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Chronic obstructive pulmonary disease is associated with a higher level of serum uric acid. A systematic review and meta-analysis

Abstract

Introduction: Recent studies have suggested that patients with chronic obstructive pulmonary disease (COPD) may have a higher level of serum uric acid compared with individuals without COPD, although the data are still limited. The current systematic review and meta-analysis was conducted to summarize all available data.

Material and methods: A systematic review was performed using the MEDLINE and EMBASE databases from their inception to July 2019. Studies that were eligible for the meta-analysis must have consisted of two groups of participants, patients with COPD and individuals without COPD. The eligible studies must have reported either mean or median level of serum uric acid and its standard deviation (SD) or interquartile range of participants in both groups. Mean serum uric acid level and SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then computed by combining MDs of each study using random effects model.

Results: A total of eight studies with 1,612 participants met the eligibility criteria and were included in the data analysis. The serum uric acid level among patients with COPD was significantly higher than individuals without COPD with the pooled MD of 0.91 mg/dL (95% CI: 0.45–1.38; $I^2 = 89\%$).

Conclusions: The current study found a significantly higher level of serum uric acid among patients with COPD than individuals without COPD.

Key words: chronic obstructive pulmonary disease, serum uric acid, meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common pulmonary disorders worldwide. The disease is characterized by persistent respiratory symptoms due to airflow limitation. Airway and/or alveolar abnormalities of COPD are usually caused by significant exposure to noxious particles or gases [1]. COPD is currently the fourth leading cause of death globally according to the World Health Organization (WHO) and is predicted to become the third leading cause of mortality by 2030 [2]. Mechanisms that lead to airway destruction include oxidant/antioxidant imbalance, unopposed protease activity, inflammation, autoimmunity and enhanced apoptosis [3–6].

Hyperuricemia is a common metabolic abnormality that can lead to various clinical phenotypes, ranging from asymptomatic incidental laboratory abnormality to acute gouty arthritis and urate nephropathy [7–8]. Recent studies have suggested that serum uric acid level could be used as a marker of tissue hypoxia, particularly among patients with pulmonary diseases [9–10]. The increased level of serum uric acid is thought

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to be a consequence of increased purine catabolism in the presence of tissue hypoxia [11]. The current systematic review and meta-analysis was conducted to compare serum uric acid level between patients with COPD, a common hypoxemic disorder, and individuals without COPD [12–19].

Material and methods

Search strategy

Three investigators (P.W., P.R., N.C.) independently searched for published studies indexed in EMBASE and MEDLINE from their inception to July 2019. Search terms were compiled from terms related to COPD and uric acid. The detailed search strategy is provided in the supplementary data 1. No language limitation was applied. References of the included studies were also manually reviewed for additional eligible studies. This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which is available as supplementary data 2.

Inclusion criteria

Studies that were eligible to be included into the meta-analysis must have consisted of two groups of participants, patients with COPD and individuals without COPD, and have reported either mean or median level of serum uric acid of participants in both groups and its standard deviation (SD), standard error of the mean (SE) or interquartile range, regardless of study design.

Study eligibility was independently determined by the three investigators (P.W., P.R., N.C.). Different opinions were resolved by conference with the senior investigator (P.U.). The quality of each study was jointly evaluated by all investigators using the Newcastle-Ottawa quality assessment scale for cohort studies [20] and the modified Newcastle-Ottawa quality assessment scale as described by Herzog *et al.* for cross-sectional studies [21].

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, country where the study was conducted, study design, year of publication, total number of participants, recruitment of patients with COPD and individuals without COPD, average age of participants, percentage of females and methods used to diagnose COPD. This data extraction was independently performed by the same three investigators (P.W., P.R., N.C.) to minimize error. Any discrepancies found in the case record forms were resolved by referring back to the original articles.

