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Metabolic status is not related to dietary acid load in polycystic ovary syndrome

Polikistik over sendromunda metabolik durum diyet asit yükü ile ilişkili değildir

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ABSTRACT

AIM:

Women with polycystic ovary syndrome (PCOS) are at high risk for obesity-related disorders, insulin resistance (IR), and metabolic syndrome (MS). Adopting potent approaches to diet enhances cardiometabolic risk profile and reproductive function. Different types of diets have provided conflicting results so far. We aimed to investigate whether dietary acid load (DAL) contributed to the metabolic process in PCOS.

MATERİAL AND METHOD:

This study included 46 newly diagnosed PCOS patients and 46 healthy individuals with matched age, sex, and BMI. Clinical, anthropometric, and biochemical measurements were obtained. We extracted net endogenous acid production (NEAP) and potential renal acid load (PRAL) scores from 24-hour dietary data recorded on a nutrient database program for three days (BeBiS software program).

RESULTS:

We concluded no statistically significant difference between the groups by NEAP (p=0.569) and PRAL (p=0.969).Patients with PCOS had higher fasting insulin levels and HOMA-IR (p<0.001 and p<0.001 respectively.); however, fasting serum glucose and HbA1c levels were similar (p=0.077 and p=0.859, respectively). Both NEAP and PRAL presented positive correlations with waist circumference (WC) (r=.236, p=0.023 and r=.290, p=0.005), hip circumference (HC) (r=.229, p=0.028 and r=.241, p=0.021), respectively. PRAL negatively correlated with total testosterone(r=-.383, p<0.001), while NEAP did not (r=-0.135, p=0.218).

CONCLUSION:

We concluded that the PCOS patients and healthy controls had similar diets in acid load. Both NEAP and PRAL were associated with WC, HC. In addition, there was a positive correlation between PRAL and BMI and negative correlation with total testosterone. The results presented no significant association between DAL and IR.

Keywords:

Polycystic ovary syndrome; insulin resistance; dietary acid load; potential renal acid load; net endogenous acid production.

ÖZET

AMAÇ:

Polikistik over sendromlu (PKOS) kadınlar obezite ile ilişkili hastalıklar, insülin direnci (İD) ve metabolik sendrom (MS) açısından yüksek risk altındadır. Güçlü diyet yaklaşımlarının benimsenmesi, kardiyometabolik risk profili ve fertilite işlevini geliştirir. Bugüne kadar farklı diyet türleri çelişkili sonuçlar sunmuştur. Biz de diyet asit yükünün (DAL) PKOS'ta metabolik sürece katkıda bulunup bulunmadığını araştırmayı amaçladık.

GEREÇ VE YÖNTEM:

Bu çalışmaya yeni tanı konmuş 46 PKOS hastası ve aynı yaş, cinsiyet ve VKİ'ye sahip 46 sağlıklı birey dahil edildi. Klinik, antropometrik ve biyokimyasal ölçümleri alındı. Net endojen asit üretimi (NEAP) ve potansiyel renal asit yükü (PRAL) skorlarını, üç gün boyunca (BeBiS yazılım programı) bir besin veri tabanı programında kaydedilen 24 saatlik diyet verilerinden hesapladık.

BULGULAR:

NEAP (p=0,569) ve PRAL (p=0,969) açısından gruplar arasında istatistiksel olarak anlamlı bir fark olmadığı sonucuna vardık. PKOS'lu hastaların açlık insülin düzeyleri ve HOMA-IR düzeyleri daha yüksekti (sırasıyla p<0,001 ve p<0,001); ancak açlık serum glukozu ve HbA1c seviyeleri benzerdi (sırasıyla p=0.077 ve p=0.859). Hem NEAP hem de PRAL, bel çevresi (BÇ) (r=.236, p=0.023 ve r=.290, p=0.005), kalça çevresi (KÇ) (r=.229, p=0.028 ve r=.241, p=0.021) ile pozitif korelasyon gösterdi, sırasıyla. PRAL toplam testosteron ile negatif korelasyon gösterirken (r=-.383, p<0.001) NEAP göstermedi (r=-0.135, p=0.218).

