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

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What is already known on this topic?

To date, no studies have investigated muscle strength and thickness in adolescents with polycystic ovary syndrome.

What this study adds?

Quadriceps muscle thickness and strength were comparable between adolescents with polycystic ovary syndrome and healthy controls. Girls using levonorgestrel showed significantly greater gains in quadriceps muscle strengths than those using cyproterone acetate.

Abstract

Objective: To date, muscle strength and thickness have not been investigated in adolescents with polycystic ovary syndrome (PCOS). This study aimed to investigate whether differences exist in these parameters between adolescents with PCOS and healthy controls. Additionally, we evaluated the effects of six months combined oral contraceptive (COC) treatment on quadriceps muscle characteristics.
Methods: The study included adolescents diagnosed with PCOS and healthy peers. Dynamometers were used to measure knee muscle and hand grip strengths, and ultrasound was used to measure quadriceps muscle thickness. In the PCOS group, all measurements were repeated after six months of COCs treatment.
Results: There were 20 participants in each of the PCOS and control groups. There were no significant differences between the groups in terms of age, weight, height, pubertal stage, Physical Activity Questionnaire scores, quadriceps muscle thickness, grip strength and isokinetic knee strengths at baseline. Within the PCOS group, significant increase were observed in weight, height, quadriceps strength and lipid levels after six months of treatment (all $p < 0.05$). Subgroup analysis of COC treatments revealed significantly greater gains in quadriceps muscle strength among levonorgestrel users (n = 6) compared to those using cyproterone acetate users (n = 13).
Conclusion: Quadriceps muscle thickness and strength were comparable between adolescent with PCOS and controls, indicating no intrinsic muscular deficit. However, significantly greater improvements in quadriceps muscle strength were observed in those using levonorgestrel-containing COCs users compared to cyproterone acetate users. These findings suggest a potential role of progestin androgenicity in muscle strength. Further longitudinal studies with larger cohorts are warranted to validate these preliminary findings and to explore the impact of COCs with varying androgenic properties.
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 characterized by hyperandrogenism and chronic anovulation. Symptoms may appear in adolescence, and the condition is associated with various 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 adults are not considered valid in adolescents, and it is often difficult to diagnose PCOS in adolescents. The diagnosis is typically made when irregular menstrual bleeding persists for at least two years post-menarche, accompanied by clinical and/or biochemical hyperandrogenism (1,2).

Hormonal and metabolic changes such as hyperandrogenism, hyperinsulinism, and hyperlipidemia may lead to alterations in muscle morphology and strength in with PCOS patients. However, there is a paucity of publications on this subject, especially in adolescents with PCOS, and there are conflicting results (3,4,5,6). As androgens and insulin have anabolic effects on skeletal muscle, they may influence muscle mass and/or strength (7,8,9,10,11,12,13). Furthermore, progesterone in combined oral contraceptives (COCs), commonly prescribed to treat PCOS, may have androgenic or antiandrogenic effects (14), potentially causing muscle changes.

Therefore, the aim of this study was to investigate whether there are differences in quadriceps muscle thickness and strength between adolescents with PCOS and controls of similar age, anthropometric characteristics, and pubertal stage. The quadriceps muscle was selected for the study due to its functional importance and substantial muscle mass (15,16). Additionally, we aimed to evaluate the effects of different COCs treatments on this muscle. We found no published studies investigating quadriceps muscle thickness by using musculoskeletal ultrasound (US) in adolescents diagnosed with PCOS.

Methods

This study was conducted at the Departments of Adolescent Health and Physical Medicine and Rehabilitation, Hacettepe University Faculty of Medicine, Türkiye. Approval was obtained from the Hacettepe University Faculty of Medicine Local Ethics Committee (decision number: KA-20083, date: 20.10.2020). The study met the standards of the Declaration of Helsinki for human experimentation. The study group consisted of adolescents with PCOS and healthy controls of similar 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 all participants and their families. PCOS diagnosis was made using the 2015 Pediatric Endocrine Society criteria (17). Biochemical hyperandrogenism was defined as a total testosterone level >42 ng/dL, and clinical hyperandrogenism was considered by a modified Ferriman-Gallwey score was ≥8 (1,2).