Statistical analysis

Mean serum uric acid level and SD of participants in both groups were extracted from each study and the mean difference (MD) was calculated. Pooled MD was then computed by combining MDs of each study using random effects model. If the study provided median and interquartile range instead of mean and SD, median would be used as an estimate for mean and SD would be estimated from interquartile range divided by 1.35. The heterogeneity of the MDs across the included studies was quantified using the Q statistic, which is complemented with I^2 statistics. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity [22]. Visual inspection of funnel plots was used to assess for the presence of publication bias. Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

Results

The systematic search identified 526 potentially relevant articles (412 articles from EMBASE and 114 articles from MEDLINE). After the exclusion of 100 duplicated articles, 426 articles underwent title and abstract review. A total of 406 articles were excluded at this stage as they clearly did not fulfill the eligibility criteria based on the type of article, study design, participants and outcome of interest. A total of 20 articles were retrieved for full-length article review and 12 articles were excluded at this stage as they did not report the level of serum uric acid among participants with and without COPD. Finally, eight studies [12–19] with 1,612 participants were eligible for the meta-analysis. The literature retrieval, review and selection process are shown in Figure 1. The characteristics of the included studies and their quality assessment are described in Table 1.

Serum uric acid level among patients with COPD versus individuals without COPD

The pooled analysis found a significantly increased serum uric acid level among patients with COPD compared with individuals without COPD with the pooled MD of 0.91 mg/dL (95% CI: 0.45–1.38). The between-study heterogeneity was high with an I^2 of 89%. Figure 2 demonstrated the forest plot of the included studies.

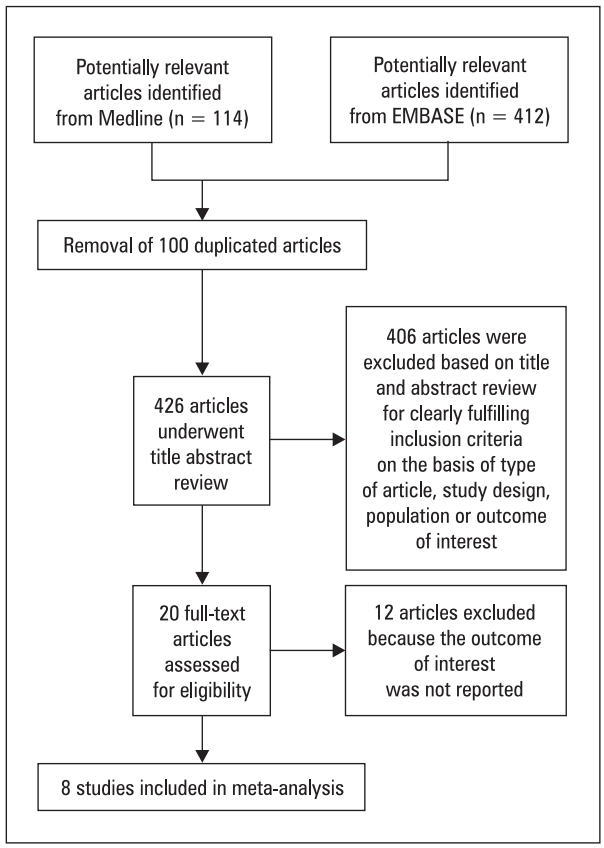

Figure 1. Literature review process

Evaluation for publication bias

Funnel plot was used to evaluate for the presence of publication bias as shown in Figure 3. The plot was relatively asymmetric and may suggest the presence of publication bias.

Sensitivity analysis

A sensitivity analysis was conducted to exclude two studies [17–18] that reported median and interquartile range and, thus, mean and SD had to be approximated using the technique described under Methods. Exclusion of these two studies from the pooled analysis only slightly increased pooled MD to 1.16 and remained statistically significant (95% CI: 0.57–1.75; I^2 88%), suggesting that the approximation did not have a substantial impact on the pooled result (supplementary data 3).

Discussion

The current study is the first systematic review and meta-analysis that summarized data from all available studies that compared the level of serum uric acid among patients with COPD versus individuals without COPD. We found that, on average, patients with COPD had a higher level of serum uric acid level than individuals without COPD with the difference of almost 1 mg/dL, which is approximately the same as the magnitude of uric acid reduction clinicians can expect from patients with gout/hyperuricemia who follow low-purine diet [23]. This observation may reinforce the hypothesis that tissue hypoxia can increase the rate of purine catabolism. In fact, *in vitro* and animal studies have indicated that hypoxic state can reversibly enhance oxidation of xanthine dehydrogenase into xanthine oxidase [12, 24–26]. Since significant number of patients with COPD has systemic hypoxia at rest or during acute exacerbation as a result of decreased oxygen diffusion capacity and alveolar hypoventilation, higher xanthine oxidase activity and increased serum uric acid level could be expected.