SONUÇ:

PKOS hastaları ile sağlıklı kontrollerin asit yükü açısından benzer diyetleri olduğu sonucuna vardık. Hem NEAP hem de PRAL, BÇ, KÇ ile ilişkilendirildi. Ayrıca PRAL ve VKİ arasında pozitif, total testosteron ile negatif korelasyon vardı. Sonuçlar, DAL ile İR arasında anlamlı bir ilişki olmadığını gösterdi.

Anahtar Kelimeler:

Polikistik over sendromu; insülin direnci; diyet asit yükü; potansiyel renal asit yükü; net endojen asit üretimi.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the leading endocrine disorder in women of reproductive age and involves about 5–15% of such women.1 It is characterized by clinical or biochemical hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology and the diagnosis requires at least two of these features.2 Its etiopathogenesis is largely unknown but now is accepted to be caused by both genetic and environmental influences.3

PCOS is manifested by hyperandrogenism (including acne, hirsutism and male pattern alopecia) and reproductive dysfunction (including oligo-amenorrhea and subfertility).4 and is also shown to be linked with abnormalities in the metabolism (e.g., type 2 diabetes (T2DM), dyslipidemia, obesity, and atherosclerotic heart disease).5

It is known that there is a close relationship between obesity and PCOS. In epidemiological studies, 38-88% of women with PCOS were shown to be overweight or obese.6 Although PCOS is associated with insulin resistance (IR) independently of obesity, it increases the degree and prevalence of obesity .6 Compensatory hyperinsulinemia occurs in approximately 70% of the patients and exacerbates the symptoms.7 Hyperinsulinemia promotes ovarian hyperandrogenism (mainly ovarian synthesis and release of androgens) in 60-80% of women with PCOS.8 Also, PCOS is closely related to factors such as T2DM, impaired glucose tolerance, nonalcoholic fatty liver disease (NAFLD), dyslipidemia, hypertension (HT), atherosclerosis, and obstructive sleep apnea syndrome, which predispose to cardiovascular disease development.9 Strategies to reduce IR constitute an essential part of the treatment to improve symptoms and reproductive abilities and prevent the development of metabolic complications.

It may be challenging for women with PCOS to lose the weight they have gained.10 Evidence-based guidelines recommend weight management (combination of diet, exercise, and behavior modification) through lifestyle modification as first-line therapy. Due to probable interactions between foodstuff, nutritionists prefer to approach diet holistically rather than evaluating individual foods. Dietary acid load (DAL) is among the indices used to evaluate the whole diet.

Many studies investigating the effects of the Western diet highlighted the place of dietary low-grade metabolic acidosis in the pathogenesis of metabolic diseases.11 Diet can alter acid-base stability in the body due to the content of acid precursors (e.g., sulfuric acid) or base precursors (e.g., citrate and bicarbonate).12 While foods containing sulfate and phosphorus (fish, meat, cheese, rice, and cereals) contribute to the acid load 12, foods rich in magnesium, potassium, bicarbonate, and calcium (fruits, vegetables, legumes, and potato) elevate the alkaline load.12 DAL is estimated by calculating net endogenous acid production (NEAP) and potential renal acid load (PRAL) based on the magnesium, protein, calcium, potassium, and phosphorus content in foods.13 The increase of NEAP and PRAL is shown to be linked with the elevated acid load.14

Various studies investigating the relationship between the likelihood of chronic disease and DAL reveal that following a diet with high acidifying potential may boost the risk of obesity 15, HT 16, diabetes 17, hyperlipidemia 18, NAFLD 19, chronic kidney disease 20 and cardiovascular death.13 However, some studies failed to establish a relationship between DAL and fasting blood sugar , triglyceride (TG), and high-density lipoprotein (HDL-C).18,21

To the best of our knowledge, there is no study in the literature investigating the relationship between PCOS and DAL. Considering that nutritional parameters may also be effective in the emergence of many metabolic disorders in addition to genetic predisposition in PCOS, we hypothesized that the metabolic state is affected by DAL in PCOS. Therefore, we aimed to investigate whether DAL contributed to the metabolic process in women with PCOS.

