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Effect of healthy lifestyle promotion on anthropometric variables, eating behavior and cardiometabolic risk factors in women with polycystic ovarian syndrome

Latifa Imen Benharrat [1], Azzedine Senouci [1], Wassila Benhabib [2], Khedidja Mekki [1] *

[1] Laboratory of Clinical and Metabolic Nutrition, University Oran 1, Oran 31100, Algeria
[2] Department of Epidemiology, University Hospital of Oran, Oran 31037, Algeria

Abstract

Background: In women with Polycystic Ovarian Syndrome (PCOS), metabolic abnormalities are common, including insulin resistance, obesity, and dyslipidemia, suggesting an increased risk for cardiovascular disease (CVD). **Objectives:** To evaluate the effect of healthy lifestyle promotion on eating behavior and metabolic biomarkers in women with PCOS. **Subjects and Methods:** The study was carried out in 102 women (30±7 years) with PCOS. Patients received nutritional counseling based on Mediterranean diet principles and recommendations to practice a regular physical activity, and were followed up during six weeks. Dietary survey and biomarkers analysis were assessed at baseline (T0), after three weeks (T1) and 6 weeks (T2). **Results:** After six weeks of intervention, there was a significant decrease in total energy intake by (-30%) at T1 and (-32%) at T2 ($p<0.001$), compared to baseline. Significant decrease was recorded in carbohydrates, proteins and lipids intake at T1 and T2 ($p<0.001$). An increase in monounsaturated fatty acid intake was noted at T1 and T2 ($p<0.001$). The body mass index (BMI) diminished at T2 ($p<0.01$), and waist circumference at T1 and T2 ($p<0.001$). Glucose values decreased at T1 ($p<0.05$) and T2 ($p<0.001$). Total cholesterol decreased at T1 ($p<0.05$) and T2 ($p<0.01$). HDL-C increased at T1 ($p<0.001$) and T2 ($p<0.001$), when CRP values remained unchanged. A decrease in Thiobarbituric acid reactive substances concentrations was observed at T1 and T2 ($p<0.05$). Superoxyde Dismutase, Catalase activities and thiols amount increased at T2 ($p<0.001$). **Conclusion:** In the long term, healthy lifestyle promotion could be beneficial to prevent or reverse the clustering of metabolic abnormalities and prevent CVD in women with PCOS.

Keywords: Polycystic ovary syndrome, Metabolic abnormalities, Healthy Lifestyle, Mediterranean diet, Cardiometabolic risk.

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1 Introduction

Polycystic ovarian syndrome (PCOS) is a complex disorder affecting 5%-10% women of childbearing age [1]. Based on the Rotterdam Criteria; PCOS can be diagnosed by at least two of the following three criteria: clinical and/ or biochemical signs of hyperandrogenism, oligo and/ or anovulation and polycystic ovary on ultrasound [2]. Short-term comorbidities of PCOS include dermatological, reproductive and mood disorders, while long-term comorbidities of PCOS include vascular dysfunction, neoplastic and mental health disorders [3]. The etiology of PCOS has not yet been clearly identified and probably results from a combination of several factors essentially genetic factors [3], exposure to high levels of androgens during the prenatal period, epigenetic and environmental factors [4] such as nutritional status that plays a crucial role, physical activity, smoking and stress [5]. Moreover, women with PCOS tend to have other disorders such as: hypertension, insulin resistance, glucose intolerance, type 2 diabetes, lipid disorders and cardiovascular diseases [6]. Metabolic disturbances are well-known clinical features of PCOS including metabolic syndrome (MS) that play a significant role in its development [7]. It has been shown that PCOS women with high body mass index (BMI) present a higher risk of developing metabolic syndrome compared to women with normal BMI [8]. Dyslipidemia constitutes a special common metabolic disorder in women with PCOS, with a prevalence of over 70% [9] when insulin resistance represents a major pathophysiological condition in PCOS with a prevalence of 50-60% approximately[10]. Dyslipidemia in women with PCOS may therefore be consistent with that observed in the insulin-resistant state; decreased levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A-I, and increased levels of triacylglycerols (TG) and low-density lipoprotein cholesterol (LDL-C) [11]. Overweight and obesity, especially abdominal obesity in adolescence and adulthood, are predictors of hirsutism and menstrual disorders in PCOS [12]. Hence, there is a solid association between PCOS and obesity, so that an obese patient with PCOS presents a greater higher metabolic risk than a patient who is only obese. Studies showed that 40-60% of PCOS cases are overweight or obese [13]. A healthy lifestyle, based on a balanced diet and regular physical activity, is the best strategy to improve insulin sensitivity in this syndrome, especially in cases of overweight and obesity, and

