

Nutritional support and dietary interventions for women with polycystic ovary syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in reproductive-aged women, which leads to reproductive, metabolic and hormonal abnormalities. Hyperinsulinemia, insulin resistance, androgen excess, ovulatory dysfunction, polycystic ovaries, gonadotropin abnormalities, obesity, adipose tissue dysfunction, difficulty to conceive and high-risk pregnancy are the most common PCOS-associated complications. The aim of this review was to describe and evaluate the effects of dietary interventions on PCOS-associated outcomes and to provide some evidence-based dietary advice for use in clinical practice. There is no optimal diet or macronutrient composition for PCOS. However, lifestyle modification, including a small-to-moderate weight loss of 5–10% (combined diet with regular physical activity) with any dietary pattern of choice, depending on the individuals' preferences, culture, habits and metabolic needs (ie, Mediterranean diet, Dietary Approaches to Stop Hypertension [DASH] diet or moderately low-carbohydrate diets [30–45% of energy]), as well as alternative dietary interventions, including small, frequent meal (five to six meals daily) consumption at regular times, with the majority of carbohydrates consumed at lunch time or equally distributed throughout the day, seems to offer the evidence-based first-line strategy for the management of PCOS symptoms and insulin resistance. No conclusions can be drawn at this time for high protein diets, polyunsaturated fatty acids or micronutrient supplementation.

Keywords: nutrition, meal frequency, dietary strategies, insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder in reproductive-aged women with a prevalence from 4% up to 18%, is the most common cause of infertility and is associated with reproductive, metabolic and hormonal dysfunction and higher association of pregnancy complications.^{1–8} Women with PCOS with menstrual irregularities, related to anovulation, may have difficulties to conceive.⁵ The majority of women with PCOS have hyperinsulinemia and insulin resistance (IR), which have a significant role in the pathogenesis of the syndrome and in the long run may lead to impairment of glucose metabolism, androgen excess with hyperandrogenic symptoms, gonadotropin abnormalities, ovulatory dysfunction and polycystic ovaries, higher intra-abdominal fat and adipose tissue dysfunction, independently of body mass index (BMI).^{5,9–18}

Women with PCOS usually weigh more than women without PCOS, and many studies show that more than half of women with PCOS are found to be obese and tend to gain more weight longitudinally compared to women without PCOS.^{5,19–22}

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However, despite the fact that the majority of women with PCOS are overweight or obese, many lean women with PCOS are also considered to be at increased risk for metabolic disturbances.^{23,24} Central obesity, race and age are positively associated with IR.^{14,25,26} Central obesity and excess body fat exacerbate IR, dyslipidemia and hormonal dysfunction.^{5,26–29} Moreover, women with PCOS have increased risk of metabolic syndrome, gestational diabetes, type 2 diabetes and cardiovascular diseases.^{8,22,26,29,31–33}

The main cause of infertility in women with PCOS is anovulation, whereas obesity seems to exacerbate symptoms and reduces conceiving rates.^{5,30} Some of the mechanisms involved in infertility may be ovarian hyperandrogenism, including luteinizing hormone (LH) hypersecretion, relative follicle-stimulating hormone (FSH) insufficiency, hyperinsulinemia and high anti-Mullerian hormone (AMH) inhibiting aromatase activity.⁵ Some adipokines secreted by adipose tissue may also be involved in obesity-mediated infertility, including low levels of adiponectin, related to androgen excess, and increased visfatin levels, related to glucose dysmetabolism.^{5,16} Leptin, resistin and retinol-binding protein 4 do not seem to play a significant role in PCOS with obesity-related infecundity.^{5,16} However, leptin is positively associated with BMI and LH, but not insulin, in women with PCOS.³⁴

Diet and its effect on metabolic outcomes should be more thoroughly examined in women with PCOS. Women with PCOS seem to have a greater appetite, consume more energy-dense high glycemic index (GI) foods and saturated fat, have inadequate fiber intake and have low scores for PCOS-related quality of life, although their overall energy intake, physical activity and resting metabolic rate are similar to controls.^{21,35–37}

Reduction in IR has been suggested as the principal goal of PCOS treatment. Lifestyle changes (diet plus physical activity), along with weight loss (5–10%), are proposed as the first-line strategy for amelioration of IR, ovulatory function and decreased free testosterone levels in women with PCOS.^{38–45} Trunk fat, waist circumference (WC) and BMI are the best predictors of IR in PCOS.⁴⁶ Other dietary interventions, including carbohydrate distribution, meal frequency and timing, adequate intake of n-3 fatty acids and/or vitamin D supplementation, have been suggested to offer some additional benefits for markers of glucose and energy metabolism and reproductive hormonal regulation. In this review, we discuss nutritional support and dietary interventions for women with PCOS and attempt to derive to some evidence based conclusions for use in clinical practice. Tables 1 and 2 summarize the dietary interventions for women with PCOS.

Table 1 Effects of nutritional support and dietary interventions for women with PCOS

Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Dietary interventions with varying macronutrient composition and dietary patterns						
Marzouk and Sayed Ahmed ⁷⁷	17–24 36.0±4.7/35.8±4.8	6 months RCT	60	Weight loss group Control group	Deficit of 500 kcal/day 15–20% PRO 50–55% CHO 30% FAT 15–20% PRO 50–55% CHO 30% FAT	Significant reduction: BMI (–2.8 kg/m ²) WC (–7.8 cm) Hirsutism (modified FG score, –4.2)
Wong et al ⁸⁶	15.4±1.3/16.3±2.2 36.2±5.3/33.9±4.7	6 months RCT	16	LGL diet LF diet	20% PRO 45% CHO 35% FAT low-GI sources of carbohydrates 20% PRO 55%CHO 25% FAT	Decreased in both groups: BMI percentile (–1.7±0.7) Body fat percentage (–1.0±0.7%) Trunk fat (–1.1±0.7 kg) The decrease in BMI percentile was greater for the LF group (–2.0±0.6) compared to LGL group (–0.4±0.1)

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Table I (Continued)

Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Barr et al ⁹⁵	31.5±6.9 29.0±5.9	36 weeks Nonrandomized clinical trial	21	Control phase (weeks 0–12) LGI dietary intervention phase (weeks 12–24) Follow-up phase (weeks 24–36)	Following their habitual diet Replace high-GI and medium-GI foods with LGI foods No dietary intervention or support	The LGI diet resulted in: Increased insulin sensitivity Decreased NEFAs Small reduction in HDL
Mehrabani et al ⁸³	28.5±5.2/30.5±6.4 31.1±4.6/31.9±4.0	3 months RCT	49	CHCD MHCD	Deficit of 500– 1000 kcal 15% PRO 55% CHO 30% FAT Deficit of 500– 1000 kcal 40% CHO low and medium GL 30% PRO 30% FAT Limitation of high glycemic foods	Both hypocaloric diets led to equal changes in: BW (CHCD: –3.3±0.62%, MHCD: –4.1±0.58%) LDL-C (CHCD: –23.7±13.8%, MHCD: 25.5±10.5%) DHEAS (CHCD: –32.0±8.9 ng/mL, MHCD: –42.1±16.1 ng/mL) SHBG (CHCD: 10.6±4.1 nmol/L, MHCD: 8.8±2.8 nmol/L) MHCD induced concomitant reductions in: Insulin (–3.6±0.7 mIU/L) HOMA-IR (–0.8±0.2) hsCRP (–0.9±0.4 mg/L) LGI diet improved post- OGTT insulin sensitivity Subjects on LGI diet who were prescribed metformin therapy achieved greater improvements in insulin sensitivity compared to those on LGI diet not on metformin More women who consumed the LGI diet showed improved menstrual cyclicity (95% compared to 63%) Serum fibrinogen concentrations showed significant differences between diets (LGI: –0.2±0.1 g/L compared to CHD: 0.2±0.1 g/L)
Marsh et al ⁷⁹	31.0±0.7/29.3±0.8 34.3±1.0/34.7±0.9	12 months or until they achieved a 7% weight loss	96	LF, LGI diet LF CHD	23% PRO 50% CHO 27% FAT 23% PRO 50% CHO 27% FAT	LGI diet improved post- OGTT insulin sensitivity Subjects on LGI diet who were prescribed metformin therapy achieved greater improvements in insulin sensitivity compared to those on LGI diet not on metformin More women who consumed the LGI diet showed improved menstrual cyclicity (95% compared to 63%) Serum fibrinogen concentrations showed significant differences between diets (LGI: –0.2±0.1 g/L compared to CHD: 0.2±0.1 g/L)

