Paraoxonase 1 and chronic obstructive pulmonary disease: A meta-analysis (protocol)

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Abstract

Introduction: Oxidative stress is a driving factor in the pathophysiology of chronic obstructive pulmonary disease (COPD). While paraoxonase 1 (PON1) is an antioxidant enzyme, a potential biomarker of this disease, data regarding the relationship of PON-1 with COPD appear to show some controversy. In this regard, to shed light on this issue, we will aim to perform a meta-analysis of data on PON1 activity in COPD.

Methods: Electronic databases (MEDLINE, Embase and CENTRAL) will be searched for available studies on PON1 activity in patients with stable COPD published before October 2021. A meta-analysis will be performed using random-effects models.

Key words: antioxidant; arylesterase; chronic obstructive lung disease; reactive oxygen species; paraoxonase

Introduction

Chronic obstructive pulmonary disease (COPD), a progressive airway disorder, is a major cause of death and disability worldwide, and the number of patients is increasing [1]. Smoking, air pollution and increased free radicals in the respiratory tract cause an increased burden of oxidative stress, leading to the development and progression of COPD [2,3]. Oxidative stress is reported to induce structural changes in the essential components of the lung, including irreversible damage to both the parenchyma and airway wall [4]. In this process, various molecules, such as nucleic acids, lipids and proteins, are oxidized [5]. Currently, oxidative stress is considered a crucial contributor to the pathophysiology of COPD [6–8].

The burden of oxidative stress is modified by the antioxidant balance. Paraoxonase 1 (PON1), which is known as an antioxidant enzyme, is composed of 354 amino acids with a molecular weight 43 kDa and is encoded by the *PON1* gene [9]. PON1 activity is determined by the substrates used to measure it, in particular, arylesterase (when using phenylacetate) and paraoxonase (when using paraoxon). PON1 is a high-density lipoprotein (HDL)-associated lipolactonase that has promiscuous activity as an esterase [10–15]. Based on the antioxidant properties of PON1, there have been studies regarding the roles of PON1 in various pathologies, including

cardiovascular disease, kidney failure, diabetes mellitus, neurological disorders, and sleep apnea [11,12,16,17]. While the relationship between PON1 and COPD is also of interest, the results on their relationship have appeared to be mixed or inconclusive.

To date, there is no general consensus on circulating PON1 activity in patients with COPD. Given the putative importance of PON1 as a biomarker of this disease, the present study will aim to explore PON1 activity in COPD via a meta-analysis of available clinical studies.

Materials and Methods

This systematic review was conducted in accordance with the reporting guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [18]. We will publish this protocol in protocols.io (https://www.protocols.io/).

A search of the MEDLINE, Embase and CENTRAL electronic databases will be performed. The following keywords will be applied to search for studies published: ‘PON1’, ‘paraoxonase’, ‘arylesterase’ and ‘chronic obstructive pulmonary disease’ were applied to the search (Appendix 1). The inclusion criteria will be clinical studies that focused on PON1 activity in patients with stable COPD in comparison to healthy

controls. The exclusion criteria will be studies without healthy controls or studies that focused on PON1 in asthma patients. There will be no restrictions on language, country, observation period, or year of publication. The reference lists of eligible studies will be searched.

First, all retrieved candidate articles will be independently screened according to their titles and summaries. The full texts of potentially relevant summaries will be independently evaluated for eligibility. Original articles that did not focus on PON1 in patients with COPD in comparison to healthy controls will be excluded. An article will be considered eligible when the two researchers are in agreement. The risk of bias will be evaluated using the Newcastle-Ottawa Quality Rating Scale, NOS [19]. Then, a summary table for each article will be extracted and created.

