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Increased inflammatory markers in women having Polycystic ovarian disorder (PCOS)

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Abstract
Background
Polycystic ovarian disorder (PCOS) is a condition in which the ovaries produce an abnormal amount of androgens, male sex hormones that are usually present in women in small amounts. The name polycystic ovary syndrome describes the numerous small cysts (fluid-filled sacs) that form in the ovaries. Most of the symptoms of PCOS are caused by higher-than-normal levels of certain hormones, called androgens. PCOS is associated with a significant elevation of multiple markers of inflammation including CRP, IL-18, MCP-1, and white blood count. Furthermore, PCOS is associated with other derangements associated with inflammation such as increased oxidative stress and endothelial dysfunction.
Purpose
Since PCOS is known to be associated with reproductive morbidity and increased risk for endometrial cancer, diagnosis is especially important because PCOS is now thought to increase metabolic and cardiovascular risks. PCOS is associated with a significant elevation of multiple markers of inflammation including CRP, IL-18, MCP-1, and white blood count. Furthermore, PCOS is associated with other derangements associated with inflammation such as increased oxidative stress and endothelial dysfunction. PCOS patients showed significant reductions in quality-of-life, increased psychological disturbances, and decreased sexual satisfaction when compared with healthy controls.
Methods
The authors reviewed all relevant case series, case reports, RCTs and clinical trials via systematic evaluation of abstracts and titles available on PubMed, sci-hub and Medline database within the range of past 10 years for better analysis excluding the articles which were not including the specifications regarding increased inflammatory markers in women having PCOS.Data on women's age, BMI, season, irregular menstrual cycle, smoking habits, history and presentation of other diseases were taken from medical records.
Results
38 studies involving the mean number of 108 consenting female participants were evaluated. Their median age at diagnosis was found to be 26.55 years and median of their BMI was calculated to be 25.51 kg/m^2. A significant relationship between obesity, hyperandrogenism and PCOS was observed. Significant elevated levels of serum CRP were also noted in most of the studies conducted.
Conclusion
It was found that women with PCOS present with hyperinsulinemia and a higher incidence of HoMA-IR, which demonstrates the association of the hyperandrogenic phenotypes with increased HoMA-IR incidence in women with PCOS. Increased risk of diabetes, hyperinsulinemia, hyperglycaemia, dyslipidaemia and systemic hypertension were the common symptoms associated with increased inflammatory markers in PCOS. Additionally, it was also noted that Women with PCOS presents with higher total cholesterol, triglyceride, and LDL levels than women without PCOS.

Keywords
Polycystic Ovary Syndrome (PCOS), body mass index (BMI), body composition, C-reactive protein (CRP), chronic inflammation, insulin resistance, Inflammatory markers, Cardiovascular disease, Low-density lipoprotein, impaired glucose tolerance, cytokine ratio, hyperandrogenism, adhesion molecules, adipokines, androgen.

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I. Introduction

Polycystic ovary syndrome (PCOS), characterized by high androgen levels, ovulatory dysfunction, and polycystic ovary, is one of the most common endocrinopathies in reproductive-aged women with a prevalence of 7–10%[1]. PCOS is also associated with an increased number of cardiovascular risk factors, such as oxidative stress, elevated homocysteine (Hcy), and increased C-reactive protein (CRP); it can also affect female fertility[2]. The etiopathogenesis of polycystic ovarian syndrome, a complicated and multifaceted disease with metabolic abnormalities, is not well understood. Patients with PCOS frequently have a pro-inflammatory condition, obesity, and IR together. It impacts metabolism (insulin resistance, impaired glucose tolerance, etc.), psychological traits, and reproduction.It is characterized by visceral obesity, glucose intolerance, insulin resistance,dyslipidemia, all of which may increase the risk of Type 2 diabetes and cardiovascular diseases. Lately, there is a rise of numerous inflammatory markers observed in women with PCOS. In these patients, elevation in white blood cell (WBC) count, C-reactive protein (CRP), and some cytokine concentrations, including interleukin 6 (IL-6), interleukin 18 (IL-18), and tumor necrosis factor-α (TNF-α), is found[3]. Recent evidence indicates that chronic inflammation may play an important role in PCOS and its complications. Women with PCOS have elevated serum inflammation factors which inhibit insulin secretion, reduce insulin signal transduction, and give rise to glucose intolerance[4]. Controversial studies have indicated that PCOS per se could promote an inflammatory state, where serum levels of IL-6 and C-reactive protein (CRP) are elevated like obesity instead, TNF-α levels are highly related to body mass index (BMI) and obesity state, rather than to PCOS condition alone[5]. The current study, we wanted to completely analyze the fact that, when compared to the respective BMI-matched control groups, lean and obese patients with PCOS have elevated inflammatory markers.