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Table 1 (Continued)

Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Sørensen et al ⁸⁷	27.7±5.5/28.4±5.8 30.6±7.8/30.5±8.5	6 months RCT	27	HP diet SP diet	>40% PRO <30% CHO 30% FAT Ad libitum diet <15% PRO >55% CHO 30% FAT Ad libitum diet	Compared to SP, HP resulted in significantly greater decreases in: BW (-4.4 kg) Fat mass (-4.3 kg) WC (-3.7 cm), but both diets equally decreased Glucose (HP: 5.2 mmol/L, SP: 5.4 mmol/L) Between the two groups, there were no significant differences in changes of: SHBG Total and free testosterone C-peptide
Toscani et al ⁸⁸	22.72±5.68 29.35±5.74	8 weeks RCT	40	HP diet NP diet	30% PRO 40% CHO 30% FAT 20–30 kcal × BW/day 15% PRO 55% CHO 30% FAT 20–30 kcal × BW/day	Decreased significantly after both diets in both groups: BW BMI WC Body fat % Sum of trunk skinfolds No changes in lipid profile with either diet. Total testosterone decreased in both PCOS and controls, independently of diet composition
Kasim-Karakas et al ⁸⁹	18–45 38.9±1.6/35.4±1.8	2 months RCT	24	PRO: deficit of 450 kcal/day (energy intake was reduced by 700 kcal) plus a 240-kcal supplement containing whey PRO Simple sugar: deficit of 450 kcal/day (energy intake was reduced by 700 kcal) plus a 240-kcal supplement containing simple sugars	1379 kcal/day 33.7% PRO 39.5% CHO 26.2% FAT 1352 kcal/day 16.6% PRO 56.7% CHO 25.9% FAT	The PRO group lost more: BW (-3.3±0.8 kg vs -1.1±0.6 kg) Fat mass (-3.1±0.9 kg vs -0.5±0.6 kg) The PRO group had greater decreases in: Serum cholesterol (-33.0±8.4 mg/dL vs -2.3±6.8 mg/dL) HDL (-4.5±1.3 mg/dL vs -0.4±1.3 mg/dL) Apolipoprotein B (-20±5 mg/dL vs 3±5 mg/dL) There were no significant changes between the two groups in fasting glucose, insulin, HOMA, HbA1c, TGs and hs-CRP

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Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Mavropoulos et al ⁸⁵	34.5 38.5	6 months Nonran- domized clinical trial without a control group	5	LCKD (≤20 g CHO/day)	Diet included unlimited consumption of animal foods (meat, chicken, turkey, other fowl, fish, shellfish), cheeses (up to 4 and 2 ounces per day) unlimited eggs, non- starchy vegetables (two cups per day), and limited intake of starchy vegetables (one cup per day)	Significant reductions from baseline to 24 weeks with the LCKD in: BW (−12%) Percent-free testosterone (−22%) LH/FSH ratio (−36%) Fasting insulin (−54%)
Stamets et al ⁴²	29±4/26±4 38±4/37±5	1 month RCT	26	HP energy- restricted diet (1000-kcal deficit per day) High- carbohydrate energy- restricted diet (1000-kcal deficit per day)	30% PRO 40% CHO 30% FAT 15% PRO 55% CHO 30% FAT	Significant BW loss with both diets: HP (−3.7±1.9 kg) High-carbohydrate (−4.4±1.5 kg) No differences between diets on a variety of measures (circulating androgens, measures of glucose metabolism, leptin) The effects of a hypocaloric diet per se showed significant changes and reductions in: DHEAS (161 ng/mL) Fasting insulin (5 mIU/L) 3-h OGTT AUC for insulin (−5.823 mIU/L×min) Fasting leptin (−11 ng/mL) 3-h OGTT AUC for leptin (−1.854 mIU/L×min) Total cholesterol (−22 mg/dL) LDL-C (−12 mg/dL)
Moran et al ⁴¹	33±0.84 37.4±1.24	16 weeks (12 weeks of energy restriction, followed by 4 weeks of weight maintenance) RCT	28	LP: 15% PRO 55% CHO 30% FAT HP: 30% PRO 40% CHO 30% FAT	Isocaloric diets energy-restricted diet (6000 kJ/day) was prescribed for 12 weeks, followed by a weight maintenance diet for the final 4 weeks with the same dietary composition in both phases plus advice for weekly exercise	Both diets resulted in decreased: BW (−7.7±0.7 kg) Total fat mass (−14.4%) Total lean mass (−3.4%) Abdominal fat (−12.5%) Total cholesterol (−8.8%) TGs (−12.5%) LDL-C (−9.8%) Fasting insulin (−20%) HOMA (−9%) The LP diet decreased HDL-C (−10%) No association between dietary composition and reproductive clinical parameters

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Table 1 (Continued)

Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Phy et al ⁹⁶	29.8±4.0 38.3±5.5	2 months Nonran- domized clinical trial without a control group	24	Ad libitum low starch/low dairy diet	Participants were instructed to eat animal PRO (meat and poultry), fish and shellfish, eggs, non- starchy vegetables, low-sugar fruits (berries, apples, oranges, plums, etc), avocados, olives, nuts and seeds and oils (olive and coconut)	Significant reductions in: BW (-8.61±2.34 kg) BMI (-3.25±0.88 kg/m ²) WC (-8.4±3.1 cm) WHR (-0.05±0.02 inches) Fasting insulin (-17.0±13.6 mIU/L) 2-hour insulin (-82.8±177.7 mIU/L) HOMA-IR (-1.9±1.2) Total testosterone (-10.0±17.0 ng/dL) Free testosterone (-1.8 pg/dL) FG scores (2.1±2.7 points)
Foroozanfard et al ¹⁰⁵	27.1±4.7 32.3±4.6	3 months RCT	53	Low-calorie DASH diet Control diet	Calorie-restricted (350–700 kcal less) 16–18% PRO 52–55% CHO 30% FAT (rich in fruits, vegetables, whole grains, LF dairy products and low in saturated fats, cholesterol, refined grains and sweets) Calorie-restricted (350–700 kcal less) 52–55% CHO 16–18% PRO 30% FAT (different in food groups contained)	Adherence to the DASH diet, compared to the control diet, resulted in significant decreases in: BW (-4.3±1.4 vs -3.2±1.9 kg) BMI (-1.6±0.5 vs -1.2±0.7 kg/m ²) AMH (-1.1±3.1 vs +0.3±0.7 ng/mL) Insulin (-25.2±51.0 vs -1.2±28.8 pmol/L) HOMA-IR score (-0.9±2.0 vs -0.1±1.0) FAI (-0.03±0.09 vs +0.06±0.21) Malondialdehyde levels (-0.5±0.4 vs +0.2±0.3 µmol/L) Significant increases in: Quantitative insulin sensitivity check index (+0.01±0.03 vs -0.004±0.01) SHBG (+3.7±8.5 vs -1.5±7.2 nmol/L) Nitric oxide (+9.0±4.9 vs +0.6±2.3 µmol/L)
Perelman et al ⁹⁰	30±7 39±7	Two phases of 3-week isocaloric program RCT crossover design	6	Eucaloric diet ↑poly- and monounsa- turated fat	15% PRO 40% CHO 45% FAT 7% saturated fat Ratio of poly to mono=1.0 200 mg Cholesterol 20 g fiber No weight loss	AUC for insulin concentrations were 30% lower on the low- CHO/fat-enriched diet (-194±148 mIU/L × 8 h) LDL-C was significantly lower on the low- CHO/fat-enriched diet (-12±60 mg/dL)

