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CIRCULATING INFLAMMATORY MARKERS IN POLYCYSTIC OVARY SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

Héctor F. Escobar-Morreale, M.D., Ph.D.[*,†], **Manuel Luque-Ramírez, M.D., Ph.D.**[*], and **Frank González, M.D.**[‡]

[*] Department of Endocrinology, Hospital Universitario Ramón y Cajal & Universidad de Alcalá, Madrid, and Centro de Investigaciones Biomédicas en Red de Diabetes y Enfermedades Metabólicas Asociadas CIBERDEM, Spain

[†] Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, Madrid, Spain

[‡] Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, U.S.A

Abstract

Objective—To review and meta-analyse the studies evaluating the status of serum inflammatory markers in women with Polycystic Ovary Syndrome (PCOS).

Design—Systematic review and meta-analysis of articles published in English before January 2010 and identified using the Entrez-PubMed engine.

Setting—Academic hospital

Interventions—Measurement of serum concentrations of inflammatory markers by high-sensitivity techniques.

Main Outcome Measures—Meta-analyses of the mean difference in serum C-reactive protein (CRP), interlekin-6 (IL-6) and tumor necrosis factor-α (TNF-α) concentrations among patients with PCOS and appropriate controls, applying random-effects models to limit interstudy variability, and using appropriate estimates of evidence dissemination bias.

Results—Meta-analysis of the 31 articles meeting inclusion criteria showed that circulating CRP was 96% higher in women with PCOS compared to controls (95% confidence interval 71% – 122%, z = 7.32, $p < 0.0001$) without evidence dissemination bias (Egger's regression intercept 0.45, 95% confidence interval −2.30 – 3.21, $P = 0.739$). These findings persisted after excluding five studies with mismatches in body mass and/or frequency of obesity between women with PCOS and controls. Meta-analyses involving 10 studies of IL-6, and 9 studies of TNF-α revealed no statistically significant differences between PCOS and controls.

CORRESPONDENCE AND REPRINTS: Héctor F. Escobar-Morreale, M.D., Ph.D.; hescobarm.hrc@salud.madrid.org.

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Conclusion—Women with PCOS exhibit elevation in circulating CRP that is independent of obesity. This finding corroborates existing molecular evidence of the chronic low-grade inflammation that may underpin the pathogenesis of this disorder.

Keywords

Chronic low-grade inflammation; adipose tissue; insulin resistance; obesity; glucose tolerance

Introduction

Chronic low-grade inflammation is involved in the pathogenesis of obesity-related diabetic syndromes. Leukocytes present in both the circulation and adipose-tissue are capable of promoting insulin resistance in obesity and type 2 diabetes (1). Polycystic Ovary Syndrome (PCOS) is also a proinflammatory state. Recent studies demonstrate that a dietary trigger such as glucose is capable of inciting an inflammatory response in mononuclear cells (MNC) of women with PCOS independent of body mass (2–5). There is also an association between inflammation at the molecular level and insulin resistance in the disorder (3–5). Elevations of a number of circulating proatherogenic inflammatory mediators have been independently reported in PCOS (6–9), and corroborated by preliminary reports of glucose-stimulated upregulation of proatherogenic molecular pathways in the disorder (10–12). It remains to be established whether the proinflammatory state in PCOS is primarily a result of inflamed adipose tissue since there is increased prevalence of abdominal adiposity in PCOS across all weight classes (13).

There is a genetic basis for the inflammation observed in PCOS (14). Variants in genes encoding several proinflammatory cytokines and their receptors associated with insulin resistance, obesity and/or diabetes have also been found to be associated with PCOS (15–21). Moreover, variants in the genes encoding tumor necrosis factor-α (TNF-α) (16), type 2 TNF receptor and interleukin-6 (IL-6) (18–20) and its signal transducer (21) have been reported in association with PCOS in European populations. These findings are in conceptual agreement with a common evolutionary background for PCOS and metabolic disorders.