II. Methods

The rise in inflammatory markers in PCOS-affected women was the subject of a thorough literature search on the databases of PubMed, Medline, and Google Scholar, which included case series, case reports, retrospective case control studies, various clinical trials, and RCTs. Medical records were used to gather information on women's age, BMI, season, irregular menstrual cycle, smoking habits, history, and presentation of other disorders. 108 consenting female participants who had been informed of the procedures, advantages, and hazards of participation were evacuated. The permission form also stated the study's objective. A description of how to obtain the research's findings, the availability of counseling services, voluntary involvement, and the researchers' contact information were all considered.In addition, relevant articles were searched for in the references of a few systematic reviews and randomized control trials. All the original studies were gathered using the advanced search function in PubMed. The syntaxes which were used to collect the relevant articles were a) Increased inflammation markers in women having PCOS b) Increased inflammation markers in women having PCOS AND clinical findings c) Increased inflammation markers in women having PCOS AND symptoms d) Increased inflammation markers in women having PCOS AND diagnosis and e) Increased inflammation markers in women having PCOS AND treatment.

Inclusion criteria

The studies a) which investigated increased inflammatory markers and its clinical findings, b) which examined its treatment and management plan and c) which included women having PCOS met the inclusion criteria.

Exclusion Criteria

Studies which were in languages other than English and the ones which involved animal models were excluded.

Data extraction

Reviewers independently gathered information from each publication about PCOS inflammatory indicators that had been published. The following details were taken from all the pertinent studies: first author, publication year, nation, research design, participant count, and age at diagnosis. Discharge disposition and treatment given to the participants were recorded. outcomes examined include Cardiovascular disease, Diabetes Mellitus, obesity, renal disease, myocardial disease, irregular menses, smoking, acne, hirsutism, alopecia, and seborrhea. progression to other diseases and symptoms were also recorded. Lab values including insulin, fasting glucose, HoMA-IR, fibrinogen, hs-CRP, FSH, LH, FBG, estradiol, progesterone, triglycerides, HDL, LDL and total cholesterol were also mentioned. Discharge disposition and treatment given to the participants were recorded.

Mean was the first choice during data collection of lab values. When the mean value was not available, the median of the data was calculated.

III. Results

A total of 291 publications met the initial criteria of which 38 papers, providing all necessary data, were selected in this meta-analysis (Search flow chart is presented in fig.1). Characteristics of the included articles are summarized in table 1.

In terms of geographic region, the papers were widely selected from all over the world. Countries like China and Brazil gave the mostnumber of selectable papers. No region was mentioned for 11 papers.

For study design, there were 25 case series and 13 case reports. Of the studies that could be pooled, most provided data in more than 1 outcome: 17 provided data on Obesity, 7 on cardiovascular diseases, 3 on Diabetes Mellitus, 12 on Irregular Menses, 7 on Acne, 12 on Hirsutism, 4 on Alopecia and 1 on Smoking, Renal Disease, Myocardial Disease and Seborrhea. In some studies, the results are not pooled and instead are represented as their median. 34 papers, which are case reviews and randomized controlled trials, are also included in the study. 20 papers about vaccines and treatments are also taken into consideration. Based on the 38 pooled studies, the categories which are highly associated with PCOS are found to be Obesity, Irregular Menses, Hyperandrogenism and CVD. Polycystic Ovary Syndrome is a complex phenomenon accompanied by metabolic dysfunction, adiposity and low grade chronic inflammation[6]. PCOS patients have demonstrated Oxidative Stress (OS) due to hyperglycemia, Insulin Resistance (IR) and Chronic Inflammation. OS is increased due to IR as hyperglycemia and higher levels of free fatty acid leads to excess production of Reactive Oxygen Species (ROS)[7].