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Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
				Eucaloric diet ↑CHO	15%PRO 60% CHO 25% FAT 7% saturated fat Ratio of poly to mono=1.0 200 mg Cholesterol 20 g fiber No weight loss	Fasting plasma total cholesterol, TG and HDL-C concentrations did not differ between diets
Asemi and Esmailzadeh ⁷⁸	30.7±6.7/29.4±6.2 29.1±3.2/31.5±5.7	2 months RCT	48	Control diet: calorie- restricted diet	Deficit of 350–700 kcal/day 18% PRO 52% CHO 30% FAT Designed based on Iranian traditional dietary pattern	Adherence to the DASH eating pattern, compared to the control diet, resulted in significant reductions in: Insulin (–1.88 μIU/mL) HOMA-IR (–0.45) Serum hs-CRP levels (–763.29) WC (–5.2 cm) HC (–5.9 cm)
Asemi et al ¹⁰⁶	30.7±6.7/29.4±6.2 29.1±3.2/31.5±5.7	2 months RCT	48	Control diet: calorie- restricted diet	Deficit of 350–700 kcal/day 18% PRO 52% CHO 30% FAT Designed based on Iranian traditional dietary pattern	Adherence to DASH diet, compared to the control diet, resulted in a significant decrease in: BW (–4.4 kg) BMI (–1.7 kg/m ²) Serum TGs (–10.0 mg/dL) VLDL-C levels (–2.0 mg/ dL)
				DASH diet: calorie- restricted diet	Deficit of 350–700 kcal/day 18% PRO 52% CHO 30% FAT Rich in: fruits/ vegetables/whole grains/LF dairy products low in: saturated fats/ cholesterol/refined grains/sweets	Significantly increased concentrations of: Plasma total antioxidant capacity (+98.6 mmol/L) Total glutathione (+66.4 μmol/L)

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Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Goss et al ¹⁷⁶	31±5.8 31.8±5.7	2 months/ 2 months RCT crossover design	23/27	1800 kcal Standard diet 1800 kcal Reduced CHO diet	18% PRO 55% CHO 27% FAT 19% PRO 41% CHO 40% FAT	Significant reduction in body fat (reduced CHO diet: -3.7%, standard diet: -2.2%). The reduced CHO diet induced a greater decrease in: Intra-abdominal adipose tissue (-7.1%) Subcutaneous abdominal adipose tissue (-4.6%) Intermuscular adipose tissue (-11.5%) The standard diet induced a decrease in total lean mass (-1.3%) Low CHO diet induced significant decreases in: Basal beta-c response (-1.7 × 10 ⁹ /min) Fasting insulin (-15.6 pmol/L) Fasting glucose (-0.26 mmol/L) HOMA (-0.7) Total testosterone (-0.55 nM) Cholesterol (-0.53 mmol/L) LDL-C (-0.41 mmol/L) HDL-C (-0.11 mmol/L) Significant increases in: Insulin sensitivity index (+1.2) Dynamic beta-cell response to glucose (+96.1 10 ⁹ /min)
Gower et al ⁹¹	31.2±5.8 31.8±5.7	Two phases of 8-week isocaloric program RCT crossover design	27	Standard eucaloric diet Low- carbohydrate eucaloric diet	18% PRO 55% CHO 27% FAT 19% PRO 41% CHO 40% FAT	Low CHO diet induced significant decreases in: Basal beta-c response (-1.7 × 10 ⁹ /min) Fasting insulin (-15.6 pmol/L) Fasting glucose (-0.26 mmol/L) HOMA (-0.7) Total testosterone (-0.55 nM) Cholesterol (-0.53 mmol/L) LDL-C (-0.41 mmol/L) HDL-C (-0.11 mmol/L) Significant increases in: Insulin sensitivity index (+1.2) Dynamic beta-cell response to glucose (+96.1 10 ⁹ /min)
Turner-McGrievy et al ¹⁵²	27.8±4.5 39.9±6.1	6 months RCT (randomized controlled feasibility study)	18	LF and LGI vegan diet Low-calorie diet	Plant-based diet (fruits, vegetables, whole grains and legumes/beans, excluding all animal products) 1200 kcal/day for participants weighing ≤90 kg and 1500 kcal/day for participants weighing ≥90 kg	LF, LGI vegan diet produced significantly greater BW losses at 3 months (-1.8 kg) Greater improvements in dietary intake at 6 months (-265 kcal/day) compared to a standard low-calorie dietary approach No significant differences in changes in any of the domains of the PCOS Health-Related Quality of Life Questionnaire (emotional health, body hair, BW, infertility, menstrual concerns)

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Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Douglas et al ⁹²	33±6 30.0±3.7	3×16-day dietary treatment RCT crossover design	11	Standard eucaloric diet Low CHO eucaloric diet High MUFA eucaloric diet	16% PRO 56% CHO 31% FAT 15% PRO 43% CHO 45% FAT 55% CHO 15% PRO 33% FAT	Fasting insulin was lower following the Low CHO diet relative to the STD diet (-3.2 mIU/L) Acute insulin response to glucose was lower following the low CHO diet relative to the MUFA diet (-97.7 mIU/L × 10 minutes) No differences in: Fasting glucose Insulin sensitivity Circulating concentrations of reproductive hormones
Moran et al ⁸¹	32.1±5.2 34.9±7.0	8 weeks weight loss 6 months weight maintenance RCT (Phase I: all subjects followed the same intervention, Phase II: randomly assigned to a carbohydrate counting group [CC], with ≤120 g carbohydrate/ day; or a fat counting [FC] group with ≤50 g carbohydrate/ day)	34 completed Phase I 23 completed Phase II	Phase I Phase II	8 weeks of energy restriction in which two meals/ day were replaced with commercially available meal replacements (two- meal replacements/ day, 4904.4±127 kJ) 8000 steps/day 24 weeks of weight loss maintenance during which subjects followed either a carbohydrate counting (≤120 g/ day; CC) or fat counting (≤50 g/day; FC) protocol 8000 steps/day	Phase I: significant reductions in BW (-5.6±2.4 kg) WC (-6.1±2.5 cm) Body fat (-4.1±2.2 kg) Insulin (-2.8±1.1 mIU/L) Total testosterone (0.3±0.7 nmol/L) FAI (-3.1±4.6) These changes were sustained during Phase II. Improvements in menstrual cyclicity occurred for 16 (57.1%) of 28 subjects. Moderate fat or carbohydrate restriction was equally effective in maintaining weight reduction and improving reproductive and metabolic variables
Alternative dietary interventions						
Papakonstantinou et al ¹³²	27±6 Whole sample (n=40, 27±6) Normal weight (n=20, 24±1.22) Overweight/obese (n=20, 30±1.21)	24-week crossover design, RCT trial	40	Weight maintenance, isocaloric diet consumed as a three-meal pattern Weight maintenance, isocaloric diet consumed as a six-meal pattern	25% PRO 40% CHO 35% FAT 25% PRO 40% CHO 35% FAT	Six meals decreased significantly vs three meals: Fasting insulin (three meals: 112±10 pmol/L, six meals: 92±10 pmol/L) Post-OGTT insulin sensitivity (Matsuda index, three meals: 3.80±0.31, six meals: 5.25±0.67) Trend toward significance (p=0.063): HOMA-IR (three meals: 2.94±0.25, six meals: 2.45±0.31)

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Table 1 (Continued)

