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SYSTEMATIC REVIEW/META-ANALYSIS

Association of Superoxide Dismutase Level in Women with Polycystic Ovary Syndrome

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Abstract

Several biomarkers involved in oxidative stress may influence polycystic ovary syndrome (PCOS). Superoxide dismutase (SOD) has been commonly identified as dismutase enzyme catalyzes the conversion of superoxide to hydrogen peroxide and elemental oxygen, and could serve as an important biomarker in this direction. The objective of the present study to determine the precise role of SOD levels in women with PCOS using a meta-analysis approach. The electronic databases like PubMed, Google Scholar, Web of Sciences, Clinical trial.gov, Cochrane Database of Systematic Review were searched for obtaining relevant studies on the association of SOD level in women with PCOS. Pooled standardized mean difference with 95% CI was computed using the DerSimonian and Liard method. A total of 267 articles were screened, out of which 12 articles fulfilled the inclusion criteria of the present meta-analysis involving 558 cases and 529 controls. Analysis including overall studies observed a higher SOD level (statistically non-significant) in women with PCOS compared to controls (SMD 0.35, 95% CI −0.91 to 1.62, $P=0.58$), however, statistically significant higher SOD levels were noted in studies using serum as a source of sample (SMD 1.53, 95% CI 0.25 to 2.81, $P=0.019$). In conclusion, women with PCOS exhibited increased SOD levels compared to controls suggesting that the byproduct of oxidative damage is expected to be increased in women with PCOS.

Keywords PCOS · Polycystic ovary syndrome · Superoxide dismutase · SOD

Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrine abnormalities in women with controversial diagnosis and management [1]. It occurs in 5 to 10% of women of reproductive age [2]. There is increasing evidence in literature suggesting the role of oxidative stress in PCOS leading to mitochondrial and genomic DNA damage, thereby leading to reduced fertility [3]. Oxidative stress is commonly referred to as the condition in which imbalance between the oxidant and anti-oxidants occurs which leads to the formation of an excessive quantity of reactive oxygen species (ROS). Several studies have shown that oxidative stress markers increase in women with PCOS as compared to normal women and play an important role in the pathogenesis of PCOS. SOD has been commonly identified as an antioxidant enzyme that plays an important role in the elimination of superoxide anions. It is a dismutase enzyme that catalyzes the conversion of superoxide to hydrogen peroxide and elemental oxygen. This reaction occurs between two identical molecules in which one is oxidized and other reduced. The reaction causes conversion of two molecules of

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superoxide anions into molecular oxygen and hydrogen peroxide. Three common forms of SOD is present in humans, SOD1, SOD2, and SOD3 which are located in the cytoplasm, mitochondria, and extracellular space, respectively. The reactive center contains copper in SOD1 and SOD3; however, SOD2 which is located in mitochondria has manganese in the reactive center [4]. SOD exhibits an important role in the primary line deference for antioxidant reaction against the reactive oxygen species (ROS) by dismutation reaction. An optimal level of SOD in the follicular fluid may have a good correlation with embryo quality, fertilization rate, pregnancy rate, and successful live birth.

Literature suggests conflicting results in association between the level of SOD and PCOS [5]. Few of the studies have shown increased levels of SOD in patients with PCOS as compared to control [6] in contrast to this finding, some studies have shown a lower level of SOD in subjects with PCOS [7, 8]. The differences between the methodologies used in the SOD biochemical measurement, selection of cases and control, differences in the study settings may explain the inconsistent results shown in the literature. It is important to determine the precise association between SOD level and women with PCOS as it could be used as an important biomarker for PCOS pathogenesis and also help in the optimal treatment of women with PCOS.

A meta-analysis is a powerful tool in the era of evidence-based diagnostic that provides precise evidence by combining multiples studies addressing the same research question using robust statistical power. Therefore, we have conducted a meta-analysis to determine the pooled effect size of SOD levels in women with PCOS.