MATERIAL AND METHOD

Study population

The study included a total of 92 participants aged 18-40, 46 of whom were newly diagnosed with PCOS by modified Rotterdam criteria. Diagnosis requires at least two of the three criteria for chronic ovulatory dysfunction, hyperandrogenism, or polycystic-appearing ovaries.2 Ovulatory dysfunction was defined as persistent anovulatory menstruation shown by mid-luteal serum progesterone of <3 ng/mL or ≤8 bleeding within a year or intermenstrual interval of ≥ 45 days. Hyperandrogenism has been defined as clinical hirsutism by a modified Ferriman-Gallwey Score (mFGS) ≥ 6 or a center-specific high serum testosterone (T) value. Polycystic appearance was determined by the presence of 12 or more antral follicles of 2-9 mm or an enlarged ovarian volume (≥ 10 cm3) on transabdominal ultrasound. We excluded other disorders mimicking PCOS with the help of 1 mg dexamethasone suppression and 17-hydroxyprogesterone tests and measurements of thyrotropin (TSH) and prolactin.

We recruited the remaining 46 subjects with regular menstruation and no hirsutism in the healthy control group. None of the participants had any known chronic illness or medication use.

Compliant with the Declaration of Helsinki, Ankara Training and Research Hospital Ethical Committee provided the study with ethical approval (No.E-93471371-514.10) and we obtained written informed consent from each participant.

Anthropomorphic Measurements and Serum Testing

We reviewed the medical histories of the participants thoroughly and examined the participants physically. We measured height using an unstretched meter with participants standing upright in a normal position. We measured weight with a portable digital scale (Tanita TBF-300 model). Body mass index (BMI) was calculated by dividing body weight (in kilograms) by the square of height. We measured waist circumference (WC) at navel level with a single layer of light clothing. Also we measured the hip circumference (HC) by measuring the distance around the widest part of the hip.

We assessed hirsutism using mFGS.22 We followed the procedure below for biochemical analyses of fasting blood samples. We calculated insulin and glucose levels by chemiluminescent method with Beckman Coulter DXI 800 immunoassay analyzer (Beckman Coulter Inc., Brea, CA) and a colorimetric method with Beckman Coulter AU 860 (Beckman Coulter Inc., Brea, CA), respectively. We calculated the homeostasis model (HOMA-IR) using the equation (HOMA-IR = fasting glucose (mg/dL) × fasting insulin (mIU/mL) / 405) and accepted a cutoff of ≥ 2.5 as IR.23 We measured TG, total cholesterol (CHOL-C), and HDL-C spectrophotometrically using the Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea, CA) instrument. Finally, we determined LDL cholesterol (LDL-C) with Friedewald's equation method.

Total testosterone (TT) and Dehydroepiandrostenedione sulfate (DHEA-S) were analyzed by electrochemiluminescence immunoassay method (Cobas E601; Roche Diagnostics GmbH, Mannheim, Germany).

Dietary assessment and definition of DAL

We asked the participants to keep a record of the amount of food they consumed for three consecutive days. The days had to include two weekdays and one weekend day with usual eating habits. The same dietician gave both written and verbal instructions to the participants on how to weigh and record the daily food consumption. We extracted PRAL and NEAP scores of 24-hour dietary records from a licensed nutrient database program (BeBiS software program).

We calculated PRAL scores using the algorithm of Remer et al 24 :

PRAL (mEq/day) =[0.4888 x protein (g/day) +0.0366 x phosphorus (mg/day) - 0.0205 x potassium (mg/day) – 0.0125 x calcium (mg/day) – 0.0263 x magnesium (mg/day)]

In addition, we obtained NEAP scores following the algorithm below 25 :

NEAP (mEq/day)= [54.5 x protein (g/day) / potassium (mEq/day)] – 10.2

Data Analysis

We utilized IBM SPSS version 25 for all statistical analyses in the study. The Kolmogorov–Smirnov test helped us to check whether continuous variables showed a normal distribution. We presented the results as median and interquartile ranges (IQ). We ran the Mann-Whitney U test to compare groups. We sought correlations between the variables using Pearson's or Spearman's rank correlation coefficients. P-value below 0.05 was accepted as significant in all

statistical analyses.