Study	Age (years) BW category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Dietary intervention	Clinical outcome measures
Jakubowicz et al ¹³³	25–39 23.7±0.2	3 months RCT	51	Isocaloric diet High-calorie BF	1800±25 kcal/day (42% PRO 27% CHO 31% FAT) BF (980 kcal, 54% daily energy intake) Lunch (640 kcal, 35% daily energy intake) Dinner (190 kcal, 11% daily energy intake)	The BF group has significant changes in: Fasting glucose (–8%) Insulin (–53%) HOMA-IR (–56%) HOMA-B (–35%) ISI (135%) Compared to baseline, the BF group had significantly lower: AUC glucose (–20%) AUC insulin (–49%) Androstenedione (–34%) DHEAS (–35%) Total testosterone (–47%) Free testosterone (from 3.4±0.2 to 1.7±0.1 ng/dL) Compared to baseline, the BF group had significantly higher: SHBG (from 2±0.1 to 4.1±0.2 µg/dL)
				Isocaloric diet High-calorie dinner	BF (190 kcal, 11% daily energy intake) Lunch (640 kcal, 35% daily energy intake) Dinner (980 kcal, 54% daily energy intake)	

Abbreviations: AMH, anti-Mullerian hormone; AUC, area under the curve; BF, breakfast; BMI, body mass index; BW, body weight; CC, clomiphene citrate; CHCD, conventional hypocaloric diet; CHD, conventional healthy diet; CHO, carbohydrates; DASH, Dietary Approaches to Stop Hypertension; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; FAT, dietary fat content; FG, Ferriman–Gallwey; FSH, follicle-stimulating hormone; GI, glycemic index; GL, glycemic load; HbA1c, hemoglobin A1c; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HOMA-B, homeostatic model assessment for B-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; HP, high protein; hsCRP, high-sensitivity C-reactive protein; ISI, insulin sensitivity index; LCKD, low-carbohydrate ketogenic diet; LF, low fat; LGI, low glycemic index; LGL, low glycemic load; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; MHCD, modified hypocaloric diet; MUFA, monounsaturated fatty acid; NEFA, non-esterified fatty acids; NP, normal protein; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PRO, protein; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; SP, standard protein; TGs, triglycerides; VLDL-C, very low-density lipoprotein cholesterol; WC, waist circumference.

Options for PCOS treatment

Typical treatment modalities used in women with PCOS include lifestyle modification (LSM; diet, physical activity and cognitive behavior therapy) and pharmacotherapy, such as clomiphene citrate (CC), aromatase inhibitors, low-dose human menopausal gonadotropin (hMG) or FSH, insulin sensitizers, laparoscopic ovarian drilling and in vitro fertilization (IVF).^{5,47–50} CC is the first-line therapy for ovulation induction in anovulatory infertile women with PCOS, although almost 20% of patients are unresponsive.^{47,51} Results from a three-arm randomized, parallel, controlled, assessor-blinded clinical trial investigating the effects of a 6-week intervention with structured exercise training and hypocaloric diet on probability of ovulation after CC in overweight and obese CC-resistant PCOS women showed that structured exercise training combined with hypocaloric diet was effective in increasing the response to CC and the ovulation rate in overweight and obese PCOS patients.⁵² Results from a study comparing immediate treatment with

CC to delayed treatment with CC after preconception treatment with continuous oral contraceptives, LSM (including caloric restriction, antiobesity medication, behavioral modification and exercise) or the combination of both showed benefit of improved ovulation and live birth with delayed infertility treatment with CC when preceded by LSM with weight loss compared to immediate treatment.⁵³ Moreover, a preconception lifestyle intervention leading to 6–7% weight loss eliminated the adverse metabolic oral contraceptive effects and led to higher ovulation rates.⁵⁴

Aromatase inhibitors, such as letrozole, are also used for ovulation induction.⁴⁷ A recent Cochrane review showed that letrozole appeared to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to CC.⁵⁵ There seems to be no difference in effectiveness between letrozole and laparoscopic ovarian drilling.⁵⁵ A recent meta-analysis investigating the comparative efficacies of ovulation induction treatments of 26 randomized clinical trials with 2722 participants and nine types of therapies (CC,

Table 2 Nutrition interventions with PUFAs in women with PCOS

Study	Age (years)/ body weight category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Characteristics/ interventions	Main conclusions
Cussons et al ¹¹⁷	32.7±7.7 34.8±6.8	8 weeks RCT Double-blind, randomized crossover study design	25	n-3 PUFA	4 g n-3/day (4×1 g capsules of 56% DHA and 27% EPA)	n-3 PUFA compared to placebo significantly decreased: Liver fat content TGs Systolic blood pressure Diastolic blood pressure Hepatic fat in women with hepatic steatosis
Karakas et al ¹⁰⁹	31.7±7.8 36.3±7.8	6 weeks RCT Three parallel- arm, randomized, double-blind study design	51	Fish oil (n=17)	Fish oil (3.5 g n-3 PUFA, six capsules/ day; each capsule contained 358 mg EPA and 242 mg DHA)	Effects of fish oil and soybean oil on plasma aromatic amino acids were similar and differed significantly from those of flaxseed oil Dietary PUFA may influence insulin secretion and resistance directly and alter plasma aromatic amino acids indirectly Dietary PUFA may directly affect aromatic amino acid metabolism and the changes in insulin secretion and resistance may be secondary
Khani et al ¹²⁰	31.0±5.0 29.2±6.7	6 months Double-blind Placebo- controlled	87	n-3 PUFA (n=43) Placebo (n=44)	2 g n-3 (two capsules/day) containing 180g EPA and 120 mg DHA Two olive oil capsules	n-3 PUFA compared to placebo decreased: BMI WC TG Interval between periods n-3 PUFA compared to placebo increased: HDL
Kalgaonkar et al ¹⁰⁸	36.2±1.7 35.1±1.8	6 weeks RCT Parallel, randomized controlled study design	31	Almonds	46 g of almonds (2.4 g saturated fat, 19.5 g MUFA, 7.5 g linoleic acid)	Walnuts increased the n-3/n-6 essential PUFA in the diet and plasma phospholipids Walnuts significantly decreased LDL-C (−6%) and apolipoprotein B (−11%) Walnuts significantly increased insulin response during OGTT (26%) Both walnuts and almonds significantly increased adiponectin Walnuts decreased HbA1c with significant intergroup difference from almonds Walnuts increased SHBG and almonds reduced FAI
Nasri et al ¹¹³	27.5±5.7 27.1±4.6	12 weeks RCT	60	n-3 PUFA (n=30)	2 g n-3 from flaxseed oil containing 800 mg ALA/day	n-3 PUFA supplementation had beneficial effects on gene expression of PPAR-γ and LDLR, gene expression involved in insulin and lipid signaling pathways

(Continued)

Table 2 (Continued)

Study	Age (years)/ body weight category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Characteristics/ interventions	Main conclusions
Nadjarzadeh et al ¹¹²	26.92±5.46 31.69±4.84	8 weeks RCT Parallel, randomized, double-blind, placebo- controlled study design	78	Placebo (n=30)	Paraffin	n-3 PUFAs significantly decreased testosterone compared to the placebo group FAI and the concentration of sex hormone-binding protein did not differ
				Flaxseed oil (n=17)	Flaxseed oil (3.5 g n-3 PUFA, six capsules/day; each capsule contained 545 mg ALA)	
Oner et al ¹¹⁵	22.6±4.75 22.4±3.1	6 months Nonrandomized clinical trial	45	Soybean oil placebo (n=17)	Soybean oil (six capsules/day; each capsule contained 200 mg oleic acid, 429 mg LA, 57 mg ALA)	Insulin levels and HOMA-IR significantly decreased during treatment Serum LH, total testosterone, free testosterone and androstenedione levels decreased significantly SHBG levels and TNF- α levels were significantly increased at 6 months
				n-3 (n=39)	3 g/day n-3	
Mohammadi et al ¹¹⁴	27.3±4.27 28.7±3.21	8 weeks RCT Parallel, double- blind, randomized controlled study design	61	Placebo (n=31)	Paraffin	Supplementation with n-3 PUFA compared to placebo: Increased adiponectin (19.5%) and HDL-C (7.4%) Glucose (-11.4%) Insulin (-8.4%) HOMA-IR (-21.8%) TC (-8.1%) LDL-C (-14.9%)
				n-3 (n=30)	4 g n-3/day (720 mg EPA and 480 mg DHA)	
Vargas et al ¹¹⁶	31.7±7.8 36.3±7.8	6 weeks RCT Three parallel- arm, randomized, double-blind, placebo- controlled study	51	Fish oil (n=17)	Fish oil (3.5 g n-3 PUFA, six capsules/ day; each capsule contained 358 mg EPA and 242 mg DHA)	Fish oil and flaxseed oil lowered TGs Soybean oil increased glucose at 30 and 60 min and AUC for glucose during OGTT and reduced testosterone Fish oil significantly increased glucose at 120 min of OGTT and significantly decreased Matsuda index
				Flaxseed oil (n=17)	Flaxseed oil (3.5 g n-3 PUFA, six capsules/day; each capsule contained 545 mg ALA)	
				Soybean oil placebo (n=17)	Soybean oil (six capsules/day; each capsule contained 200 mg oleic acid, 429 mg LA, 57 mg ALA)	