Considering that the mean age of menarche in Turkish females is 12.2 ± 0.9 years (18) participants were selected from adolescents aged 14 to 18 years whose menarche had already occurred, and pubertal development was Tanner stage ≥4. Adolescents engaged in regular training or sports, having chronic systemic diseases, on prescription or non-prescription drugs (including those affecting testosterone metabolism), or with mentally disabilities were excluded.

Study Protocol

Each participant's height and weight were measured using a stadiometer and a digital scale. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and expressed as BMI standard deviation (SD) score (BMI Z-scores) based on national data for Türkiye. Adolescents with a BMI at or above the 95th percentile were classified as obese, and those with BMI between the 85th and 94.9th percentiles as overweight, and those with BMI between the 5th and 84.9th percentiles as normal weight (19). Pubertal staging was done according to the Marshall-Tanner system (20). Hair growth in the patient group was assessed using the modified Ferriman-Gallwey scale (FGS) (21).

Lifestyle changes, healthy nutrition, and walking for 30-45 minutes at least 3 days a week, 15 minutes of weight training, and 15 minutes of muscle-strengthening exercise were recommended for all participants. In addition, a weight-loss diet was also recommended for both overweight and obese patients. Patients were monitored monthly to compliance with these suggestions. All patients were prescribed either COCs or with progestin-only drugs if COCs were contraindicated. COC regimens included 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®), while norethisterone (Primolut®) was used for progestin-only drug. In our routine clinical practice, Microgynon® and Diane 35® were the preferred COCs.

Laboratory Measurements

At the start of the study, serum samples were collected to diagnose PCOS, evaluate metabolic and hormonal changes, and exclude other differential diagnoses. To evaluate the

metabolic/hormonal changes, biochemical and hormonal tests were also performed after sixth month of treatment. Serum samples for glucose, insulin, triglyceride, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and total were obtained after an 8-hour fast at 8:00 AM. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the standard formula: 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 strength on the dominant side using the Biodex System 3 Pro device (Biodex Medical Systems, Shirley, NY, USA) (22). After a 5-minute warm-up, 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 two cm above the malleoli. The thighs/trunk were secured to the seat with straps to prevent force distribution and ensure stabilization. The concentric strengths of the quadriceps and hamstrings muscles were measured for five repetitions at 60°/sec and 15 repetitions at 180°/sec, with 60-second rest intervals, and verbal motivation was provided during the test (23). Peak torque values were recorded for analyses.

Grip Strength Assessment

Dominant hand grip strength was measured 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. They were asked to perform three maximal grip strength trials, and the highest value 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 US measurements were performed on the dominant hand side with minimal compression. Muscle thickness 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 a physiatrist (MK) experienced in musculoskeletal US.

Physical Activity Evaluation

The Physical Activity Questionnaire in Adolescents (PAQ-A) was used to assess the physical activity level over the last seven days of the school term (24). It consists of eight questions, scored from 1 (low activity) to 5 (high activity), and nine questions about barriers to physical activity in the past week, and was adapted for the Turkish population (25).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 23, IBM Inc., Armonk, NY, USA). Descriptive statistics are presented as mean ± SD or median (interquartiles) for numerical variables. Normality was tested using the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test was used to compare the variables between the groups, and paired t-test or Wilcoxon test was used to compare within-group/subgroup comparisons. Fisher's exact test was used for categorical variables. Correlations between continuous variables were assessed using Pearson or Spearman's correlation analysis. A $p < 0.05$ was considered statistically significant.

Results

A total of 20 adolescents with PCOS and 20 control adolescents were included in the study. Weight distribution in comparable between the groups, with the majority of participants classified as having normal weight (13 individual; 65% in each group). Table 1 shows the comparison of the clinical parameters between the groups. There were no significant differences between the groups in terms of o age, weight, height, pubertal stage, PAQ-A scores, quadriceps muscle thickness, grip strength, or isokinetic knee muscle strength parameters.

Among the PCOS group, 10 participants (50%) had clinical hyperandrogenism only, two (10%) had biochemical hyperandrogenism only, and eight (40%) presented with both. Of the 13 normal-weight patients, only four (30.7%) adhered to dietary recommendations and seven (53.8%) followed the walking recommendations of the exercise program. None of the overweight (n = 2) or obese (n = 5) patients adhered to either dietary or exercise program. Regarding pharmacologic treatment, six patients (30%) received Microgynon® (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg), 13 patients (65%) received Diane 35® (cyproterone acetate 2 mg and ethinyl estradiol 0.035 mg), and one patient (5%) received Primolut® (norethisterone). All patients reported regular use of medication for six months.

