



Original Article

The effect of bariatric surgery on inflammatory markers in women with polycystic ovarian syndrome



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ABSTRACT

Aim: The aims of this study is to address the improvement in CRP and adiponectin in obese PCOS and non PCOS after bariatric surgery, and to show that obese PCOS women have a slower rate of improvement when compared to obese non PCOS women.

Methods: This is a prospective case-control study evaluating the effect of weight loss by sleeve gastrectomy among obese PCOS patients.

Results: There was a 36.28% of weight loss among obese PCOS and 33.04% among the control group at 12 months. Both groups showed a significant increase in the adiponectin levels at 3, 6 and 12 months' post-surgery. The rate of increase was higher in the obese non PCOS women (4.93 ± 1.79 – 9.79 ± 3.9) compared to obese PCOS women (5.05 ± 1.98 – 7.25 ± 0.21). The CRP levels decreased with weight loss after the surgery to reach statistical significance at 3 months in obese PCOS group (4.18 ± 3.94 , $p = 0.048$).

Conclusion: The degree of weight loss after surgery was effective in lowering CRP and increasing adiponectin levels in PCOS women. However, this improvement was slower compared to obese non PCOS patients. A genetic predisposition to insulin resistance might explain these findings.

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1. Introduction

Polycystic Ovary Syndrome (PCOS) affects 6–10 % of obese and non-obese women of reproductive age [1]. It is characterized by oligo-ovulation or anovulation, hyperandrogenism or hyperandrogenemia, and polycystic ovaries on ultrasound [2]. Thirty percent of women with PCOS are obese where obesity is associated with insulin resistance, dyslipidemia, and hypertension [3,4]. In addition, PCOS women are at increased risk of cardio-vascular diseases compared to their age-matched control displaying higher oxidative stress and dysfunction of the adipose tissue [5].

As a known marker of inflammation, C-reactive protein (CRP) is secreted by the liver, in response to cytokines (IL-6, TNF- α) [6,7]. The levels are increased with insulin resistance, metabolic syndrome and diabetes [8]. Its positive correlation with obesity is well established too; adipose tissue contributes to the elevation of CRP levels through the secretion of cytokines [9]. However, CRP

elevation in obese patients is not consistent. Such an observation is explained by inter-individual genetic polymorphism [10].

Adiponectin is another inflammatory substance secreted by adipocytes in adipose tissue, with insulin sensitizing, and anti-inflammatory effects [11]. Obese patients were found to have lower levels of adiponectin [12].

There is an inverse relationship between adiponectin and CRP [13], thus a higher level of adiponectin is beneficial in terms of insulin sensitivity and anti-inflammatory properties. It has been acknowledged, that obese PCOS patients, have high CRP levels [14,15] and low adiponectin levels [16–18]. Many studies have shown that weight loss decreases CRP in obese PCOS women [19] and obese non PCOS women [20,21]. However, weight loss increases adiponectin levels in obese PCOS and non PCOS women, paralleled by improved insulin sensitivity [22].

Lifestyle changes is considered the first line treatment for PCOS [23]. World Health Organization (WHO) has recommended weight loss as one of the most important parameter in the management of PCOS [24]. However, maintenance of weight loss is hard to achieve, thus the need for an intervention that results in a permanent lasting reduction in weight [25].

The effect of bariatric surgery has been studied on menstrual irregularities, hormonal changes and hyperandrogenemia in obese

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PCOS patients [26–28]. It has been established that bariatric surgery is effective in the management of morbid obesity, with improved insulin sensitivity [27,29]. Nevertheless, less is known regarding the effect of bariatric surgery on inflammatory markers (adiponectin and CRP) and anthropometric measurements in obese PCOS patients [27].

