Archives of Gynecology and Obstetrics (2019) 300:771–776
https://doi.org/10.1007/s00404-019-05229-2

Is muscle mechanical function altered in polycystic ovary syndrome?

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Received: 7 April 2019 / Accepted: 19 June 2019 / Published online: 1 July 2019

Abstract

Purpose Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age. The aim of the current study was to assess muscle mechanical function in PCOS and its relationship with hormonal and metabolic features of the syndrome.

Methods The study included 44 women with PCOS, all having clinical or biochemical hyperandrogenism, chronic oligo-anovulation and PCOM, and 32 age- and BMI-matched healthy women. Anthropometric, hormonal and biochemical measurements were performed. Muscle mechanical function including lower limb explosive strength and average power (AvP) was measured using isokinetic dynamometry, a valid and reliable instrument for measuring muscle strength.

Results The mean age and BMI of the women with PCOS and controls were 21.8 ± 3.2 versus 22.8 ± 3 years and 26.1 ± 5.4 versus 25.5 ± 5.7 kg/m^2, respectively (p = NS for both). PCOS patients had higher androgen levels, whereas total and regional fat and lean body mass and insulin resistance parameters were similar between the groups. The peak muscle force output defined as the peak torque of knee extensor and flexor muscles was higher in normal weight women compared to overweight and obese ($p < 0.05$ for both) but did not differ in patients and controls. AvP determined by the time-averaged integrated area under the curve at 60°/s angular velocity was higher in the PCOS group for extension and flexion (50.3 ± 21.2 vs 42.1 ± 11.6 and 35.3 ± 27 vs 22.2 ± 11.1, respectively, $p < 0.05$ for both). These measurements were correlated with bioavailable testosterone ($r = 0.29$, $p = 0.012$, $r = 0.36$, $p = 0.001$, respectively).

Conclusion Muscle mechanical function is altered in PCOS. Women with PCOS have increased average lower limb power that is associated with hyperandrogenism.

Keywords PCOS · Androgen excess · Muscle strength · Muscle power · Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is characterized by androgen excess, ovulatory dysfunction and polycystic ovarian morphology (PCOM), and affects up to 1 in 7 women worldwide [1]. PCOS is associated with increased risk of several comorbidities including type 2 diabetes, hepatic steatosis, dyslipidemia, hypertension, infertility and obstetric complications and endometrial cancer [2].

Clinical and/or biochemical hyperandrogenism is a cardinal feature of PCOS that is observed in the vast majority of the patients [2]. Androgen excess is also implicated in the pathophysiology and development of the syndrome [3]. It is well known that testosterone is a key determinant of muscle strength irrespective of being endogenous or exogenous [4]. Increased muscle mass and power performance that correlates with mildly increased circulating testosterone

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in the high-normal female range has been reported in elite female athletes [5]. Accordingly, it is of interest whether mild androgen excess in women with PCOS is related to alterations in muscle strength.

A few studies are available in the literature evaluating muscle strength in women with PCOS by a variety of methods. Limited data from these studies suggest either unaltered or increased muscle strength in the syndrome [6–9]. The purpose of the current study was to determine whether muscle mechanical function is altered in women with PCOS and to investigate its potential relationship with hormonal and metabolic features of the syndrome.

Material and methods

Participants

Forty-four women with PCOS were recruited from the Outpatient Clinic of Endocrinology and Metabolism at Hacettepe University between February and October 2018. Diagnosis of PCOS was based on the Rotterdam criteria after exclusion of the related disorders as suggested [10]. Clinical and biochemical hyperandrogenism, oligo-anovulation and polycystic ovarian morphology on ultrasound (PCOM) were defined as previously described [11]. All patients fulfilled three diagnostic criteria of the Rotterdam (phenotype A). The control group included 32 age- and body mass index (BMI)-matched healthy women with regular menstrual cycles and without clinical or biochemical hyperandrogenism or PCOM.

All participants were sedentary women aged 18–30 years and had been weight stable (< 10% weight change) for at least 6 months prior to enrollment. Exclusion criteria included smoking, regular exercise at least once a week, use of contraceptives or any other medications for treatment of PCOS within the past 6 months, any degree of glucose intolerance, hypertension, hepatic or renal disease or any other systemic illness. Participants with a history of angina or any other cardiac, pulmonary or physical symptom that would potentially limit exercise performance were also excluded.