Methods

Search Strategies

The electronic databases like PubMed, Google Scholar, Web of Science, Clinical trial.gov, Cochrane Database of Systematic Review were used for obtaining relevant studies on PCOS and SOD levels. The gray literature, conference abstracts, and scientific proceedings were also searched for obtaining additional relevant studies. The keywords used for obtaining the relevant studies were "PCOS" OR "polycystic ovary syndrome" OR "Ovarian Disease" OR "Ovary syndrome" OR "polycystic ovarian syndrome" OR "polycystic ovarian disease" OR "polycystic ovaries" OR "PCO" OR "PCOD" OR AND "SOD" OR "Superoxide dismutase" with the filter applied only to human subjects. Two authors extracted the data, and any inconsistency was resolved by consensus. The search strategy was limited to the English language.

Selection Criteria

Studies were included if they fulfilled the following criteria: studies reporting the SOD level with standard deviation comparing PCOS and Controls; Studies having sufficient information to extract the relevant data; Reporting at least one value of SOD; Studies have used case–control as study design. Studies were excluded if they were case reports, editorial, leading opinion, or review articles.

Data Extraction

The general relevant information like author, year of publication, country, and study population, method of diagnosis for PCOS, the total number of subjects included, mean, and standard deviation of SOD in both cases and control were extracted from the published studies.

Study Question in PICO

Patients: Women with PCOS.

Exposure: Serum/Follicular fluid SOD level.

Comparator: Women without PCOS.

The outcome of interest: The primary outcome was the difference in the SOD level in women with PCOS as compared to control.