There are numerous studies in the literature reporting elevations of circulating inflammatory molecules in PCOS, it remains unclear whether their elevations are related to PCOS itself, or are a function of obesity and/or abdominal adiposity. There is also controversy regarding the relevance of circulating inflammatory molecules because most proinflammatory mediators exert their effect in tissue in an autocrine and paracrine fashion. In the case of TNF-α, the metabolic effects of this known mediator of insulin resistance are typically estimated indirectly by the soluble fraction of its type 2 receptor (1,22–24). In contrast, IL-6 is an endocrine cytokine produced by MNC and adipose tissue that is directly responsible for stimulating hepatic C-reactive protein (CRP) synthesis (25–28). CRP in turn, has emerged as a major predictor of metabolic dysfunction in asymptomatic individuals, and is also produced by adipose tissue (29,30).

We have conducted a systematic review of the studies published to date addressing the status of circulating inflammatory markers in PCOS compared to non-hyperandrogenic controls. We also performed meta-analyses of studies reporting circulating CRP, TNF-α and IL-6 levels in PCOS to determine whether they reflect the chronic low-grade inflammation intrinsic to the disorder to be of clinically utility.

Materials and Methods

PubMed searches of studies published before January 2010 that addressed PCOS and inflammatory markers were conducted as described in Supplemental Data Table 1. The studies identified were considered for further review only if they fulfilled the following criteria:

- **i.** Strict definition of PCOS according to National Institute of Health (NIH) criteria (31), European Society of Human Reproduction and Embryology / American Society of Reproductive Medicine (ESHRE / ASRM) Rotterdam criteria (32) or Androgen Excess and PCOS Society (AEPCOS) criteria (33).
- **ii.** Cross-sectional comparison of reproductive-age women with PCOS and non-hyperandrogenic controls.
- **iii.** Measurement of circulating inflammatory molecules concentrations by high-sensitivity methods.

Meta-analyses of CRP, IL-6 and TNF-α serum concentrations were limited to studies that included a minimum of 25 women with PCOS and a similar number of non-hyperandrogenic controls defined as the absence of androgen excess or ovulatory dysfunction. If a series of articles by the same authors was identified, the report with the larger sample size was selected for inclusion in the meta-analysis to avoid over-representation of cases.

The absolute mean concentrations and standard deviations of CRP, IL-6 and TNF-α were standardized as the percent mean in which control groups means represented 100% to adjust for the large difference in absolute means among individual studies. This large difference most likely reflects variability among assays used for measurement.

A separate random-effects model was constructed for each inflammatory marker using the DerSimonian and Laird weighting method, which incorporates between-study variability into the calculations. We selected this method because of the high likelihood that there was empirical heterogeneity resulting from the variability in the ethnicity and race of the subjects, differences among studies in the criteria used to define PCOS, and inconsistent control of confounding factors such as obesity. All calculated *p*-values are two-sided, and an α level of 0.05 was used to determine statistical significance. Evidence dissemination bias was estimated by funnel plot asymmetry and Egger's regression test.

Studies reporting the status of circulating inflammatory markers in PCOS other than CRP, IL-6 and TNF-α were systematically reviewed and summarized. However, the paucity of studies (i.e. three or less) addressing each marker precluded performance of meta-analyses.

Results

Meta-analysis of serum CRP concentrations in women with PCOS and controls

Supplemental Data Figure 1 includes the QUORUM flowcharts for the separate meta-analysis of serum CRP, IL-6 and TNF-α concentrations. We identified 125 studies to screen for retrieval that were potentially relevant to serum CRP levels and PCOS (2,6,7,19,20,34–152).

Twelve review articles were immediately excluded (40,43,46,55,60,62,76,89,117,122,128,136), and the remaining 113 studies were retrieved for a more detailed evaluation.

Twenty four studies were subsequently excluded for the following reasons: 1) Standard assays were used for measuring CRP instead of high-sensitive assays in 7 studies (34,36,37,53,59,63,146); 2) Serum CRP concentrations were not measured in 1 study (145); 3) The relatives of women with PCOS were evaluated instead of actual patients in 2 studies (83,106); 4) Patients with androgen excess disorders other than PCOS were evaluated in 4 studies (50,70,104,127); 5) Only pregnant women with PCOS were evaluated in 3 studies (41,65,108); 6) PCOS was diagnosed with criteria other than the NIH, ESHRE / ASRM or AEPCOS definitions in 7 studies (38,42,44,47,67,75,132).

