Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial

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Context: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of reproductive age. Hyperandrogenism is the central feature of PCOS. Studies on isolated ovarian theca-interstitial cells suggest that resveratrol, a natural polyphenol, reduces androgen production.

Objective: This study was designed to evaluate endocrine and metabolic effects of resveratrol on PCOS.

Design and Setting: This was a randomized (1:1) double-blind, placebo-controlled trial that evaluated the effects of resveratrol over a period of 3 months in an academic hospital.

Patients and Other Participants: Subjects with PCOS were identified according to the Rotterdam criteria. Thirty-four subjects were enrolled and 30 subjects completed the trial. Evaluations were performed at baseline and repeated after 3 months of treatment.

Intervention: Resveratrol (1,500 mg p.o.) or placebo were administered daily.

Main Outcome Measure: Primary outcome was the change in the serum total T.

Results: Resveratrol treatment led to a significant decrease of total T by 23.1% ($P = .01$). In parallel, resveratrol induced a 22.2% decrease of dehydroepiandrosterone sulfate ($P = .01$), a decrease of fasting insulin level by 31.8% ($P = .007$) and an increase of the Insulin Sensitivity Index (Matsuda and DeFronzo) by 66.3% ($P = .04$). Levels of gonadotropins, the lipid profile as well as markers of inflammation and endothelial function were not significantly altered.

Conclusions: Resveratrol significantly reduced ovarian and adrenal androgens. This effect may be, at least in part, related to an improvement of insulin sensitivity and a decline of insulin level. **(*J Clin Endocrinol Metab* 101: 3575–3581, 2016)**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age and is primarily characterized by hyperandrogenism and ovulatory dysfunction. Depending on the diagnostic criteria, the prevalence of PCOS has been estimated to be in the range of 6–18% (1–4). In addition to reproductive dysfunction, PCOS is associated with a wide range of endocrine and metabolic derangements including insulin resistance, dyslipidemia, systemic inflammation, and endothelial dysfunction (5–8). Although the etiology, or more likely multiple etiologies of PCOS are still poorly understood, extensive evidence points to hyperandrogenism as

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Abbreviations: BMI, body mass index; CRP, C-reactive protein; CYP17, 17α-hydroxylase/C17-20-lyase; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OC, oral contraceptive; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; QUICKI, Quantitative Insulin Sensitivity Check Index; sICAM-1, soluble intracellular adhesion molecule–1; sVCAM, soluble vascular cell adhesion molecule 1.

the key aspect of this condition. Excessive ovarian androgen levels are a result of increased production of androgens by the hyperplastic theca compartment and the markedly elevated expression and activity of several enzymes involved in steroidogenesis (9–12). Adrenal glands also contribute to hyperandrogenism in PCOS, as evidenced by the enlargement of adrenal glands and increased levels of dehydroepiandrosterone sulfate (DHEAS) (13–15).

The development of effective treatments of PCOS remains challenging, given that the use of antiandrogens such as spironolactone, flutamide, or cyproterone acetate and the suppression of ovarian function (eg, by combination oral contraceptive [OC] pills) is often clinically unacceptable. Ideally, a reduction of androgen production may be accomplished by decreasing the growth of theca cells and the inhibition of expression and/or activity of relevant enzymes regulating steroidogenesis, especially 17α-hydroxylase/C17-20-lyase (CYP17; Cyp17a1), the key rate-limiting enzyme in androgen biosynthesis.

Our recent in vitro studies identified resveratrol (trans-3,5,4′′-trihydroxystilbene) as a potentially promising novel treatment of ovarian hyperandrogenism. Resveratrol is a natural polyphenol found in grapes, nuts, and berries with noted anti-inflammatory, antioxidant, and cardioprotective properties. Exposure of rat theca-interstitial cells to resveratrol resulted in a potent concentration-dependent inhibition of cell growth via a reduction of DNA synthesis and stimulation executioner caspases leading to apoptosis (16). These effects were related to a resveratrol-induced inhibition of mevalonate pathway through mechanisms partly comparable and partly complementary to the effects of statins (17). Subsequently we found that resveratrol reduces androgen production by theca-interstitial cells by inhibition of Cyp17a1 mRNA expression (18). Importantly, it seems that resveratrol actions on ovarian steroidogenesis are selective, given that it has no effect on progesterone production by theca cells. In granulosa cells, resveratrol has cytostatic but not cytotoxic effect and reduces the expression of vascular endothelial growth factor but not anti-Müllerian hormone (19).