Fig.1 Search Flow Chart

Table.1 Characteristics of the Included Articles

S.No.	Author	Year	No. of Participants	Age at Diagnosis	BMI	Month/ Season	Country
1	Doddappa M Bannigida	2020	100	18-40	n=50 21.6 n=50 32.7	NA	NA
2	E Rudnicka	2020	200	18-40	24.86	NA	Poland
3	Y Çakıroğl	2016	146	29.85	26.45	May	Turkey
4	RaziyeKeskin Kurt	2014	62	32.2	27.15	NA	NA
5	Nearmeen M Rashad	2013	107	28.7	29.8	August	Egypt
6	Ana Celly Souza Dos Santos	2015	20	17-40	<24.9	NA	Brazil
7	Celia Bañuls	2017	116	25.1	25.9	NA	NA
8	Sibel Sak	2018	46	23.45	29.5	April	NA
9	Frank González	2012	14	25	22.4	NA	NA
10	Sebastião Freitas de Medeiros	2021	235	28.3	27.9	NA	Brazil
11	IlijanaMažibrada	2018	26	16.2 ± 1.0	22.4 ± 2.1	NA	Belgrade
12	Varalakshmi Desai	2014	25	20-38	24.40 ± 2.07	NA	India
13	P. Maidana	2019	73	26.9±5.5	18.6–46.9	NA	Argentina
14	RaziyeKeskin Kurt	2014	62	28-37	28	NA	Turkey
15	Yue Liu	2020	86	20-32	23.9	NA	China
16	Iva PerovićBlagojević	2018	114	25.5 (22.0-29.2)	24.2 (21.2–29.7)	October 2015 – June 2017	Belgrade
17	HongyingKuang	2020	49	29.32	22.479	NA	China
18	LianLian Wang	2017	99	26.755	23.265	February 2013 and December 2014	China
19	MałgorzataMizgier	2021	59	14-18	NA	2018 to 2020	Poland
20	Fatemeh Esfahanian	2012	40	20-30	31	February	NA
21	MinjooKim	2013	273	60.6	27.3	January	Korea
22	Renjiao Zhang	2016	544	20-40	23.09	NA	China
23	MałgorzataKałużna	2020	270	18-40	26.33	September	NA
24	Melissa Pawelczak	2014	23	15.2	20.7	NA	New York
25	EsraNurTola	2017	34	18.41	23.3	NA	NA

26	Shirin Kalyan	2018	200	28.4	29	NA	Bahrain
27	Cristian-IoanIuhas	2012	31	32.26	30.69	NA	NA
28	M. Razavi	2016	64	25.1	25.3	october	Iran
29	Q. Cheng	2014	96	25.48	23.14	November	China
30	LangQin	2016	40	20-33	23.78	NA	China
31	CeliaBañuls	2017	148	26.8	29.65	NA	NA
32	RaziyeKeskin Kurt	2014	62	32.2	27.15	NA	NA
33	GültekinAdanaş	2020	36	26.86	28.19	June	Bursa
34	Daiana Cristina ChielliPedrosoM.Sc	2015	150	13-45	29.9	NA	Brazil
35	Mohd Ashraf Ganie	2014	160	22.3	23.7	January	India
36	N. Unni C. Sumithra	2014	61	18-40	23.51	October	India
37	Szu-Hung Shen	2015	165	27	24.4	January	Taiwan
38	B.Ün	2016	75	21	22.77	November	Turkey

IV. Discussion

PCOS is associated with low-grade systemic inflammation as evidenced by elevation of multiple markers of inflammation such as C-reactive protein, interleukin-18, monocyte chemo-attractant protein-1 and white blood count as well as endothelial dysfunction and increased oxidative stress. To date studies have been limited concluding whether chronic inflammation is secondary to obesity or not. Insulin resistance has never been included in the diagnostic criteria of this syndrome, although it is present in 50–70% of PCOS women and is a triggering factor in the pathogenesis of ovarian and adrenal hyperandrogenism. Additionally, obesity is linked to insulin resistance and many PCOS patients suffer from obesity[8].Hyper-insulinemia and IR are regarded as the core mechanism in both obese and non-obese polycystic ovary syndrome (PCOS) pathogenesis[7]. Women with PCOS have statistically significantly higher WBC and CRP concentrations in comparison with their normal-ovulating, non-hyper androgenic, age- and BMI-matched peers[3].In summary, we suggest that PCOS is associated with increased WBC and CRP concentrations, which supports the evidence that PCOS is associated with low-grade inflammation. The main predicting factors of increased CRP are BMI and insulin resistance, but there is a relationship between WBC counts in PCOS and androgen concentration itself so that inflammation may be mediated not only through adiposity but also through increased androgen concentration. However, due to many factors that can affect WBC and CRP levels, further studies are needed to understand the precise mechanism of chronic low-grade inflammation in women with PCOS.