(Continued)

Table 2 (Continued)

Study	Age (years)/ body weight category (kg/m ²)	Duration and design of dietary intervention	Sample size	Description of groups	Characteristics/ interventions	Main conclusions
Phelan et al ¹⁰	18–40 years 35.07±6.10	6 weeks RCT Randomized double-blind, placebo- controlled, crossover design study	22	LC n-3 PUFA supplementation	4×1 g capsules/day 2.4 g LC n-3 PUFAs that contained 1.9 g EPA and DHA/d in a ratio of EPA to DHA of 1.49:1	LC n-3 PUFA supplementation increased plasma concentrations of n-3 PUFAs and had an antiandrogenic effect in PCOS Significant increase in plasma EPA and DHA concentrations after LC n-3 PUFA supplementation Bioavailable testosterone concentrations were significantly reduced after LC n-3 PUFA supplementation than after placebo intake
				Placebo olive oil	4×1 g olive oil capsules/day	
				Walnuts	36 g of walnuts (2.9 g saturated fat, 4.5 g MUFA, 19.2 g LA and 4.3 g ALA)	
Kasim-Karakas et al ¹⁸	34±5 34.0±1.9	3 months control and then 3 months intervention Nonrandomized clinical trial	17	Walnuts	48 g walnuts/800 kcal energy intake (19 g LA and 3.3 g ALA)	PUFA-rich diet significantly increased fasting glucose and AUC for glucose Fasting plasma-free fatty acids decreased and ketone bodies decreased Plasma testosterone, free testosterone, SHBG, DHEAS, LH, FSH, and urinary estrogen conjugates did not change
				Placebo	Olive oil (4×1000 mg capsules of olive oil containing 67% oleic acid)	

Abbreviations: ALA, α -linolenic acid; AUC, area under the curve; BMI, body mass index; DHA, docosahexaenoic acid; DHEAS, dehydroepiandrosterone sulfate; EPA, eicosapentaenoic acid; FAI, free androgen index; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LA, linoleic acid; LC, long-chain fatty acids; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LH, luteinizing hormone; MUFA, monounsaturated fatty acid; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PPAR- γ , peroxisome proliferator-activated receptor gamma; PUFAs, polyunsaturated fatty acids; RCT, randomized controlled trial; SHBG, sex hormone-binding globulin; TC, total cholesterol; TGs, triglycerides; TNF- α , tumor necrosis factor- α ; WC, waist circumference.

metformin, letrozole, FSH, hMG, unilateral laparoscopic ovarian drilling, bilateral laparoscopic ovarian drilling, the combination of metformin with letrozole and the combination of metformin with CC) showed that FSH, hMG and the combination of metformin with letrozole were potentially more effective therapies in improving reproductive outcomes compared to the other therapies.⁵⁶ Obesity seems to affect the responsiveness to hMG and FSH with increased dose needed, although this needs further investigation.^{5,47}

Insulin sensitizers, such as metformin, are recommended for women with PCOS with impaired glucose tolerance.⁵¹ A meta-analysis of 12 randomized controlled trials (RCTs) with 608 women with PCOS showed that the combination of lifestyle intervention and metformin was associated with lower BMI and subcutaneous adipose tissue and improved menstruation compared to lifestyle and placebo over 6 months,

without significant differences between metformin alone compared to lifestyle on body weight loss.⁵⁷

IVF is a third-line treatment for PCOS indicated in those who have not responded to first- or second-line ovulation induction therapies or in those who require IVF for other indications and can be used with the safer gonadotropin-releasing hormone antagonist protocol and metformin as an adjunct, although no ideal protocol has been identified yet and no dietary associations with IVF have been reported.^{5,47,58} Obesity increases the risk of conception failure with IVF.^{5,47,58} Fertility in women with PCOS is maintained until the age of 38 years using IVF, but thereafter pregnancy rates decrease.⁵⁹ Women with PCOS who conceive singleton pregnancies after IVF may be at increased risk of pregnancy complications and may require close antenatal monitoring.^{7,60} In conclusion, PCOS therapy should be individualized.^{50,60} There is

a need for well-designed, long-term, with adequate sample size, studies to evaluate the effectiveness of pharmacological PCOS treatments, alone or in combination with dietary interventions to ameliorate PCOS symptoms and fertility outcomes.

LSM programs and PCOS

Lifestyle intervention (diet plus physical activity) leading to a small to moderate weight loss of about 5–10% is sufficient to significantly improve IR, restore ovulation and improve menstrual regularity and conception, as well as ameliorate hyperandrogenism, hirsutism and dyslipidemia.^{15,16,48,49,58,60–64} Results from a cross-sectional study showed that women with PCOS were more likely to follow a number of both healthy body weight management practices (balanced diet, reduced fat or sugar intake, adoption of a low-GI diet) as well as paradoxical nonhealthy attitudes (ie, increased smoking, use of laxative and diet pills) compared to women without PCOS.⁶⁵

Although most clinicians are in favor of lifestyle changes for the management of PCOS, the majority of women with PCOS reported that they rarely receive lifestyle advice from their therapists.^{66,67} LSM programs combine dietary recommendations aiming at a small-to-moderate weight loss or maintenance, physical activity patterns and behavioral and cognitive approaches. Several studies have shown that LSM programs may prevent or delay the onset of type 2 diabetes in people with impaired glucose tolerance and women with PCOS.^{15,68,69} LSM programs, including diet and exercise, with or without dedicated stress reduction techniques, may offer significant benefits for amelioration in anthropometric, reproductive (hyperandrogenism, menstrual function, ovulation, pregnancy, conception), metabolic (glucose metabolism, IR, dyslipidemia) and quality of life parameters.^{38,48,49}

Results from five meta-analyses of RCTs with women with PCOS supported the benefits of LSM programs on decreased BMI, fasting blood glucose, IR, FSH, sex hormone-binding globulin (SHBG), total testosterone, androstenedione, free androgen index (FAI) and Ferriman–Gallwey (FG) score and improved cardiorespiratory fitness, but not on glucose tolerance or lipid profiles.^{57,63,70–72} No studies have assessed the effects of LSM programs on clinical reproductive outcomes, quality of life or treatment satisfaction in women with PCOS.^{2,70} A 1-year randomized, placebo-controlled trial compared the effects of four interventions: 1) metformin 850 mg two times daily, 2) LSM plus metformin 850 mg two times daily, 3) LSM plus placebo and 4) placebo group on anthropometric and hormonal parameters, and showed that the combined LSM plus metformin group offered greater

changes in body weight (–9 kg), total testosterone (–27 ng/dL) and FAI (–9).⁷³ Results from a study investigating the effects of a 3-month LSM in overweight/obese women with PCOS with anovulation, hyperandrogenism and polycystic ovaries compared to BMI-matched regularly menstruating controls, normal weight PCOS and normal weight controls showed that women with PCOS exhibited lower levels of insulin receptor substrate-1 and glucose transporter-4 (GLUT4) mRNA in their proliferative endometrium compared to BMI-matched controls, whereas LSM led to decreased body weight, improved menstrual regularity and increased endometrial insulin sensitivity.⁶¹