RESULTS

The mean ages and body mass indices were not different between the groups. Table 1

Table 1. Baseline characteristics, hormonal and metabolic features of all participants

	PCOS (n:46) median (IQR)	Control group (n:46) median (IQR)	*P*
Age (y)	24(21-29.5)	25.5(22-30)	0.294
BMI (kg/m^2)	27.2(23.8-30.6)	24(20.8-29)	0.056
WC (cm)	92(84-100.3)	83.5(77.5-95.3)	**0.027**
HC (cm)	108(101.8-116)	103.5(94.5-110)	**0.032**
Body fat percentage (%)	33.8(28.2-39.6)	29.4(20.6-36.3)	**0.018**
Whole body fat mass (kg)	23.9(17.7-32.7)	18.9(10.3-26.4)	**0.026**
Lean body mass (kg)	47.4(44.4-49.9)	44.7(41.1-48.5)	**0.045**
FSG (mg/dL)	92(86-97)	87.5(83-94.3)	0.077
Fasting serum insulin (mIU/L)	14.7(10.2-21.4)	9.4(6.9-12.5)	**<0.001**
HOMA-IR	3.3(2.1-4.9)	2.1(1.4-2.9)	**<0.001**
HbA1c (%)	5.4(5.2-5.5)	5.4(5.3-5.6)	0.859
ALT (U/L)	16(12.5-24.5)	12(9.8-16.3)	**0.002**
AST (U/L)	17(13.5-20)	16(14-18)	0.400
GGT (U/L)	14(11-17)	12(8.8-14)	**0.008**
eGFR (mL/ min/1.73 m2)	120(109.5-125)	122.5(113-126)	0.494
CHOL-C (mg/dL)	170(147.3-196.5)	157(135.8-182.5)	0.089
HDL-C(mg/dL)	54(46-64)	53(47-64)	0.622
LDL-C (mg/dL)	93.5(75.3-108.8)	81(71.8-104.5)	0.201
TG-C (mg/dL)	95.5(69-132.8)	80(57.5-106)	0.051
TSH (mIU/ml)	2.2(1.5-2.8)	2.1(1.6-2.7)	0.812
TT (ng/dL)	41.9(28.8-59.7)	28(14.6-40.1)	**<0.001**
DHEA-S (µg/dL)	290.9(211.3-422)	271.2(171.1-345.9)	**0.048**
NEAP (mEq/day)	47.6(36.9-57.2)	46.1(35.9-54.7)	0.569
PRAL (mEq/day)	5.7328(-1.3-13.6)	4.9(-1.8-12.7)	0.969

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; FSG: Fasting serum glucose; HOMA IR: homeostasis model assessment -insulin resistance; HbA1c: Glycated hemoglobin A1c; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; eGFR: Estimated glomerular filtration rate; CHOL -C: Total Cholesterol; HDL -C: High-density lipoprotein; LDL -C: Low-density lipoprotein; TG-C: Triglyceride; TSH: Thyrotropin;TT: Total testosterone; DHEA -S: Dehydroepiandrosterone s ulfate; NEAP: Net endogenous acid production; PRAL: Potential renal acid load.
p<0.05 denoted as statistically significant (in bold).

outlines the clinical characteristics and biochemical data of the groups. We reached no statistically significant difference between the groups by NEAP (p= 0.569) and PRAL(p= 0.969). Besides, we found PRAL to correlate with NEAP positively (r= .949, p <0.001).

As expected, fasting insulin levels and HOMA-IR were detected significantly higher in patients with PCOS than in the control group (p<0.001 and p<0.001, respectively). Nevertheless, FSG and HbA1c values were similar (p= 0.077 and p= 0.859, respectively).

Table 2

Table 2. Correlations between NEAP, PRAL and metabolic parameters and steroid hormones in participants

