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Research article

Assessment of Quadriceps Muscle Strength and Thickness in Adolescents with Polycystic Ovary Syndrome: A Case-control and Longitudinal Follow-up Study

Güven AG et al. Muscle Strength and Thickness in PCOS adolescents

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What is already known on this topic?
No studies have investigated muscle strength and thickness in adolescents with polycystic ovary syndrome.

What this study adds on this topic?
Quadriceps muscle thickness and strength were comparable between patients and controls. The users of levonorgestrel showed a significantly greater increase in the strength of the quadriceps muscle than the users of cyproterone acetate.

Abstract
Objective: No studies have investigated muscle strength and thickness in adolescents with polycystic ovary syndrome (PCOS). We investigated whether there were changes in quadriceps muscle thickness and strength between adolescents with PCOS and controls. Secondly, we evaluated the effects of six months of combined oral contraceptive (COC) treatment on the quadriceps muscle.
Materials and Methods: The study included 20 adolescents with PCOS and 20 healthy adolescents. The isokinetic dynamometer for the knee muscle strengths and hand dynamometer for grip strength, and ultrasound for quadriceps muscle thickness were used. These measurements were repeated after six months of COCs treatment in the patient group.
Results: Age, weight, height, pubertal stage, Physical Activity Questionnaire scores, quadriceps muscle thickness, grip strength and all isokinetic knee strength values were similar between patients and controls (all $p>0.05$). Compared to baseline, weight, height, quadriceps strength and lipid profile increased (all $p<0.05$). According to subgroup analyses, significant (and greater) increases in quadriceps muscle strength were found in COC-containing levonorgestrel users (n=6) than in cyproterone acetate users (n=13) (both $p<0.05$).
Conclusion: Quadriceps muscle thickness and strength values were similar between PCOS patients and controls. Significant and greater increases were observed in quadriceps muscle strength in levonorgestrel users than cyproterone acetate users. Further longitudinal studies with larger samples evaluating the COCs with different androgenic capacity are awaited to confirm our preliminary findings.
Keywords: PCOS, isokinetic, ultrasound, levonorgestrel, oral contraceptive

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous condition that occurs most commonly in women of reproductive age. It is characterised by hyperandrogenism and chronic anovulation. Its symptoms may appear in adolescence and it may be associated with many comorbidities such as insulin resistance/hyperinsulinemia, impaired glucose tolerance, hypertension, non-alcoholic fatty liver disease, dyslipidemia and sleep apnea (1). The criteria for diagnosing PCOS in adult women are not considered valid in adolescents, and it is often difficult to diagnose PCOS in adolescents. The diagnosis is made when irregular menstrual bleeding persisting for at least two years after menarche is associated with clinical and/or biochemical hyperandrogenism (1,2).
There may be changes in muscle morphology and strength due to hormonal and metabolic changes in patients with PCOS (e.g. hyperandrogenism, hyperinsulinism, hyperlipidemia), but there is a paucity of publications on this subject in the literature, especially in adolescents, and there are conflicting results (3-6). As androgens and insulin have anabolic effects on skeletal muscle, they may cause changes in muscle mass and/or strength (7-13) In addition, the progesterone in combined oral contraceptives (COCs) used to treat PCOS patients may also have androgenic (or antiandrogenic) effects (14), causing changes in muscle.
Therefore, in this study we investigated whether there were changes in quadriceps muscle thickness and strength between adolescents with PCOS and controls of similar age, anthropometric characteristics, and pubertal stage. Secondly, we evaluated the effects of different COCs treatment on the quadriceps muscle, which is functionally important and has a large muscle mass in the body (15,16). In this regard, no study has yet been published in the literature evaluating quadriceps muscle thickness by using musculoskeletal ultrasound (US) in adolescents with PCOS.