In view of the profound metabolic derangements in obese PCOS patients, the primary objective of this study is to address the improvement in the inflammatory markers (CRP and adiponectin) as well as anthropometric measurements in both obese PCOS and non PCOS patients after bariatric surgery. The secondary objectives are to show that obese PCOS women have a slower rate of improvement in these parameters after surgery compared to obese non PCOS women, and to assess the correlation between the change in CRP, adiponectin and metabolic profile after weight loss via sleeve gastrectomy.

2. Materials and methods

2.1. Subjects

In a prospective case-control study, we approached patients at the American University of Beirut Medical Center from November 2015 to November 2018.

Twenty-five obese patients presenting to bariatric surgery unit at AUBMC for sleeve gastrectomy were evaluated for PCOS according to Rotterdam criteria [1]. Six patients were diagnosed with PCOS and 19 patients had no PCOS. The study was approved by the Institutional Review Board committee. Informed consent was obtained from each participating subject.

Obesity was defined on the basis of body mass index (BMI) greater or equal than 40 kg/m^2 or greater than 35 kg/m^2 with severe obesity related conditions (diabetes, hypertension, dyslipidemia). All women were between 18 and 45 years of age, determined to undergo bariatric surgery. Exclusion criteria were pregnancy, BMI less than 40 kg/m^2 , history of cancer or liver disease and a previous history of bariatric surgery. Patients were also excluded if they were trying to conceive.

Consort criteria are documented in Fig. 1.

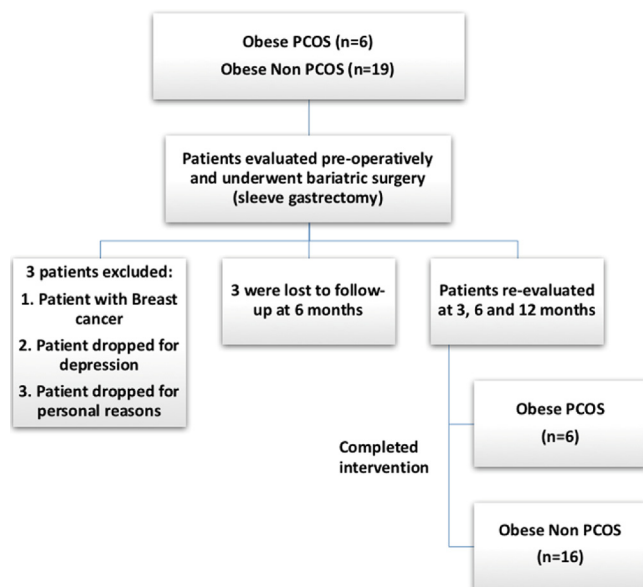


Fig. 1. Flow diagram of subjects with and without PCOS who completed a 12 months' follow-up after bariatric surgery.

2.2. Study design

The study was conducted on an outpatient basis over 12 months. Subjects attended the clinic periodically at 3, 6 and 12 months, and were weighed in light clothes with no shoes.

Ferriman Gallwey score was also evaluated at the different time points and a score >8 was considered as clinical hirsutism [30]. All anthropometrical measurements were made by the same trained staff. Weight was measured to the nearest 0.1 kg, height was measured to the nearest 0.5 cm, and BMI (kg/m^2) was computed.

2.3. Metabolic parameters, CRP and adiponectin measurement

Overnight fasting blood samples were collected for evaluation of glucose, insulin, testosterone, Sex Hormone Binding Globulin (SHBG), lipid profile, CRP and adiponectin. We measured adiponectin using a commercial immunoassay (Human Resistin ELISA Kit) and CRP using spectrophotometric commercial kit.

2.4. Statistical analysis

Results were presented for 22 subjects. For all included patients, descriptive and comparative statistics of demographics were analyzed. Summary statistics were presented as percentages for categorical variables compared using the Chi-square test, and mean \pm standard deviation (SD) were used for continuous variables and compared using Student's *t*-test or one-way analysis of variance. Inflammatory markers were also correlated with biochemical parameters and the results were analyzed using Pearson's correlation coefficient. Statistical analysis was performed using SPSS IBM version 24 software, and a value of $p < 0.05$ was considered to be statistically significant.