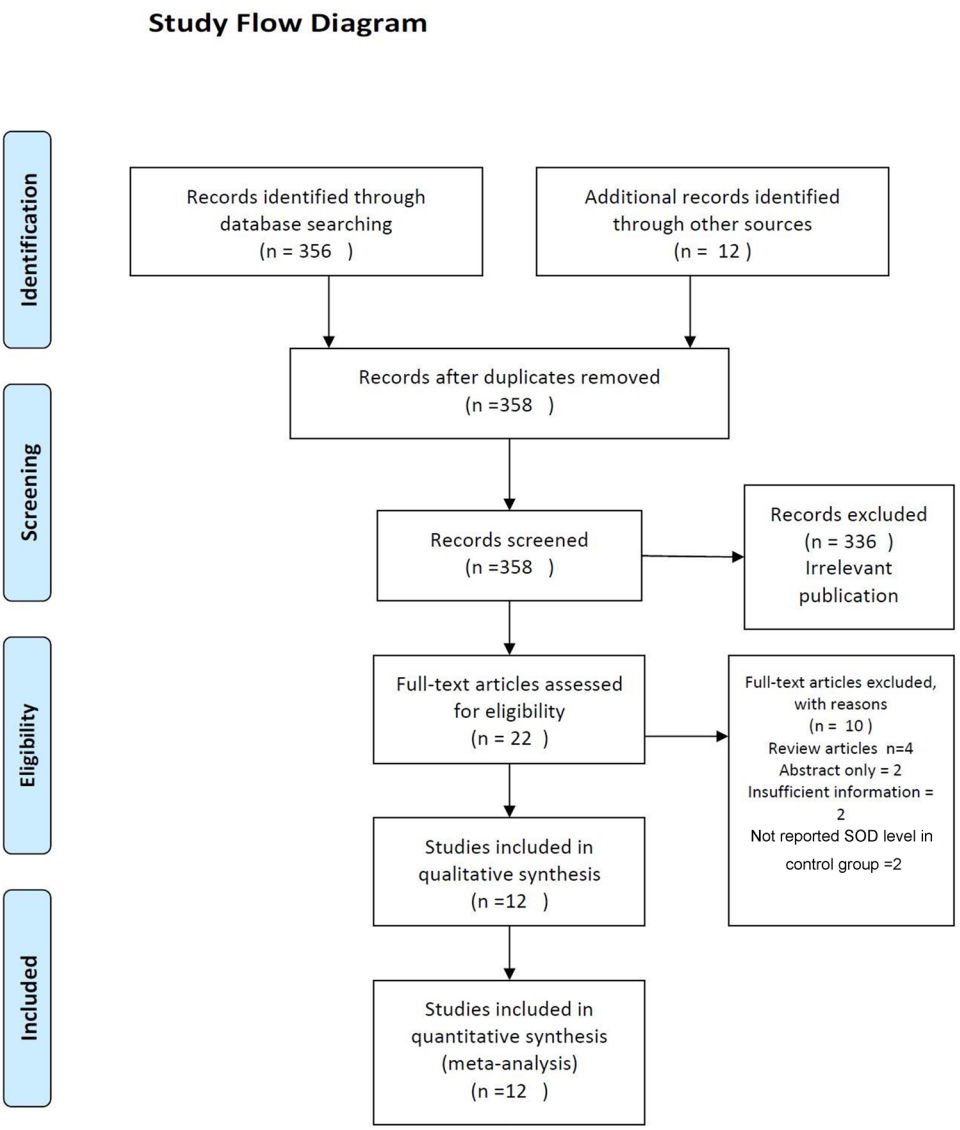
Statistical Analyses

Pooled standardized mean difference with 95% CI of SOD between PCOS and control was computed using the DerSimonial and Liard method for all three groups i. overall studies, ii. Studies using serum as source samples iii studies used follicular fluid as a source sample. Heterogeneity was examined by using I^2 test. The I^2 was more than 50% significant heterogeneity was considered. The random-effects model was used in the synthesis if heterogeneity was noted ($I^2 > 50\%$) otherwise fixed-effect model was used. Publication bias was assessed using funnel plot and Begg and Egger test. All the statistical analyses were conducted using statistical software STATA version 13.

Results

Our initial search obtained a total of 267 articles out of which 22 articles were screened in detail. Out of 22 studies, 10 studies were excluded due to the following reasons i. not a relevant research question for the present study

Fig. 1 Study flow diagram



($n=8$), ii. Studies did not show SOD activity in the control group ($n=2$). The remaining 12 articles (3,6–16) fulfilled the inclusion criteria of the present meta-analysis involving 558 cases and 529 controls. The study flow diagram as per PRISMA guidelines is shown in Fig. 1. The characteristics of the studies included are shown in Table 1. The standardized mean difference between cases and control for individual studies are given in Table 2.

The result of the three analyses was i. The analysis including overall ($n=12$) studies, observed no statistically significant difference in the SOD level between women with PCOS and controls (SMD 0.35, 95%Cl −0.91 to 1.62, $P=0.58$) (Fig. 2). We used the random effect model because significant heterogeneity was observed between the studies ($I^2=98.4\%$, $P<0.0001$). ii. In the stratified analysis of studies using serum as a source of the sample, we observed statistically significantly higher SOD levels as compared to controls (SMD 1.53, 95% CI 0.25 to 2.81, $P=0.019$) (Fig. 3), iii. We did not observe a statistically significant difference in SOD level between cases and controls including the studies conducted on follicular fluid (SMD −3.79, 95% CI −8.46 to 0.88, $P=0.11$) (Fig. 3). We did not observe significant publication bias indicated by Begg ($P=0.55$), Egger test ($P=0.63$), and in funnel plot (Fig. 4).

Discussion

The present meta-analysis demonstrated that there is higher SOD level (statistically non-significant) in women with PCOS compared to controls in overall studies, however, a significant association was observed when analysis was restricted to studies that used serum samples for biochemical measurement of SOD levels.

SOD is an important antioxidant enzyme that provides the defense that removes superoxide anions (O2-), by