In view of the above observations, we proposed that resveratrol may be effective in treatment of hyperandrogenism in conditions such as PCOS. This study evaluated the effects of resveratrol on the endocrine and metabolic function of women with PCOS during a 3-month placebo-controlled randomized clinical trial. For the first time we show that resveratrol significantly reduces T level. Furthermore, resveratrol also decreases adrenal androgen production, as evidenced by lowering levels of circulating DHEAS.

Materials and Methods

Subjects

All subjects fulfilled PCOS criteria as defined by the Rotterdam consensus and had at least two of the following: 1) clinical or chemical hyperandrogenism; 2) oligo- or amenorrhea; and/or 3) polycystic ovaries as viewed by transvaginal ultrasound (20). Congenital adrenal hyperplasia was excluded on the basis of a morning follicular phase 17-hydroxyprogesterone less than 2 ng/mL. None of the subjects had elevated prolactin, thyroid disease, Cushing's disease, or diabetes mellitus. No clinical signs or symptoms of any other endocrinopathy were identified in any participants. All subjects had normal baseline renal function tests, bilirubin, and aminotransferases. During the 3 months before the study, none of the study subjects used any form of OCs, other steroid hormones, or any other treatments likely to affect ovarian function, insulin sensitivity, or lipid profile. All subjects were recruited at the Poznan University of Medical Sciences between December 2013 and March 2015. Informed consent was obtained from all participants. Approval of the study was obtained from the Institutional Review Board at the Poznan University of Medical Sciences and the Institutional Review Board at the University of California–San Diego. The study was registered at www.clinicaltrials.gov with the identifier NCT01720459.

Procedures

The flowchart of this study is summarized in Figure 1. A total of 41 women were screened, and 34 (83%) were randomly assigned to two treatment groups: Resveratrol group (receiving micronized transresveratrol; 1500 mg/d orally) and Placebo group. Resveratrol was obtained from RevGenetics and the placebo was provided by Adamed sp. z o.o., Adamed Group. The resveratrol and placebo pills were identical in appearance. Randomization was performed using a 1:1 allocation ratio with blocks of set size (six subjects per block). Patient allocation was obtained using GraphPad QuickCalcs (GraphPad Software Inc.). Investigators and patients were blinded to treatment and could not identify the actual treatment throughout the study. The primary endpoint was change of total T.

Study design and assays

All participants were evaluated at baseline during the follicular phase of a natural cycle or after medroxyprogesterone-induced menses. All evaluations were performed at baseline and after 3 months of treatment.

Clinical assessments included determinations of body mass index (BMI), hirsutism (using Ferriman and Gallwey score), and acne score. Acne was scored using a four-point scale described previously (21). Transvaginal ultrasonographic evaluations were performed using Aloka ProSound α7 (Aloka Co, Ltd.); ovaries were measured in three perpendicular diameters. Ovarian volume was determined using the prolate ellipsoid formula.

Endocrine and metabolic tests were performed after 3 days of carbohydrate intake of 300 g/d to standardize conditions before glucose tolerance test. Venous blood was collected between 0700 and 0800 hours after an overnight fast. Serum specimens were stored at −70°C until analysis was performed. A 2-hour oral glucose tolerance test (OGTT) was performed with determinations of glucose and insulin in the fasting state as well as after a 75-g glucose load at 30, 60, 90, and 120 minutes. Glucose was