* **Corresponding author:** Khedidja Mekki, Laboratory of Clinical and Metabolic Nutrition, University Oran 1, Oran 31100, Algeria. Tel: (+213) 552649929, E-mail: khmekki@hotmail.com

should be adopted as first-line therapy [14]. Among the various nutritional strategies, the Mediterranean diet (MD) is generally recognized as a health-promoting diet due to its particular characteristics, including regular consumption of unsaturated fats, carbohydrates with low glycemic index, fibers, vitamins and antioxidants, and moderate rates of animal proteins [15].

The aim of the current study was to assess the impact of healthy lifestyle promotion on anthropometric variables, food behavior and cardiometabolic biomarkers in women with polycystic ovarian syndrome. Aiming to reach this objective, women received nutritional counseling based on Mediterranean diet principles and physical activity, and were followed up for six weeks.

2 Subjects and Methods

2.1 Subjects

A cross-sectional study was conducted from September 2018 to June 2019 at the Public Health (EPSP) of Es Senia, Oran (Western Algeria).

One hundred and two fertile women (age < 40years) with PCOS (30±7 years) were included and presented some metabolic abnormalities such as: high waist circumference, dyslipidemia, high blood pressure, and hyperglycemia. The patients were diagnosed according to the Rotterdam Consensus criteria 2003, two of these three are required: Clinical and/or biochemical hyperandrogenism, oligo/amenorrhea, anovulation and polycystic ovaries appearance on ultrasound [1]. On the 102 women, 87% were overweight, 94% had abdominal obesity, 47% high blood pressure, 24% had an insulin resistance and 79% a dyslipidemia.

Twenty-two percent of the study population already suffered from comorbidity diagnosed prior their inclusion in the study. Only 27% of them take their treatment regularly. These illnesses were primarily diabetes (40% of the pathologies) treated with insulin aspartate rapid and insulin glargine. Women with dyslipidemia were treated with statins and those with high blood pressure or ischemic heart disease received betablockers, diuretics, statins, and converting enzyme inhibitor.

The purpose of the study was clarified to all subjects and the investigation was carried out with their consent. All women signed the informed consent.

2.1.1 Nutritional intervention

All women received nutritional counseling based on the Mediterranean diet. They were therefore asked to consume olive oil for seasoning, wholegrain cereals (50 g of bread at each meal, 250 g of cereals or starch once a day), fruit (once a day), vegetables (200 g twice a day) and fish (twice a week) [16]. Portion and serving sizes of commonly consumed foods were also specified using household measures. A list of manufactured foods and sweet products to avoid was provided. In addition, women received guidance about cooking methods best suited for adherence to current dietary guidelines. Moreover, at least 30 minutes of daily physical activity such as brisk walking was recommended.

2.1.2 Assessment of dietary intake

Nutritional surveys were carried out at baseline (T0), at three weeks (T1) and six weeks (T2) further the start of nutritional intervention.