Clinical Presentation

PCOS is one of the most commonly diagnosed endocrinologist diseases that has been shown to affect 5-10% of women in reproductive age[7]. PCOS is an intricate and multi-factorial pathological disease with the etiopathogenesis being not well established[6]. PCOS has shown to have significant clinical implications, namely hyperinsulinemia, glucose intolerance, reproductive disorders, metabolic disorders, obesity, abnormal blood lipid level, ovulating dysfunction and hyperandrogenism[3,6]. Recent emerging data suggests that chronic low grade inflammation has also been involved in PCOS. Meta analysis of 31 studies that included 2359 women and 1289 controls showed that C Reactive Protein (CRP) levels are higher in women with PCOS[6].

All subjects of Liu et al.'s research met all criteria for the Rotterdam Diagnostic test including criteria such as : polycystic ovaries confirmed by ultrasound examination, biochemical and/or clinical hyperandrogenism, oligomenorrhea or amenorrhea, clinically manifested hirsute acne (excluding Kaohsiung caused by other diseases)[9,10,11]. PCOS is also often seen to be associated with obesity: mainly central abdominal obesity[12]. This disease has also been characterized by chronic oligoovulation/ anovulation , hirsutism and an increased risk of endometrial cancer[13].

PCOS is also now believed to be associated with an assemblage of cardiovascular risks and metabolic derangements including type in hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, endothelial dysfunction, subclinical inflammation, and insulin resistance[14]. Early manifestations of PCOS are menstrual abnormalities (amenorrhea or oligomenorrhea), hirsutism, insulin resistance and infertility while long term complications include type II Diabetes Mellitus, cardiovascular disease, endometrial and breast cancer[11].

PCOS causes a variety of problems that ranges from reproductive pathology to long term metabolic pathology[15].

All these associations with PCOS is evidenced by the increased plasma concentrations of inflammatory cytokines like: tumor necrosis factor- alpha (TNF alpha), CRP and interleukin-6 (IL-6)[16].

Diagnosis

PCOS remains a diagnosis of exclusion of other similar diseases presenting with the same symptoms[17].

To accurately diagnose women suspected of PCOS, clinicians need to factor out other potential endocrinopathies that might mimic the same symptoms that PCOS presents[18].

These possible disorders would include androgen producing tumors, non-classic adrenal hyperplasia, Cushing's Syndrome, and drug induced androgen excess[18].Furthermore, clinicians should also rule out other causes of ovulatory dysfunction. This would include hyperprolactinemia, thyroid dysfunction as well as pregnancy in reproductive age[18].

The first differential diagnosis would be Hyperprolactinemia. Early morning prolactin levels should be measured to exclude hyperprolactinemia. Clinicians should also be on the watch out for signs and symptoms that correlate with prolactinoma (eg: galactorrhoea)[17]. The next differential diagnosis would be Androgen secreting tumors. Laboratory reference range that shows marked increased testosterone levels that exceed two or three times the upper limit suggests an androgen secreting tumor. Testosterone levels that are significantly raised with an acne onset and rapid progression of clinical hyperandrogenism should be evaluated as an androgen secreting tumor until it is proved otherwise[17].Another possible diagnosis may also be Non classic congenital adrenal hyperplasia (NC-CAH; 21-hydroxylase deficiency). Since clinical presentation may not differ from that of PCOS (hirsutism and/or hyperandrogenism), early morning plasma levels of 17-hydroxyprogesterone (17-OHP) or 60 minutes after stimulation of intravenous ACTH should be measured to exclude NC-CAH due to 21-hydroxylase deficiency to check for increased levels[17]. The next diagnosis could possibly be Primary Hypothyroidism. Primary hypothyroidism may also potentially present with oligomenorrhea or amenorrhea. Hence, TSH lab values should be checked to rule out possible hypothyroidism[17].Yet another differential diagnosis could be Cushing's Syndrome. Cushing's Syndrome also may present with hirsutism and/or hyperandrogenism, oligomenorrhea or amenorrhea. Hence this disease should be ruled out testing 24-hour free cortisol levels[17].Again, Premature ovarian failure could be another probable diagnosis. This may present with oligomenorrhea or amenorrhea. Increased plasma levels of FSH with normal or decreased levels of estradiol helps in ruling out this disease[17]. Another possibility could be drug induced androgen excess. This may present with hirsutism and/or hyperandrogenism. Oligomenorrhea or amenorrhea may potentially be present. Hence a detailed history of any use of exogenous androgen and drug induced androgen excess (eg: androgenic or anabolic steroids, valproic acid, danazol) must be taken[17].

According to recent guidelines by the Endocrine Society, early morning plasma levels of TSH, 17-OHP and TSH should be measured routinely in the diagnostic evaluation of PCOS to exclude thyroid disorders (particularly hypothyroidism), hyperprolactinemia, NC-CAH (primarily 21-hydroxylase deficiency) respectively[17].