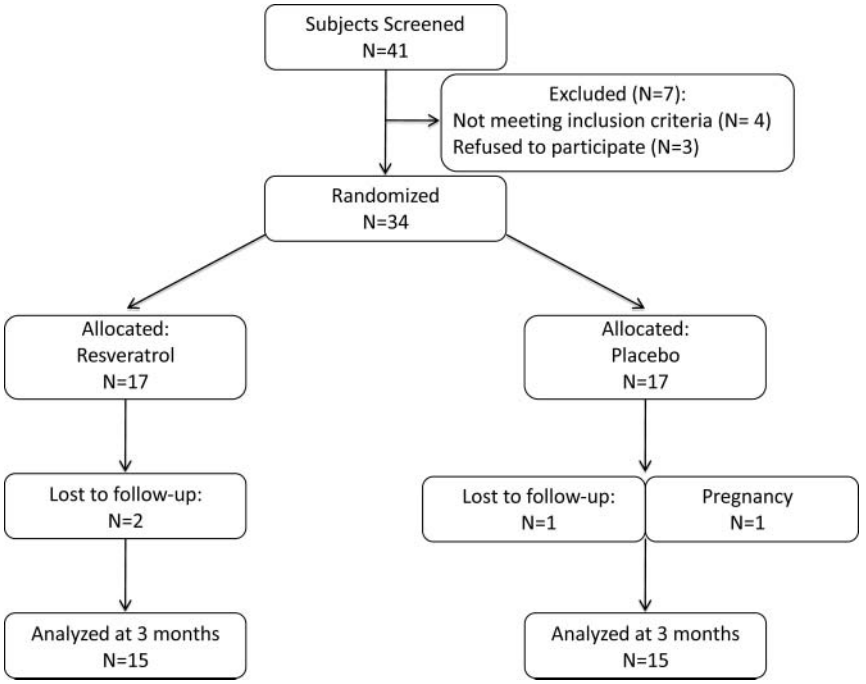

Figure 1. Flow diagram of the trial.

determined using the enzymatic reference method with hexokinase on Roche Cobas 6000 System (Roche Polska sp z o.o.).

Insulin, total T, LH, FSH, prolactin, SHBG, 17-hydroxyprogesterone, DHEAS, and high-sensitivity C-reactive protein (CRP) (hs-CRP), were determined using specific electrochemiluminescence assays (Automated Cobas 6000 System; Roche Polska sp z o.o.). Evaluation of insulin sensitivity using fasting measures used the method described by Katz et al (22): Quantitative Insulin Sensitivity Check Index (QUICKI) = 1/[log(fasting insulin) + log (fasting glucose)]. The insulin sensitivity index was calculated using glucose and insulin levels obtained during an OGTT as described by Matsuda and DeFronzo: Insulin Sensitivity Index = 10,000/square root of [(fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT)] (23). Total cholesterol and triglycerides were determined by enzymatic colorimetric assays (Automated Cobas 6000 System; Roche Polska sp z o.o.). High-density lipoprotein (HDL) was separated by precipitating apolipoprotein-B (Roche Polska sp z o.o.). Low-density lipoprotein (LDL) was calculated using the Friedwald formula. Soluble vascular cell adhesion molecule 1 (sVCAM) and soluble intracellular adhesion molecule–1 (sICAM-1) were determined using a human Quantikine ELISA kit from R&D Systems. Neopterin was determined using ELISA kit from Demeditec Diagnostics, GmbH.

Statistical analysis

Analysis was carried out using JMP pro 11 statistical software (SAS Institute). Power analysis assumed enrollment of 34 subjects with anticipated 15% dropout rate, a coefficient of variation of primary outcome at 20% (based on previous studies) and a 25% effect of treatment with power of 0.9 and alpha error of 0.05. Comparisons between groups were performed using unpaired *t* test. Comparisons of baseline and follow-up values were performed using paired *t* test. In the absence of a normal distribution (tested by Shapiro-Wilk test), logarithmic transformations or nonparametric testing (Wilcoxon/Kruskal Wallis, Wilcoxon Signed Rank) was carried out. Correlations between variables were evaluated by a determination of the Pearson product–moment correlation coefficient or Spearman's rank correlation coefficient.