Meta-analyses will be performed using random-effects models in Review Manager 5.4.1 (RevMan 2020) [20]. The standard mean difference (SMD) and 95% confidence interval (CI) of paraoxonase and arylesterase activity will be calculated. If missing data exist, standard deviations will be calculated based on the methods of the Cochrane handbook [21]. The statistical heterogeneity will be evaluated by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 0% to 40%: might not be important; 30%to 60%: may represent moderate heterogeneity; 50% to

90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) [21]. When heterogeneity will be identified (I^2 statistic >50%), the possible source of heterogeneity will be examined in subgroup analyses of the severity of COPD (studies including severe COPD versus studies of mainly non-severe COPD). The studies on severe or non-severe COPD will be judged based on the description of the prevalence of patients with severe COPD or the use of home oxygen therapy, suggesting a severe state of COPD [21].

When original studies only report standard error or p-value, the standard deviation will be calculated based on the method by Altman [22]. If these values were unknown, standard deviation will be calculated by confidence interval and t-value based on the method by Cochrane handbook [21], or validated method [23].

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Appendix 1

MEDLINE via PubMed

#1. "Aryldialkylphosphatase"[Mesh]

#2. "aryldialkylphosphatase"[tiab]

#3. "arylesterase"[tiab]

#4. "paraoxonase"[tiab]

#5. #1 OR #2 OR #3 OR #4

#6. "Lung Diseases, Obstructive"[Mesh]

#7. "Pulmonary Disease, Chronic Obstructive"[Mesh]

#8. emphysema*[tiab]

#9. chronic*[tiab] AND bronchiti*[tiab]

#10. obstruct*[tiab] AND (pulmonary[tiab] OR lung*[tiab] OR airway*[tiab] OR airflow*[tiab] OR bronch*[tiab] OR respirat*[tiab])

#11. COPD[tiab] OR COAD[tiab] OR COBD[tiab] OR AECB[tiab]

#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13. #5 AND #12

CENTRAL via Cochrane Library

#1. MeSH descriptor: [Aryldialkylphosphatase] explode all trees

#2. aryldialkylphosphatase:ti,ab,kw (Word variations have been searched)

#3. arylesterase:ti,ab,kw (Word variations have been searched)

#4. paraoxonase:ti,ab,kw (Word variations have been searched)

#5. #1 OR #2 OR #3 OR #4

#6. MeSH descriptor: [Lung Diseases, Obstructive] explode all trees

#7. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees

#8. emphysema*:ti,ab,kw (Word variations have been searched)

#9. (chronic* AND bronchiti*):ti,ab,kw (Word variations have been searched)

#10. (obstruct* AND (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)):ti,ab,kw (Word variations have been searched)

#11. (COPD OR COAD OR COBD OR AECB):ti,ab,kw (Word variations have been searched)

#12. #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13. #5 AND #12

Embase via Proquest

S1 EMB.EXACT.EXPLODE("aryldialkylphosphatase")

S2 ab(aryldialkylphosphatase) OR ti(aryldialkylphosphatase)

S3 ab(arylesterase) OR ti(arylesterase)

S4 ab(paraoxonase) OR ti(paraoxonase)

S5 S1 OR S2 OR S3 OR S4

S6 EMB.EXACT.EXPLODE("obstructive lung disease")

S7 EMB.EXACT.EXPLODE("chronic obstructive lung disease")

S8 ab(emphysema*) OR ti(emphysema*)

S9 EMB.EXACT.EXPLODE("chronic obstructive lung disease")

S10 ab(emphysema*) OR ti(emphysema*)

S11 (ab(chronic*) OR ti(chronic*)) AND (ab(bronchiti*) OR ti(bronchiti*))

S12 (ab(obstruct*) OR ti(obstruct*)) AND ((ab(pulmonary) OR ti(pulmonary)) OR (ab(lung*) OR ti(lung*)) OR (ab(airway*) OR ti(airway*)) OR (ab(bronch*) OR ti(bronch*)) OR (ab(respirat*) OR ti(respirat*)))

S13 (ab(COPD) OR ti(COPD)) OR (ab(COAD) OR ti(COAD)) OR (ab(COBD) OR ti(COBD)) OR (ab(AECB) OR ti(AECB))

S14 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S15 S5 AND S14