3. Results

A total of twenty-two subjects completed the intervention (6 PCOS and 16 non-PCOS) with 0% dropout rate. The mean age in non PCOS women was 27.06 years and 23.83 years in PCOS women. The mean preoperative BMI in obese non PCOS women was found to be $40.54 \pm 6.85 \text{ kg/m}^2$ compared to $41.05 \pm 5.08 \text{ kg/m}^2$ in PCOS women with an overall mean BMI of 40.49 kg/m^2 . We followed the changes in inflammatory markers, lipid profile and anthropometric measurements at 3, 6 and 12 months after sleeve gastrectomy. The surgery was well tolerated by all subjects with no adverse events documented.

Baseline demographics between Obese PCOS and Obese non PCOS subjects are summarized in Table 1. The 2 groups were comparable at the baseline level except for the Ferriman Gallwey score, testosterone levels and SHBG levels which were significantly higher in the obese PCOS group ($p = 0.001$, 0.043 and 0.008 respectively) justifying the higher incidence of hirsutism in this group.

3.1. Weight loss and body composition

BMI was dramatically reduced 1 year after surgery with significant difference in weight loss between women with and without PCOS ($36.28\% \pm 2.93$ vs $33.04\% \pm 6.84$ respectively, $p = 0.002$). A reduction in the waist to hip ratio was seen at 3, 6 and 12 months after the surgery, however this reduction was not significantly different between the 2 groups (0.9 ± 0.04 vs 0.88 ± 0.07 , $p = 0.639$).

3.2. Fasting lipids, FBS, adiponectin, and CRP levels

3.2.1. Lipids

LDL cholesterol and triglycerides were significantly reduced at 3, 6 and 12 months in both groups (Table 2a), and HDL cholesterol

Table 1
Baseline demographics between Obese PCOS and Obese non PCOS women.

	Obese Non PCOS (n = 16)	Obese PCOS (n = 6)	P value
Age (years)	28 ± 7	24 ± 5	0.175
Age at menarche (years)	12 ± 1	12 ± 1	0.242
Ferriman Gallwey Score	5 ± 5	17 ± 10	0.001
Waist circumference (cm)	117.88 ± 16.92	120.33 ± 13.65	0.753
Hip circumference (cm)	132.93 ± 13.06	133.67 ± 9.87	0.901
Waist/Hip ratio	0.88 ± 0.07	0.9 ± 0.04	0.639
BMI (kg/m ²)	40.54 ± 6.85	41.05 ± 5.08	0.867
Albumin (g/L)	44.94 ± 2.26	42.67 ± 1.86	0.041
HDL-cholesterol (mg/dL)	49.47 ± 11.72	47.33 ± 9.22	0.688
LDL-cholesterol (mg/dL)	119.77 ± 28.2	114.67 ± 25.71	0.698
Triglyceride (mg/dL)	122.16 ± 98.91	104.67 ± 34.82	0.679
CRP (mg/L)	10.04 ± 5.85	6.63 ± 4.12	0.203
Testosterone (ng/dL)	13.18 ± 6.37	21.62 ± 11.99	0.043
Adiponectin (ug/mL)	4.86 ± 1.74	5.05 ± 1.98	0.83
Fasting blood sugar (mg/dL)	101.66 ± 35.42	94.5 ± 9.73	0.634
Sex Hormone Binding Globulin (nmol/L)	31.72 ± 7.86	40.43 ± 36.34	0.008

Results are expressed as mean ± standard deviation.

was significantly increased in both groups at 3, 6 and 12 months. However, the rate of increase in HDL was slower in obese PCOS patients (Table 2a).

3.2.2. FBS

There was a significant change in fasting glucose with weight loss in both groups with 102.13 ± 37.65 to 87.29 ± 14.26 in non

PCOS women ($p < 0.001$) and from 94.5 ± 9.73 to 85 ± 7.81 in PCOS women ($p = 0.003$) (Table 2a).