Results

Comparison of groups at baseline

Table 1 summarizes the baseline characteristics of 34 subjects enrolled onto the study. Hyperandrogenism (defined as Ferriman and Gallwey score ≥8 and/or total T > 0.50 ng/mL) was identified in 68% of the subjects. Overall, randomization in the Resveratrol and Placebo groups resulted in comparable populations of subjects with the exception of significantly higher total cholesterol in the Resveratrol group. The flow diagram of the study (Figure 1) demonstrates that 30 subjects (88%) completed the 3-month trial.

Effects of treatments

Results of the trial are presented in Table 2 and Table 3. Table 2 presents baseline and post-treatment values for the Resveratrol group and the Placebo group separately whereas Table 3 compares the changes between groups. Total T level (primary outcome) declined only in the Resveratrol group (by 23.1%; $P = .01$), whereas it minimally increased by 2.9% ($P = .78$) in the Placebo group; the difference between groups was statistically significant ($P = .04$). In a similar fashion, DHEAS, an androgen nearly exclusively produced by the adrenals, also significantly declined in the Resveratrol group (by 22.2%), whereas its level in the Placebo group modestly increased by 10.5% ($P = .08$); the difference between groups was significant ($P = .002$). Improvement of hyperandrogenemia in the Resveratrol group was paralleled by a decline of fasting insulin (by 31.8%; $P = .007$) and increase of the Insulin Sensitivity Index (by 66.3%; $P = .04$). However, resveratrol had no significant effect on BMI, ovarian volume, gonadotropins, lipid profile, or markers of inflammation and endothelial function. Notably, when evaluating baseline vs 3-month data (Table 2), several significant changes were observed in the Placebo group including a reduction of ovarian volume and an increase of total cholesterol and HDL cholesterol.

Table 1. Baseline Parameters in Individual Groups

Variable	Resveratrol (n = 17)	Placebo (n = 17)	Comparison Between Groups *P*-Value
Age, y	26.8 ± 1.1	26.8 ± 1.5	1.00
BMI, kg/m^2	27.1 ± 1.5	27.6 ± 3.9	.77
Hirsutism, Ferriman/Gallwey score	6.8 ± 1.3	7.9 ± 1.2	.52
Acne score	0.7 ± 0.2	0.4 ± 0.2	.15
Ovarian volume, both ovaries, mL	20.3 ± 1.2	20.2 ± 1.7	.94
Total T, ng/mL	0.55 ± 0.04	0.47 ± 0.05	.28
DHEAS, μmol/L	8.41 ± 0.69	8.09 ± 0.88	.78
SHBG, nmol/L	48.2 ± 5.0	43.5 ± 6.9	.58
LH, mIU/mL	9.6 ± 1.4	8.4 ± 1.0	.52
FSH, mIU/mL	5.8 ± 0.3	5.1 ± 0.4	.14
Prolactin, ng/mL	14.1 ± 1.8	15.3 ± 2.1	.67
Total cholesterol, mg/dL	200.1 ± 8.2	169.1 ± 8.6	.01
LDL cholesterol, mg/dL	117.9 ± 7.8	117.9 ± 7.8	.08
HDL cholesterol, mg/dL	56.0 ± 3.3	51.3 ± 3.2	.31
Triglycerides, mg/dL	119.3 ± 16.9	89.4 ± 14.9	.19
hs-CRP, mg/L	1.8 ± 0.4	2.7 ± 0.8	.31
sVCAM, ng/mL	434 ± 52	472 ± 59	.64
sICAM-1, ng/mL	262 ± 12	233 ± 18	.19
Neopterin, nmol/L	8.6 ± 1.4	8.6 ± 0.9	.99
Fasting glucose, mg/dL	87.5 ± 1.8	90.4 ± 2.1	.31
Fasting insulin, μU/mL	14.3 ± 1.6	13.2 ± 1.2	.59
QUICKI	0.330 ± 0.007	0.330 ± 0.005	.98
Insulin sensitivity index	3.1 ± 0.4	3.6 ± 0.5	.48

Each value represents mean ± SEM.