Another possible explanation is associated with an increased oxidative stress, which is a prominent feature of COPD [27]. Uric acid is classified as a low molecular weight water soluble antioxidant [12] that takes part in protecting the lungs from oxidative stress by inhibiting lipid peroxidation and scavenging reactive oxygen species and reactive nitrogen species [28]. Therefore, it is possible that the higher level of serum uric acid is a counter-response to a higher burden of oxidative stress among patients with COPD [3, 29].

Because of the observational nature of the included studies, it is also possible that the observed association between COPD and higher serum uric acid level is not causal with no direct mechanistic link. A recent systematic review found that metabolic syndrome is common among patients with COPD that is found in about one-third of them [30]. Since there is a strong association between insulin resistance, metabolic syndrome and hyperuricemia, [31] the observed higher level of serum uric acid level could be confounded by co-morbidities rather than COPD itself.

The results of this systematic review and meta-analysis may suggest that patients with COPD could be at a higher risk of hyperuricemia and serum uric acid may be worth checking for patients with COPD who exhibit signs and symptoms of complications of hyperuricemia, such as acute arthritis and kidney stones.

Few limitations of this systematic review and meta-analysis should be noted. First, between-study heterogeneity was high in this analysis, suggesting that the results of the primary studies could be too heterogeneous to combine together. The difference in background popula-

Table 1. Baseline characteristics of studies included in the meta-analysis

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Nicks *et al.* 2011 [12]	United States	Cohort study	**Cases:** Cases were smokers (at least a 10-pack year smoking history) with COPD who were recruited from the community of Denver, Colorado. Diagnosis of COPD was made based on GOLD criteria. **Comparators**: Comparators were smokers (at least a 10-pack year smoking history) without COPD who were recruited from the same community	Cases: 367 Comparators: 136	Mean age: Cases: 66.0 years Comparators: 57.0 years Percentage of female: Cases: 44.0% Comparators: 55.0% BMI Cases: 27.2 Comparators: 29.2 Smoking (Pack-Years) Cases: 57.0 Comparators: 42.0 Predicted FEV_1% Cases: 50.0% Comparators: 80.0% FEV_1/FVC Cases: 0.48 Comparators: 0.77	Selection: 4 stars Comparability: 1 star Outcome: 3 stars
Kocak *et al.* 2016 [14]	Turkey	Cohort study	**Cases:** Cases were patients with stable COPD (i.e., not in current COPD exacerbation or had history of exacerbation during the previous four weeks) who were recruited from the outpatient clinic of the study center between August 2014 and April 2015. Diagnosis of COPD was made based on GOLD criteria. **Comparators:** Comparators were subjects without COPD who were recruited from the same center. Subjects with chronic renal failure (serum creatinine levels > 3 mg/dL or glomerular filtration rate < 30 mL/min), gout disease or those who used any drugs that might affect serum UA levels, including allopurinol, febuxostat, probenecid, losartan, fenofibrate, pyrazinamide, ethambutol, cyclosporine and heparin, were excluded	Cases: 110 Comparators: 52	Mean age: Cases: 65.4 years Comparators: 62.7 years Percentage of female: Cases: 16.3% Comparators: 28.8% Current smoker: Cases: 18.1% Comparators: 26.9% Smoking (pack-years): Cases: 34.2 Comparators: 13.6 BMI (kg/m^2): Cases: 27.0 Comparators: 27.5 Urea (mg/dL): Cases: 27.1 Comparators: 31.1 Creatinine (mg/dL): Cases: 0.9 Comparators: 0.8	Selection: 4 stars Comparability: 1 star Outcome: 3 stars

Table 1. Baseline characteristics of studies included in the meta-analysis [cont.]