Table 1 Characteristics of studies included in the meta-analysis

Author/year	Country	Sample size	Source of samples	Unit	Method of assessment
Enechukwu CI 2019	Nigeria	100	Blood	U/l	Spectrophotometry
Masjedi F 2019	Iran	100	Follicular fluid	*IU/ml*	Spectrophotometry
Isık H 2016	Turkey	73	Blood	U/ml	Sandwich enzyme-linked immunosorbent assay (ELISA)
Jeelani H 2019	India	190	Blood	U/ml	Beauchamp and Fridovich
KUS NK 2009	Turkey	54	Blood	NR	Spectrophotometry
Sumithra NUC 2009	India	122	Blood	U/gmHb	Spectrophotometry
Sabuncu T 2001	Turkey	45	Blood	MU/mol Hb	Colorimetry
Mohan SK 2009	India	112	Blood	U/gm of Hb	Spectrophotometry
Bausenwein J 2010	Germany	84	Follicular Fluid	U/mg protein	Colorimetry
Macut 2011	Serbia	57	Blood	U/ml	Spectrophotometry
Seleem A 2014	Egypt	40	Blood	U/mg protein	Spectrophotometry
Seleem AK 2014	Egypt	40	Follicular Fluid	U/mg protein	Spectrophotometry
Rasool M 2019	Pakistan	70	Blood	ng/ml	Spectrophotometry

NR Not reported

Table 2 Standardized mean the difference between PCOS and control

Study	No of cases	No of controls	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Enechukwu CI 2019	50	50	100	−1.130	0.214	−1.554–−0.705			13.04	7.89
Masjedi F 2019	50	50	100	−7.939	0.595	−9.120 –−6.757			1.68	7.45
Isık H 2016	42	31	73	−0.948	0.247	−1.441 –−0.455			9.78	7.86
Jeelani H 2019	95	95	190	4.800	0.285	4.236–5.363			7.32	7.83
KUS NK 2009	31	23	54	0.954	0.286	0.379–1.528			7.28	7.83
Sumithra NUC 2009	61	61	122	0.490	0.183	0.129–0.852			17.89	7.90
Sabuncu T 2001	27	18	45	0.607	0.306	−0.00937–1.224			6.39	7.81
Mohan SK 2009	56	56	112	1.649	0.218	1.218–2.080			12.60	7.88
Bausenwein J 2010	22	62	84	0.101	0.246	−0.388–0.590			9.86	7.86
Macut 2011	34	23	57	1.019	0.283	0.452–1.586			7.46	7.83
Seleem A 2014	20	20	40	−2.241	0.399	−3.048–−1.434			3.76	7.72
Seleem AK	20	20	40	−3.485	0.498	−4.493–−2.477			2.41	7.59
Rasool M 2019	50	20	70	12.167	1.061	10.050–14.284			0.53	6.53
Total (fixed effects)	558	529	1087	0.364	0.0773	0.212–0.515	4.710	< 0.001	100.00	100.00
Total (random effects)	558	529	1087	0.357	0.641	−0.901–1.616	0.557	0.578	100.00	100.00

catalyzing to H_2O_2 and elemental oxygen. A study published by Sabuncu et al. in 2001[14] observed that women with PCOS had a higher level of SOD as compared to control ($P = 0.048$), however, a study published by Zhang et al. observed that SOD level is lower (statistically significant) as compared to control ($P < 0.05$) [17]. An earlier meta-analysis published in 2013 observed that 34% (SMD 1.0, 95% CI 0.5–1.4) increase in the level of the SOD in PCOS patients as compared to controls [5]. Another study that examined the SOD level in both serum and follicular fluid in women with PCOS demonstrated a significant decrease in SOD activity in both serum and follicular fluid, in women with PCOS as compared to the control group. Due to inconsistent evidence available in the literature now it becomes essential to elucidate the role of SOD in women with PCOS. In the present meta-analysis, we have included a total of 12 studies, for more accuracy to establish more association of SOD with PCOS subjects as compared to control. We observed significant heterogeneity between the studies ($I^2 = 98.21\%$) which suggests huge variations between the studies reported in the literature regarding the association of SOD activity in patients with PCOS. The