3.2.3. Adiponectin levels

Adiponectin levels were comparable at baseline between the 2 groups with non-significant higher levels observed in PCOS group (5.05 ± 1.98 compared to 4.93 ± 1.79). Both groups showed a

Table 2a
Effect of weight loss on biochemical parameters, C-reactive protein and adiponectin levels before and after bariatric surgery.

		Obese Non PCOS (n=16)	P value	Obese PCOS (n=6)	P value
HDL-c (mg/dL)	Pre-operative	49.47 ± 11.72		47.33 ± 9.22	
	3 months	51.5 ± 13.41	<0.001	46.17 ± 10.7	<0.001
	6 months	54.78 ± 13.5	<0.001	52.67 ± 3.21	0.001
	12 months	64.86 ± 22.43	<0.001	58.33 ± 7.09	0.005
LDL-c (mg/dL)	Pre-operative	119.77 ± 28.2		114.67 ± 25.71	
	3 months	116.86 ± 34.55	<0.001	106.83 ± 38.15	0.001
	6 months	124.67 ± 39.7	<0.001	105 ± 15.72	0.007
	12 months	124.43 ± 38.22	<0.001	101 ± 3	<0.001
Triglyceride (mg/dL)	Pre-operative	122.16 ± 98.91		104.67 ± 34.82	
	3 months	95.43 ± 55.13	<0.001	81.67 ± 24.88	<0.001
	6 months	99 ± 34.8	<0.001	85.67 ± 7.57	0.003
	12 months	81.14 ± 24.35	<0.001	65.67 ± 4.04	0.001
CRP (mg/L)	Pre-operative	10.04 ± 5.85		6.63 ± 4.12	
	3 months	4.51 ± 3.44	<0.001	4.18 ± 3.94	0.048
	6 months	4.21 ± 2.48	<0.001	1.2 ± 0.79	0.120
	12 months	2.14 ± 1.15	0.003	1.5 ± 1.74	0.275
Testosterone (ng/dL)	Pre-operative	13.18 ± 6.37		21.62 ± 11.99	
	3 months	7.13 ± 5.33	<0.001	10.29 ± 6.39	0.011
	6 months	6.85 ± 5.24	0.003	14.81 ± 15.15	0.232
	12 months	6.87 ± 4.96	0.003	10.01 ± 9.45	0.208
Adiponectin (ug/mL)	Pre-operative	4.86 ± 1.74		5.05 ± 1.98	
	3 months	8.23 ± 2.86	<0.001	6.74 ± 2.98	0.007
	6 months	7.5 ± 3.54	<0.001	6.4 ± 2.34	0.042
	12 months	9.79 ± 3.9	0.001	7.25 ± 0.21	0.013
Insulin (μU/mL)	Pre-operative	18.53 ± 13.9		23.98 ± 7.06	
	3 months	7.98 ± 4.53	<0.001	14.45 ± 7.49	0.05
	6 months	7.03 ± 4.12	<0.001	5.97 ± 3.27	0.087
	12 months	5.09 ± 2.71	0.003	6.1 ± 1.71	0.025
FBS (mg/dL)	Pre-operative	101.66 ± 35.42		94.5 ± 9.73	
	3 months	87.36 ± 18.05	<0.001	88.33 ± 5.2	<0.001
	6 months	104.7 ± 68.39	0.001	81.33 ± 3.51	0.001
	12 months	87.29 ± 14.26	<0.001	85 ± 7.81	0.003
SHBG (nmol/L)	Pre-operative	31.72 ± 7.86		40.43 ± 36.34	
	3 months	77.38 ± 28.83	<0.001	58.62 ± 30.44	0.005
	6 months	76.95 ± 30.22	<0.001	67.1 ± 57.87	0.110
	12 months	133.09 ± 162.25	0.073	62.8 ± 29.3	0.065

Results are expressed as mean ± standard deviation.