	NEAP *r*	NEAP *p*	PRAL *r*	PRAL *p*
Age (y)	0.179	0.088	0.179	0.088
BMI (kg/m^2)	0.194	0.063	.274*	**0.008**
WC (cm)	.236	**0.023**	.290*	**0.005**
HC (cm)	.229	**0.028**	.241	**0.021**
Bodyfat percentage (%)	.238	**0.022**	.289*	**0.005**
Whole body fat mass (k	.249	**0.016**	.287*	**0.006**
Lean body mass (kg)	.273*	**0.009**	.293*	**0.005**
FSG (mg/dL)	0.123	0.246	0.175	0.097
Fasting serum insulin (mIU/L)	0.103	0.332	-0.084	0.428
HOMA-IR	0.127	0.229	-0.069	0.516
HbA1c (%)	0.117	0.276	.383*	**<0.001**
ALT (U/L)	0.206	0.051	-0.049	0.641
AST (U/L)	0.106	0.319	-0.167	0.113
GGT (U/L)	.292*	**0.005**	.241	**0.022**
eGFR (mL/ min/1.73 m	-0.193	0.066	-.329*	**0.001**
CHOL-C (mg/dL)	-0.104	0.329	-0.053	0.617
HDL-C(mg/dL)	-0.026	0.808	0.055	0.607
LDL-C (mg/dL)	-0.074	0.486	-0.047	0.658
TG-C (mg/dL)	-0.035	0.747	0.135	0.205
TSH(mIU/ml)	0.145	0.170	0.165	0.118
TT (ng/dL)	-0.135	0.218	-.383*	**<0.001**
Free T (ng/dl)	0.099	0.516	-0.122	0.425
DHEAS (µg/dL)	-0.146	0.178	-0.128	0.239
NEAP (mEq/day)	1		.949*	**<0.001**
PRAL (mEq/day)	.949*	**<0.001**	1.000	

*Correlation is significant at the 0.05 level
**Significant when p<0.01

presents the correlations of NEAP and PRAL with the specified parameters. Both NEAP and PRAL showed positive correlations with WC (r= .236, p= 0.023 and r= .290, p= 0.005), HC (r= .229, p= 0.028 and r= .241, p= 0.021), whole body fat mass (r= .249, p= 0.016 and r= .287, p= 0.006), lean body mass (r= .273, p= 0.009 and r= .293, p= 0,005). Also PRAL was positively correlated with BMI (r=0.274, p=0.008) while NEAP was not (r= 0.194, p=0.063). While both NEAP and PRAL did not correlate with aminotransferases, they positively correlated with GGT (r= .292, p= 0.005 and r= .241, p= 0.022, respectively).PRAL negatively correlated with TT (r= -.383, p<0.001), whereas NEAP did not (r= -0.135, p= 0.218).

DISCUSSION

To the best of our knowledge, our study is the first in the literature to have evaluated the association between metabolic indices and DAL in adults with PCOS. We concluded a positive and robust relationship between NEAP and PRAL. Nonetheless, we could determine no significant correlation between NEAP and PRAL and age, FSG, fasting serum insulin, HOMA-IR, aminotransferases, cholesterols, TG, and DHEA-S. On the other hand, we found positive correlations between NEAP and PRAL and WC, HC, whole-body fat mass, lean body mass, and GGT, while there was a positive correlation between PRAL and BMI and HbA1c but negative correlation with TT.

Manifesting the impacts of eating on body acid-base status, DAL is a rather new diet concept. Two indices that are used to predict DAL from dietary intake are PRAL and NEAP.18 Previously, several potential underlying mechanisms were suggested to clarify the relationship between metabolic disturbances and DAL. It was proposed that the association between IR and high DAL was led by excessive administration of calcium and magnesium in urine, increased cortisol, decreased urinary citrate excretion, and increased fatty acid oxidation and organic acid production, which can be reversed with the help of high vegetable and fruit consumption.26 It was also revealed that acidogenic diets were linked with elevated weight gain and obesity.

PCOS is commonly characterized by obesity, particularly visceral origin, which remarkably influences both cardiometabolic and reproductive functions in patients. In a comprehensive meta-analysis, the prevalence of obesity in women with PCOS was found to be 49% 27. PCOS also leads to IR, known as impaired response to endogenous and exogenous insulin.28 Although its mechanism in PCOS has not been fully elucidated, the latent defect has previously been reported to occur in the post-receptor phosphatidylinositol 3-kinase (PI3-K) insulin pathway.6 Increased plasma T levels (both in adulthood and prenatal period) and increased androgen receptor sensitivity may contribute to the development of IR.29 In addition, suppressed serum adiponectin levels may further contribute to its development.30 PCOS is shown to be related to IR, independent of obesity; however, obesity enormously boosts its prevalence and degree.6 In our study, although BMIs were matched between the PCOS and control groups, there was a significant difference between the groups by HOMA-IR and fasting insulin levels, and, as expected, they were higher in the PCOS group.