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Ozanturk *et al.* 2016 [13]*	Turkey	Cohort study	**Cases:** Cases were patients with COPD who were recruited from the study center. COPD was diagnosed from a history of ≥ 10 pack-years of smoking or a history of biomass exposure AND FEV_1 of < 80% of the predicted value after bronchodilator AND FEV_1/FVC of ≤ 0.7 after bronchodilator use. **Comparators:** Comparators were subjects without COPD who were recruited from the same center. Subjects with the following conditions were excluded: gout, diabetes mellitus, hemolytic anemia, myelolymphoproliferative disease, psoriasis, Paget's disease, glucose-6-phosphatase deficiency, glycogen storage disease, renal failure, acidosis, sarcoidosis, lead intoxication, berylliosis, use of some medication (salicylic acid, diuretic,cyclosporine, levodopa, phenylbutazone, ethambutol, pyrazinamide, nicotinic acid,nitroglycerin, theophylline, and allopurinol)	Cases: 15 Comparators: 15	Mean age: Cases: 58.0 years Comparators: 46.2 years Percentage of female: Cases: 6.6% Comparators: 60.0% Current smoker: Cases: 40.0% Comparators: 20.0% BMI (kg/m^2): Cases: 27.2 Comparators: 27.5	Selection: 4 stars Comparability: 1 star Outcome: 3 stars
Antus *et al.* 2017 [16]	Hungary	Cohort study	**Cases:** Cases were patients with stable COPD who were recruitedthe study center. **Comparators:** Comparators were subjects without COPD who were recruited from the same center	Cases: 34 Comparators: 29	NA	Selection: 2 stars Comparability: 0 star Outcome: 2 stars
Sarangi *et al.* 2017 [15]	India	Cohort study	**Cases:** Cases were patients with stable COPD who were recruited from the study center between 1st June 2016 and 31st July 2016. Diagnosis of COPD was made based on presence of persistent cough with or without sputum production and breathlessness, followed by spirometric evaluation (post bronchodilator FEV_1 to FVC ratio less than 0.7). **Comparators:** Comparators were nonsmoker, nonalcoholic subjects who came for routine health checkup at the same center. Comparators had no history of any respiratory signs or symptoms in the last three months. They were age and sex matched to cases	Cases: 39 Comparators: 46	Mean age: Cases: 62.97 years Comparators: 48.76 years Percentage of female: Cases: 46.2% Comparators: 43.4%	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars
AbdelHalim *et al.* 2018 [19]	Egypt	Cohort study	**Cases:** Cases were male patients with stable COPD (i.e., no exacerbation within 4 weeks prior to recruitment) who were recruited from the study center between August 2014 and April 2015. Diagnosis of COPD was made based on GOLD criteria. **Comparators:** Comparators were males without COPD who were recruited from the same center. Subjects with the following conditions were excluded: other chronic lung diseases, gouty arthritis, chronic renalfailure, malignancies, and use ofmedications that may affect the serum level of either UA or Cr, for example, allopurinol, ethambutol, pyrazinamide, cyclosporine, probenecid, heparin, fenofibrate and losartan	Cases: 283 Comparators: 123	Mean age: Cases: 55.9 years Comparators: 56.1 years Percentage of female: Cases: 0.0% Comparators: 0.0% BMI (kg/m^2): Cases: 25.9 Comparators: 25.3 CRP (mg/dl): Cases: 3.2 Comparators: 0.6	Selection: 4 stars Comparability: 1 star Outcome: 2 stars

Table 1. Baseline characteristics of studies included in the meta-analysis [cont.]

Study	Country	Study design	Study subjects	Number of subjects	Baseline characteristics of subjects	Quality assessment
Bačura *et al.* 2018 [18]	Croatia	Cohort study	**Cases:** Cases were patients with stable COPD who were recruited from the study center. **Comparators:** Comparators were subjects without COPD who were recruited from the same center	Cases: 137 Comparators:95	NA	Selection: 3 stars Comparability: 1 star Outcome: 2 stars
Lee *et al.* 2018 [17]	South Korea	Cohort study	**Cases:** Cases were never-smokers with COPD who were recruited from 6 administrative districts of South Korea in the Kangwon and Chungbuk provinces between October 2012 and November 2014. Diagnosis of COPD was made based on clinical presentation and evidence ofairflow limitation (post-bronchodilator FEV_1 to FVC of $< 70\%$). **Comparators:** Comparators were never-smokers without COPD who were recruited from the same areas	Cases: 77 Comparators : 54 Comparators: 54	Mean age: Cases: 74.0 years Comparators: 73.0 years Percentage of female: Cases: 57.0% Comparators: 38.0% BMI (kg/m^2): Cases: 24.1±3.1 Comparators: 23.9±3.2 Extra-pulmonary comorbidities Diabetes mellitus: Cases: 11.7% Comparators: 13.0% Cerebrovascular disease: Cases: 9.1% Comparators: 9.3% Malignancy: Cases: 3.9% Comparators: 5.6% Chronic liver disease: Cases: 3.9% Comparators: 3.7% Chronic kidney disease: Cases: 1.3% Comparators: 3.7%	Selection: 4 stars Comparability: 1 star Outcome: 3 stars