In conclusion, LSM (diet plus regular physical activity) should be the first-line strategy for the management of PCOS. The main challenge remains the long-term maintenance of healthy dietary attitudes and insulin sensitivity. A team-based approach along with lifestyle interventions may be more suitable for the management and treatment of PCOS.^{49,58,74,75}

Negative energy balance and PCOS

Several studies assessing the effects of caloric restriction along with modified dietary macronutrient composition on multiple health outcomes and biochemical indices have shown that there is no optimal dietary macronutrient composition or dietary pattern for PCOS.^{38,41,76} Overall, there is little variation in weight loss with different diets, and this variation may be due to the differences in compliance and not how the body handles different macro- or micronutrients. Negative energy balance (with a deficit of 350–1000 kcal/day) seems to be the key factor leading to successful body weight and fat loss and amelioration of menstrual cycle and insulin sensitivity, irrespectively of the adopted dietary pattern.^{42,77–82}

Results of a 1-month trial comparing the effects of two hypocaloric diets, differing in macronutrients, on a variety of clinical measures in women with PCOS, showed that negative energy balance alone resulted in significant weight loss (–4 kg) and decreased testosterone (–9 ng/dL), fasting insulin (–5 mIU/L), area under the curve (AUC) for insulin (–5.823 mIU/L·min), fasting leptin (–11 ng/mL), AUC for leptin (–1.854 ng/mL·min), total cholesterol (–22 mg/dL) and low-density lipoprotein (LDL) cholesterol (–12 mg/dL), independently of macronutrient composition of the tested diets.⁴² Similarly, results from another trial comparing the effects of two hypocaloric diets with different macronutrient composition and GI in women with PCOS showed that negative energy balance resulted in successful weight loss (–4%), decreased dehydroepiandrosterone sulfate (DHEAS) and increased SHBG concentrations.⁸³ Moreover, results from

a 6-month study comparing the effects of two hypocaloric diets (energy deficit -500 kcal/day), differing in macronutrient composition, showed that negative energy balance per se resulted in body weight and fat loss, amelioration of menstrual dysfunction (more regular menstrual episodes reported after weight loss) and hirsutism.⁷⁷

In conclusion, negative energy balance is a key strategy for the management and treatment of PCOS. The size of the caloric deficit should be determined according to the individuals' needs (dietary preferences, habits, culture and metabolic goals) and physical activity patterns.

Dietary carbohydrates and PCOS

The "low-carbohydrate diet" is typically defined as having $<20\%$ carbohydrates (equivalent to $20-60$ g carbohydrates/day).⁸⁴ Out of 12 studies reporting effects of low-carbohydrate diets, only one, nonrandomized 24-week trial with small sample size met the criteria of the low-carbohydrate definition with PCOS subjects instructed to limit carbohydrate intake to ≤ 20 g/day.⁸⁵ One trial included a diet with $<30\%$ carbohydrates, six trials included diets with 40% carbohydrates and four studies with $41-45\%$ carbohydrates.^{41,42,76,83,86-92}

Douglas et al⁹² compared the effects of three eucaloric diets: 1) standard (16% protein, 56% carbohydrate, 31% fat), 2) moderately low-carbohydrate (15% protein, 43% carbohydrate, 45% fat) and 3) high monounsaturated fatty acid (MUFA) diets (15% protein, 55% carbohydrate, 33% fat) on glucose and insulin responses in women with PCOS and reported greater reductions in fasting insulin (-3 mIU/L) and lower acute insulin response to glucose (-98 mIU/L \times 10 minutes) with the moderately low-carbohydrate diet compared to other two diets. In contrast, results from two clinical trials reported no significant differences in glucose or energy metabolism with moderately low-carbohydrate diets.^{41,42}

Carbohydrate distribution may be a significant component for glucose metabolism and IR. One study provided evidence showing that the consumption of the majority of carbohydrates (50%) at lunch time resulted in the lowest postprandial glucose spikes and improved glycemic control, compared to the majority of carbohydrates consumed at breakfast, dinner or equally distributed throughout the day, in people with type 2 diabetes.⁹³ Moreover, another study showed that consumption of a high-carbohydrate breakfast ($>45\%$ of energy from carbohydrates) may have detrimental effects in people with impaired glucose regulation and it should be avoided.⁹⁴

In conclusion, there is no optimum amount of carbohydrate intake for women with PCOS, and, therefore, any range of dietary carbohydrates may be adopted, according to the

individuals' dietary assessment, metabolic goals, dietary habits and preferences. However, it may be advantageous to consume the majority of carbohydrates at lunch time, with the second best option, ie, their equal distribution in meals throughout the day, and to avoid a high-carbohydrate breakfast.

GI, glycemic load (GL) and PCOS

Five available clinical trials examined the effects of low GI on glucose or energy metabolism and hormonal responses in women with PCOS and reported successful weight loss, irrespective of GI.^{77,79,83,86,95} Out of the five trials, two showed increased insulin sensitivity^{79,95} and one showed decreased insulin levels, IR, DHEAS and high-sensitivity C-reactive protein (hsCRP) with adoption of low-GI diet.⁸³

Results from one trial showed that a high-protein, moderately low-carbohydrate with low and medium GL resulted in significant reductions in blood insulin (-4 mIU/L), IR (homeostatic model assessment for IR [HOMA-IR], -0.8) and hsCRP (-0.9 mg/L) levels compared to a conventional diet.⁸³ Similarly, results from a 12-month dietary intervention with two similar macronutrient composition, energy-reduced, low-fat, low-saturated fat, moderate-to-high fiber diets (23% protein, 50% carbohydrates, 27% fat), low or high GI, showed that the low-GI diet provided a threefold greater improvement in whole-body insulin sensitivity and improved menstrual regularity and better emotional scores, compared to a conventional hypocaloric, low-fat diet.⁷⁹ However, both the low-GI and the conventional diets led to similar improvements or changes in blood lipids and androgenic hormone concentrations, markers of inflammation and other measures of quality of life.⁷⁹ Wong et al⁸⁶ showed that a low-GI diet led to a greater decrease in BMI percentile in adolescents with PCOS. In a nonrandomized clinical trial, participants replaced high-GI and medium-GI with low-GI foods, and findings showed possible improvements in metabolic risk factors (ie, insulin sensitivity).⁹⁵

In conclusion, results from a few available studies suggest that consumption of low-GI foods may have a small additional beneficial impact on some outcome measures in women with PCOS.

Dietary protein and PCOS

Out of seven available trials comparing the effects of high-protein hypocaloric diets compared to low-protein diets on several outcomes in women with PCOS, four found no significant effects of dietary protein on indices of energy metabolism or androgenic parameters,^{42,80,85,96} two reported

greater weight loss with higher protein intake^{87,89} and three reported greater reductions in body fat with higher protein diets.^{87–89} Only one trial reported greater reductions in glucose levels with higher protein diets.⁸⁷