In Summary, the diagnostic criteria for PCOS is based on expert concurrence, not evidence. The consensus opinion has generally agreed that the ovary is central to the disorder and it is imperative to exclude other endocrinological disorders before making the final diagnosis[18].

S No.	No. of participants	BMI	Insulin	Fasting Glucose	HoMA-IR	Fibrinogen	hs-CRP	FSH	LH
1	100	n=50 21.6 n= 50 32.7	9.47-15.83	90-120	NA	NA	10.88-13.4	NA	NA
2	200	24.86	NA	NA	NA	NA	NA	4.96	7.19
3	148	26.45	NA	NA	1.95	NA	NA	6.55	7.1
4	62	27.15	11.5	5.8	2.6	NA	5.5	5.95	11.9
5	107	29.8	14.9	88.5	3.24	NA	1	8.2	11.4
6	20	<24.9	5.69	76.5	1.07	NA	Elevated	5.32	10.35
7	116	25.9	9.3	83.8	2.67	NA	1.67	4.64	6.07
8	46	29.5	NA	86.97	NA	NA	NA	5.88	9.04
9	14	22.4	92	83	NA	NA	0.37	NA	13.2
10	235	27.9	NA	NA	1.68	NA	0.96	5.8	9.4
11	26	22.4	NA	NA	2.0	3.1	0.4	5.1	14.0
12	25	24.4	14.96	94.24	3.63	NA	NA	NA	NA
13	73	18.6-46.9	12.7	NA	3.46	NA	2.38	NA	NA
14	62	28	13.5	6.2	3.15	NA	5.9	6.85	13.15
15	86	23.9	12.69	5.4	2.89	NA	NA	5.93	6.99
16	114	24.2	NA	NA	NA	NA	1.90	NA	NA
17	49	22.479	NA	NA	NA	NA	NA	4.825	6.669

18	99	23.625	8.715	5.24	2.07	NA	1.485	6.61	NA
19	59	NA	16.44	88.945	3.77	NA	1.19	NA	NA
20	40	31	13.4	93.5	3.0	NA	5.2	NA	NA
21	273	27.3	10.4	90.4	2.34	NA	Elevated	NA	NA
22	544	23.09	102.28	5.4	3.67	NA	NA	6.09	14.4
23	270	26.33	11.8	88	2.41	NA	1.3	5.9	8.8
24	23	20.7	21.12	88.63	4.79	NA	NA	NA	NA
25	34	23.3	14.93	89.15	3.29	NA	4.21	6.85	8.64
26	200	29	NA	NA	3.8	NA	15.5	NA	NA
27	31	30.69	NA	NA	NA	NA	NA	NA	NA
28	64	25.3	NA	NA	NA	NA	1.82	6.27	10.76
29	96	23.14	10.2	5.19	NA	NA	1.22	NA	NA
30	40	23.78	NA	NA	3.0	NA	NA	3.61	12.34
31	148	29.65	16.58	89.3	5.07	NA	4	4.57	5.64
32	62	27.15	11.5	5.8	2.6	NA	5.5	5.95	11.9
33	36	28.19	11.45	89.69	NA	NA	NA	4.66	5.6
34	150	29.9	9.8	105.95	2.63	NA	5.52	NA	7.51
35	160	23.7	10.9	91.1	2.38	NA	1.82	5.8	6.7
36	61	23.51	7.35	96.28	NA	NA	4.35	4.03	9.07
37	165	24.4	103.7	5.09	3.48	NA	0.21	NA	NA
38	75	22.77	9.7	NA	2.22	NA	0.21	4.76	5.58