Study protocol

The study protocol was approved by the Ethical Committee of Hacettepe University and all participants provided written informed consent.

A standardized medical form was completed and anthropometric measurements including weight, height, waist and hip circumferences (waist: midway between the lower rib margin and the iliac crest, hip: widest circumference over the great trochanters) were determined. The BMI [weight (kg)/height $(m)^2$] and waist-to-hip ratio (WHR) were calculated. Total and regional body fat, lean mass and bone mineral density were measured using a Bioelectrical Impedance Segmental Body Analysis Monitor (TANITA, BC-418 MA type, Tokyo, Japan).

Blood samples were collected in early follicular phase between 8.00 and 10.00 a.m. on day 2–5 of the menstrual bleeding after an overnight fast. All subjects underwent a 75 g 2 h oral glucose tolerance test. Centrifuged serum and plasma samples were stored at − 80 °C.

Assessment of muscle mechanical function

The muscle strength measurement of the participants with isokinetic dynamometer was performed by the same sports physician at the Department of Sports Medicine at Hacettepe University and using the single isokinetic dynamometer; Biodex® System 3 (Biodex Corp., Shirley, NY, USA). The participants were given a warm-up exercise at 6 km/h for 15 min on the treadmill (G-THORC TX4000. SAS SPORT, TR) before muscle strength analysis with an isokinetic dynamometer.

The dominant leg was determined based on the leg which the subject prefers to kick a ball with, and all isokinetic measurements were done using the dominant leg. The orientation of the dynamometer was maintained at 0° and 0° tilt. The seat orientation was also done at 0°. The participants were seated on the dynamometer seat, the trunk was fixed with restraint straps placed on the pelvis and thigh, and the entrance axis of the dynamometer was aligned with the dominant axis of knee rotation. The range of motion was kept between 0° and 90° for the knee joint. The non-dominant leg was rested on the supporting device.

Following the gravitational correction procedure of the device, a submaximal reconstruction was performed three times in the perceived effort of each participant in the knee extension and knee flexion for the acquaintance of the isokinetic dynamometer equipment and the working procedure. Immediately after the warm-up exercises, each participant was asked to perform three maximum repetitions as fast and as explosive as possible at an angular speed of 60°/s. The participants started when the knee joint was in 90° flexion. Then, the movement of the dominant leg in the range of 90°–180° in the range of motion of the limbs was followed [12–14].

Isokinetic (concentric/concentric) knee flexion and knee extension measurements of the quadriceps and hamstring muscles were performed with three repetitions at an angular velocity of 60°/s in the dominant leg. The results of extensor peak torque and flexor peak torque in the dominant legs are in Newton/meter (N m) according to the international system of units, while the average power (AvP) is in watts (W).

The peak muscle force output during the assessment was defined as the peak torque (PT) and was reported as body

weight-normalized PT (N m/kg). AvP was determined by the time-averaged integrated area under the curve at 60°/s angular velocity.

Laboratory measurements

Laboratory data included total testosterone, sex hormone binding globulin (SHBG), fasting and 2 h glucose and insulin levels during OGTT.

Serum total testosterone level was measured by chemiluminescent microparticle immunoassay (CMIA) method (Abbott Diagnostics, GmbH, Co, KG, Germany). Intra-assay and inter-assay coefficient of variability (CV) are calculated as 3.7% and 4.7%, respectively. Serum SHBG level was measured by two-step immunoenzymatic sandwich method (Beckman Coulter, Inc., USA). Intra- assay and inter-assay CV for SHBG are calculated as 4.0% and 6.3%, respectively. Plasma insulin level was measured by a single-step immunoenzymatic method (Beckman Coulter, Inc., USA). The coefficients of intra-assay and inter-assay variation are 4.5% and 5.6%. Plasma glucose was measured by the hexokinase method in AU 5600 (Beckman Coulter, Inc., USA). The coefficients of intra-assay and inter-assay variation are 1.9% and 2.2%.

Bioavailable testosterone (bT) was calculated using the formula of Vermeulen et al. [15] and homeostasis model assessment index-insulin resistance (HOMA-IR) was calculated by the following equation; HOMA-IR = [fasting insulin (μIU/ml) × fasting plasma glucose (mg/dl)/405].