The remaining 89 studies were considered potentially appropriate. An additional 58 studies were excluded for the following reasons: 1) Less than 25 subjects with PCOS were included in 14 studies (2,49,54,57,67,69,78,82,107,118,121,135,141,147); 2) No controls were included in 28 studies (51,56,66,68,71,74,77,80,81,84–87,95,98,100,102,105,112,115,119,120,123,126,139,143,148,152); 3) Patients and controls were also included in ulterior extended series by the same authors in 14 studies (7,35,58,92–94,101,110,113,116,125,131,149,150); 4) CRP concentrations were measured as a function of a polymorphism in the gene encoding the progesterone receptor, and not in PCOS and controls separately in 1 study (73); 5) It was unclear whether CRP was measured using a high sensitivity assay in 1 study, and there was no response from the corresponding author to a request for clarification (137).

The remaining 31 studies containing usable information by outcome were used to perform the meta analysis (6,19,39,45,48,52,61,64,72,79,88,90,91,94,96,97,99,103,109,111,114,124,129,130,133,134,138,140,142,144,151).

The CRP meta-analysis included 3,648 women (2,359 women with PCOS and 1,289 controls). Mean serum CRP levels were 96% higher in women with PCOS compared to controls (95% confidence interval 71% − 122%, z = 7.32, $p < 0.0001$, Figure 1). There was no evidence dissemination bias in the CRP meta-analysis (Egger's regression intercept 0.45, 95% confidence interval −2.30 – 3.21, $P = 0.739$, Figure 1). The results were similar after excluding 5 studies (19,48,60,103,114) with mismatches in body mass and/or frequency of obesity between women with PCOS and controls (102% relative increase in PCOS compared to controls, 95% confidence interval 73% − 131%, z = 6.93, $p < 0.0001$; Egger's regression intercept −0.79, 95% confidence interval −3.85 – 2.26, $P = 0.598$).

Meta-analysis of serum IL-6 concentrations in women with PCOS and controls

We identified 49 studies that were potentially relevant to serum IL-6 levels and PCOS (19,20,35,54,60,78,82,88,96,97,99,116–118,121,126,129,138,140,143,150,153–180).

Eight review articles were immediately excluded (60,117,159,165,166,170,171,177), and the remaining 41 studies were retrieved for a more detailed evaluation.

Fifteen studies were subsequently excluded for the following reasons: 1) Basal serum IL-6 levels were not reported in 6 studies (20,116,129,150,157,163); 2) A standard assay was used to measure IL-6 instead of a high-sensivity assay in 1 study (99); 3) IL-6 was only measured in follicular fluid in 2 studies (153,156); 4) IL-6 was only measured in cell culture supernatants in 3 studies (169,173,179); 5) IL-6 was measured in animals in 2 studies (155,175); 6) Subjects who did not have PCOS were evaluated in 1 study (162).

The remaining 26 studies were considered potentially appropriate. An additional 16 studies were excluded for the following reasons: 1) Less than 25 PCOS patients were included in 8 studies (54,78,82,118,121,158,174,176); 2) No controls were included in 6 studies

(126,143,154,160,161,164); 3) Patients and controls were also included in ulterior extended series by the same authors in 1 study (178); 4) Serum IL-6 was measured in only 8 controls in 1 study (180).

The remaining 10 studies containing usable information by outcome were used to perform the IL-6 meta analysis (19,35,88,96,97,138,140,167,168,172). This meta-analysis included 852 women (522 women with PCOS and 330 controls). There was no significant difference in serum IL-6 levels in women with PCOS compared to controls, with a 15% relative difference in group means (95% confidence interval −15% – 45%, z = 0.97, $P = 0.331$, Figure 2). There was no evidence dissemination bias in the IL-6 meta-analysis (Egger's regression intercept −1.62, 95% confidence interval −6.27 – 3.02, $P = 0.443$, Figure 2). The results were similar after excluding one study (19) with body mass mismatches between women with PCOS and controls (18% relative increase in PCOS compared to controls, 95% confidence interval −13% – 50%, z = 1.13, $p = 0.257$; Egger's regression intercept −1.49, 95% confidence interval −6.98 – 4.00, $P = 0.541$).