Table 2. Lab values

S No.	No. of participants	BMI	FBG	Estradiol	Progesterone	Triglyceride	HDL	LDL	Total Cholesterol
1	100	n=50 21.6 n= 50 32.7	NA	NA	NA	NA	NA	NA	NA
2	200	24.86	NA	41.75	NA	93.96	57.22	105.2	180.29
3	148	26.45	NA	48.65	NA	NA	NA	NA	NA
4	62	27.15	NA	55.3	NA	1.35	1.27	3.35	5.3
5	107	29.8	NA	NA	NA	218.4	40.6	133.7	217.6
6	20	<24.9	NA	44.32	0.5	94.6	46.3	110.8	171.5
7	116	25.9	NA	NA	NA	62.5	51.6	102.5	169.3
8	46	29.5	NA	NA	NA	NA	NA	NA	NA
9	14	22.4	NA	NA	NA	NA	NA	NA	NA
10	235	27.9	NA	199.6	NA	NA	NA	NA	NA
11	26	22.4	NA	116.5	2.5	0.73	1.3	2.3	4.0
12	25	24.4	NA	NA	NA	NA	NA	NA	NA
13	73	18.6-46.9	NA	NA	NA	NA	NA	NA	NA
14	62	28	NA	57.55	NA	1.65	1.41	3.75	5.8
15	86	23.9	NA	34.9	NA	NA	NA	NA	NA
16	114	24.2	NA	NA	NA	0.840	1.40	2.84	4.76
17	49	22.479	NA	NA	NA	NA	NA	NA	NA
18	99	23.625	NA	NA	NA	NA	NA	NA	NA
19	59	NA	NA	NA	NA	NA	54.16	83.07	NA
20	40	31	NA	NA	NA	147	35	105	203
21	273	27.3	NA	NA	NA	185.7	43.9	128.1	207.6
22	544	23.09	NA	307.82	NA	1.36	1.4	2.55	4.42
23	270	26.33	NA	40.5	NA	81.5	62	96.57	177.75
24	23	20.7	NA	NA	NA	NA	NA	NA	NA
25	34	23.3	NA	37.15	NA	84.61	62.88	68.5	148.6
26	200	29	NA	NA	NA	NA	NA	NA	NA
27	31	30.69	NA	NA	NA	154.96	54.47	115.1	200.89
28	64	25.3	NA	NA	NA	NA	NA	NA	NA
29	96	23.14	NA	NA	NA	1.42	1.04	1.94	4.06
30	40	23.78	NA	NA	NA	NA	NA	NA	NA
31	148	29.65	NA	NA	NA	109.9	43.7	114.0	183.05
32	62	27.15	NA	55.3	NA	1.35	1.26	3.35	5.3
33	36	28.19	NA	35.97	NA	101.44	48.53	106.5	177.06
34	150	29.9	NA	92.03	NA	126.75	54.83	125.6	208.02
35	160	23.7	NA	NA	NA	129.9	NA	NA	165.9
36	61	23.51	NA	NA	NA	136.37	47.96	134.2	221.36

S No.	No. of participants	BMI	FBG	Estradiol	Progesterone	Triglyceride	HDL	LDL	Total Cholesterol
1	100	n=50 21.6 n= 50 32.7	NA	NA	NA	NA	NA	NA	NA
2	200	24.86	NA	41.75	NA	93.96	57.22	105.2	180.29
3	148	26.45	NA	48.65	NA	NA	NA	NA	NA
4	62	27.15	NA	55.3	NA	1.35	1.27	3.35	5.3
5	107	29.8	NA	NA	NA	218.4	40.6	133.7	217.6
6	20	<24.9	NA	44.32	0.5	94.6	46.3	110.8	171.5
7	116	25.9	NA	NA	NA	62.5	51.6	102.5	169.3
8	46	29.5	NA	NA	NA	NA	NA	NA	NA
9	14	22.4	NA	NA	NA	NA	NA	NA	NA
10	235	27.9	NA	199.6	NA	NA	NA	NA	NA
11	26	22.4	NA	116.5	2.5	0.73	1.3	2.3	4.0
12	25	24.4	NA	NA	NA	NA	NA	NA	NA
13	73	18.6-46.9	NA	NA	NA	NA	NA	NA	NA
14	62	28	NA	57.55	NA	1.65	1.41	3.75	5.8
15	86	23.9	NA	34.9	NA	NA	NA	NA	NA
16	114	24.2	NA	NA	NA	0.840	1.40	2.84	4.76
17	49	22.479	NA	NA	NA	NA	NA	NA	NA
18	99	23.625	NA	NA	NA	NA	NA	NA	NA
19	59	NA	NA	NA	NA	NA	54.16	83.07	NA
20	40	31	NA	NA	NA	147	35	105	203
21	273	27.3	NA	NA	NA	185.7	43.9	128.1	207.6
37	165	24.4	NA	NA	NA	1.2	1.4	2.99	5
38	75	22.77	NA	35	NA	75	47	102	164

Table 3. Lab values

Management & Treatment

Weight loss and lifestyle modifications such as physical activity is the first line of treatment in the management of PCOS. Furthermore, the use of oral contraceptive pills and metformin may help induce regular menses and reduce hyperinsulinemia and ovarian androgens production in these women[19]. Visceral obesity, which is believed to be a result of IR, is associated with increased incidence of Diabetes and cardiovascular disease in patients with PCOS. For this reason, it has been suggested that PCOS should no longer be considered a purely gynecological disorder, but rather a complex endocrine disorder[20]. The role of omega-3 fatty acid supplementation in controlling oxidative stress and chronic low-grade inflammation in women with PCOS is still uncertain[21] but it is found in other studies that omega-3 fatty acid supplementation tends to increase insulin sensitivity, plasma adiponectin levels and decrease the levels of plasma triglycerides, liver fat and reduces hyperinsulinemia. DASH (dietary approaches to stop hypertension) diet is proved to be beneficial in maintaining lower body fat although no significant beneficial effects on metabolic profiles and biomarkers of oxidative stress in women with PCOS has been found.