METHODS

This study was conducted at the Departments of Adolescent Health and Physical Medicine and Rehabilitation, Hacettepe University. Approval was obtained from the local ethics committee (decision number: KA-20083). The study met the standards of the Declaration of Helsinki for human experimentation. The study group consisted of 20 adolescents with PCOS and 20 healthy controls matched for age, weight, height and pubertal stage who were admitted to the Adolescent Health Unit between September 2020 and December 2022. Informed consent was obtained from the participants and their families. The diagnosis of PCOS was made using the 2015 Pediatric Endocrine Society criteria (17). Biochemical hyperandrogenism was considered if the total testosterone level was >42 ng/dl, and clinical hyperandrogenism was considered if the modified Ferriman-Gallwey score was ≥8 (1,2).

Since the mean age of menarche in Turkish females has been reported as 12.2±0.9 years (18) the participants in our study were selected from adolescents aged between 14 and 18 whose menarche had occurred, and pubertal development was at Tanner stage ≥4. Subjects participating in regular training or sports, having a chronic systemic disease, using prescription (including drugs that affect testosterone metabolism) or non-prescription drugs, and being mentally disabled were excluded. Healthy adolescents similar in age, weight, height and pubertal age with PCOS patients were taken into control group.

Study Protocol

Each participant's height was measured with a stadiometer, body weight was measured with a digital scale. Body mass index (BMI) was calculated as weight (in kg) divided by height squared (m^2) and expressed as BMI standard deviation score (BMI SDs) based on national data for Turkey. Adolescents in the obesity group were classified as as having a BMI at or above the 95th percentile. Overweight adolescents were categorized within the BMI range of the 85th to 94.9th percentiles, while normal-weight adolescents were defined as having a BMI between the 5th and 84.9th percentiles (19). Pubertal staging was done according to the Marshall-Tanner staging system (20). The hair growth scores in the patient group were calculated using the Modified Ferriman-Gallwey scale (FGS) (21).

The following treatment was suggested to patients. Initially, lifestyle changes, healthy nutrition, and walking for 30–45 minutes at least 3 days in a week, 15 minutes of weight training, and 15 minutes of muscle-strengthening exercise were recommended for all patients. A weight-loss diet was also recommended for obese patients. In addition, patients were called monthly to determine to what extent they complied with these suggestions. All patients were treated with combined oral contraceptives (COCs) or progestin-only who could not use COCs due to contraindications. 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol (Microgynon®) or a combination of 2 mg cyproterone acetate and 0.035 mg ethinyl estradiol (Diane 35®) was used as COC, and norethisterone (Primolut®) was used as a progestin-only drug. In our clinic, we did not interfere with the physicians' drug preferences in the treatment of PCOS. In our clinical practice, one of the COCs can be preferred in the treatment of adolescents with PCOS.

Laboratory Measurements

At the beginning of the study, serum samples were taken to diagnose PCOS, to evaluate the metabolic and hormonal changes in patients, and to exclude other diseases in the differential diagnosis. To evaluate the metabolic/hormonal changes, biochemical and hormonal tests were performed at the end of the 6th month of the treatment as well. Serum samples were taken for glucose, insulin, triglyceride, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, and luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone at 8:00 in the morning after an 8-hour fasting. Homeostasis Model Assessment Index (HOMA-IR) was calculated as insulin resistance (HOMA-IR = [fasting insulin (uU/mL) x fasting plasma glucose (mg/dL)]/405).

Isokinetic Muscle Strength Assessment

Prior to treatment, all participants underwent isokinetic measurement of knee extension and flexion muscle strength on the dominant side using the Biodex System3 Pro device (Biodex Medical Systems Shirley N.Y. 11967 USA) (22). After a 5-minute warm-up on the treadmill, participants were seated with the hip/knee joints in 90° flexion, the lateral femoral condyle of the femur positioned through the center of motion of the dynamometer and secured to the distal end of the dynamometer with a strap 2-cm above the malleoli. The thighs/trunk were secured to the seat with straps to prevent force distribution and ensure stabilisation. The concentric strength of the quadriceps and hamstrings was measured for 5 repetitions at an angular velocity of 60°/sec, 15 repetitions at an angular velocity of 180°/sec, with a rest period of 60 seconds between each test, and during the test the subjects were asked to go "faster and stronger" with verbal motivation (23). After the test, peak torque (PT) values were recorded for analysis.