To determine whether any of the tested baseline parameters correlated with a change of T level in the Resveratrol group, correlations were assessed; the only variable predicting a reduction of serum T was BMI, whereby leaner subjects had a significantly greater decrease of T in response to resveratrol than subjects with greater BMI (Spearman's $\rho = 0.63$; $P = .01$) (Figure 2). Two patients in the Resveratrol group described tran-

Table 2. Comparison of Tested Parameters at Baseline and After 3 Months of Treatment

Variable	Resveratrol		Effect of Resveratrol vs Baseline *P*-Value	Placebo		Effect of Placebo vs Baseline *P*-Value
	Baseline (n = 15)	3 Mo		Baseline (n = 15)	3 Mo	
BMI, kg/m^2	27.38 ± 1.69	26.65 ± 1.67	.23	28.09 ± 0.97	27.92 ± 0.95	.23
Hirsutism, Ferriman/Gallwey score	6.9 ± 1.4	6.9 ± 1.4	1.0	8.1 ± 1.3	8.4 ± 1.4	.16
Acne score	0.7 ± 0.2	0.7 ± 0.2	1.0	0.4 ± 0.2	0.5 ± 0.2	.16
Volume of both ovaries, mL	19.8 ± 1.2	22.9 ± 2.5	.21	20.1 ± 1.7	17.6 ± 1.5	.01
Total T, ng/mL	0.53 ± 0.04	0.41 ± 0.04	.01	0.48 ± 0.07	0.49 ± 0.06	.78
DHEAS, μmol/L	8.05 ± 0.73	6.26 ± 0.64	.01	8.08 ± 0.99	8.90 ± 1.17	.08
SHBG, nmol/L	50.2 ± 5.3	52.3 ± 6.6	.64	43.0 ± 7.9	43.9 ± 7.5	.74
LH, mIU/lmL	10.1 ± 1.5	11.1 ± 1.3	.52	8.2 ± 1.1	10.2 ± 1.7	.31
FSH, mIU/mL	5.9 ± 0.3	5.2 ± 0.4	.85	5.0 ± 0.4	5.1 ± 0.4	.85
Prolactin, ng/mL	13.8 ± 2.0	10.1 ± 1.3	.04	16.5 ± 2.2	14.4 ± 1.8	.17
Total cholesterol, mg/dL	205.8 ± 8.2	203.2 ± 7.9	.74	172.9 ± 8.8	183.8 ± 8.2	.005
LDL cholesterol, mg/dL	120.1 ± 8.6	118.4 ± 9.0	.58	102.2 ± 6.6	106.2 ± 6.2	.18
HDL cholesterol, mg/dL	57.6 ± 3.4	61.7 ± 5.3	.28	52.0 ± 3.4	57.0 ± 3.9	.001
Triglycerides, mg/dL	123.0 ± 18.9	112.3 ± 21.1	.64	93.2 ± 16.7	103.7 ± 15.6	.32
hs-CRP, mg/L	2.0 ± 0.5	2.7 ± 0.9	.40	2.8 ± 0.8	2.3 ± 0.6	.27
sVCAM, ng/mL	444 ± 60	438 ± 33	.89	468 ± 66	462 ± 74	.80
sICAM, ng/mL	264 ± 13	259 ± 12	.53	234 ± 19	237 ± 14	.88
Neopterin, nmol/L	9.2 ± 1.9	7.4 ± 1.1	.41	8.6 ± 1.0	9.5 ± 1.3	.29
Fasting glucose, mg/dL	87.2 ± 1.7	86.0 ± 1.4	.58	90.2 ± 2.3	92.1 ± 3.3	.46
Fasting insulin, μU/mL	14.5 ± 1.8	9.8 ± 1.5	.007	13.8 ± 1.2	13.8 ± 2.5	1.00
QUICKI	0.331 ± 0.008	0.353 ± 0.009	.002	0.328 ± 0.006	0.337 ± 0.010	.31
Insulin sensitivity index	3.11 ± 0.41	5.12 ± 1.10	.04	3.57 ± 0.53	3.98 ± 0.95	.45

Each value represents mean ± SEM; data below represent only subjects who completed 3 months of treatment.