DASH Diet

DASH diet is a low glycemic index low-energy index low energy-dense diet. It reduces testosterone levels which is a key component in PCOS. Consumption of DASH diet resulted in significant increase in plasma TAC and total GSH levels among overweight and obese women with PCOS. Increased contents of dietary fiber, antioxidants, phytoestrogens and isoflavones along with its low glycemic index might help PCOS patients to control their increased levels of lipid profile and oxidative stress[19].

The decrease of reactive oxygen species by vitamin D supplements may contribute to its beneficial effects on oxidative stress[22]. Vitamin D-K-calcium co-supplementation reduced serum free testosterone, DHEAS, plasma MDA and a significant increase in plasma TAC concentration but did not affect endocrine profiles, inflammatory markers and GSH concentration.

Metformin

Both metformin D-chiro-inositol (DCI) together showed positive effects by decreasing oxidative damage on follicular fluid protein as well as in recovering good quality oocytes. Many patients treated with metformin referred to serious side effects such as nausea, vomiting, gastric pain leading to interruption of therapy, where DCI did not have any adverse consequences[23]. On the other hand, empagliflozin was found to have significant

improvement in anthropometric improvements and body composition after 12 weeks of treatment which metformin could not do[24].

Resveratrol
ER stress is a potential therapeutic target for patients with PCOS. Administration of Resveratrol in women with PCOS decreased the serum levels of pro-inflammatory factors such as IL-6, IL-18, TNF-alpha, IL-1beta and CRP. Resveratrol has anti-inflammatory effects due to the inactivation of NF-kB-dependent signaling which plays an important role in inflammation-induced cellular transformation[25].

Liraglutide
26-week intervention of liraglutide found to be affective for weight loss in obese women having PCOS. It is found to have beneficial effects on markers of VTE and CVD risk. Liraglutide was well tolerated but one should be aware of the risk of weight loss-related gall bladder stone attacks in a population of young overweight women[26].

Atorvastatin
12-weeks of atorvastatin treatment significantly decreased the markers of adipose tissue dysfunction and inflammation, namely ASP, IL-6 and MCP-1 in obese women with PCOS. Changes in adipose tissue markers were significantly associated with substantial improvements in HoMA-IR, testosterone, and hs-CRP levels[27]. Women with PCOS have elevated levels of hs-CRP that is an independent risk marker of early CVD. There was 25% reduction in hs-CRP levels after atorvastatin treatment[27].

Sitagliptin
It is found that sitagliptin, a DPP4 inhibitor, lowered blood glucose level by increasing GLP-1 and enhancing early insulin secretion. Although BMI and weight remained stable, body composition was found to be improved due to decrease in VAT, sitagliptin did not increase mean overnight GH but did enhance GH half-life[28].

Pioglitazone
The beneficial effects of pioglitazone treatment could involve both improving insulin sensitivity of inflammatory cells[29].

Melatonin
Administration of melatonin supplementation for 12 weeks to women with PCOS significantly reduced hirsutism, total testosterone, hs-CRP, and MDA, while increased TAC and GSH levels. In addition, melatonin administration reduced gene expression of IL-1 and TNF-alpha[30].

Zinc
Few RCTs showed that zinc supplementation markedly reduced plasma CRP concentration, particularly at high dosage (500mg/day) and in patients with kidney dysfunction[31]. Zinc plays anti-oxidant and anti-inflammatory roles in the human body.

Clomiphene
PCOS patients with clomiphene resistance had lower antioxidant (catalase and ferroxidase) levels compared to those who were sensitive to clomiphene and who did not have PCOS[32].

There is wide range of treatment options for managing metabolic comorbidities in women having PCOS such as lifestyle modifications, intervention of insulin sensitizing agents, thiazolidinediones, metformin, glucagon-like peptide-1 receptor analogue, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter-2 inhibitors, myo-inositol, statins, weight loss medications etc.[33].