During the initial study, for dietary survey, a food frequency questionnaire was developed and adapted to the studied cohort in order to evaluate their food habits. The questionnaire was organized by meal and every meal was structured in starter, main course, side dish and dessert. Food groups were used as a basis for meals structure. The patients were asked about their usual consumption of the seven days preceding the interview. A 24h ″Recall and Record″ method was used to validate the food frequency questionnaire. A pilot survey was conducted on a sample of 10 women, and it was used to correct and adapt all questions. We collected information about the quantity and the frequency of consumption of different foods. Food Composition Database CIQUAL of Anses was used to convert foods into energy and nutrients.

In order to follow the advancement of the provided advice, a 24-hour Recall and Record survey has been carried out at T1 (3 weeks) and T2 (6 weeks) after the initiating study. Women were asked to recall everything they had eaten or drunk during the 24 h preceding the interview.

All patients were treated at the gynecology department of the Es Senia Oran public health establishment. Overall steps of the study were explained to our patients, then the consent was accepted and signed.

2.2 Methods

Blood samples were drawn at baseline (T0), at three weeks (T1) and six weeks (T2) after the beginning of nutritional intervention. Samples were collected by low-speed centrifugation at 4000 × g at 5° for 20 minutes and stored with sodium heparin (NH).

2.2.1 Glucose and lipid analysis

Blood glucose, triacylglycerols (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were measured by a colorimetric method (Kits Biolabo, France). Low-density lipoprotein cholesterol (LDL-C) was determined using the Friedwald formula.

2.2.2 C - reactive protein (CRP) analysis

The analysis of C-reactive protein (CRP) was performed by colorimetric method to analyze inflammation (kits, Latex, Cobas C 111, France, CRPLX: ACN 019).

2.2.3 Lipid and protein peroxidation

Thiobarbituric acid (TBARS) was used to analyze serum lipid peroxidation according to Quintanilha *et al.* method [17], using malondialdehyde (MDA) as a standard which happens to be one of many low molecular weight end products formed by the decomposition of certain primary and secondary lipid peroxidation products. One milliliter of diluted sample (protein approximately 2 mg/mL) was added to 2 mL of thiobarbituric acid

(final concentration, 0.017 mmol/L) and butylated hydroxytoluene (concentration, 3.36 mmol/L), and incubated for 15 minutes at 100°C. After cooling and centrifugation, the absorbance of the supernatant was measured at 535 nm. Data were expressed in mmol of TBARS produced/L of serum. Carbonyl concentrations were measured by estimating the oxidized proteins according to the method of Levine *et al.*, [18] using 2,4-dinitrophenylhydrazine to obtain aldehyde derivatives and ketones. The absorbance of the supernatant was measured between 250 and 300 nm.

2.2.4 Antioxidant Measurements

Superoxide dismutase (SOD) was determined by the method of Marklund & Marklund [19], based on a competition between the oxidation reaction of pyrogallol by O_2^- and the dismutation of O_2^- by SOD. The product of the auto-oxidation and O_2^- both absorb at 325 nm. The spectrophotometric determination of hydrogen peroxide (H_2O_2) was performed to evaluate the determination of catalase activity by the Goth method [20], which form stable complex with ammonium molybdate that absorbs at 405 nm. The determination of Thiols was carried out by a colorimetric method according to Sedlak *et al.*, [21] based on the oxidation reaction of -SH groups with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), thereby releasing thionitrobenzoic acid (TNB) of yellow color, which absorbs at 412 nm.

2.3 Statistical Analysis

The data were presented as mean ± standard errors, and have been analyzed by Student's t test. The level of $p < 0.05$ was considered significant. Data were compared: Over time, *T1 and T2 compared to T0.

3 Results

Table 1: Clinical characteristics of study patients

	Baseline T0	T1	T2
Patients (n)	102	102	102
Age (years)	30 ± 7	30 ± 7	30 ± 7
Smokers (%)	1	1	1
Employed (%)	56	56	56
SBP (mm Hg)	125.1±12.9	124.0± 8.2	123.8±8.6
DBP (mm Hg)	79.6±9.5	79.4 ± 7.4	79.5 ± 6.5

Data are expressed as mean ± SD; SBP: Systolic blood pressure; DBP: diastolic blood pressure.