Grip Strength Assessment

Participants' dominant hand grip strength was assessed using a hydraulic dynamometer (JAMAR Baseline Hydraulic Hand Dynamometer, Irvington, NY, USA). Participants were positioned in a standing position with the shoulder in full adduction, the elbow in 90° flexion and the hand in neutral and were asked to push the dynamometer with their maximum force. The test was performed three times, and the maximum was recorded.

Ultrasonographic Measurements

Prior to treatment, all participants underwent muscle US to assess quadriceps muscle thickness using a 7-12 MHz linear probe (Logiq P5, GE, Medical Systems, AD). All ultrasound (US) measurements were performed on the dominant hand side. US images were acquired without compression. Muscle thickness (distance between the superior fascia of the rectus femoris and the periosteum of the femur) was measured in axial view at the 50% level between the anterior superior iliac spine and the patella, with the participants in the supine position. Measurements were performed by an experienced physiatrist (MK) experienced in musculoskeletal US.

Physical Activity Evaluation

The Physical Activity Questionnaire in Adolescents (PAQ-A) was used to assess the level of physical activity in secondary school students aged 14–20 years during the last seven days of the school term (24). It consists of eight questions, scored from 1 to 5, and nine questions about barriers to physical activity in the past week. The total score ranges from 1 (low-intensity physical activity) to 5 (high-intensity physical activity) (25). According to the PAQ-A, the mean score reflects the physical activity levels as 1.0-1.9; very low physical activity, 2.0-2.9; low physical activity, 3.0-3.9; moderate physical activity, and 4.0-5.0; high physical activity (25).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences 23 program. Descriptive statistics are presented as mean±SD or median (interquartile 25%-75%) for numerical variables, where appropriate. The normal distribution of the data was tested using the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test was used to compare baseline values between patients and controls, and paired t-test or Wilcoxon test was used to compare within-group/subgroup comparisons of treatment effects, as appropriate. Fischer's exact test was used for categorical variables. The relationship between numerical variables was examined using Pearson correlation analysis. A p-value <0.05 was considered statistically significant.

RESULTS

According to the weight distribution in both groups, the participants were mostly of normal weight (13 vs. 13). Table 1 shows a comparison of the clinical findings of the patients and controls. The groups were similar with regarding age, weight, height, pubertal stage, PAQ-A, quadriceps muscle thickness and grip strength and all isokinetic knee muscle strengths (all p>0.05).

In the PCOS group, 10 (50%) had clinical hyperandrogenism only, two (10%) had biochemical hyperandrogenism only, and eight (40%) had both biochemical and clinical hyperandrogenism. When analysing the compliance of the normal weight patients (n=13), only four (30.7%) of

them followed the healthy diet recommendations and seven (53.8%) only followed the walking recommendation of the exercise program. None of the obese (n=5) or overweight (n=2) patients adhered to the prescribed diet and exercise program. Microgynon® (0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol) was prescribed to six patients (30%), Diane 35® (2 mg cyproterone acetate and 0.035 mg ethinyl estradiol) to 13 patients (65%) and Primolut® (norethisterone) to one patient (5%). All patients took their medication regularly for six months.

In the PCOS group, positive correlations were found between weight and quadriceps muscle thickness (r=0.462), knee muscle strength values at 60° extension (r=0.496), 60° flexion (r=0.514), and 180° flexion (r=0.545), and handgrip strength (r=0.475) (all $p<0.05$). Similarly, positive correlations were observed between BMI Z-score and quadriceps muscle thickness (r=0.672), and knee muscle strengths at 60° extension (r=0.633), 60° flexion (r=0.786), and 180° flexion (r=0.591) (all $p<0.01$).

In the PCOS group, positive correlations were found between serum insulin levels and knee muscle strength values at 60° extension (r=0.498), 60° flexion (r=0.457), and 180° flexion (r=0.565) (all $p<0.05$). No correlations were found between height, modified FGS scores, disease duration, fasting blood glucose (FBG), testosterone levels and all knee muscle thickness and muscle strength values (all $p>0.05$).