Statistical analysis

Statistical analyses were performed using the IBM SPSS for Mac version 24 program. Numerical variables are summarized with mean, median, standard deviation, minimum and maximum values. Categorical variables are indicated by number and percentage. In the binary comparison of the groups in the study sample, independent sample *t* test (independent two samples *t* test) was used to compare whether the two independent samples were different in terms of a given variable. In addition, the relationship between hormone values and muscle strength analysis results was determined by Pearson correlation analysis. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

Clinical, anthropometric and body composition measurements are shown in Table 1. There were no differences between the patient and control groups for age, BMI, waist, WHR, body fat, lean mass and bone mineral content. Bone mineral density in all regions of the body were also similar between the patients and controls (data not shown).

Hormonal and metabolic features are shown in Table 2. PCOS patients had higher levels of total and bioavailable testosterone, whereas glucose and insulin measurements during OGTT were similar between the two groups. None of the participants had glucose intolerance.

Table 1 Clinical, anthropometric and body composition measurements of women with PCOS and healthy controls

Variable	PCOS ($n=44$)	Control ($n=32$)	p value
Age (years)	21.8 ± 3.2	22.8 ± 3	0.17
BMI (kg/m^2)	26.1 ± 5.4	25.5 ± 5.7	0.63
Waist circumference (cm)	81.8 ± 15	80.5 ± 12	0.67
Hip circumference (cm)	102.7 ± 13.5	103 ± 11.7	0.91
Waist/hip circumference ratio	0.8 ± 0.06	0.78 ± 0.06	0.26
Whole body fat mass (kg)	28.6 ± 11.7	28.7 ± 12	0.97
Lean body mass (kg)	39.6 ± 5.9	37.7 ± 5.4	0.14
Bone mineral content (kg)	2.5 ± 0.4	2.4 ± 0.4	0.51
mFG score	9.7 ± 4.7	1.0 ± 1.0	< 0.01

Data is shown as mean ± SD

PCOS polycystic ovary syndrome, *BMI* body mass index, *mFG* modified Ferriman Gallwey

Table 2 Hormonal and metabolic features of women with PCOS and healthy controls

Variable	PCOS ($n=44$)	Control ($n=32$)	p value
Total testosterone (ng/dl)	61.6 ± 18.6	31.7 ± 7	< 0.01
SHBG (nmol/l)	36.6 ± 24	39.1 ± 16.4	0.59
bT (nmol/l)	0.30 ± 0.20	0.10 ± 0.05	< 0.01
FPG (mg/dl)	84.3 ± 6	85.2 ± 7.4	0.55
Fasting insulin (μIU/ml)	9.9 ± 7.2	7.9 ± 5.8	0.22
Homa-IR	2 ± 1.5	1.6 ± 1.2	0.18
OGTT 2 h glucose (mg/dl)	88.4 ± 17.7	88.4 ± 13.8	0.99
OGTT 2 h insulin (μIU/ml)	40 ± 40.4	40 ± 37.3	0.90

Data is shown as mean ± SD

SHBG sex-hormone binding globulin, *bT* bioavailable testosterone, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model assessment-insulin resistance, *OGTT* oral glucose tolerance test

Comparison of muscle mechanical function between the groups

The normalized values of knee extensor and flexor PT at 60°/s were higher in normal weight individuals compared to overweight–obese individuals (1.5 ± 0.39 vs 1.2 ± 0.42, $p = 0.003$; and 0.7 ± 0.15 vs 0.58 ± 0.32, $p = 0.008$, respectively). These values were similar between patients and controls (Table 3).

The AvP at 60°/s with extension and flexion was significantly higher in PCOS group (Table 3). These measurements were correlated with bT ($r = 0.29$, $p = 0.012$; and $r = 0.36$, $p = 0.001$, respectively) (Fig. 1).

Discussion

In this study, we evaluated muscle mechanical function in PCOS by isokinetic dynamometer which is the current gold standard for the measurement of muscle strength. Our main finding is that the women with PCOS compared to healthy women have higher lower extremity dynamic muscle power that is positively correlated with androgen excess. On the other hand, peak muscle force output is higher in obese women but do not differ between PCOS and controls.