Some studies have attempted to separate the effects of high-protein intake (from diet alone or supplementation) from low-carbohydrate intake (diets typically with $\geq 20\%$ protein, $\leq 45\%$ carbohydrates, varying in fat content). Two studies found greater improvements in anthropometric and other outcome measures with high-protein diets,^{87,89} whereas three found no differences between high- and low-protein diets.^{41,42,88} Sørensen et al⁸⁷ demonstrated that a high-protein, low-carbohydrate diet ($\sim 40\%$ protein, 30% carbohydrate, 30% fat) decreased significantly more body weight (-4.4 kg), fat mass (-4.3 kg), WC (-3.7 cm) and glucose concentrations (-0.2 mmol/L) compared to a low-protein, high-carbohydrate diet ($\sim 15\%$ protein, 55% carbohydrate, 30% fat). However, no differences between diets were found for SHBG, total and free testosterone and C-peptide.⁸⁷ Toscani et al⁸⁸ compared the effects of two diets, a high-protein, moderately low-carbohydrate diet (30% protein, 40% carbohydrate, 30% fat) or a low-protein, high-carbohydrate (15% protein, 55% carbohydrate, 30% fat) diet, and reported equal reductions in body weight, BMI, WC, body fat and the sum of trunk skinfolds with both diets. Similarly, results from another study comparing the effects of a high-protein, moderately low-carbohydrate (30% protein, 40% carbohydrate, 30% fat) vs a low-protein, high-carbohydrate diet (15% protein, 55% carbohydrate, 30% fat) showed successful weight loss and improvement in reproductive and metabolic abnormalities with both diets.⁴¹

Results from one trial comparing the effects of a high whey protein, moderately low-carbohydrate diet vs normal protein, high simple carbohydrate diet on glucose metabolism, body composition, blood lipids and indices of inflammation in patients with PCOS, using two types of hypocaloric diets, a high-protein, moderately low-carbohydrate ($\sim 34\%$ protein, 40% carbohydrate, 26% fat) or a low-protein, high simple carbohydrate diet ($\sim 17\%$ protein, 57% carbohydrate, 26% fat), showed greater weight and fat mass loss with the high whey protein, moderately low-carbohydrate diet.⁸⁹ However, no differences were found for fasting glucose, insulin, IR, glycated hemoglobin A1c (HbA1c), triglycerides (TGs) or hsCRP between diets.⁸⁹ A meta-analysis of RCTs suggested that high-protein, moderately low-carbohydrate diets (within 6 months) may have some beneficial effects on weight loss, HbA1c and blood pressure in patients with impaired glucose metabolism.⁹⁷ Moreover, our group has shown that, in obese people with

and without type 2 diabetes, dietary protein did not have an important effect on glucose metabolism,⁹⁸ but others have shown that it increases insulin response.⁹⁹ Some proposed mechanisms for the beneficial effects of higher protein diets on body composition and weight loss include increased protein-induced thermogenesis^{100,101} and increased satiety, possibly due to enhanced cholecystokinin production.^{102,103} Moreover, a meta-analysis of RCTs reported that the majority of RCTs (35 out of 51) demonstrated a benefit of fat-free mass preservation with higher protein diets.¹⁰⁴

In conclusion, although some studies support that higher protein diets may result in several positive health outcomes, including lean mass preservation during weight loss and maintenance, better glycemic control and amelioration of other cardiovascular disease risk factors, such as blood pressure, it is not clear yet whether these effects are due to the higher protein or lower carbohydrate intake, and no recommendations can be made currently. Nevertheless, the addition of $7\text{--}15$ g of dietary protein in meals and snacks may offer some additional health benefits for women with PCOS, including amelioration of insulin sensitivity and lower postprandial glucose fluctuations, but this still needs to be confirmed.

Dietary fat and PCOS

Eight clinical trials compared the effects of hypocaloric low- vs high-fat diets, typically using diets with a mean of $20\text{--}30\%$ energy from fat or dietary patterns (ie, Dietary Approaches to Stop Hypertension [DASH]), on energy metabolism in women with PCOS, and all reported significant reductions in body weight and composition with adoption of low-fat diets.^{76,78,90–92,105,106,152}

Moderately low-carbohydrate, high-fat diets have been shown to decrease fasting insulin and AUC for insulin and to increase insulin sensitivity in three trials in women with PCOS.^{90–92} In one trial, a high-fat, moderately low-carbohydrate eucaloric diet resulted in greater reductions in body fat, intra-abdominal adipose tissue, subcutaneous abdominal adipose tissue and intermuscular adipose tissue compared to a control diet.⁷⁶ Results from another trial comparing two isocaloric diets – a low-fat, low-saturated fat, high-carbohydrate ($\sim 15\%$ protein, 60% carbohydrate, 25% fat, 7% saturated fat) or a high-fat, low-saturated fat, moderately low-carbohydrate diet ($\sim 15\%$ protein, 40% carbohydrate, 45% fat, 7% saturated fat) – showed a 30% greater reduction in AUC for insulin and blood lipids with the high-fat, low-saturated fat, moderately low-carbohydrate diet, in the absence of weight loss.⁹⁰ Results from a short-term, crossover trial showed that a moderately low-carbohydrate (43%), high unsaturated fatty acids (mono-

unsaturated fatty acids, MUFA: 18%; polyunsaturated fatty acids, PUFA: 17%) diet, led to a greater decrease in fasting insulin concentrations and the acute insulin to glucose response compared to the control diet.⁹² Results from another crossover clinical trial showed that a high-fat and moderately low-carbohydrate (~41% carbohydrate, 19% protein and 40% fat) diet induced significant glucose metabolism improvements (decreased basal β -cell response, fasting insulin, fasting glucose and IR), hormonal responses (lower testosterone) and decreased blood lipids and adipose tissue (intra-abdominal adipose tissue [-7.1%], subcutaneous abdominal adipose tissue [-4.6%] and intermuscular adipose tissue [-11.5%]).^{76,91}

DASH diet is a low-GI, low-energy-density, high in complex carbohydrates, high fiber diet (~18% protein, 52% carbohydrate, 30% fat), which has been shown to produce significantly lower blood pressure and glycemic responses.^{99,107} Asemi and Esmailzadeh⁷⁸ demonstrated that adherence to DASH eating pattern, compared to a control diet based on Iranian traditional foods, resulted in greater reductions in body weight, BMI, WC, hip circumference (HC), serum insulin levels, IR, hsCRP and TG compared to the control diet in women with PCOS.¹⁰⁶ Similarly, another trial showed that adherence to the DASH diet for 12 weeks had beneficial effects on weight loss, serum AMH, markers of insulin metabolism, SHBG, FAI, plasma nitric oxide and malondialdehyde levels among women with PCOS.¹⁰⁵

In conclusion, replacement of dietary carbohydrate with MUFA and/or PUFA in a reduced energy diet may offer additional health benefits in the management of PCOS. The adoption of healthy dietary patterns such as DASH or the Mediterranean-style diets should be encouraged among women with PCOS, as they are rich in dietary fiber, antioxidants and anti-inflammatory nutrients, lead to greater satiety and have anti-hyperlipidemic, antihypertensive and antidiabetic properties.^{78,103,106}

PUFA and PCOS

PUFAs, particularly the marine n-3 PUFA (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), have been studied for their metabolic effects on insulin sensitivity, IR, androgen status and anti-inflammatory markers in women with PCOS.^{16,108–111} Mainly, most of the clinical trials of PUFA supplementation were of short duration (6–12 weeks) and the supplementation dose ranged between 2 and 4 g PUFAs per day.^{108–110,112–118} A recent meta-analysis of eight clinical trials with a total of 298 females with PCOS showed a slight reduction in serum total testosterone levels following n-3 PUFA supplementation among females with PCOS, without

significant impact on SHBG and DHEAS levels.¹¹⁹ Results from a cross-sectional study showed that increased plasma n-6 PUFAs or increased n-6:n-3 PUFA ratio was associated with greater circulating androgen concentrations, whereas increased long-chain n-3 PUFA in plasma was associated with decreased blood lipids in women with PCOS.¹¹⁰ Subsequently, results from a crossover, placebo-controlled, RCT showed that long-chain n-3 PUFA supplementation (4×1 g capsules/day, containing 2.4 g total long-chain n-3 PUFAs, 1.9 g EPA and DHA/day in a ratio of EPA to DHA of 1.49:1) resulted in increased plasma concentrations of n-3 PUFAs and had an antiandrogenic effect in women with PCOS.¹¹⁰ Results from a double-blind RCT, providing n-3 PUFA supplementation (3 g/day) for 8 weeks, showed that n-3 PUFA led to a greater reduction in serum testosterone, but not SHBG, compared to the placebo group.¹¹² Results from another double-blind RCT, providing n-3 PUFA supplementation (2 g/day) for 6 months in PCOS, showed that n-3 decreased lipid profiles, WC and interval between periods, with no changes in body weight, HC, fasting glucose, number of ovarian follicles, size of ovary, bleeding volume, menstrual bleeding and hirsutism score.¹²⁰