Increased IR and metabolic dysfunction are likely via hepatic and visceral fat in women with PCOS. In a study by Kucharska AM et al, the prevalence of BMI and WC was higher in the highest quintile of NEAP.31 Although Murakami K et al. reported higher WC in the highest quintile of PRAL among Japanese adults; yet, they have not found any significant difference in BMI.18 However, some studies did not note any relationship between DAL and central and general obesity indices. According to a large meta-analysis, higher PRAL scores were correlated with higher prevalence of obesity in females, whereas this was the case when males had higher NEAP scores.15

A positive correlation was observed between PRAL and BMI in our study. The similarity of BMI between the groups may explain the lack of difference between these groups by NEAP and PRAL; otherwise, we would expect these parameters to be high in the PCOS group. However, we found a significant difference between the groups in terms of WC, which is responsible for visceral adiposity and IR, favoring the PCOS group. Moreover, we reached positive correlations between WC and HC and NEAP and PRAL. In the study of Akter et al., there was no

relationship between DAL and HbA1c and FSG values.11 Also, in a review, DAL was found to have no relationship with FSG, HbA1c, serum insulin and HOMA-IR.34 However, some studies, which evaluated the dietary intakes only by diet history surveys and FFQ, reached a significant direct association between DAL and HbA1c and FSG values. In our study, there was no difference in fasting blood glucose and HbA1c values between the two groups. Nevertheless, we could not establish any correlations between NEAP and PRAL and fasting blood glucose and HOMA-IR values, although PRAL positively correlated with HbA1c.
Previously, it was shown that high DAL only reduces lean body mass in women, eventually resulting in increased body fat synthesis. Besides, alkali-rich diets have been reported to be associated with excess skeletal muscle mass in women. Women with PCOS have elevated an increased number of visceral adipose tissues and global adiposity, particularly in mesenteric and intraperitoneal stores. In addition, mesenteric fat thickness and fasting insulin were found to be independent determinants of fatty liver in patients with PCOS. In our study, we did not find any difference between the groups in terms of BMI. Yet, we found a significant difference between the groups by lean mass and fat mass, which were both higher in the PCOS group. Interestingly, both NEAP and PRAL positively correlated with both masses.

Early diagnosis of NAFLD is important because it can occur at earlier ages in PCOS patients. In addition, more histological NAFLD is seen in PCOS patients than women with similar laboratory profiles and clinics Because liver biopsy is not feasible and cost-effective, it is needed to optimize non-invasive tests. Ultrasound should usually be evaluated together with aminotransferase levels to detect NAFLD. What needs to be investigated is to determine the abnormal upper limit of the aminotransferase value. In our study, there were significant differences in GGT and ALT between the two groups, while there was no difference in AST. In addition, there was no correlation between both NEAP and PRAL and both ALT and AST, except for GGT.

In accordance with the role of IR in pathophysiology, women with PCOS are known to have a higher prevalence of metabolic syndrome (MS). In a meta-analysis, the number of PCOS subjects was reported to be three times higher regarding MS prevalence in BMI-matched studies. Atherogenic dyslipidemia, a vital component of MS, is a widespread metabolic disorder in PCOS. Androgen excess is shown to produce more atherogenic LDL-C particles in the early stages of PCOS development. Regardless of BMI, the lipid profile in women with PCOS includes high TG, normal or elevated total and LDL-C concentrations, and reduced HDL-C levels. Women with PCOS need to be recruited for CVD risk assessment at all ages to detect their glucose levels, lipid profile, blood pressure, WC, physical activity, nutrition, and smoking. The previous studies revealed a positive relationship between DAL and TG, CHOL-C and LDL-C; nevertheless, it correlated with HDL-C inversely. The underlying mechanisms of why higher PRAL scores are linked with increased TG concentrations are not well suggested, but a few proposed mechanisms may be impaired insulin sensitivity and increased cortisol secretion. In our study, there were no differences in total and LDL-C, HDL-C, and TG between the groups, and these parameters did not correlate with NEAP and PRAL.