The PAQ-A of the patients and controls were mostly in the very low or low physical activity levels. Only three individuals in the patient group, and two adolescents in the control group engaged in moderate physical activity. No correlations were found between PAQ-A levels with muscle thickness or strength values in the PCOS group.

When compared to baseline in the PCOS group (Table 2), weight and height, quadriceps muscle strengths, and LDL, total cholesterol, triglyceride, and HDL values increased, however, LH, FSH and total testosterone values decreased after the treatment (all $p<0.05$). There were no differences in PAQ-A, quadriceps muscle thickness and grip strength values with the treatment (all $p>0.05$). In addition, after the treatment, we found no significant relationships among weight and height changes and knee muscle strength changes (all $p>0.05$).When subgroup analyses were performed according to COC use (Table 3), significant increases were observed in all knee muscle strength measurements among users of levonorgestrel and ethinyl estradiol, while in the cyproterone acetate and ethinyl estradiol group, this increase was significant only in 180° extension strength (all $p<0.05$). Both groups demonstrated significant increases in LDL, total cholesterol, and triglyceride levels (all $p<0.05$); however, a significant increase in HDL was noted exclusively in the cyproterone acetate plus ethinyl estradiol group ($p=0.001$).

Additionally, significant decreases in LH, FSH, and total testosterone levels were identified in the levonorgestrel and ethinyl estradiol group (all $p<0.05$). In contrast, in the cyproterone acetate and ethinyl estradiol group, the decrease reached statistical significance only in LH levels ($p=0.023$). When comparing the post-treatment changes between the two groups, significant differences were found in knee extensor strength at 60° ($p=0.009$) and HDL levels ($p=0.001$).

DISCUSSION

In this study, we aimed to investigate whether there were changes in quadriceps muscle thickness and strength between adolescents with PCOS and healthy controls, and we also evaluated the effects of different COCs treatments on quadriceps muscle thickness and strength. We found that quadriceps thickness and strength were similar between the PCOS patients and controls. In addition, increases in weight, height, quadriceps muscle strength and lipid profiles were seen in patients who received six months of COC treatment. These increases in quadriceps muscle strength appeared to be caused by levonorgestrel use, while increases in lipid profile and hormone suppression were seen in both COC users.

Although there is strong evidence that anabolic androgens lead to an increase in muscle mass, there is no clear data on their effects on muscle strength (9-11). Studies investigating the effects of hyperandrogenism in PCOS on skeletal muscle are insufficient in adults and lacking in the adolescents (3-6). In this regard, Thomson et al. (4) compared 10 adult patients with PCOS to 16 healthy controls by using isokinetic dynamometer and did not find any difference on quadriceps muscle strength. Like our study, the muscle strength values of the two groups were similar and the fact that testosterone levels were not found to be related to quadriceps muscle strengths in the patient group may suggest that hyperandrogenism may not be a major factor for muscle strength in PCOS, which is still discussed in the literature (26).

A recent meta-analysis (26) investigating the relationship between muscle strength and mass in adults reported that PCOS patients had higher total muscle mass compared to controls. Although no correlation was found between total muscle mass and total testosterone levels, a significant correlation was observed between BMI and total muscle mass. The meta-analysis also highlighted conflicting findings in the literature regarding muscle strength in PCOS, with some studies suggesting an increase and others a decrease, ultimately concluding that further research is needed to clarify this issue (26).

In our study, quadriceps muscle thickness, recognized as a valid and reliable metric in current sarcopenia guidelines, was measured and compared to the muscle mass assessment methods referenced in the meta-analysis. We found no significant differences in quadriceps muscle mass or strength measurements between adolescents with PCOS and controls. Consistent with the meta-analysis findings, quadriceps muscle thickness was correlated with BMI-Z scores, but not with testosterone or insulin levels. However, a correlation was observed between insulin levels and certain knee muscle strength parameters.