Meta-analysis of serum TNF-α concentrations in women with PCOS and controls

We identified 52 studies that were potentially relevant to serum TNF-α levels and PCOS (2,5,17,35,40,54,78,82,99,107,111,129,138,140,153,155,157–159,165–169,171–174,176,177,179,181–201).

Thirteen review articles were immediately excluded (40,159,165,166,171,177,181,185,188,191,193,194,199), and the remaining 39 studies were retrieved for a more detailed evaluation.

Eighteen studies were subsequently excluded for the following reasons: 1) Basal serum TNF-α levels were not reported in 5 studies (17,129,157,186,190); 2) TNF-α was only measured in follicular fluid in 1 study (153); 3) TNF-α was only measured in cell culture supernatants in 6 studies (2,169,173,179,182,189); 4) TNF-α was measured in animals in 4 studies (155,187,196,198); 5) Subjects who did not have PCOS were evaluated in 1 study (200); 6) PCOS was not defined by strict criteria in 1 study (183).

The remaining 21 studies were considered potentially appropriate. An additional 12 studies were excluded for the following reasons: 1) Less than 25 women with PCOS were included in 11 studies (5,54,78,82,107,158,174,176,192,197,201); 2) No controls were included in 1 study (195).

The remaining 9 studies containing usable information by outcome were used to perform the TNF-α meta-analysis (35,99,111,138,140,167,168,172,184). This meta-analysis included 726 women (398 women with PCOS and 328 controls). There was no significant difference in serum TNF-α levels in women with PCOS compared to controls, with a 5% relative difference in group means (95% confidence interval −12% – 23%, z = 0.58, $P = 0.561$, Figure 3). There was also evidence of a significant publication bias favoring studies underestimating the differences in TNF-α levels between women with PCOS and controls (Egger's regression intercept −4.71, 95% confidence interval −8.18 – −1.25, $P = 0.015$, Figure 3). The results were similar after excluding one study (184) with body mass mismatches between women with PCOS and controls (1% relative increase in PCOS compared to controls, 95% confidence interval -18% - 20%, z = 0.14, $p = 0.887$; Egger's regression intercept -5.78, 95% confidence interval -8.56 -3.00, $P = 0.002$).

Systematic review of other serum inflammatory markers in PCOS patients and controls

Table 1 describes the few studies about serum inflammatory markers other than CRP, IL-6 and TNF-α that included more than 25 women with PCOS and an appropriate number of

controls. PCOS and obesity appeared to independently and consistently contribute to serum IL-18 elevations (150,202,203). Circulating sICAM-1 was increased in women with PCOS in 2 of 3 studies, although obesity played a contributing role in this increase (6,35,204). The white blood cell count (WBC) was also higher in women with PCOS, compared to controls with obesity contributing to the elevation in the smaller of the 2 studies (53,205). sTNF receptor levels measured in 2 studies yielded conflicting results regarding the circulating status, and the effects of PCOS and obesity (35,172). Finally, single studies reported elevated levels of sVCAM-1, MMP-9, MCP-1, MIP-1α, TIMP-1, sE-selectin, sCD40L and soluble CD36, and decreased levels of neutrophil gelatinase-associated lipocalin and its complex with MMP-9 in women with PCOS (6,92,96,134,206,207).

In studies including less than 25 women with PCOS, circulating levels of IL-1Ra, sICAM-1, MCP-1, MMP-2, MMP-9, MIF, neopterin, TIMP-1 and WBC were elevated in the disorder (8,54,57,121,208), although the MMP-2, MMP-9 and WBC elevations were no longer significant when controlling for indexes of fat mass (54) or obesity (8). Finally, one study reported high IL-1β levels and low IL-7 levels in obese women with PCOS (174).