Androgens may carry IR with direct effects on skeletal muscle and adipose tissue by altering adipokine secretion and increasing visceral adiposity. mTORC1 should be considered as an important point in cell signaling as it integrates many intracellular and extracellular signals such as growth factors (insulin, IGF-1), energy sensing signals (glucose, AMP/ATP regulating the ratio).40 T increases the phosphorylation of mTOR , which may be shown as the most crucial system to induce IR. The Western diet provides ample glucose, fat and energy to suppress AMPK activity, which increases mTORC1 signaling. Metformin inhibits mTORC1 activity by antagonizing both leucine-mediated activation of mTORC1 and AMPK-mediated suppression of mTORC1 activity.42 The literature informs that using insulin-sensitizing drugs, such as metformin and thiazolidinediones, to reduce insulin levels can lower circulating androgen levels and increase SHBG levels, which may lead to the restoration of ovulation menstrual cycles in patients with PCOS.43 Dietary management is critical in the follow-up of patients with PCOS in terms of the relationship between both androgens and IR. Although we found a significant difference between the groups in terms of TT and DHEA-S in our study, we could not find significant relationship between these parameters and NEAP and PRAL. Moreover, there was no correlation between both TT and DHEA-S and fasting blood glucose and BMI, while fasting insulin significantly correlated with DHEA-S but not with TT.

Recent studies investigating the relationship between PCOS and compositional differences in the gut microbiome suggest that there are various changes in microbiota characteristics that may be associated with the disease state. While circulating metabolites associated with the gut microbiota and lipopolysaccharides leaking from the gut barrier may cause hyperandrogenism; Prenatal androgen exposure is associated with gut microbial dysbiosis, suggesting a bidirectional interaction between androgens and gut microbiota. Although the close relationship of nutrition with microbiota is well known, the effect of improvement in hyperandrogenic state in patients with PCOS and the effects of any therapeutic approach on gut microbial composition are still unknown.44 Guzelce et al. showed that muscle mechanical function is altered in PCOS and mean lower extremity strength is increased in women with PCOS, which is associated with hyperandrogenism and possibly nutrition. However, we did not focus on this issue in our study.45

Our study has several limitations and strengths, in particular being a cross-sectional study with a small sample size. Evidence has shown that both systolic and diastolic blood pressures are significantly increased in PCOS patients 46, and DAL was associated with HT. Besides, we did not record the patients' blood pressure, which is a component of MS, in our study. The food frequency questionnaire covers various dietary components and emphasizes regular intake over a short period of time, giving more accurate results than the 24-hour recall method. However, we used the 24-hour dietary record system for three days instead of the FFQ. Better results would have been provided if the study employed an interventional design.

In conclusion, PCOS is a common disease often associated with endocrine, metabolic and reproductive disorders. Metabolic complications lead to dyslipidemia, HT, more severe obesity, diabetes, and cardiovascular diseases, which are mainly associated with hyperinsulinemia. Numerous preventive actions and therapeutic options for the treatment of hyperinsulinemia and IR have failed to gain clinical relevance so far.

Our study is remarkable for being the first study evaluating the relationship between DAL with a number of obesity-related parameters in patients with PCOS. In this study, we found no difference between patients with PCOS and healthy individuals in terms of NEAP and PRAL, which were calculated from their dietary records. NEAP and PRAL correlated to each other strongly and positively. Also, we found positive correlations between NEAP and PRAL and WC, HC, lean body mass, whole-body fat mass and GGT and between PRAL and BMI and TT. Nevertheless, the results indicated no significant association between DAL and fasting blood glucose, IR, and lipid profiles.

Even a five percent weight loss in PCOS provides significant improvements in symptoms, hormonal profile, and metabolic risk. Reducing calorie intake alone is not enough to be successful in weight loss, and dietary content regulation is an integral part of disease management. The results of significant weight loss and changes to metabolic/hormonal parameters are contradictory in studies conducted with different diet types in PCOS. Although diets reducing metabolic risks and focusing on dietary acid content have recently come to the fore, the primary therapeutic approach is a lifestyle change. In this study, we could not prove the importance of DAL in patients with PCOS; therefore, the issue needs to be clarified with future randomized and controlled intervention studies.

Author's Contribution
TO established the conception and design of the study and were involved in the data collection. FHZ entered dietary records in the nutritional database program. TO led the data analysis. SA and CC assisted with the statistical analysis and interpretation of data. TO wrote the initial draft of the manuscript. All authors approved the final version of the manuscript submitted for publication.
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Conflict of interest
The authors declare no conflicts of interest.

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