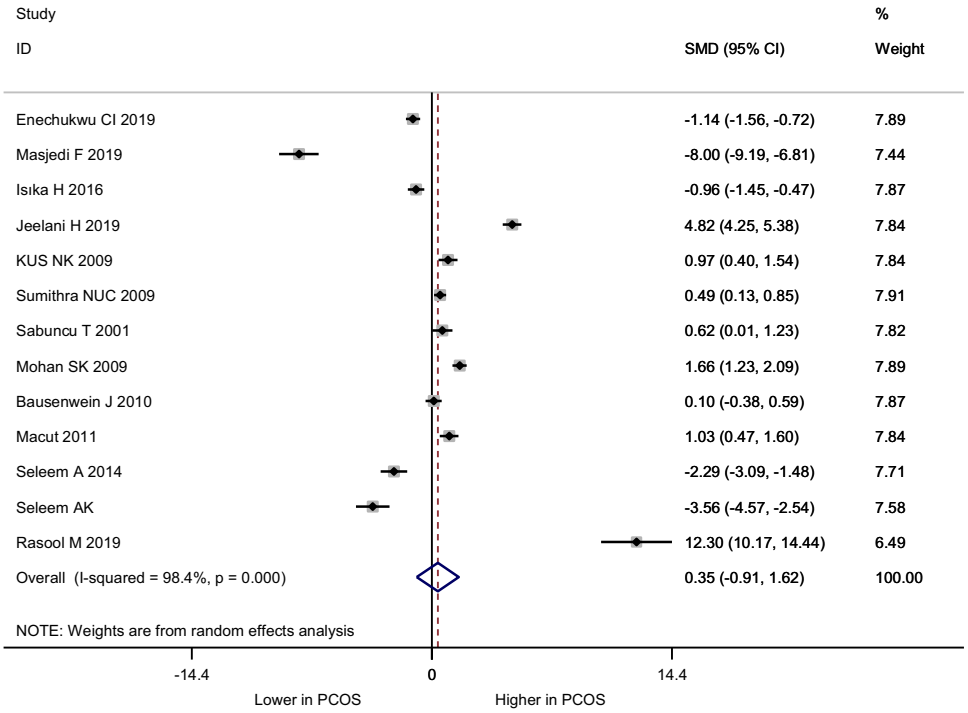


Fig. 2 Forest plot showing association of SOD levels in PCOS and control including all studies

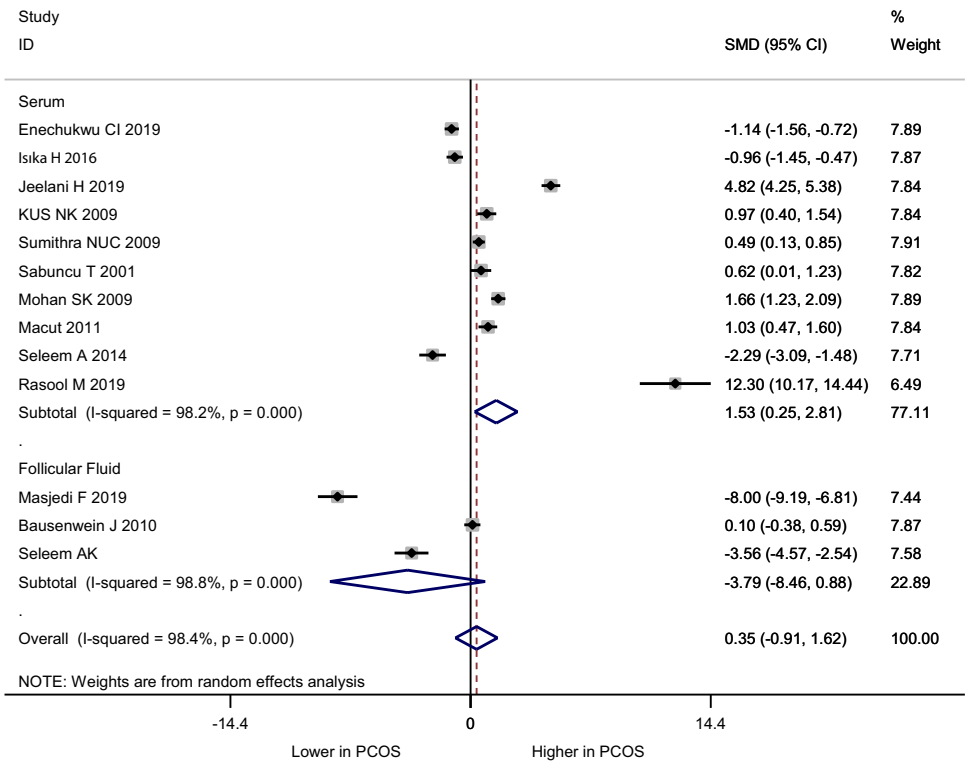


Fig. 3 Forest plot showing stratified analysis of association of SOD levels in PCOS and control