A few studies assessing muscle strength by different methods reported varying results in women with PCOS. The earliest study that looked at hand grip and pinch strength in women with PCOS and controls reported similar strength for all parameters [9]. The diagnosis of PCOS was based on Rotterdam criteria. Even though specific information was not given regarding phenotypes of the syndrome, the average total testosterone level of control group was 0.75 ng/ml suggesting that there were hyperandrogenic women among controls [9]. The study might have failed to detect a difference in strength due to heterogeneity of the PCOS group and presence of hyperandrogenic women in controls. Also, handheld dynamometry test shows some correlations with the gold standard isokinetic dynamometry [16], but it does not seem to be a reliable indicator of global muscle strength and could be affected by many variables including daily activity, individual's work or pathological processes such as carpal tunnel syndrome [17–19].

Table 3 Isokinetic dynamometer analyses in women with PCOS and healthy controls

	PCOS ($n = 44$)	Control ($n = 32$)	p value
Knee extensors			
PT (N m)	94.2 ± 34.8	82.4 ± 21.8	0.09
PT/BW (%)	1.4 ± 0.47	1.28 ± 0.37	0.14
AvP (W)	50.2 ± 21.1	42.1 ± 11.6	0.035
Knee flexors			
PT (N m)	43.6 ± 15.5	39.8 ± 11.1	0.24
PT/BW (%)	0.65 ± 0.21	0.61 ± 0.18	0.37
AvP (W)	35.3 ± 26.9	22.2 ± 11.2	0.005

Data is shown as mean ± SD. Measurements were performed with an angular velocity of 60°/s

PT peak torque (N m): Newton meter, *AvP* average power/W: Watt, *PT/BW* peak torque/body weight

The only previous study that used isokinetic dynamometer included 10 PCOS patients with an average age of 33.6 years and a BMI of 34.1 kg/m^2 and compared with age- and BMI-matched controls [8]. Free androgen index measurements were similar between the groups. In contrast to our findings, this study reported no difference in maximal isometric and isokinetic knee extensor strength between patients and controls. The difference between our results and the results of this study might be due to sample size, patient characteristics including age, BMI and phenotypic features, particularly hyperandrogenism.

Two studies from the same group reported increased muscle strength in PCOS [6, 7]. The first study published in Portuguese included 27 women with PCOS and 28 controls and found increased strength in hand grip, bench press and leg extension in the PCOS group [6]. Expanding their population to 40 patients with PCOS (phenotype A and C) and 40 women with regular cycles (a third having hyperandrogenism), same investigators showed that bench press maximal dynamic muscle strength, leg extension and isometric handgrip strength were greater in patients with PCOS. BMI was associated with all strength measurements whereas androgens were correlated with leg extension only [7]. Our results in patients with classical phenotype using the gold standard isokinetic dynamometer are in line with the results of these previous studies.

Available data in the literature suggest an inverse relation between insulin resistance and muscle strength both in middle-aged and elderly individuals in the setting of metabolic syndrome, obesity and type 2 diabetes [20, 21]. A recent study evaluating middle-aged obese women with metabolic syndrome reported an association of insulin resistance with decline in muscle strength proposing the term "dynapenic obesity" for this phenotype [22]. It is well known that women with PCOS are likely to develop metabolic alterations including insulin resistance and type 2 diabetes as they get older [23]. Accordingly, our finding of increased muscle power in relatively young PCOS patients might not be persistent throughout reproductive age.

The strengths of the current study include enrollment of well-phenotyped patients and controls and use of a technique that is gold standard for the assessment of muscle mechanical function in the clinical setting. Another strength is assessment of both muscle power and strength which gives information about muscle performance from different aspects. However, some limitations should be noted. First,