Prognosis
Polycystic ovary syndrome is a heterogeneous syndrome with endocrine abnormalities and metabolic dysfunction that affect reproduction from folliculogenesis to implantation[6]. PCOS affects potentially more than 1 in 7 women of reproductive age, this poses a major burden on healthcare systems[34]. These adverse outcomes may partially be attributed to hyperandrogenaemia and increased intrafollicular androgen levels, thereby increased follicular degeneration[6]. PCOS has significant implications for women regarding their reproductive potential: increased risk of anovulatory infertility, increased risk of miscarriage and increased pregnancy related

complications[34]. The link between insulin resistance, hyperandrogenism, and ovulatory disorder is very complex in PCOS[6]. In addition, women with PCOS are at a markedly increased risk of type-II diabetes and potentially, of cardiovascular disease, in later life[34]. Most of the women with PCOS suffer from hirsutism, acne, oligomenorrhea and androgenic alopecia, which impair the quality of life in these women[30]. The reason for increased inflammation in PCOS has not been clarified yet, and it remains uncertain whether it is associated with PCOS itself or the accompanying obesity[35]. Evidence for the presence of chronic low-grade inflammation in PCOS is mixed, with reports of either normal or elevated circulating levels of inflammatory cytokines[29].

V. Conclusion

PCOS is associated with dyslipidaemia, metabolic syndrome and CVD risk factors, especially elevated triglycerides which serve to increase the substrate for free radicals which are not neutralised by the defective antioxidant system[36]. Increased oxidative stress and low-grade inflammation was indicated by elevated levels of MDA and CRP in women with PCOS irrespective of obesity[7]. The main predicting factors of increased CRP are BMI and insulin resistance, but there is a relationship between WBC count in PCOS and androgen concentration itself so that inflammation may be mediated not only through adiposity but also through increased androgen concentrations[3]. No association of cortisol levels were found between PCOS patients and the controls. It is analysed that lean and obese patients with PCOS have increased inflammatory markers when compared to the corresponding BMI-matched control groups. NLR and PLR were significantly increased in all PCOS subjects compared to controls. PLR was significantly increased in NW-PCOS compared to control and OB-PCOS[6]. There are increased levels of NLR independent of obesity. Increased inflammation and oxidative stress, together with ER stress, contribute to the enhanced interaction between these cells and the endothelium, thereby increasing the risk of CVD[37]. Higher levels of hs-CRP and fibrinogen were associated with unfavourable lipid profile[38]. The association of AA with markers of oxidative stress and CRP suggests that excess AA is an additional source of oxidative stress in normal weight women with PCOS[39]. Relationship between IL-6 levels and metformin in PCOS was systematically reviewed. Metformin may influence IL-6 levels and ameliorate the state of chronic inflammation in PCOS women that receive early metformin therapy[40]. 12 weeks of atorvastatin treatment reduced MDA concentrations in patients with PCOS[41]. Various RCTs showed that zinc supplementation markedly reduced plasma CRP concentration in patients with kidney dysfunction. Beneficial effects of pioglitazone treatment could involve both improving insulin sensitivity of muscle and reversing the augmented sensitivity of inflammatory cells[29]. Consumption of the DASH diet for 8 weeks led to a significant reduction in serum insulin, triglycerides and VLDL-C and a significant increase in TAC and GSH levels[19]. Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should still be considered the first line of treatment for overweight/obese women with PCOS for reduction in body weight, central obesity and insulin resistance[24].

VI. Limitations

Several limitations needed to be noted in this meta-analysis. To begin with, the results were possibly impacted by potential confounding factors. We extracted median from included studies when they were available and calculated mean when only raw data was accessible. Our meta-analysis was limited to publications written in English and there is the possibility of unidentified articles in other databases. Also, we did not include unpublished literature. Due to the possibility of incorrect diagnosis or mis-diagnosing of PCOS in adolescents, a limitation in the diagnostic approach was suggested to girls with the highest probability for the disorder. One of the main limitations of the present study is the small sample size. BMI may be insufficient to reflect regional body fat, it would have been better to include measurements that reflect visceral obesity in lean PCOS, such as waist circumference.

Abbreviations

IL- Interleukins
TNF- Tumor necrosis Factor
CRP- C-reactive Protein
OS- Oxidative stress
MDA- Malondialdehyde
CVD- cardiovascular disease
HOMA-IR- Homeostasis model assessment- estimated insulin resistance
FSH- Follicle stimulating hormone
LH- Luteinizing hormone
TSH- Thyroid stimulating hormone
FBG- fasting blood glucose

HDL- high cholesterol level
LDL- low cholesterol level
HCy- Homocysteine

Conflict of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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