HDL-c: HDL-cholesterol, LDL-c: LDL-cholesterol, CRP: C-reactive protein, FBS: Fasting Blood Sugar, SHBG: Sex Hormone Binding Globulin.

significant increase in the adiponectin levels at 3, 6 and 12 months' post-surgery (Table 2a). The rate of increase seen was higher in the obese non PCOS women (4.93 ± 1.79 – 9.79 ± 3.9) compared to obese PCOS women (5.05 ± 1.98 – 7.25 ± 0.21) (Table 2a).

3.2.4. CRP levels

At baseline, CRP was higher in obese non PCOS group (9.55 ± 5.14) compared to obese PCOS group (6.63 ± 4.12), however not statistically significant ($p = 0.329$). The CRP levels decreased with weight loss after the surgery to reach statistical significance and normal values at 3 months in obese PCOS group (4.18 ± 3.94 , $p = 0.048$). As for the non PCOS group, the CRP levels continued to decrease significantly at 3, 6 and 12 months ($p < 0.001$, $p < 0.001$, $p = 0.003$ respectively) (Table 2a).

3.3. SHBG, testosterone and insulin levels

3.3.1. SHBG

In PCOS women, SHBG increased significantly at 3 months (58.62 ± 30.44 , $p = 0.005$). However, this increase plateaued at 6 and 12 months after surgery. In non PCOS women, it more than doubled significantly at 3 (77.38 ± 28.83 , $p < 0.001$) and 6 months (76.95 ± 30.22 , $p < 0.001$).

3.3.2. Testosterone levels

In contrast, total testosterone decreased significantly, about 50% during the first three postoperative months (7.13 ± 5.33 , $p < 0.001$ in non PCOS and 10.29 ± 6.30 , $p = 0.011$ in PCOS) in both groups. The drop in testosterone was significantly higher in non PCOS patients. Nevertheless, it remained constant thereafter in PCOS group at 3, 6 and 12 months.

3.3.3. Insulin levels

Insulin levels were significantly higher in the obese PCOS group at baseline with 23.98 ± 7.06 $\mu\text{U/mL}$ compared to 16.68 ± 9.48 $\mu\text{U/mL}$ in non PCOS ($p = 0.049$). It showed a decreased trend after weight loss in both groups, and it improved markedly within the first 3 postoperative months in PCOS women (14.45 ± 7.49 , $p = 0.005$) and 1 year after the surgery (6.1 ± 1.71 , $p = 0.025$). However, the rapid drop in insulin was more statistically significant in obese non PCOS as compared to obese PCOS women.

3.4. Anthropometrical measurements

The weight loss was most rapid during the first three post-operative months with a BMI of 41.05 – 33.2 in PCOS women and 40.54 to 32.82 in non PCOS women. In both groups, the BMI continued to decrease, yet not as rapid as before and the decrease was slower in PCOS patients.

Following surgery, waist circumference decreased rapidly with weight loss at 3 months in both groups and remained more or less constant thereafter.

The waist/hip-ratio declined after three months (0.90 to 0.81 in PCOS and 0.88 to 0.84 in non PCOS) and remained stable thereafter. Anthropometric measurements changed significantly after bariatric surgery in both groups, however PCOS women had a slower rate of improvement (Table 2b).

In obese PCOS group, preoperative levels of CRP correlated negatively only with HDL cholesterol ($r = -0.943$, $p < 0.01$). In the control group, the CRP levels correlated positively with BMI ($r = 0.736$, $p < 0.01$) and the adiponectin levels correlated positively with TG ($r = 0.661$, $p < 0.01$).

For obese PCOS women, the change in CRP correlated with the change in BMI at 6 months ($p < 0.01$). However, it did not correlate in case of non PCOS status.