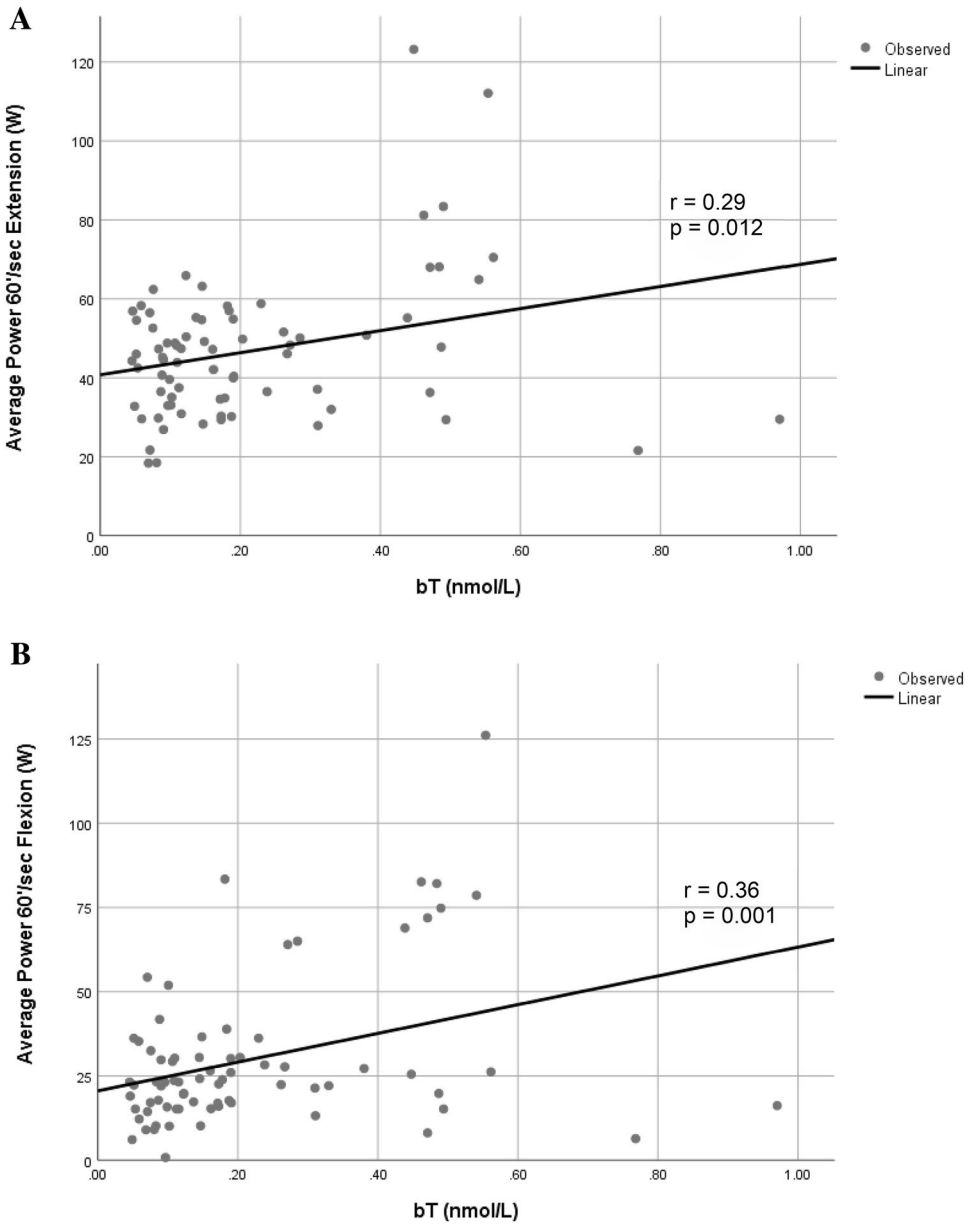

Fig. 1 Correlations of bioavailable testosterone (bT) with average power 60°/s extension (**a**) and flexion (**b**)

cross-sectional design of the study precludes making causal inferences. Second, we have included only patients with all three features of the syndrome (phenotype A) and, therefore, our findings might not be applicable for other phenotypes of the syndrome, particularly for non-hyperandrogenic women. Third, our patients were sedentary and had an average BMI of 26 kg/m^2. Thus, the study is unable to provide information regarding muscle mechanical function in physically active or morbidly obese women with PCOS.

In conclusion, our results suggest an increased muscle power associated with hyperandrogenism and unaltered peak muscle torque in women with PCOS. Evaluation of muscle strength might be relevant in designing effective and adequate exercise protocols for the long-term management of the syndrome in addition to medical therapy. Studies investigating the relationship between muscle mechanical function and muscle tissue function are needed to clarify potential involvement of altered muscle mechanical function in pathophysiology of PCOS.

Author contributions ECG: data collection and analysis, manuscript writing. DE: data collection and analysis. ST: data collection and analysis. FA: data collection. OP: data collection and analysis. HD: protocol development and manuscript writing. BOY: protocol development and manuscript writing. All authors reviewed the manuscript.

Data availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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