7.13 ± 0.29 (3.31–8.33)</td>
</tr>
<tr>
<td>PRL (µg/l)</td>
<td>8.8 ± 0.6 (4.9–12.4)</td>
<td>8.6 ± 0.4 (5.4–12)</td>
</tr>
<tr>
<td>17αOH-P (nmol/l)</td>
<td>1.82 ± 0.09 (1.18–2.42)</td>
<td>2.64 ± 0.12 (1.14–4.24)</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>61.1 ± 2.0 (46–72)</td>
<td>38.4 ± 1.7 (26–58)</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>0.41 ± 0.01 (0.32–0.51)</td>
<td>1.56 ± 0.05 (0.84–2.01)</td>
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</table>

*P < 0.001 versus controls (unpaired Student’s t-test).

Results are expressed as mean ± SEM with the range in parentheses.

BMI = body mass index; DHEAS = Dehydroepiandrosterone sulphate; PRL = Prolactin; 17αOH-P = 17-hydroxyprogesterone; SHBG = sex hormone binding globulin. Normal values: LH = 5–17 IU/l; FSH = 5–15 IU/l; Testosterone = 0.35–2.78 nmol/l; Androstenedione = 1.75–9.78 nmol/l; DHEAS = 3.25–9.76 µmol/l; PRL = 5–20 µg/ml; 17αOH-P = 0.30–2.42 nmol/l; SHBG = 39–77 nmol/l.
Table II. Clinical and endocrine parameters of PCOS patients before (pre) and after (post) treatment with placebo or acarbose for three months

<table>
<thead>
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<th>Placebo</th>
<th>Acarbose</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.5 ± 0.9 (16–26)</td>
<td>20.6 ± 0.73 (16–26)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.07 ± 0.46 (20.31–25.81)</td>
<td>22.63 ± 0.47 (20.31–25.81)</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>19.07 ± 0.73 (14.8–23)</td>
<td>18.47 ± 0.73 (14–24)</td>
</tr>
<tr>
<td>Acne/Seborrhea score</td>
<td>8.71 ± 0.14 (1–2.5)</td>
<td>1.83 ± 0.15 (1–3)</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>6.2 ± 0.5 (3.2–10.2)</td>
<td>6.7 ± 0.5 (3.2–10.6)</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>3.19 ± 0.10 (2.67–3.82)</td>
<td>3.09 ± 0.07 (2.74–3.82)</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>8.73 ± 0.45 (5.94–11.52)</td>
<td>7.13 ± 0.31 (6.15–10.48)</td>
</tr>
<tr>
<td>DHEAS (μmol/l)</td>
<td>7.08 ± 0.40 (4.12–8.67)</td>
<td>7.44 ± 0.27 (5.28–8.97)</td>
</tr>
<tr>
<td>PRL (μg/l)</td>
<td>8.8 ± 0.5 (6.4–11.6)</td>
<td>8.5 ± 0.5 (5.8–12.6)</td>
</tr>
<tr>
<td>I7αOH-P (nmol/l)</td>
<td>2.61 ± 0.18 (1.45–3.94)</td>
<td>2.45 ± 0.12 (1.51–3.3)</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>35.6 ± 2.1 (26–52)</td>
<td>35.2 ± 1.8 (26–48)</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>1.59 ± 0.06 (1.19–1.98)</td>
<td>1.52 ± 0.04 (1.32–1.81)</td>
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*P < 0.05 versus all other groups (ANOVA followed by Duncan’s multiple range test). Results are expressed as mean ± SEM with the range in parentheses. For abbreviations and normal values see Table I.

Figure 2. Glycaemia (upper panel) and insulin (lower panel) responses to an oral glucose load (75 g) in patients with PCOS before (pre) and after (post) treatment with placebo or acarbose for three months. *Indicates a statistically significant difference (P < 0.05, 1-way ANOVA followed by Duncan’s test) versus time zero for each respective treatment group.

steroidogenesis by inhibiting type 1 11β-hydroxysteroid dehydrogenase (11β-HSD) which predominantly acts as a reductase in vivo, catalysing the conversion of inactive cortisone to active cortisol in many human tissues, including liver and adipose tissue. Indeed, an impaired cortisone to cortisol conversion, due to decreased 11β-HSD activity in subjects with central adiposity has been demonstrated, and increased abdominal adipose tissue represents a frequent clinical feature in both obese and non-obese PCOS women.