Table 3. Change of Parameters after 3 Months of Treatment in Comparison With Baseline Values

Variable	Resveratrol (n = 15)	Placebo (n = 15)	Comparison Between Groups *P*-Value
BMI, kg/m^2	−0.73 ± 0.58 (−2.6%)	−0.17 ± 0.58 (−0.6%)	.41
Hirsutism, Ferriman/Gallwey score	0.0 ± 0.0 (0%)	0.27 ± 0.18 (0.3%)	.15
Acne score	0.0 ± 0.0 (0%)	0.14 ± 0.10 (40%)	.31
Volume of both ovaries, mL	3.32 ± 2.51 (16.9%)	−2.31 ± 0.79 (−11.5%)	.04
Total T, ng/mL	−0.12 ± 0.04 (−23.1%)	0.01 ± 0.05 (2.9%)	.04
DHEAS, μmol/L	−1.79 ± 0.62 (−22.2%)	0.85 ± 0.45 (10.5%)	.002
SHBG, nmol/L	2.09 ± 4.34 (4.1%)	0.97 ± 2.91 (2.3%)	.83
LH, mIU/lmL	0.95 ± 1.42 (9.4%)	2.00 ± 1.88 (24.5%)	.66
FSH, mIU/mL	−0.64 ± 0.42 (−10.9%)	0.11 ± 0.57 (2.2%)	.30
Prolactin, ng/mL	−3.48 ± 1.59 (−25.8%)	−2.13 ± 1.45 (−12.9%)	.54
Total cholesterol, mg/dL	−2.7 ± 7.9 (−1.3%)	11.0 ± 3.3 (6.4%)	.12
LDL cholesterol, mg/dL	−2.4 ± 4.3 (−2.1%)	4.1 ± 2.9 (4%)	.75
HDL cholesterol, mg/dL	4.1 ± 3.6 (7.1%)	5.0 ± 1.2 (9.6%)	.81
Triglycerides, mg/dL	−10.6 ± 22.0 (−8.6%)	10.4 ± 10.1 (11.1%)	.39
hs-CRP, mg/L	0.64 ± 0.74 (31.7%)	−0.49 ± 0.43 (−17.6%)	.19
sVCAM, ng/mL	−5.7 ± 40.9 (−1.3%)	−5.2 ± 23.6 (−1.1%)	.99
sICAM-1, ng/mL	−5.5 ± 8.5 (−2.1%)	2.7 ± 17.3 (1.2%)	.68
Neopterin, nmol/L	−1.74 ± 2.0 (−19.0%)	0.84 ± 0.77 (9.7%)	.24
Fasting glucose, mg/dL	−1.2 ± 2.1 (−1.4%)	2.0 ± 2.6 (2.2%)	.36
Fasting insulin, μU/mL	−4.6 ± 1.5 (−31.8%)	0.0 ± 2.4 (0%)	.11
QUICKI	0.022 ± 0.006 (6.6%)	0.008 ± 0.008 (2.4%)	.18
Insulin sensitivity index	2.04 ± 0.88 (66.3%)	0.58 ± 0.73 (17.0%)	.21

Each value represents mean ± SEM; percent change in brackets.

sient numbness of hands, all remaining patients had no complaints.

Discussion

This study, to our knowledge, is the first clinical trial evaluating the effects of resveratrol on PCOS. It is apparent that resveratrol significantly reduces serum levels of T and DHEAS, suggesting an effect on ovarian as well as adrenal androgen production. The magnitude of improvement of hyperandrogenemia observed in response to resveratrol is comparable to or greater than that found in response to OC pills or metformin, with the exception of preparations containing cypretorone acetate, which are not available in the United States. In the present study, a 3-month course of resveratrol led to a 23.1% decline of total T, whereas a 12-month treatment with OC pill (150 mg desogestrel and 30 μg ethinyl estradiol) resulted in a 19% reduction of T level; in the same trial metformin alone was also associated with a 19% decrease of T (24). In another study, 6 months of metformin treatment resulted in a nonsignificant decrease of T by 8.2% (25). A reduction of T following pharmacological interventions seems usually to occur gradually over a period of many months; thus, for exam-

