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Review article

Subclinical atherosclerosis risk markers in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis

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ABSTRACT

Background and aims: Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality. Identifying early changes of cardiovascular system before the occurrence of fatal clinical event is critical for the management of COPD. We performed a meta-analysis to investigate the associations between COPD and subclinical markers of cardiovascular risk.

Methods: We searched PUBMED, EMBASE for studies published before Aug 1st, 2016, on the association between COPD and carotid intima-media thickness (CIMT), prevalence of carotid plaques, flow-mediated dilation (FMD), pulse-wave velocity (PWV) and augmentation index (AIx).

Results: Thirty-two studies (3198 patients, 13867 controls) were included. Compared with controls, COPD patients had significantly higher CIMT (MD: 0.10 mm; 95% CI: 0.04, 0.16; $p = 0.0007$), PWV (SMD: 0.70; 95% CI: 0.52, 0.88; $p < 0.0001$), AIx (MD: 4.60%; 95% CI: 0.52, 8.68; $p = 0.03$), AIx@75 (AIx normalized to a heart rate of 75 beats per minute) (MD: 4.59%; 95% CI: 2.80, 6.38; $p < 0.0001$), prevalence of carotid plaque (OR: 2.54; 95% CI: 2.04, 3.15; $p < 0.0001$), and significantly lower FMD (MD: −4.21%; 95% CI: −6.71, −1.71; $p = 0.001$). Sensitivity and subgroups analyses substantially confirmed our results. Meta-regression analysis revealed that spirometry (as expressed by FEV_1%predicted) might influence on PWV.

Conclusions: These findings indicate that COPD, even in mild to moderate patients, had greater impaired markers of subclinical atherosclerosis and cardiovascular risk. However, further studies are still needed to address confounders, such as age, smoking, hypertension, diabetes etc, which might affect the associations in COPD patients.

Contents

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1. Introduction

Accumulating evidence has demonstrated that chronic obstructive pulmonary disease (COPD) is a pulmonary disease characterized also by extra-pulmonary manifestations and co-morbidities [1,2]. Of these, cardiovascular diseases are the most common co-morbid conditions affecting COPD patients, and contribute substantially to the severity and prognosis of COPD [1,3,4].

Although cardiovascular risk scores [5] have been proposed to assess the effect of cardiovascular co-morbidities on COPD mortality, better understanding the association between COPD and early changes of cardiovascular system before the occurrence of fatal clinical events (i.e. myocardial infarction, stroke), has incremental implications for disease management at an individual level, such as early-targeted prevention and intervention for individuals classified as high cardiovascular risk stratum. Several subclinical vascular markers have been generally validated in the cardiovascular field, including carotid intima-media thickness (CIMT) [6], endothelial function (flow-mediated dilation [FMD]) [7], and arterial stiffness measurements (pulse wave velocity [PWV], and augmentation index [AIx]) [8,9], and these non-invasive, reproducible, and relatively easy imaging test have been accepted as surrogate markers for predicting major cardiovascular events (stroke, myocardial infarction, or cardiac death) in previous studies [10–12]. Recently, independent studies have been reported increased subclinical atherosclerosis in patient with COPD compared to healthy subjects, and this was summarized in a recent narrative review [13]. However, no previous study has provided a comprehensive information about this issue using quantitative evidence synthesis.

With this in mind, we perform a systematic review and meta-analysis of the available literatures to investigate the associations between COPD and these cardiovascular risk markers; and assess the validity of the associations and potential sources of heterogeneity with modern statistical approaches.

2. Methods

2.1. Data sources and searches

L.Y.W. and Y.N.Z. independently searched MEDLINE (via PUBMED) and EMBASE databases to identify publications reporting associations between COPD and cardiovascular risk markers (i.e. CIMT, FMD, NMD, PWV, AIx and AIx@75) from observational data published before Aug 1st, 2016 without any language restriction. The following key terms were used: “chronic obstructive pulmonary disease”, “COPD”, “intima-media thickness”, “carotid plaques”, “atherosclerosis”, “flow-mediated dilation”, “endothelium-dependent dilation”, “endothelium-independent dilation”, “endothelial dysfunction”, “pulse wave velocity”, “augmentation index”, “arterial stiffness”. Additionally, we reviewed references of retrieved articles for other potential eligible publications that were not identified in the initial search.

2.2. Study selection

Studies were included for this meta-analysis if they met all the following criteria: (1) had a control group; (2) evaluated the relationship between steady-state COPD, defined as no exacerbations or antibiotic treatment of respiratory infection within 4 weeks, and markers of cardiovascular risk, including at least one variable among the following: carotid artery IMT (CIMT), brachial artery FMD, PWV measured at any anatomical region, aortic AIx, and aortic AIx@75; (3) had sufficient data to generate means with standard deviation (SD), or reporting the prevalence of carotid plaques. However, case-reports, case-series without a control group, reviews and animal studies were excluded. In studies with multiple measures over time, we used baseline data. When studies had the same study population or reported a subgroup of other studies, only the largest one was included.

Conference abstracts or website materials were also excluded, because these data have not been peer-reviewed and their inclusion may bias the results of this meta-analysis.

2.3. Data extraction and quality assessment

From each included study, the following data were extracted: sample size, major clinical and demographic variables, the means and SD of CIMT, FMD, PWV, AIx, AIx@75, and prevalence of carotid plaques in COPD patients and controls, respectively.

We assessed the quality of each study using the Newcastle–Ottawa Scale (NOS) for case-control studies [14] to ascertain the quality of selection, comparability, exposure, and outcome of