3.1 Food intake composition

After 6 weeks of lifestyle intervention, there was a significant decrease in total energy intake (TEI) by (- 30%) at T1 ($p<0.001$) and (- 32%) at T2 ($p<0.001$), compared to baseline (Table 2).

The distribution of energy intake through the day showed a significant decrease for each meal. Breakfast energy intake was reduced by (- 39%) at T1 ($p<0.01$) and by (- 45%) at T2 ($p<0.01$), respectively, compared to T0. There was a decrease in lunch energy intake values by (- 39%) at T1 ($p<0.001$) and T2 ($p<0.001$). And for dinner we observed a significant decrease by (- 36%) at T1 ($p<0.01$) and T2 ($p<0.01$), respectively, compared to T0. However, a significant increase was noted in afternoon snack by (+ 27%) at T1 ($p<0.01$) and by (+ 18) at T2.

Lunch was the eating occasion with the highest energy intake (33.7%), followed by dinner (30.7%), breakfast (19.8%) and snacking (12%) (Table 2).

Table 2: Distribution of energy intake throughout the day in PCOS women after lifestyle counseling

	Baseline T0	T1	T2
Total Energy Intake			
MJ/day	9.1 ± 1.5	6.4 ± 1.9***	6.2 ± 1.3***
Breakfast			
MJ/day	1.8 ± 1.0	1.1 ± 0.6**	1.0 ± 0.4**
% of TEI	(19.8%)	(17.2%)	(16.1%)
Lunch			
MJ/day	3.4 ± 0.9	2.1 ± 0.9***	2.1 ± 0.7***
% of TEI	(37.4%)	(32.8%)	(33.9%)
Afternoon snack			
MJ/day	1.1± 0.8	1.4 ± 0.7**	1.3 ± 0.7
% of TEI	(12.1%)	(21.9%)	(21.0%)
Dinner			
MJ/day	2.8 ± 0.9	1.8 ± 0.9***	1.8 ± 0.7***
% of TEI	(30.7%)	(28.1%)	(29.0%)

T0: The beginning of life style intervention; T1 (3 weeks) and T2 (6 weeks) after initiating lifestyle counselling. Values are in MJ/day and % of total energy intake (TEI). Data are presented as mean ± standard error. * Significant difference in relation to the baseline (student test). * $p<0.05$. **$p<0.01$. ***$p<0.001$

Food intake composition, showed a significant decrease in protein intake by (-36%) at T1 ($p<0.001$) and T2 ($p<0.001$) (Table 3). Carbohydrates intake was decreased by (-32%) at T1 ($p<0.001$) and T2 ($p<0.001$), respectively, compared to T0. There was a decrease in lipids intake by (- 37%) at T1 ($p<0.001$) and T2 ($p<0.001$). Proteins energy intake was about 15 to 16 %, carbohydrates 44 to 46 % and lipids 38 to 40 %. Qualitative nutritional evaluation showed a significant decrease in plant proteins intake by (-23%) at T1 ($p<0.001$) and at T2 ($p<0.001$), respectively, compared to T0 (Table 3). This intake represented 47 to 61% of total energy protein intake. Starchy food lowered by (-20%) at T1 ($p<0.001$) and (-18%) at T2 ($p<0.001$). Similar sugar intake was observed at T1, T2 compared to baseline. A significant decrease was noted for fiber values by (-25%) at T2 ($p<0.001$).