Some have proposed that n-3 PUFAs may improve insulin sensitivity by decreasing the production of inflammatory cytokines including tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6) and increasing secretion of the anti-inflammatory hormone adiponectin.¹²¹ However, results from clinical trials on IR and insulin sensitivity remain controversial in women with PCOS. Nasri et al¹¹³ reported that 2 g n-3 PUFA supplementation from flaxseed oil (800 mg α -linolenic acid [ALA]/day) had beneficial effects on peroxisome proliferator-activated receptor gamma (PPAR- γ) and LDL receptor gene expression involved in the insulin and lipid signaling pathways. Similarly, Mohammadi et al¹¹⁴ showed that 4 g n-3 PUFA supplementation (720 mg EPA and 480 mg DHA) resulted in a 20% increase in adiponectin and decreased glucose (-11%) and insulin (-8%) concentrations. However, a recent meta-analysis with three available trials of small sample size reported no beneficial effects of n-3 PUFAs on IR or other clinical outcome measures in women with PCOS.¹²¹

In conclusion, although some studies have reported some beneficial health effects of PUFAs, particularly n-3 marine PUFAs, there is still a lot of controversy and no conclusions can be drawn at this point.

Meal frequency, meal timing and PCOS

Meal frequency and meal timing seem to be valuable components of lifestyle changes, although there are only limited

data on women with PCOS. Some argue that frequent meal consumption is detrimental to body composition and indices of glycemic control, because it may lead to weight gain due to increased lipogenesis or fat deposition after meals or by simply increasing the overall energy intake.^{122–125} Furthermore, it has been suggested that increased meal frequency may increase postprandial glucose, insulin, IR and blood lipids and may have a negative impact on the fatty acid composition of serum phospholipids.^{126–129} In contrast, others propose that increased meal frequency may exert a beneficial effect on body weight and indices of glycemic control, which may be attributed to nutrient load spreading, producing lower postprandial insulin concentrations, hunger reduction, inhibitory effects of free fatty acids on glucose uptake suppression and increased glucose clearance from the circulation with a significant economy in insulin secretion.^{130,131}

In a 24-week crossover RCT, our group reported a beneficial effect of a six-meal pattern, without energy restriction, on amelioration of post-oral glucose tolerance test (OGTT) insulin sensitivity and reduction in subjective hunger in lean and obese women with PCOS compared to a three-meal pattern.¹³² Another study by Jakubowicz et al¹³³ compared two isocaloric diets (high-kilocalorie breakfast vs high-kilocalorie dinner) in lean women with PCOS and reported that high-energy intake at breakfast resulted in reduced food intake at dinner, which in turn led to improved insulin sensitivity and markers of reproductive function.

The timing of food intake has gained considerable interest in the past few years as it is found to affect metabolism and insulin secretion.¹³⁴ It has been suggested that postprandial glycemia is under circadian regulation and that its misalignment may lead to glucose intolerance.¹³⁰ Eating late during the day was associated with decreased resting-energy expenditure, decreased fasting carbohydrate oxidation, decreased glucose tolerance, blunted daily profile in free cortisol concentrations and decreased thermal effect of food on wrist temperature in normal weight, healthy females.¹³⁵ People with prediabetes preferring to consume their main meal in the evening (later chronotype) had higher HbA1c compared to those consuming their main course at lunch time, and thus, had higher risk of developing type 2 diabetes sooner.¹³⁶ The American Heart Association in their recent scientific statement concluded that meal frequency and timing may be important parameters in the nutrition management of chronic diseases, leading to healthier lifestyle and reduction in cardiometabolic risk factors.¹²⁸

Vitamin D and PCOS

Epidemiological studies have shown inconsistent results for vitamin D status between women with and without PCOS.¹³⁷ Some studies have demonstrated lower serum vitamin D concentrations in women with PCOS compared to women without PCOS, whereas a case–control study, with 85 women with PCOS and 115 healthy controls, found higher serum vitamin D concentrations in women with PCOS compared to controls.^{138–140} Low serum vitamin D levels or insufficiency has been positively associated with PCOS-related symptoms, such as central obesity, IR, infertility and hirsutism, whereas serum 25-hydroxy vitamin D (25OHD) seems to be an independent predictor of measures of reproductive success following ovulation induction.^{141–144}

A recent systematic review and meta-analysis showed that vitamin D supplementation significantly decreased total testosterone, without any effects on serum SHBG and free testosterone.¹³⁷ Another systematic review discussed the association between vitamin D status and metabolic disturbances and suggested an inverse association between vitamin D status and IR in women with PCOS.¹⁴⁵ One study showed that 1000 mg/day calcium plus 50,000 IU/week vitamin D supplementation for 8 weeks among vitamin D-deficient women with PCOS had beneficial effects on serum insulin levels, IR, TG and very-LDL (VLDL) levels, without affecting fasting glucose and other lipid profiles.¹⁴⁶ Another study showed that the combination of 1500 mg/day metformin plus 1000 mg/day calcium and 100,000 IU/month vitamin D supplementation for 6 months had positive effects on weight loss, follicle maturation, menstrual regularity and improvement in hyperandrogenism in infertile women with PCOS.¹⁴⁷

In conclusion, few available studies have found some, but limited, benefits of vitamin D supplementation among women with PCOS, and it remains a controversial topic. Systematic reviews and meta-analyses support that currently no recommendations can be made about vitamin D supplementation for PCOS, due to conflicting study results, small sample sizes, lack of adjustments for confounders, use of different definitions for PCOS, use of different assays for serum 25OHD measurement, short trial duration and use of varying amounts of vitamin D supplementation.¹⁴⁵

PCOS and micronutrients

Few available studies have examined the effects of micronutrient supplementation on PCOS symptoms and biochemical indices. One study showed that 220 mg zinc sulfate supplementation per day for 8 weeks among PCOS had beneficial

effects on fasting glucose, insulin, IR and TG.¹⁴⁸ It has been reported that 200 mg/day selenium supplementation for 8 weeks among PCOS had beneficial effects on fasting insulin, IR, insulin sensitivity, TG and VLDL levels, without affecting fasting glucose and other lipid profiles.¹⁴⁹ Another study found that 200 mg/day chromium supplementation for 8 weeks among PCOS had favorable effects on fasting insulin, IR and insulin sensitivity.¹⁵⁰ Moreover, 5 mg/day folate supplementation for 8 weeks among PCOS had beneficial effects on inflammatory factors and biomarkers of oxidative stress.¹⁵¹ In conclusion, there is insufficient evidence to recommend micronutrient supplements for women with PCOS at this time.

In summary, this review aimed to discuss the effects of nutritional support and dietary interventions on various clinical outcome measures in women with PCOS. The results indicate that there is still a great need for well-designed, long-term, with adequate sample size, clinical trials examining all aspects of overall nutrition (ie, patterns, habits and alternative nutrition interventions) and nutrient effects (ie, micronutrients) in women with PCOS. From the available current trial data, we can conclude that LSM, including a small-to-moderate weight loss of about 7% achieved with any dietary pattern of choice, depending on the individuals' preferences, culture, habits and metabolic needs (ie, DASH diet, moderately low-carbohydrate diets [40–45% of energy] or substitution of carbohydrates for MUFA or PUFA in the diet), as well as alternative dietary interventions, including increased meal frequency and regular meal timing, with the majority of carbohydrates consumed at lunch time, seems to offer the evidence-based nutritional support strategy for IR and the management and treatment of PCOS.

Disclosure

The authors report no conflicts of interest in this work.

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