Discussion

The present meta-analysis of the mean differences in CRP, IL-6 and TNF-α clearly indicates that CRP is a circulating marker of the proinflammatory state in PCOS as evidenced by the 2-fold elevation in circulating CRP in women with disorder compared to controls. There is no difference in the levels of IL-6 or TNF-α among both groups with the latter finding affected by evidence dissemination bias cautioning interpretation of the results. There are less consistent changes in other circulating inflammatory markers in studies with insufficient numbers to perform a meta-analysis, many of which are isolated reports. Nevertheless, the limited evidence to date suggests that in PCOS, elevations in serum IL-18 concentrations (150,202,203) and WBC (53,57,205) can be independent of obesity.

Elevated circulating CRP in PCOS is independent of obesity since this finding persisted after excluding all the studies with mismatches in frequency of obesity or body mass between groups from the meta-analysis. This is important because obesity is a well documented proinflammatory state independently associated with elevations in all three of these markers (209–211), and inflamed adipose tissue is a known source of IL-6 and TNF-α (26,212) the former of which stimulates CRP synthesis in the liver (28). There is a high prevalence of obesity in the women with PCOS some of the studies analyzed. The degree of elevation in circulating levels of CRP and IL-6 in PCOS is much greater when obesity is also present (39,45,79,88,90,114,133,138,144). In fact, several studies show that serum CRP elevations in women with PCOS are no longer statistically significant when controlling for indices of obesity such as body mass index (6,72), or that obesity alone is responsible for the CRP increase (19,35,103,129). Similarly, the highest circulating TNF-α levels are evident in the obese regardless of PCOS status, as demonstrated in the initial report of increased serum TNF-α in normal weight women with PCOS (184), and in the largest report to date of increased serum TNF-α in the disorder (138).

The limitations of our meta-analyses include the sole use of the PubMed Entrez search engine to identify studies, and the exclusion of studies written in languages other than English. Despite the effort to minimize interstudy variability using random-effects models, the following additional study design limitations may have influenced our interpretation:

- **i.** Small sample sizes, and uncontrolled confounding variables, with inadequate matching for body mass and prevalence of obesity arising most frequently.
- **ii.** Lack of uniform diagnostic criteria for PCOS.

iii. Exclusion of studies using standard assays insensitive to small differences between groups.

iv. Time-dependent individual variation in circulating levels.

v. Concomitant subclinical inflammatory illnesses that confound the results by altering circulating levels.

vi. Evaluation only in the fasting state in most studies.

The relevance of the last concern is based on the new awareness that dietary components can stimulate inflammation which may accentuate clinically relevant differences between women with PCOS and controls (2–5,121). These differences may in turn, reflect molecular inflammatory responses involved in the promotion of insulin resistance and atherogenesis.

In conclusion, our meta-analysis of the most comparable studies indicate that circulating CRP is elevated in PCOS reflective of the chronic low-grade inflammation present in the disorder. In contrast, the trend towards slightly greater circulating levels of IL-6 and TNF-α among women with PCOS is far from reaching statistical significance. Because the CRP elevation attributable to PCOS is relatively small, caution is merited in using CRP to attribute metabolic and cardiovascular risk to PCOS *per se*. Finally, our review brings to the forefront factors that should be considered in designing future studies. Some examples include cross-sectional comparison of patients and controls using power analyses-based sample sizes, use of quality-controlled high-sensitivity assays, proper control of confounders, repeated measurements over time, and evaluation of diet-induced changes in the circulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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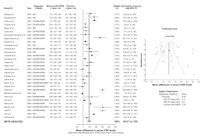

Figure 1.
Meta-analysis of serum C-reactive protein (CRP) levels in women with PCOS and controls. Evidence dissemination bias was assessed by funnel plot and Egger's regression. NIH, National Institute of Health, ESHRE/ASRM, European Society of Human Reproduction and Embryology / American Society of Reproductive Medicine.