Results showed a decrease in polyunsaturated fatty acids (PUFA) intake at T1 ($p<0.05$) and T2 ($p<0.01$), compared to baseline. On the other hand, we noticed a significant increase in monounsaturated fatty acids intake (MUFA) after 3 (T1) and 6 weeks ($p<0.05$) of lifestyle intervention, compared to baseline. Saturated fatty acids (SFA) intake was decreased at T1 and T2 ($p<0.001$), compared to T0. Dietary cholesterol consumption was about 315 mg at baseline, this consumption decreased by (- 22%) at T1 ($p<0.05$) and (- 23%) at T2 ($p<0.05$), respectively, compared to T0.

Table 3: Food intake composition in PCOS women after lifestyle counseling

	Baseline T0	T1	T2	DR
Proteins	1.4 ± 0.3	0.9±0.3***	0.9 ± 0.3***	0.8
MJ/day	16	15	16	10
% of TEI	39	53	53	60
Animal (%)[a]	61	47***	47***	40
Vegetable(%)[a]				
Carbohydrates	3.8 ± 0.9	2.6± 0.9***	2.6 ± 0.9***	4.4
MJ/day	44	47	46	55
% of TEI	27	41	40	40
Sugar (%)[a]	73	59***	60***	60
Starch (%)[a]				
Lipids	3.3 ± 0.7	2.1± 1.1***	2.1 ± 1.0***	2.8
MJ/day	40	38	38	35
% of TEI	28	24*	23**	25
PUFA (%)[a]	41	48*	48*	50
MUFA (%)[a]	31	28***	29***	25
SFA (%)[a]				
Cholesterol (mg)	315	246*	244*	<300
Fiber g/d	20	20	15**	30

T0: The beginning of life style intervention; T1 (3 weeks) and T2 (6 weeks) after initiating lifestyle counseling. DR: Dietary recommendation. TEI: Total energy intake. a % of total nutrients intake. Data are presented as mean ± standard error. * Significant difference in relation to the baseline (student test). * p < 0.05. **p<0.01. ***p<0.001

Food quality analysis revealed that nutritional guidance improved starchy food consumption. An increase by (+55%) was noted at T1 (p<0.001) and by (+67%) at T2 (p<0.001) (Table 4). We also observed a significant increase in cooked vegetables consumption group at T1 (p<0.001) and T2 (p<0.001).

Compared to baseline, there was a significant increase in milk and dairy products group intake by (+22%) at T1 (p<0.001) and (+23%) at T2 (p<0.001). Meat, poultry and fish intake was decreased by (-9%) at T2 (p<0.05). Fat intake amount remained unchanged. We observed a significant decrease in sweet products group by (-32%) at T1 (p<0.001) and (-34%) at T2 (p<0.001).

Table 4: The intake of food groups in PCOS women after lifestyle counseling

Food group (g/day)	Baseline T0	T1	T2	DR
Starchy	199±62	309 ± 165***	334 ± 143***	400
Cooked vegetables and fruits	235±144	427± 138***	491 ± 140***	500
Raw vegetables and fruits	113 ± 34	105 ± 30	99 ± 31	50
Milk and dairy products	124 ± 21	152 ± 47***	153 ± 36***	180
Meat, poultry and fish	76 ± 27	70 ± 19	67 ± 15*	50
Fat	73 ± 23	71 ± 22	67 ± 19	60
Sweet products	104 ± 22	71 ± 19***	69 ± 19***	60

T0: The beginning of life style intervention; T1 (3 weeks) and T2 (6 weeks) after initiating lifestyle counseling. DR: dietary recommendations. Data are presented as mean ± standard error. *Significant difference in relation to the baseline (student test). * p < 0.05. **p<0.01. ***p<0.001

3.2 Clinical and biochemical parameters

After six weeks (T2) nutritional follow up we observed a significant decrease by (-8%) in BMI values compared to baseline (p<0.05). Also, body weight was decreased by (-8%) at T2 (p<0.05), and waist circumference decreased by (-3%) at T1 and (-8%), respectively (p<0.001), compared to T0 (Table 5).

A significative decrease was noticed in glucose level by (-5%) at T1 (p<0.05) and by (-8%) at T2 (p<0.001), compared to T0. No significant difference was observed in triacylglycerol concentrations after six weeks of lifestyle advice.