In the PCOS group, weight was positively correlated with quadriceps muscle thickness ($r = 0.462$), knee extensor strength at 60° ($r = 0.496$), knee flexor strengths at 60° ($r = 0.514$) and 180° ($r = 0.545$), and handgrip strength ($r = 0.475$) (all $p < 0.05$). Similarly, BMI Z-score demonstrated

positive correlations with quadriceps muscle thickness (r = 0.672), knee extensor strength at 60° (r = 0.633), and knee flexor strengths at 60° flexion (r = 0.786), and 180° (r = 0.591) (all $p < 0.01$). In addition, serum insulin levels were positively correlated with knee extensor strength at 60° (r = 0.498), and knee flexor strengths at 60° (r = 0.457), and 180° (r = 0.565) (all $p < 0.05$). No significant correlations were found between quadriceps muscle thickness or strength values with height, modified FGS scores, disease duration, fasting blood glucose (FBG), or testosterone levels.

The PAQ-A scores indicated that both patients and controls were predominantly in the very low or low physical activity categories. Only three patients and two controls were categorized as moderately active. However, no correlations were found between PAQ-A scores and muscle thickness or strength in the PCOS group.

Following six months of treatment (Table 2), patients demonstrated significant increases in weight, height, quadriceps muscle strengths, HDL, LDL, total cholesterol, and triglyceride levels, while LH, FSH and total testosterone levels significantly decreased (all $p < 0.05$). No significant differences were observed in PAQ-A scores, quadriceps muscle thickness, or handgrip strength (all $p > 0.05$). Additionally, changes in weight and height did not correlate with changes in knee muscle strength after treatment (all $p > 0.05$).

Subgroup analyses based on type of COC use (Table 3) revealed that all knee muscle strength parameters increased significantly among users of levonorgestrel containing COCs, however, in the cyproterone acetate group, a significant increase was observed only in knee extension strength at 180° (all $p < 0.05$). Both subgroups demonstrated significant increases in LDL, total cholesterol, and triglyceride levels (all $p < 0.05$). However, HDL levels increased significantly only in the cyproterone acetate group ($p = 0.001$). Significant decreases in LH, FSH, and total testosterone levels were found in the levonorgestrel group, while only LH levels decreased in the cyproterone acetate group (all $p < 0.05$). Comparison of the post-treatment changes between the groups showed significant differences in knee extensor strength at 60° ($p = 0.009$) and HDL levels ($p = 0.001$).

Discussion

To our best notice, this is the first study investigating quadriceps muscle thickness and strength using objective US and isokinetic assessments in adolescents with PCOS, with additional analyses following six months of different COCs treatment. Our preliminary findings suggest that while muscle strength improves with treatment, this can be more attributable to COCs type than to intrinsic effects of PCOS itself.

At baseline, quadriceps muscle thickness and strength values did not differ significantly between adolescents with PCOS and healthy controls. Following six months of COC treatment, increases were observed in weight, height, quadriceps muscle strength and lipid profiles. The increases in quadriceps muscle strengths appeared to be associated with levonorgestrel, while elevations in lipid profile and hormone suppression were observed in both groups of COC users.

Although there is strong evidence that anabolic androgens increase muscle mass, their effects on muscle strength

Table 1. Comparison of clinical parameters of groups (n = 40)

Characteristics	PCOS (n = 20)	Control (n = 20)	p	Effect size
Age (years)	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/m²)	21.6 (19.5-25.3)	21.3 (19.0-23.5)	0.808	0.075
BMI Z-score	0.74 (0-1.68)	0.80 (-0.30-1.61)	0.760	0.071
Tanner stage (4 vs. 5)	5/15	5/15	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 (interquartiles) 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/m²)	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 or median (interquartiles).
PAQ-A: Physical Activity Questionnaire in Adolescents, MT: muscle thickness, LDL: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, LH: luteinizing hormone, FSH: follicle stimulating hormone, FBG: fasting blood glucose, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SD: standard deviation, BMI: body mass index, NB: statistically significant variables are shown as bold

remain unclear (9,10,11). Studies investigating the effects of hyperandrogenism on skeletal muscle in PCOS patients are limited in adults and lacking in adolescents (3,4,5,6). Thomson et al. (4) compared 10 adult patients with PCOS to 16 healthy controls using isokinetic dynamometer measurements and found no difference in quadriceps muscle strength. Our results are consistent with these findings. Additionally, the same study also found no correlation between testosterone levels quadriceps muscle strength, suggesting that hyperandrogenism may not play a significant role in determining muscle strength in this population. Nonetheless, this relationship remains a topic of debate in the literature (26).

