Microalbuminuria as a potential novel cardiovascular biomarker in patients with COPD

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Microalbuminuria is a simple biomarker that identifies COPD patients at increased cardiovascular risk http://ow.ly/tdIAB

Chronic obstructive pulmonary disease (COPD) is now recognised as the third cause of death in the world [1]. Patients with COPD are more likely to have pre-existing cardiovascular disease (CVD) and are at high risk of acute events, hospitalisations and death from CVD [2, 3]. Furthermore, this strong association is independent of the degree of airflow limitation. Because of this, the Global Initiative for Chronic Obstructive Lung Disease initiative recognises CVD as the most important disease coexisting with COPD and suggests it should be routinely looked for, but makes no recommendation on how to do it [4].

Over the past two decades, interest in CVD prevention has expanded and now promotes not only primary prevention, but also identification of factors that could help clarify CVD pathophysiology, offer targets for intervention or lead to improved risk stratification beyond that allowed by the Framingham equations [5]. Currently, only a few biomarkers have been accepted as being clinically useful [6]. In this regard, the recent consensus of the American College of Cardiology/American Heart Association recognises family history as being useful and haemoglobin A1c measurement as reasonable in all adults. They also categorise microalbuminuria (MAB) assessment as reasonable in adults with hypertension or diabetes [7].

The discovery of novel "biomarkers" that could help identify cardiovascular risk in patients with COPD could help personalise therapy for that particular phenotype. To be clinically useful, the biomarker should be inexpensive, noninvasive and easily measurable. Therefore, MAB could be a promising biomarker to identify patients with COPD at increased risk for poor cardiovascular outcomes. The presence of MAB is consistently associated with arterial stiffness assessed by pulse wave velocity and worse cardiovascular outcomes in patients with diabetes, hypertension and, importantly, in the general population [8–10]. MAB has been shown to have a stronger association with cardiovascular events and death than C-reactive protein [11], and is thought to reflect a state of generalised endothelial dysfunction.

The limited number of studies that have investigated the presence of MAB in patients with COPD have reported a high prevalence in patients during acute exacerbations [12–14] and, importantly, also in stable state [15, 16]. Several authors have shown that after adjusting for smoking and independent of the presence of diabetes and hypertension, the prevalence is ~25% of patients with stable COPD [15, 16].

In this issue of *European Respiratory Journal* (*ERJ*), ROMUNDSTAD *et al.* [17] confirm this data in a large population-based study. A total of 3129 subjects, aged ⩾20 years, with spirometry and morning urine

samples for MAB analysis were included in the main analysis. 136 ($\sim$22%) of the 631 patients had COPD and MAB, defined as an albumin/creatinine ratio (urine albumin (mg))/(urine creatinine (mmol)) between 2.5 and 30 mg·mmol^{-1}. In this study, MAB was evaluated in three morning urine samples and the final data was defined as the mean of three albumin/creatinine ratio measurements, rendering more precision to the final estimate.

In the Nord-Trøndelag Health Study (HUNT) cohort in 2003, ROMUNDSTAD et al. [18] observed that the presence of MAB was associated with a two-fold increased risk of all-cause mortality in healthy individuals without diabetes or hypertension. In this issue of the *ERJ*, they expanded the analysis to a group of patients who had also undergone spirometry. For the first time, they showed a positive association between MAB and all-cause mortality [17]. Although others factors such as exacerbations or symptoms were not measured and residual confounding are possible, the results were based on a large cohort with long-term follow-up (mean 12 years) and a high number of deaths (319 subjects with COPD died). They also observed an association between MAB and the level of airways obstruction, similar to that reported previously in a clinical study [16]. However, the HUNT study did not evaluate other variables such as arterial oxygen tension (PaO$_2$), which was the factor most strongly associated with MAB in two previous studies [15, 16].

The association with all-cause mortality was significantly increased, even after excluding the presence of CVD at baseline. However, cardiovascular mortality was not significantly increased in this study. This suggests that MAB could reflect a low-grade systemic inflammation, independent of the process of atherosclerosis. However, it is possible that the difficulty in ascertaining accurate cause of death in COPD patients (information was from the Norway Cause of Death Registry and classified according the International Statistical Classification of Diseases) could explain the lack of association between MAB with cardiovascular death in this study.

Little is known about the factors that determine the onset of proteinuria and even less is known about the relationship between MAB and the pathogenesis of COPD. In the general population, the systolic blood pressure and fasting glucose appear to be the most important factors related to MAB, through their direct effect on the glomerular intra-renal pressure or the stimulation of the renin-angiotensin-aldosterone system [19]. Inflammation, endothelial dysfunction and thrombogenic factors have been implicated as potential mechanisms underlying the relationship between proteinuria and cardiovascular disease [20]. Indeed, circulating von Willebrand factor, soluble vascular cell adhesion molecule, fibrinogen and tissue plasminogen activator have been found to correlate with urinary albumin excretion. More recently, MAB has been associated with novel biomarkers (high-sensitivity troponin T, C-reactive protein and vascular endothelial growth factor) in addition to classical cardiovascular risk factors (HbA1c, coronary calcium and carotid intima-media thickness). However, the majority of studies demonstrating relationships between proteinuria and cardiovascular risk factors are cross-sectional and so inference regarding causality cannot be drawn. Unfortunately, biomarkers were not measured in the HUNT study, so the question remains unanswered.

The effect of the tissue hypoxia on the kidney could be another possible cause of MAB. In fact, it could explain the increase of MAB prevalence that has been reported in subjects living at high altitude even with preserved glomerular filtration rate [21]. In fact, in two recently published studies [15, 16], the PaO$_2$ was the main factor inversely associated with MAB. Interestingly, no previous studies have considered the possible association between PaO$_2$ and MAB in population cohorts or in studies in patients with diabetes or hypertension.

Given that the presence of MAB is independently associated with increased risk of death, it could be a therapeutic target for risk reduction. However, studies of earlier and aggressive intervention with renin-angiotensin-aldosterone system blocking agents have demonstrated a reduction in proteinuria, but this has not yet translated into reduction in hard cardiovascular end-points. Furthermore, these studies have also reported a greater degree of side-effects and adverse events [22], so careful studies are needed to clarify the mechanism by which MAB occurs in general and in patients with COPD in particular, and how its management may influence ultimate outcomes.

In summary, the presence of MAB is increased in patients with stable COPD and is mainly associated with hypoxaemia. As a novel and important finding in this issue of *ERJ*, MAB is associated with all-cause mortality in this population. In theory, MAB could be a promising biomarker to identify patients with COPD at increased cardiovascular risk. More carefully obtained longitudinal data of MAB and its relationship with others biomarkers and cardiovascular risk factors are urgently needed. Finally, well-designed interventional trials that can support a potential role of MAB as a target in the management of patients with COPD should be considered.

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