However, TC values decreased by (-6%) at T1 (p<0.05) and by (-11%) at T2 (p<0.01) respectively, compared to T0. A significant increase was noted in HDL-C amounts by (+12%) and (+26%) at T1 and T2 (p<0.001), respectively, compared to T0. LDL-C concentrations were decreased by (-15%) at T1 (p<0.01) and by (-30%) at T2 (p<0.01), compared to T0.

Table 5: Changes in clinical and biochemical parameters in PCOS women after lifestyle counseling.

	Baseline T0	T1	T2
BMI (kg/m²)	28.4 ± 2.4	26.1 ± 3.2	26.3 ± 1.5*
Weight (kg)	75.6 ± 7.7	73.5 ± 5.6	70.0 ± 5.4*
Waist Circumference (cm)	98.9 ± 7.1	94.6 ± 5.6***	91.3 ± 4.8***
Glucose (mmol/L)	5.39 ± 0.70	5.14 ± 0.53*	4.98± 0.47***
TG (mmol/L)	1.96 ± 0.29	1.89 ± 0.19	1.73 ± 0.15
TC (mmol/L)	5.50 ± 0.79	5.21 ± 0.55*	4.90 ± 0.50**
HDL-C (mmol/L)	1.54 ± 0.32	1.73±0.19***	1.94± 0.21***
LDL-C (mmol/L)	3.03 ± 0.85	2.58 ± 0.6**	2.14 ± 0.55**

T0: The beginning of life style intervention; T1 (3 weeks) and T2 (6 weeks) after initiating lifestyle counseling. Data are presented as mean ± standard error. *Significant difference in relation to the baseline (student test). * p < 0.05. **p<0.01. ***p<0.001

3.3 Inflammation, pro-oxidant and antioxidant parameters

There were no statistically significant differences in C - reactive protein concentrations after six weeks of nutritional monitoring (Table 6). Redox status analysis showed a significant decrease in TBARS concentrations by (-20%) at T1 (p<0.05) and by (-31%) at T2 (p<0.05), compared to T0. Carbonyls concentrations were lowered by (-30%) at T1 (p<0.001) and by (-44%) at T2 (p<0.001), compared to T0 (p<0.001) (Table 6). For antioxidant enzymes, we observed that superoxide dismutase activity was increased by (+125%) at T2 (p<0.01), compared to T0. Catalase activity was significantly elevated by (+16%) at T2 (p<0.05), compared to T0.

Thiol values were significantly increased by (+11%) and (+14%) at T1 and T2 (p<0.001) respectively, compared to T0.

Table 6: Changes in CRP, pro-oxidant and antioxidant parameters in PCOS women after lifestyle counseling

	Baseline T0	T1	T2
CRP (mg/L)	3.55 ± 1.83	3.39 ± 2.29	2.96 ± 1.36
TBARS (mmol/L)	23.81 ± 11.05	19.15 ± 8.20*	16.62 ± 8.27*
Carbonyls (mmol/L)	9.37 ± 2.82	6.65 ± 1.73***	5.30 ± 1.53***
SOD (U/mL)	308.24±193.89	394.87±196.00	695.80±584.92**
Catalase (KU/L)	5.07 ± 1.95	4.99 ± 2.15	4.26 ± 2.05*
Thiols (µmol/L)	75.57 ± 12.57	85.34±9.42***	86.63 ± 13.07***

T0: The beginning of life style intervention; T1 (3 weeks) and T2 (6 weeks) after initiating lifestyle counseling. Data are presented as mean ± standard error. * Significant difference in relation to the baseline (student test). * $p < 0.05$. **$p<0.01$. ***$p<0.001$