At 12 months, positive correlations were seen in PCOS women between adiponectin levels and the following: HDL ($r = 1$, $p < 0.01$), LDL ($r = 1$, $p < 0.01$), testosterone ($r = 1$, $p < 0.01$), FBS ($r = 1$, $p < 0.01$), and SHBG ($r = 1$, $p < 0.01$), and negative correlations with: BMI ($r = -1$, $p < 0.01$) and triglyceride ($r = -1$, $p < 0.01$). Also, CRP levels correlated positively with LDL ($r = 1$, $p < 0.01$), insulin ($r = 1$, $p < 0.01$), and negatively with FBS ($r = -1$, $p < 0.01$), and SHBG ($r = -1$, $p < 0.01$). As for the control group, adiponectin was only correlated with HDL ($r = 0.786$, $p < 0.05$) and CRP did not correlate with any of the lipid profile, testosterone, insulin and BMI (Table 3).

4. Discussion

4.1. C-Reactive protein

Our study has detected a 36.28% of weight loss in women with PCOS and 33.04% in women without PCOS. We showed a 77.3% decrease in CRP in obese PCOS women and 78.6% in obese non PCOS women. The effect of weight loss on reducing CRP in obese

Table 2b
Effect of weight loss on anthropometrical characteristics before and after bariatric surgery.

		Obese Non PCOS (n = 16)	P value	Obese PCOS (n = 6)	P value
Waist Circumference	Pre-operative	117.88 \pm 16.92		120.33 \pm 13.65	
	3 months	100.43 \pm 13.67	<0.001	99.28 \pm 8.70	<0.001
	6 months	97.60 \pm 11.79	<0.001	88.67 \pm 15.95	0.011
	12 months	90.71 \pm 6.28	<0.001	83.67 \pm 15.31	0.011
Hip circumference	Pre-operative	132.93 \pm 13.06		133.67 \pm 9.87	
	3 months	118.89 \pm 15.17	<0.001	119.92 \pm 10.40	<0.001
	6 months	114.85 \pm 11.88	<0.001	108.83 \pm 15.30	0.007
	12 months	93 \pm 29.05	<0.001	102.33 \pm 11.37	0.004
Waist/hip ratio	Pre-operative	0.88 \pm 0.07		0.90 \pm 0.04	
	3 months	0.85 \pm 0.09	<0.001	0.82 \pm 0.05	<0.001
	6 months	0.87 \pm 0.09	<0.001	0.81 \pm 0.04	0.001
	12 months	0.84 \pm 0.06	<0.001	0.81 \pm 0.05	0.001
BMI (kg/m ²)	Pre-operative	40.54 \pm 6.85		41.05 \pm 5.08	
	3 months	32.82 \pm 6.40	<0.001	33.20 \pm 5.05	<0.001
	6 months	31.41 \pm 5.13	<0.001	27.97 \pm 5.95	0.015
	12 months	28.40 \pm 3.72	<0.001	24.93 \pm 3.73	0.007
Weight (kg)	Pre-operative	107.20 \pm 22.81		111.02 \pm 16.10	
	3 months	87.81 \pm 19.20	<0.001	90.02 \pm 15.09	<0.001
	6 months	84.08 \pm 16.17	<0.001	75.80 \pm 17.57	0.017
	12 months	74.46 \pm 12.77	<0.001	67.53 \pm 11.91	0.01

Results are expressed as mean \pm standard deviation.

Table 3

Correlation coefficients at baseline between adiponectin levels, CRP, BMI and metabolic characteristics in both groups.