A recent meta-analysis (26) investigating the relationship between muscle strength and mass in adults reported that PCOS patients had greater total muscle mass compared to controls. While no association 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 emphasized the inconsistent findings in the literature regarding muscle strength in PCOS-some studies reported an increase, while others observed a decrease. The authors concluded that further research is necessary to clarify these discrepancies (26).

In the present study, quadriceps muscle thickness, recognized as a valid and reliable parameter in current sarcopenia guidelines (39), was measured and compared to the muscle mass assessment methods cited in the referenced meta-analysis. No significant differences were observed in quadriceps muscle mass or strength between adolescents with PCOS and controls. Consistent with the meta-analysis findings, quadriceps muscle thickness was positively correlated with BMI-Z scores, but not with testosterone or insulin levels. However, a significant correlation was observed between insulin levels and certain knee muscle strength parameters.

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 tests				
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. Statistically significant variables are shown in bold.
Baseline: at start of treatment period, After: following six months of treatment with the specified COC, EE: ethinyl estradiol, LDL: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, LH: luteinizing hormone, FSH: follicle stimulating hormone, COC: combined oral contraceptive, SD: standard deviation

Aksun et al. (27) reported that short-term use of COCs (121 days) did not affect muscle composition or strength in their study of 20 adult patients with PCOS, in which muscle strength and body composition were evaluated. They also identified a correlation between total testosterone levels and mean lower extremity power. In contrast, our study did not observe any association between total testosterone and muscle strength. The discrepancy may be attributed to differences in the characteristics of the study populations. Additionally, the shorter duration of COC use in the study of Aksun et al. (27) compared to the present study may have influenced the divergent muscle strength outcomes observed following treatment.

In a study by Kogure et al. (28), which evaluated physical performance in adults with 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 reported that handgrip strength was significantly higher in the PCOS group and was positively correlated with

lean body mass. However, in our study, we observed similar handgrip strength values between the patient and control groups. Furthermore, no correlation was found between BMI-Z scores and handgrip strength.

A systematic review of limited studies investigating the effects of COCs on muscle hypertrophy, power and strength adaptations to resistance exercise concluded that there is no evidence-based rationale either supporting or against the use of COCs (29). However, the presence of estrogen and progesterone receptors in skeletal muscle suggests potential direct effects of both endogenous and exogenous estrogen and progesterone hormones on muscle tissue (30). Although androgens are known to have anabolic effects on skeletal muscle (7,8), the androgenic or antiandrogenic properties of COCs vary depending on the specific progestin content. A molecular study has shown that second-generation COC use in young, untrained women led to an increase in satellite cell numbers and skeletal muscle molecular markers after 10 weeks of resistance training, compared with non-users (30). Additionally, a COC containing progestin (Dienogest) at physiologic concentrations was shown to positively influence muscle cell proliferation and myogenic potential *in vitro*, suggesting a possible anabolic effect of certain COCs *in vivo* (31).

A meta-analysis including nine studies in adults reported no significant effect of COC use on muscle strength (32). However, the limitations of this analysis included the lack of consideration for differences in progestin content across studies, small sample sizes, and methodological inconsistencies in measuring muscle mass and strength. In the present study, we examined the impact of progestin content on muscle thickness and strength in adolescents with PCOS over a 6-month treatment period. Among progestin-containing COCs, Levonorgestrel exhibits the strongest androgenic activity, whereas cyproterone acetate demonstrates anti-androgenic properties (14). Our findings revealed significantly greater improvements in all measures of knee muscle strength among girls who used levonorgestrel-containing COCs compared to those who received cyproterone acetate. These results suggest that the differing androgenic or anti-androgenic effects of progestins, despite similar ethinyl estradiol content, may account for the observed differences in muscle strength outcomes.