Regardless of the etiopathogenetic factors which determine hyperinsulinaemia in PCOS patients, it is logical to consider that if glucose absorption leads to an exaggerated insulin response, a drug able to reduce glucose absorption and to minimize the post-prandial rise in blood glucose concentrations could decrease the secretion of insulin and consequently the degree of hyperandrogenism. Hence, this drug may be employed for the treatment of PCOS patients with hyperinsulinaemia. The α-glucosidase inhibitors act by slowing the absorption of carbohydrates from the intestine and thereby minimize the post-prandial rise in blood glucose (Coniff et al., 1995). Acarbose, a member of this family, is a synthetic disaccharide that reversibly inhibits α-glucosidase in the brush-border of the intestinal mucosa. The inhibition of α-glucosidase is followed by a decrease in disaccharide digestion and by a subsequent decline of enteral monosaccharide absorption (Toeller et al., 1991). This results in a flattening of post-prandial circulating concentrations of both glucose and insulin. Enteral absorption of acarbose is extremely low (about 0.5–1.7%) and its clinical use as an anti-hyperglycaemic compound is well-established in patients with non insulin-dependent diabetes mellitus (Mahler and Adler, 1999). The side-effects are dose-dependent and limited to abdominal distension, flatulence and diarrhoea (Mahler and Adler, 1999). Gastrointestinal side-effects require gradual dosage increments over weeks or months after therapy is initiated. Serious adverse reactions are rare, and hypoglycaemia and lactatacidosis are not associated with the use of acarbose. Therefore, this drug is regarded as the first choice medical treatment of diabetes mellitus in many countries (Lebovitz, 1997). Because of its mechanism of action and safety, acarbose may represent a good therapeutic approach to patients with PCOS and hyperinsulinaemia. Accordingly, Geisthovel et al. reported a decline of ovarian hypertestosteronemia in association with a flattening of the post-prandial glucose and insulin increase in seven hyperinsulinaemic, hypertestosteronemic pre-
menopausal women treated with acarbose (Geisthovel et al., 1996).

In this study, we found that acarbose was able to reduce androgen and to increase SHBG serum concentrations. These effects were associated with a decreased insulin response to OGTT. The observed reduction of androgen concentrations during treatment with acarbose is probably related to a decreased ovarian cytochrome P450c17α activity. This effect seems to be limited to ovarian C19-steroids, since DHEAS, the major adrenal androgen, was not affected by acarbose therapy. Our study has confirmed the presence of an abnormal increase of the early phase insulin secretion to OGTT in hyperinsulinaemic PCOS patients and the pathogenetic role of hyperinsulinaemia in these patients. We observed also a significant decrease of LH serum concentrations as also reported in previous studies with octreotide (Prelevic et al., 1990b), troglitazone (Dunaif et al., 1996) and metformin (De Fronzo et al., 1991; Jakubowicz and Nestler, 1997). On the other hand, the observed reduction of LH serum concentrations during acarbose treatment could have determined and/or contributed to the decline of LH-dependent androgen ovarian production. However, the decrease of LH concentrations seems to be related only to the lowered insulin serum concentrations, because acarbose per se does not influence LH secretions or pituitary responsiveness to GnRH stimulation. In agreement with this hypothesis, in a previous study (Ciotta et al., 1999) we found that octreotide decreased LH and androgen serum concentrations only in PCOS patients with hyperinsulinaemia, but not in those with normal insulin concentrations, because in the latter octreotide did not affect insulin response to OGTT, whereas in the former it blunted significantly the insulin response. Hence, these data strongly suggests that the reduction of androgen concentrations in hyperinsulinaemic patients is linked to the decrease in insulin.

The reduction of testosterone and androstenedione concentrations and the increase in SHBG can explain the amelioration of acne/seborrhoea observed in patients treated with acarbose. The hirsutism score did not decrease significantly in any patients during treatment, even if some of them reported a lower hair growth rate during the last three weeks of therapy. Because hirsutism requires a longer treatment to reach a significant regression, it is possible to postulate acarbose may improve also the hirsutism score of PCOS patients if the treatment is administered for a longer period.

Other drugs have been shown capable of significantly decreasing insulin and androgen concentrations in PCOS women with hyperinsulinaemia and are, therefore, potential candidates for clinical use (Nestler et al., 1989; Velazquez et al., 1994; Geisthovel et al., 1996). However, several clinical, metabolic and haematochemical side-effects are reported during long-term treatment with these drugs. Despite these many side-effects, it is possible to postulate that these drugs may find a clinical application in the treatment of anovulation of PCOS patients with hyperinsulinaemia, before a conventional stimulatory therapy is given. In fact, a treatment of short duration reduces the potential clinical, metabolic and haematochemical side-effects of these drugs.

In conclusion, our study is the first report demonstrating a positive clinical effect of acarbose in PCOS women with hyperinsulinaemia. The absence of significant clinical, metabolic and haematochemical side-effects makes acarbose a drug suitable to treat the hyperandrogenic manifestations and to prevent the conversion from hyperinsulinaemia and impaired glucose tolerance to diabetes mellitus in PCOS patients. However, further long-term, double-blind studies are needed to establish whether acarbose can be used as an adjunct and/or unique therapy in such patients.

References


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