	Obese Non PCOS		Obese PCOS	
	Adiponectin	CRP	Adiponectin	CRP
BMI	−0.214	0.736**	−0.371	0.486
HDL-c	0.456	0.028	−0.714	−0.943**
LDL-c	0.186	0.193	−0.257	0.200
Triglycerides	0.661**	0.277	0.314	0.029
Testosterone	0.158	−0.110	0.371	0.143
Insulin	−0.263	0.040	−0.086	0.600
FBS	0.339	0.071	−0.257	−0.143
SHBG	0.313	0.405	0.371	−0.429

** $p < 0.01$.

patients is well documented in the literature [20,21]. However, none of these studies have focused on the effect of bariatric surgery on inflammation in obese PCOS women. A meta-analysis showing the association between elevated CRP levels and obesity has shown that BMI is significantly correlated with CRP ($r = 0.36$) [31]. We also demonstrated the positive correlation between CRP and BMI ($r = 0.736$, $p < 0.01$) in obese non PCOS women. However, this correlation was lower and not significant in obese PCOS patients ($r = 0.486$, $P > 0.05$). Based on these results, we demonstrated a significant drop in CRP levels after weight loss only at 3 months to plateau later on in obese patients with PCOS whereas the improvement in non PCOS patients was significant at all points of follow-up till 12 months. This can be explained by the fact that obese PCOS women display a high inflammatory status, that might be resistant to weight loss, secondary to genetic predisposition to insulin resistance [32].

Whilst, several studies have showed that obese PCOS patients have higher CRP levels compared to non-obese patients [14,15], a meta-analysis assessing the circulating inflammatory markers in PCOS patients indicated that CRP is the main marker of the chronic low-grade inflammatory state in PCOS. This demonstrates that CRP levels are independent of obesity in PCOS patients [33]. This is in line with our findings, where despite significant weight loss after bariatric surgery, the drop in CRP levels plateaued after 3 months.

4.2. Anthropometrical measurements

As expected, patients displayed anthropometrical abnormalities associated with morbid obesity. Measurements were comparable at baseline with non-significant higher measurements of waist circumference (WC), hip circumference (HC) and waist/hip ratio (W/H) in obese PCOS group compared to obese non PCOS. Improvements in these measurements are significant only after 10% of weight loss after diet control (WC: 100 to 86, HC: 111 to 101, W/H: 0.90 to 0.86) [34]. Our study has found a similar trend with a decrease in all 3 parameters in obese PCOS patients only after 3 months of surgery. Nonetheless, these parameters almost plateaued at 6 and 12 months in obese PCOS women compared to obese non PCOS women who displayed a continuous improvement at all levels.

4.3. Adiponectin

Despite the small sample size in the PCOS group, we detected a significant increase in adiponectin levels at 3, 6 and 12 months following bariatric surgery (6.74, $p = 0.007$, 6.4, $p = 0.042$, and 7.25, $p = 0.013$ respectively), plateauing at 3 months. Whereas, adiponectin level in obese non PCOS women continued to increase till 12 months, reaching a level of 9.79 $\mu\text{g/mL}$.

Studies in mice showed that adiponectin, a fat derived hormone secreted from adipocytes, lowers CRP along with TNF levels

resulting in an inhibition of vascular inflammation [35]. It is already proven that adiponectin possesses anti-atherogenic and anti-inflammatory properties [36]. Adiponectin, insulin and androgen levels are highly linked too. Inflammatory markers such as adipokines contribute to hyperinsulinemia [37]. Higher insulin levels increase the production of androgens, and decreases the production of SHBG leading to anovulation [38]. Previous studies have disclosed a hypo-adiponectinemia state in all PCOS patients (irrespective of weight) [39], where this was related to the intrinsic insulin resistance. This might explain the slow improvement of adiponectin in obese PCOS patients demonstrated in our study after significant weight loss when compared to obese non PCOS.

4.4. Testosterone, SHBG and insulin

Ovarian theca cells of PCOS women are well identified in the secretion of excessive androgens, favoring the deposition of visceral adiposity, and consequently the development of insulin resistance [40].