Aksun et al. (27) reported that short-term (121 days) use of COCs did not alter muscle composition or strength in their study involving 20 adult PCOS patients, where muscle strength and body composition were compared. The authors also observed a correlation between total testosterone levels and lower extremity average power. In contrast, our study did not find a correlation between total testosterone and muscle strength. Differences in patient populations may account for this discrepancy. Additionally, the shorter duration of COC use in the aforementioned study compared to our study might have contributed to the differences in muscle strength outcomes observed following treatment.

In the adult study by Kogure et al. (28), which assessed physical performance in PCOS and control groups using a hand dynamometer, 70 women in the PCOS group were compared with 93 participants in the control group. The study found that handgrip strength was significantly higher in the PCOS group and correlated with lean body mass. In our study, however, we observed similar handgrip strength values between the patient and control groups. Furthermore, unlike the findings of the aforementioned study, we did not observe any correlation between BMI-Z scores and handgrip strength.

A systematic review of limited studies examining the effects of COCs on muscle hypertrophy, power and strength adaptation to resistance exercise found that there was no evidence-based rationale for or against the use of COCs (29). However, estrogen and progesterone receptors are expressed and localised within skeletal muscle, suggesting direct effects of endogenous and exogenous estrogen and progesterone on muscle tissue (30). Although androgens have anabolic effects on skeletal muscle (7,8), COCs have various androgenic or antiandrogenic effects due to progestin content. A molecular study has shown that use of 2nd generation COCs in young untrained women increased satellite cell number and skeletal muscle molecular marker following 10-week of resistance training compared with nonusers (30). Additionally, a positive effect of COC including progestin (Dienogest) in physiologic concentrations has been shown on muscle cell proliferation and myogenic potential in vitro, demonstrating an anabolic effect of COCs (31).

A meta-analysis including nine studies in adults have shown no significant effect of COC use on muscle strength (32). The meta-analysis' limitations included the fact that the effect of COCs on muscle strength was not studied in the relevant studies due to differences in progestin content, as well as the small number of patients participating and methodological differences for measurements of muscle mass and strength. In our study, we investigated the effects of progestin content on subjects' muscle thickness and strength over a 6-month treatment period. The

levonorgestrel has the strongest androgenic capacity among progestin generations, whereas cyproterone acetate has anti-androgenic capacity (14). Our study demonstrated significantly higher increases in all knee muscle strength values in COC users containing levonorgestrel than in cyproterone acetate users. This conclusion could be attributed to the progestin content of both medications, which have different androgenic (vs. anti-androgenic) effects while containing similar quantities of ethinyl estradiol.

Although previous studies investigated the effect of COCs on exercise adaptation, its impact on exercise performance is poorly understood. Dalgaard et al. evaluated the effects of 3rd generation COCs on muscular adaptations to resistance exercise in young untrained women (33). After 10-week resistance exercise, COC use (n=14) was associated with a trend towards a higher increase in quadriceps cross sectional area (p=0.06) and type I muscle fiber area (p=0.04) compared with nonusers (n=14). Similar to our study, Ruiæ et al. compared (anti)androgenic effects of COCs on muscle strength and fat-free mass during 16-week of exercise in young women (34). They found that COC including levonorgestrel (n=24) was related with significantly higher gains in muscle strength and fat-free mass than COC including cyproterone acetate (n=26). The authors attributed this relatively low increase in the cyproacetate group to the antiandrogen effects of the drug, however, we think that like our study, the higher increase in muscle strength in levonorgestrel users than in cyproacetate users can be caused due to the high androgenicity of levonorgestrel (14).

The safety and effects of COCs on the metabolic profile of PCOS have yet to be clarified. Our patients received cyproterone acetate (n=13), levonorgestrel (n=6), and norethisterone (n=1) as progestins. Levonorgestrel containing intrauterine contraceptive devices have been used with clinically meaningful changes in clinical and metabolic parameters (35). It has been reported that COCs containing cyproterone acetate or 3rd generation progestin, caused an increase in the lipid profile (in HDL, LDL, and triglyceride levels), while not affected weight and fasting blood glucose (36). In a study including 14 to 19-year-old adolescents with PCOS who either (37) received desogestrel and ethinyl estradiol, or cyproterone acetate and ethinyl estradiol, significant increases were observed in total cholesterol, LDL, and HDL levels in both drug groups. Similarly, we detected increases in the lipids at six months, while we did not observe changes in fasting blood glucose, insulin, and HOMA values. The increase in lipids was attributed to ethinyl estradiol and/or progestin content of COCs.