differences in the methodology used, study population, diagnosis of PCOS, and lack of blinding in the biomarker assessment may explain the heterogeneity reported in the literature. Moreover, antioxidant and oxidant status greatly varies between subjects due to differences in the lifestyle, diet, and dietary antioxidant could be an important factor for the heterogeneity observed in the current study.

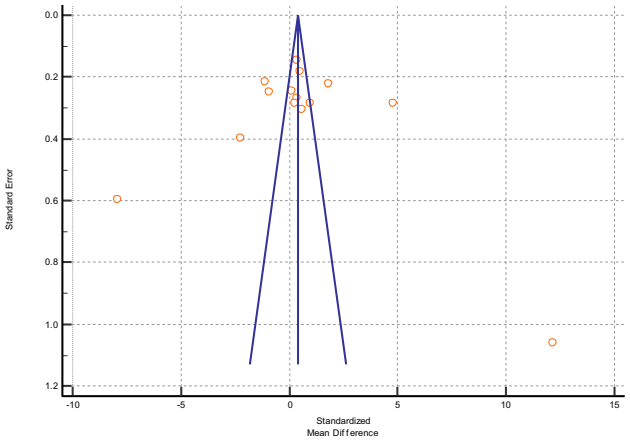


Fig. 4 Funnel plot showing publication bias

In the stratified analyses, we found an increased SOD level in subjects with PCOS when biomarker measurements were done in serum samples but not in follicular fluid samples. The follicular fluid sample is more relevant to assess the biomarker analysis as it provides an essential external microenvironment for the development of oocytes. Any change in expression of biomarkers could be captured first in most close tissue or organ which also correlates with the risk or progression of the disease. In the present study, we did not observe significant association in the follicular fluid although we cannot exclude the type II error in this findings. We may have missed the association due to inadequate power due to less number of studies reported in follicular fluid for the assessment of SOD levels.

The important question that arises is whether the generation of reactive oxygen species is related to PCOS and how the antioxidant enzymes are implicated in this complex biological process. Extracellular SOD corresponds to a major defense system against the oxidative damage caused due to superoxide ions. Our meta-analysis finding suggests the SOD levels are higher in women with PCOS in studies that used the serum samples for analysis as compared to controls. The units of measurement in the included studies are different and common reporting of the unit would further strengthen the homogeneity in the study results. The most commonly used unit is IU/ml which could be an ideal choice to report in future studies for ease of understanding for readers and also for obtaining homogenous findings in the meta-analysis.

Limitation of the study

The unit of measurement used in the studies included in the meta-analysis was not homogenous, however, we used the standardized mean difference to estimate the precise pooled effect size suggested by Cochrane Library (18) to deal with this issue to estimate the precise effect size. A huge amount of heterogeneity was noted among the studies which could be due to differences in the method used for the assessment of SOD level, differences in the location of the study site, and differences in patients' characteristics.

In conclusion, women with PCOS exhibited increased SOD levels compared to controls suggesting the byproduct of oxidative damage is expected to be increased in women with PCOS. Further, well designed, adequately powered prospective studies are needed to explore the precise role of SOD in the pathogenesis of PCOS and its use in clinical settings.

Data Availability It will be made available on request.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval It is not required as meta-analysis does not require it.

Human and Animal Participant Data were extracted from the studies on human participants which were published earlier.

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About the Author

Arshi Talat is pursuing a Ph.D. in Medical Biochemistry from Rama Medical College Kanpur, and her topic entitled polycystic ovary syndrome related to oxidative stress the marker used is Superoxide dismutase. She has a keen interest in evidence-based medicine and meta-analysis.