The effect of bariatric surgery on circulating androgen levels has been described previously, however, mechanisms remain to be established [27,41]. We showed a 50% decrease in androgen levels, especially testosterone, in obese PCOS patients during the first three postoperative months. This is in line with a prospective nonrandomized study that showed a decrease in testosterone levels by half after 6 months in PCOS patients [42]. However, levels remained constant at 3 months in our PCOS group. The decrease in testosterone is explained by the parallel increase in SHBG. Similar observation was noted for SHBG that also decreased at 3 months and plateaued thereafter. As for the obese non PCOS group, the decrease in androgens and the increase in SHBG continued till 12 months of follow-up. These findings put the intervention under question in terms of hyperandrogenemia benefits in case of PCOS patients. The intrinsic state of ovaries in case of PCOS patients is an explanation to the slow improvement observed in androgen levels after surgery.

Insulin has been demonstrated to stimulate the secretion of ovarian androgens via ovarian LH receptors [43]. Therefore, another mechanism that supports the rapid decrease at 3 months in obese PCOS patients is related to the significant improvement in insulin levels at 3 months after weight loss surgery (14.45 ± 7.49 , $p = 0.005$). Multiple studies have showed similar results with respect to the decrease in insulin concentrations and increase in SHBG after bariatric surgery [44,45]. Furthermore, a new ovarian state is reached after the surgery explained by the constant androgen levels, confirming the results observed by Skubleny and Kjær [27,29]. Nonetheless, this state that is reached after 3 months in obese PCOS patients, stabilizes whereas obese non PCOS patients continue to decrease their insulin levels resulting in a better improvement of their metabolic syndrome. These findings are replicated earlier in a case control study that suggested that PCOS associated insulin resistance (IR) is linked to a defect in insulin signaling, whereas obesity-associated insulin resistance is associated with the levels of adiponectin and CRP levels [46].

4.5. Lipid profile and FBS

Bariatric surgery has been shown to have positive effects in PCOS patients with decrease in BMI, testosterone, FBS and lipid profile [25]. This is supported by our study that illustrated a similar response for subjects with and without PCOS with respect to total cholesterol, HDL-C, LDL-C and triglycerides after bariatric surgery. However, obese PCOS patients demonstrated a plateauing in the levels of their lipid profile after 3 months, mainly LDL-c (106.83 mg/dL at 3 months, 105 mg/dL at 6 months and 101 mg/dL at 12 months) and triglycerides (81.67 mg/dL at 3 months and

85.67 mg/dL at 6 months). This finding might be related to the above discussed genetic predisposition to insulin resistance.

As for the plateauing observed in blood sugar at 3 months, the intrinsic defect in the GLUT4 glucose transporters in adipocytes among PCOS patients is a principal explanation. As a result, PCOS women experience a decrease in the adipocytes glucose uptake with diminished responsiveness to insulin [47].

4.6. Limitations and strengths

This study has several limitations including the small sample size, the challenge in recruiting obese PCOS patients willing to undergo a bariatric surgery. Several patients were lost to follow-up at 6 and 12 months. On the other hand, it shares many strengths. It's the first prospective study investigating the effect of bariatric surgery on inflammatory markers and anthropometric measurements in obese PCOS patients, thus eliminating the potential recall bias that might ensue. We included PCOS patients with uniform diagnostic criteria (Rotterdam criteria), and all patients underwent one type of bariatric surgery that was performed by two surgeons.

5. Conclusions

To our knowledge, this is the first study demonstrating that obese PCOS patients benefit from sleeve gastrectomy in terms of inflammatory markers and anthropometric measurements that become apparent very early after the surgery via improvement in insulin sensitivity. The degree of weight loss after bariatric surgery was effective in lowering CRP concentrations and increasing adiponectin levels in PCOS women. However, this improvement was slower compared to obese non PCOS patients three months after surgery. That can be explained on the basis of a possible genetic predisposition to insulin resistance and abnormal glucose metabolism. Based on these findings, the study can be used as a counseling tool to obese patients with PCOS. These patients will experience a significant improvement in anthropometric and inflammatory markers, however the effect plateaued few months after surgery.

Conflicts of interest

Authors have nothing to declare.

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