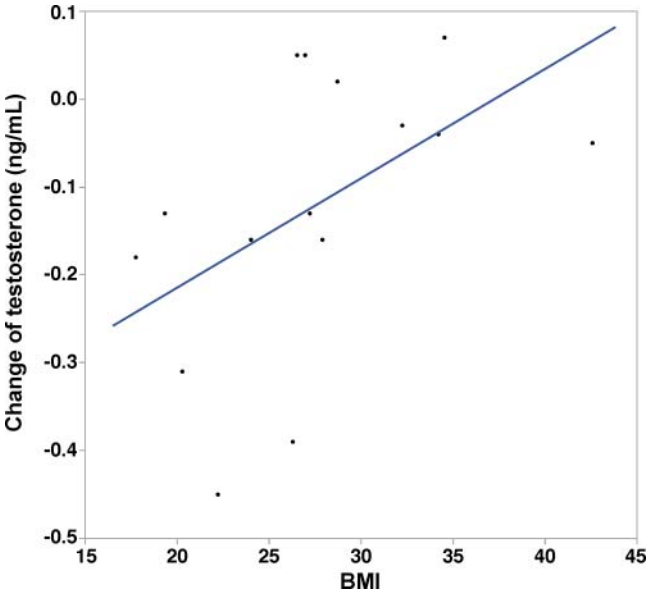

Figure 2. Effect of resveratrol on the change of total T correlated inversely with BMI.

ple, in our previous trial, metformin treatment resulted in a 13.6% decrease of T after 3 months and a 25.6% decrease after 6 months (26, 27). Consequently, a marked reduction of hyperandrogenemia observed over a period of 3 months in this trial is encouraging. Also encouraging is the observation that in contrast with most studies evaluating OC pills, resveratrol had no adverse effect on metabolic aspects of PCOS and did not significantly alter the lipid profile or markers of inflammation, but had a positive effect on insulin sensitivity and a reduction of fasting insulin level.

Although identification of the mechanisms of action of resveratrol is not possible in this clinical trial, several possible mechanisms may be considered, including the direct inhibition of 17α-hydroxylase/C17-20-lyase enzymatic activity, a reduction of growth of theca cells, and the improvement of insulin sensitivity with consequent reduction of insulin levels. Indeed, in our previous in vitro studies using rat theca-interstitial cells, we observed that resveratrol inhibits proliferation of these cells and reduces mRNA expression of Cyp17a1 (17, 18). These effects on the proliferation of theca cells are related to resveratrol-induced inhibition of mevalonate pathway, at least in part via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase expression and activity (17, 28). In contrast, the effects of resveratrol on Cyp17a1 expression are not due to an inhibition of the mevalonate pathway, but seem to be related to the inhibition of Akt/PKB-signaling pathway (18).

In the present study we did not observe any significant decline of cholesterol level in the Resveratrol group. However, in the Placebo group total cholesterol has increased; hence, one may speculate that resveratrol may have prevented an increase of cholesterol that would have occurred otherwise over time. The absence of significant inhibition of cholesterol in this study may also reflect differences between species (human vs rat), could be due to inherent difference of in vivo vs in vitro responses to resveratrol, or may be a consequence of the relatively short duration of this clinical trial. Nevertheless, the presently observed effects of resveratrol on androgen levels are unlikely to be related to significant inhibition of the mevalonate pathway, and hence are not due to a reduced proliferation of theca cells, but may be an effect of the inhibition of androgen production by both ovarian and adrenal tissues, possibly via a reduction of 17α-hydroxylase/C17-20-lyase enzymatic activity. Furthermore, given that insulin is known to stimulate androgen production in both ovarian (29, 30) and adrenal (31) tissues, it is likely that the resveratrol-induced reduction of insulin observed in the present study may have contributed to a decrease of androgen levels. An effect of resveratrol on improvement of insulin sensitivity has been demonstrated previously in some but not in other studies (32–35).

In conclusion, this study demonstrates that resveratrol reduces serum levels of both T and DHEAS in women with PCOS, indicating effects at both the ovarian and adrenal level, and in the absence of significant changes in BMI, lipid profile, and markers of inflammation/endothelial function.

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