Study Limitations: The present study has some limitations. First, the number of participants was small, and a single follow-up measurement was applicable. However, the effect of exercise or other interventions on muscles may appear gradually and more with a sequence of power, then strength, and finally and less muscle mass increase (38,39). Although we found higher increases in quadriceps muscle strengths with COC containing levonorgestrel (than cyproterone acetate) treatment, we imply that significant increase in quadriceps muscle thickness can be detected in more patients and/or longer-term treatment.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate the quadriceps muscle thickness and strength in adolescents with PCOS compared to healthy controls, as well as to examine the effects of different COC treatments on quadriceps muscle and metabolic/hormonal profile with a six-month period. Our findings showed that quadriceps muscle thickness and strength values were similar between patients and controls. Additionally, we observed increases in knee muscle strength values in adolescents with PCOS who received COCs containing levonorgestrel after six months of treatment. Further longitudinal studies with larger sample sizes are needed to validate our preliminary but novel findings and to assess the effects of COCs with varying androgenic properties

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Author Contributions

AG, MK, SG, DAA, EK, GB, HD, OD: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript. **AG, MK, GB, HD, OD**: the drafting of the article, critical revision for important intellectual content. **AG**: final approval of the version to be published. All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Table 1. Comparison of Clinical Parameters of Groups (n=40)

Characteristic	**PCOS** (n=20)	**Control** (n=20)	p	Effect size
Age (year)	15.7±0.6	15.8±1.3	0.684	0.130
Weight (kg)	67.6±20.3	58.0±9.3	0.892	0.021
Height (cm)	163.5±6.6	163.0±6.5	0.821	0.072
BMI (kg/m^2)	21.6 (19.5-25.3)	21.3 (19.0-23.5)	0.808	0.075
BMI Z-score	0.74 (0-1.68)	0.63±1.12	0.760	0.071
Tanner stage (4 vs. 5)	5/15	3/15	0.347	
PAQ-A	2.2±0.8	2.0±0.8	0.461	0.291
Quadriceps MT (mm)	42.4±7.4	40.8±8.2	0.525	0.026
Grip strength (kg)	27.0±4.1	26.5±4.5	0.746	0.024
Knee muscle strength (Nm)				
60° extension	93.2±29.1	94.5±25.5	0.889	0.002
60° flexion	44.3±17.1	43.0±11.2	0.774	0.006
180° extension	61.8±20.5	59.7±18.8	0.402	0.133
180° flexion	37.7±14.5	38.8±10.7	0.791	0.007

Data are shown as mean±SD, median (interquartile 25%-75%) or number (n).
PAQ-A; Physical Activity Questionnaire in Adolescents, MT; muscle thickness

Table 2. Clinical Parameters of the Patients at Baseline and After Treatment (n=20)