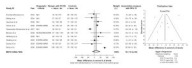

Figure 2.
Meta-analysis of serum interleukin-6 (IL-6) levels in women with PCOS and controls. Evidence dissemination bias was assessed by funnel plot and Egger's regression. NIH, National Institute of Health, ESHRE/ASRM, European Society of Human Reproduction and Embryology / American Society of Reproductive Medicine.

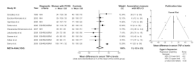

Figure 3.
Meta-analysis of serum tumor necrosis factor- α (TNF- α) levels in women with PCOS and controls. Evidence dissemination bias was assessed by funnel plot and Egger's regression. NIH, National Institute of Health, ESHRE/ASRM, European Society of Human Reproduction and Embryology / American Society of Reproductive Medicine.

Table 1

Serum inflammatory markers other than C-reactive protein, interleukin-6 and tumor necrosis factor-α in women with PCOS compared to non-hyperandrogenic controls

Authors, Year	Marker	Diagnostic criteria	Women with PCOS (n)	Controls(n)	Effects of PCOS	Effect of obesity	Comments
Escobar-Morreale *et al.*, 2004 (202)	IL-18	NIH	60	34	↑	↑	BMI-matched, age- corrected
Zhang *et al.*, 2006 (203)	IL-18	ESHRE/ASRM	42	38	↑	↑	BMI- and glucose- matched
Kaya *et al.*, 2010 (150)	IL-18	ESHRE/ASRM	60	60	↑	↑	Overall ↑ due to normal weight PCOS
Glintborg *et al.*, 2009 (207)	MCP-1, MIP-1α	NIH	30	63	↑	Directly correlated with BMI	All overweight or obese PCOS
Diamanti-Kandarakis *et al.*,2008 (92)	MMP-9,NGAL	NIH	40	40	↓in normal- and overweight PCOS	None	BMI- and age-matched
Liu *et al.*, 2008 (206)	MMP-9, TIMP-1	ESHRE/ASRM	42	40	↑		BMI- and age-matched
Glintborg *et al.*, 2008 (96)	sCD36	NIH	30	14	↑	Not assessed	Weight- and age-matched
Oktem *et al.*, 2009 (134)	sCD40L	ESHRE/ASRM	31	31	↑	None	BMI- and age-matched
Diamanti-Kandarakis *et al.*, 2006 (6)	sE-selectin	ESHRE/ASRM	62	45	↑	Directly correlated with BMI	
Escobar-Morreale *et al.*, 2003 (35)	sICAM-1	NIH	35	28	None	None	BMI-matched, age- corrected
Nasiek *et al.*, 2004 (204)	sICAM-1	NIH	57	22	↑ in obese PCOS	None	BMI- and age-matched
Diamanti-Kandarakis *et al.*, 2006 (6)	sICAM-1	ESHRE/ASRM	62	45	↑	Directly correlated with BMI	
Peral *et al.*, 2002 (17)	sTNFR2	NIH	42	36	None	↑	BMI-matched, age- corrected
Olszanecka-Glinianowicz *et al.*, 2007 (172)	sTNFR 1&2	NIH	39	34	↑	Not assesed	All obese subjects, age- matched
Diamanti-Kandarakis *et al.*, 2006 (6)	sVCAM-1	ESHRE/ASRM	62	45	None		
Orio *et al.*, 2005 (53)	WBC	NIH	150	150	↑	None	BMI- and age-matched
Kebapcilar *et al.*, 2009 (205)	WBC	ESHRE/ASRM	48	30	↑	↑	BMI- and age-matched

Symbols: ↑, increased.

Abbreviations: BMI, body mass index; ESHRE/ASRM, European Society of Human Reproduction and Embryology / American Society of Reproductive Medicine; IL, interleukin; MMP, Matrix metalloproteinase; MIP-1α, Macrophage inflammatory protein-1α MCP-1, Monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase-associated lipocain; NIH, National Institute of Health; sE-selectin, soluble endothelial leucocyte adhesion molecule; sICAM, soluble intercellular adhesion molecule; sTNFR, soluble tumor necrosis factor receptor, sVCAM, soluble vascular cell adhesion molecule; TIMP, tissue inhibitor of matrix metalloproteinase; WBC, white blood count.