4 Discussions

The study was conducted in women with PCOS to assess the effects of lifestyle promotion on eating habits, blood glucose, dyslipidemia, inflammation, lipids and protein peroxidation, and antioxidant defense. Women received nutritional counseling based on principles of Mediterranean diet and recommendations for practice moderate physical activity. Food intake and biochemical parameters and all biomarkers were assessed at baseline, and 3, 6 weeks after initiating study. This study demonstrated the beneficial effects of lifestyle promotion on food consumption, body weight, glucose levels, lipid profile and pro-oxidant and antioxidant status. Our investigation showed that in women with PCOS, a decrease in total energy intake, body weight, BMI and waist circumference tends to significantly improve the biochemical profile by noting a significant drop in blood sugar levels and this by favoring foods with a low glycemic index and abandoning sweet products, as well as total cholesterol and LDL cholesterol by highlighting unsaturated fatty acids, and to balance the pro-oxidant-antioxidant balance by adopting a diet rich in fiber and micronutrients, so regular physical activity is essential to adopt a healthy lifestyle and improve health.

There is a close connection between PCOS and obesity; studies have shown that, 40-60 percent of women with PCOS are overweight or obese [12]. It has been reported that, in PCOS women, a reduction by 5-10% of body weight can generate a decrease in the prevalence of cardiovascular risk factors, type 2 diabetes, endocrine and reproductive parameters [22]. Successful body weight loss results from a reduction in calorie intake with regular physical activity and a reduction in daily stress [12]. It is established that increased consumption of fruits, vegetables and whole grains has protective effects against cardiovascular disease and diabetes, while high consumption of animal protein increases the risk of malignancy, so it is evident that the best advice for women with PCOS includes high carbohydrate (55% of calories) and low fat (30% of calories) with moderate protein content (15%) as well as regular physical activity [13]. After six weeks of nutritional counseling follow up, we observed a reduction in glucose values. In this study, we advised the consumption of low glycemic index foods to improve insulin resistance. One of the major consequences of obesity is the development of insulin resistance [10]. Insulin resistance is at the heart of the multifactorial pathogenesis of PCOS, and is associated with metabolic syndrome components, such as cardiovascular risk, hypertension and endothelial dysfunction, which is considered the initial stage of the atherosclerosis process[13]. Almost 50–70% of all women with PCOS have some degree of insulin resistance, and this hormone insensitivity may contribute to the hyperandrogenism being responsible for the signs and symptoms of PCOS [23]. Epidemiological studies have also shown that a low glycemic index diet is associated with reduced risk of cardiovascular disease, type 2 diabetes, insulin resistance and metabolic disorders, as well as reduced risk of endometrial, breast and ovarian cancers. Thus, it appears that the type of carbohydrate intake plays a more important role in maintaining metabolic health than the total amount received[24,25].

In this study, we have noted a significant improvement in the lipid profile; significant decrease in TC and LDL-C, and an increase in HDL-C. Some studies reported lower HDL-C levels and elevated total and LDL-C levels in women with PCOS [26]. Different types of dyslipidemia in women with PCOS have been attributed to the influence of hyperandrogenism and insulin resistance that is commonly seen in women with PCOS, as well as diet, exercise, and genetic predisposition [9]. Atherogenic dyslipidemia predispose women with PCOS to an increased risk of cardiometabolic risks. Intervention strategies are required to prevent cardiovascular diseases in these women category [27]. A recent meta-analysis highlighted a significant association between BMI and LDL-C in women with PCOS [12]. Another study observed that BMI had a significant impact on HDL-C levels in women with PCOS [9]. It has been noted a substantial increase in the prevalence of dyslipidemia in PCOS women with normal BMI [3]. Further studies showed high prevalence of obesity and lipid abnormalities in women with PCOS [28,29]. Variations in body weight and composition alone may not fully explain differences in dyslipidemia in women with PCOS; other factors include genetic and environmental factors such as diet and physical activity levels [26].