Characteristic	Baseline	After treatment	p	Effect size
Weight (kg)	67.6±20.3	69.1±17.2	**0.035**	0.473
Height (cm)	163.5±6.6	163.9±6.6	**0.010**	0.640
BMI (kg/m^2)	21.6 (19.5-25.3)	23.2 (21.6-28.8)	**0.030**	0.486
BMI Z score	0.74 (0-1.68)	0.70 (0.28-1.64)	0.093	0.376
PAQ-A	2.2±0.8	1.9±0.7	0.105	0.291
Quadriceps MT (mm)	42.4±7.4	43.8±8.1	0.117	0.026
Grip strength (kg)	27.0±4.1	27.8±3.9	0.096	0.024
Knee muscle strength (Nm)				
60° extension	93.2±29.1	103.5±21.5	**0.008**	0.002
60° flexion	44.3±17.1	48.0±14.1	**0.018**	0.006
180° extension	50.2±17.0	60.7±20.8	**0.001**	0.133
180° flexion	37.7±14.4	42.4±13.1	0.075	0.007
Laboratory test				
LDL (mg/dl)	106.0±24.5	132.4±27.6	**0.001**	0.891
Total cholesterol (mg/dl)	171.0±32.7	209.2±39.0	**<0.001**	1.028
Triglyceride (mg/dl)	91.3±40.1	129.6±49.8	**0.003**	0.668
HDL (mg/dl)	52.0±11.8	58.9±11.8	**0.030**	0.486
LH (mIU/mL)	9.5±5.2	2.9±3.8	**<0.001**	0.938
FSH (mIU/mL)	5.3±1.9	3.4±3.0	**0.017**	0.606
Total testosterone (ng/dl)	45.7±21.7	29.1±13.3	**0.001**	0.890
FBG (mg/dl)	85.4±7.8	83.8±8.6	0.466	0.163
Insulin (µIU/ml)	11.1±5.0	14.0±7.9	0.126	0.342
HOMA-IR	2.9±2.2	3.0±1.5	0.204	0.284
ALT (U/L)	17.6±10.7	23.0±15.5	0.099	0.369
AST (U/L)	18.1±5.6	20.8±10.9	0.222	0.273

Data are shown as mean±SD, median (interquartile 25%-75%)
PAQ-A; Physical Activity Questionnaire in Adolescents, PT; peak torque, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, FBG: Fasting blood glucose, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.
Statistically significant variables are shown as bold.

Table 3. Clinical Parameters of the Patients at Baseline and After Treatment (n=19)

Characteristic		Levonorgestrel- EE (n=6)	Cyproterone acetate-EE (n=13)	Effect size
Knee strength (Nm)				
60° extension	Baseline	81.5±9.0	98.7±34.8	
	After	105.1±12.2	103.1±25.8	
	p	**0.002**	0.288	**0.336**
60° flexion	Baseline	41.7±16.9	45.6±18.4	
	After	55.5±12.8	45.1±14.5	
	p	**0.046**	0.919	0.132
180° extension	Baseline	54.5±12.9	47.4±18.9	
	After	68.5±11.1	56.9±24.2	
	p	**0.010**	**0.015**	0.066
180° flexion	Baseline	35.5±12.3	39.3±16.1	
	After	44.5±17.0	41.4±12.2	
	p	**0.017**	0.549	0.084
Laboratory test				
LDL (mg/dl)	Baseline	92.3±34.2	112.2±18.0	
	After	116.3±15.9	141.1±29.4	
	p	**0.039**	**0.010**	0.006
Total cholesterol (mg/dl)	Baseline	145.7±50.0	175.6±25.0	
	After	182.7±28.7	223.3±36.2	
	p	**0.034**	**0.006**	0.021
Triglyceride (mg/dl)	Baseline	80.5±29.0	99.7±44.7	
	After	109.7±20.5	144.8±52.6	
	p	**0.039**	**0.015**	0.024
HDL (mg/dl)	Baseline	54.8±8.4	47.8±7.7	
	After	52.5±10.9	62.5±11.5	
	p	0.602	**0.001**	**0.531**
LH (mIU/mL)	Baseline	8.0±3.0	10.1±6.1	
	After	2.2±2.9	3.4±4.3	
	p	**0.028**	**0.023**	0.003
FSH (mIU/mL)	Baseline	4.6±1.4	5.7±2.0	
	After	2.1±2.2	3.9±3.2	
	p	**0.029**	0.118	0.012
Total testosterone (ng/dl)	Baseline	42.6±9.1	47.2±26.4	
	After	21.6±12.4	33.3±12.8	
	p	**0.022**	0.056	0.025

Data are shown as mean±SD

EE; ethinyl estradiol, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH: Luteinizing hormone, FSH: Follicle stimulating hormone.

Statistically significant variables are shown as bold.