Although previous studies have investigated the effect of COCs on exercise adaptation, their impact on exercise performance remains poorly understood. Dalgaard et al. evaluated the effects of third-generation COCs on muscular adaptations to resistance training in young, untrained women (33). Following a 10-week resistance training program, COC users (n = 14) exhibited a trend towards a greater increase in quadriceps cross-sectional area (p = 0.06) and a significantly greater increase in type 1 muscle fiber area (p = 0.04) compared with non-users (n = 14). Similarly, Ruiæ et al. (34) examined the (anti)androgenic effects of COCs on muscle strength and fat-free mass over a 16-week of exercise program in young women. Their findings indicated that the use of COC containing levonorgestrel (n = 24) led to significantly greater gains in muscle strength and fat-free mass compared to COC containing cyproterone acetate (n = 26). The authors attributed the relatively lower increase in the cyproterone acetate group to its antiandrogen properties. In contrast, our findings suggest that the more pronounced gains in muscle strength observed in levonorgestrel users may be attributable to the higher androgenic potential of levonorgestrel (14).

The safety and metabolic effects of COCs in individuals with PCOS remain to be fully elucidated. In our study, patients received progestins in the form of cyproterone acetate (n = 13), levonorgestrel (n = 6), or norethisterone (n = 1). Intrauterine contraceptive devices containing levonorgestrel have been associated with clinically meaningful changes in clinical and metabolic parameters (35). It has been reported that COCs containing cyproterone acetate or third generation progestin can lead to elevations in the lipid parameters, without affecting body weight or FBG (36). In a study including 14 to 19 years with PCOS, treatment with either desogestrel and ethinyl estradiol or cyproterone acetate and ethinyl estradiol resulted in significant increases in lipid profile in both drug groups (37). Consistently, we observed increases in the lipid levels following six months of treatment; however FBG, insulin levels, and HOMA-IR values remained unchanged. These changes in lipids may be attributed to the ethinyl estradiol and/or progestin components of the COCs.

Study Limitations

This study has several limitations. First, the sample size was relatively small, and only a single follow-up measurement was conducted. However, it is known that the effect of exercise or hormonal interventions on muscles typically progress over time, often beginning with improvements in power, followed by strength, and eventually increases in muscle mass (38,39). Although our findings indicated greater increases in quadriceps muscle strengths with levonorgestrel containing COC treatment compared to cyproterone acetate, we hypothesize that significant increases in quadriceps muscle thickness may have been observed with a larger sample size and/or a longer duration of treatment.

Conclusion

In summary, adolescents with PCOS showed similar quadriceps muscle thickness and strengths compared to healthy controls, suggesting no intrinsic deficit in muscle thickness and function. Knee muscle strength improvements observed after six months of COC treatment seem to be more closely related to weight gain and the COC formulation (containing levonorgestrel) than changes in physical activity or muscle hypertrophy. Larger, long-term studies are needed to clarify our preliminary but novel findings.

Ethics

Ethics Committee Approval: Approval was obtained from the Hacettepe University Faculty of Medicine Local Ethics Committee (decision number: KA-20083, date: 20.10.2020).

Informed Consent: Informed consent was obtained from all participants and their families.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ayşe Gül Güven, Murat Kara, Sinem Güneri, Demet Aygün Arı, Erdem Karabulut, Hüseyin Demirbilek, Gürkan Bozdağ, Orhan Derman, Concept: Ayşe Gül Güven, Murat Kara, Hüseyin Demirbilek, Gürkan Bozdağ, Orhan Derman, Design: Ayşe Gül Güven, Murat Kara, Hüseyin Demirbilek, Gürkan Bozdağ, Orhan Derman, Data Collection or Processing: Ayşe Gül Güven, Murat Kara, Sinem Güneri, Demet Aygün Arı, Orhan Derman, Analysis or Interpretation: Ayşe Gül Güven, Murat Kara, Erdem Karabulut, Orhan Derman, Literature Search: Ayşe Gül Güven, Murat Kara, Writing: Ayşe Gül Güven, Murat Kara, Sinem Güneri, Demet Aygün Arı, Hüseyin Demirbilek, Gürkan Bozdağ, Orhan Derman.

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