Diets with high fat especially saturated and trans fatty acids primarily reduce insulin sensitivity and increase the risk of metabolic syndrome and cardiovascular disease [9]. Thus, a diet containing unsaturated fats, particularly omega-3 polyunsaturated fatty acids, tends to reduce many of metabolic risk factors observed in women with PCOS, such as elevated serum lipid levels, insulin resistance and impaired endothelial function [12].The majority of women with PCOS suffer from an undeniable chronic inflammatory condition. It is explicit that PCOS is associated with a significant increase in several markers of inflammation, including CRP [30]. CRP is an acute phase reagent produced by hepatocytes under the stimulating control of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor α (TNFα). There is growing evidence to support the concept that CRP may not only be a marker but also a mediator of inflammatory processes [31]. A recent meta-analysis has evaluated 31 clinical trials including 2,359 women with PCOS and 1,289 controls and concluded that CRP amount is on average 96%

higher compared with healthy subjects [32]. Unfortunately, in our study and after a targeted nutritional intervention, no significant decrease in CRP was observed. Our study showed a significant decrease in oxidative stress. playing a central role in PCOS pathophysiology. Several studies have shown more circulating oxidative markers in patients with PCOS than in healthy subjects and they are considered to be potential inducers of the pathogenesis of PCOS [33]. The role of oxidative stress in this pathogenesis is not yet completely understood. Studies have suggested that oxidative stress seems to be involved in PCOS by causing an alteration in steroidogenesis in the ovaries, which contributes to increased androgen levels, leading to follicular development disorders and infertility. Oxidative stress is therefore linked to factors such as obesity, insulin resistance and cardiovascular risk in women with PCOS[34]. The intervention with the Mediterranean diet showed a significant increase in antioxidant defense by improvement in SOD, catalase activities and thiols amount. It should be noticed that enzymatic antioxidants act as lines of defense in the cell against the pro-oxidant effect of free radicals [35].

SOD is a potential antioxidant defense enzyme that eliminates superoxide anions (O_2-), as major oxygen radical, by catalyzing them in H_2O_2 and finally by GPx converted to water [36]. SOD activity in the PCOS was reported in several studies. Sabuncu *et al.* determined the antioxidant status in women with PCOS and evaluated the level of SOD in the blood in patients with PCOS compared to healthy controls [37]. They showed that women with PCOS had higher levels of SOD than healthy subjects. In 2009, Kuscu *et al.* determined the role of oxidative stress in endothelial dysfunction in a group of young, non-obese patients with PCOS by measuring blood levels of SOD and showed that SOD levels were significantly higher in a PCOS group than in the control group [38]. In 2013, the result of a meta-analysis showed that mean SOD activity was 34% higher in PCOS patients than in controls[39]. Further studies are needed to examine the mechanism of SOD as an antioxidant defense in PCOS. For the rest of the antioxidant defense endpoints, there have been virtually no studies being able to analyze them. Foods rich in antioxidants could have a direct impact on hormone production and, therefore, the consumption of certain nutrients could help alleviate hormonal symptoms and have a positive effect in the management of PCOS and its complications, although more studies are required in this area because there is insufficient evidence to identify optimal management of antioxidants in women with PCOS [14]. Even if there were promising results, it is clear that if the study had been extended over time, the results would have been much more significant both on the anthropometric side (BMI, weight, waist circumference) and on the biochemical side (glycemia, lipid profile, radical attack and antioxidant defense).

In conclusion, in women with PCOS and metabolic disorders, nutritional counseling follow up, based on the principles of Mediterranean diet associated to a regular physical activity practice have a favorable effect on body weight, glycemia, and dyslipidemia. Moreover, this healthy diet improves oxidative stress by lowering prooxidant markers and enhancing antioxidant defense. At long term, this strategy could be beneficial to prevent or reverse the clustering of metabolic abnormalities and cardiovascular diseases.

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ORCID:
Khedidja MEKKI: https://orcid.org/0000-0002-3398-9041

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