*The study by Ozanturk E. *et al.* reported serum uric acid level in several groups of participants but only data from two groups of participants, individuals without COPD and obstructive sleep apnea and patients with COPD without nocturnal hypoxemia, were used for the meta-analysis. BMI — body mass index; Cr — creatinine; COPD — chronic obstructive pulmonary disease; $D_{LCO}\%$ — diffusing capacity for carbon monoxide percentages; FEV_1 — forced expiratory volume in one second; FVC — forced vital capacity; GOLD — Global Initiative for Chronic Obstructive Lung Disease; NA — not available; UA — uric acid

Study or subgroup	COPD Mead	COPD SD	COPD Total	Comparators Mean	Comparators SD	Comparators Total	Weight	Mean difference IV, Random, 95% CI	Year	Mean difference IV, Random, 95% CI
Nicks *et al.*	9.3	5	367	9.4	4.7	136	9.4%	-0.10 [-1.04, 0.84]	2011	
Ozanturk *et al.*	5.5	1.1	15	4.8	1.2	15	10.4%	0.70 [-0.12, 1.52]	2016	
Kocak *et al.*	5.9	1.5	110	4.6	1.2	52	13.6%	1.30 [0.87, 1.73]	2016	
Sarangi *et al.*	4.9	1.7	39	2.3	0.9	46	12.3%	2.60 [2.01, 3.19]	2017	
Antus *et al.*	5.4	0.3	34	4.6	0.3	29	15.2%	0.80 [0.65, 0.95]	2017	
Lee *et al.*	4.7	1.3	77	4.7	1.3	54	13.5%	0.00 [-0.45, 0.45]	2018	
Bacura *et al.*	5.4	1.6	137	4.9	1.3	95	14.0%	0.50 [0.13, 0.87]	2018	
AbdelHalim *et al.*	6.2	1.3	283	4.8	3.7	123	11.6%	1.40 [0.73, 2.07]	2018	
Total			**1062**			**550**	**100.0%**	**0.91 [0.45, 1.38]**		

Heterogeneity: $Tau^2 = 0.36$, $Chi^2 = 61.44$, df = 7 ($P < 0.0001$); $I^2 = 89\%$
Test for overall effect: $Z = 3.89$ ($P = 0.0001$)

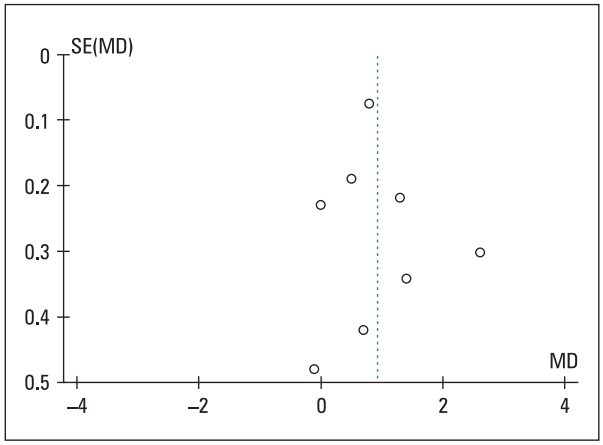

Figure 3. Funnel plot o1.1f the meta-analysis

Figure 2. Forest plot of the meta-analysis

tions of patients with COPD was the most likely explanation for the variation. Second, funnel plot of this analysis was relatively asymmetric and may suggest the presence of publication bias in favor of studies that report positive results. Third, the quality of some included studies was fairly low as reflected by low Newcastle-Ottawa scores.

Conclusions

In conclusion, this study found a higher level of serum uric acid among patients with COPD. Tissue hypoxia and increased oxidative burden are the possible explanations as well as confounding effect of co-morbidities.

Contributors

All authors designed the study. PW, NC and PR collected data and drafted the manuscript. PU performed statistical analysis and made critical revisions. All authors revised and approved the final manuscript.

Conflict of interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices or materials described in this report.

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