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# Increased oxidative stress and depleted antioxidant capacity in chronic obstructive pulmonary disease: Searching for applications

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Chronic obstructive pulmonary disease (COPD) has been rising in the prevalence as the world population ages. In the most recent iteration of the Global Burden of Disease study, there was a modest increase in global death rates attributable to COPD from 2005 to 2015. This was despite a global decline in age-standardized COPD-specific death rates, due to better healthcare.<sup>[1]</sup> These are ominous signs for the future COPD-related burden on the already stressed health-care system.<sup>[2]</sup> Strategies to predict susceptibility to COPD or its progression would be useful toward focusing limited resources. Further, the identification of potentially reversible factors is needed for better therapeutics.

The oxidant-antioxidant balance in COPD has been a longstanding topic of interest, analogous to the better-studied protease/anti-protease balance. It is believed that reactive oxygen species (ROS) that are not sufficiently counterbalanced by antioxidant factors are important in the pathogenesis of COPD. The sources of ROS are manifold; from the external environment such as cigarette puffs, to metabolically generated mitochondrial ROS, as reviewed elsewhere.<sup>[3]</sup> There is also data that there is an increase of oxidants and a decrease in some antioxidant defenses in the blood of COPD patients when compared to controls. This is the lung india paper for which I am writing the editorial. Jyoti Bajpai *et al*, Study of Oxidative Stress Biomarkers and their correlation with disease severity.<sup>[4]</sup> This is generally consistent with prior data and adds to the limited data on this subject from India. While the study also reports significant differences in oxidant/antioxidant markers between COPD and nonsmoking healthy controls, these differences can be attributed to either smoking or COPD. The authors found higher oxidative stress in higher GOLD classes of COPD (III, IV) when compared to lower classes (I, II) suggesting a COPD driven relationship. However, differences in smoking patterns could have importantly contributed, as could subpopulation characteristics such as gender, age, and sickness. Gender-related differences were seen in the study, with males showing greater oxidative stress than females. Whether this reflects true gender differences or exposure differences cannot be determined. Importantly, nonsmoking COPD was also associated with elevated oxidative stress, although less than that seen in smokers. Overall the results of this study are important toward understanding the type and extent of oxidant stress and antioxidant depletion in Indian patients. Increased lipid peroxidation, as evidenced by increased malondialdehyde,

and reduced catalase or superoxide dismutase (SOD) in patients with COPD, were consistent with existing data.<sup>[5]</sup> The relationship with iron and copper were more interesting. It is well known that anemia is more common in patients with COPD, but there is no clear consensus on whether iron supplementation would be beneficial. Iron-mediated hydroxyl radical formation and oxidative injury can be seen in the setting of high superoxide and hydrogen peroxide levels (Haber–Weiss reaction).<sup>[6]</sup> Given the reduced levels of SOD and catalase, it seems plausible that there would be accumulation of superoxide and hydrogen peroxide, which would be converted by free iron to even more toxic hydroxyl radicals.<sup>[7]</sup> This could underlie the noted association of iron with oxidative stress and COPD in this paper. However, the measurements here were made in blood, which has relevance to the systemic aspect of COPD, but misses the more important tissue aspects of inflammation and destruction. Further study in lung tissue samples would be useful. The associations with copper were more modest and it is difficult to reach substantive conclusions. Since the parameters seem to be internally correlated, higher order models are needed to more clearly define independent effects. The small sample size in this study is limiting for such analysis and larger studies will be needed to better understand the independent and interactive effects of these parameters.

A consistently disappointing aspect of the study of oxidative stress in COPD has been difficulty in relating it to susceptibility, progression, or outcome. Here, there was no significant difference in oxidative stress markers between outpatient, inpatient, or intensive care setting. Further, there was poor ( $r \sim 0.2$ , although statistically significant) correlation with functional parameters such as forced expiratory volume in 1 s or forced vital capacity. Thus, it does not seem that either outcomes or progression are likely to be well predicted by oxidative stress markers. In the absence of a prospective cohort study, it is also impossible to determine whether smokers with higher oxidative stress are more likely to progress to COPD, although there have been hints that subjects with lower antioxidant levels may be at greater risk. Unfortunately, there has been inconsistent evidence that antioxidant supplementation is effective in either preventing or treating COPD.<sup>[8,9]</sup> On the contrary, recent reports suggest that antioxidants may increase the aggressiveness of cancer, a risk that needs to be carefully evaluated for COPD in antioxidant trials.<sup>[10]</sup> In short, there is a strong

basis for oxidative stress being an important part of COPD pathogenesis, but more needs to be done before we can successfully translate the knowledge into practically useful outcomes.

**Anurag Agrawal**

*CSIR-Institute of Genomics and Integrative Biology, Delhi  
University, New Delhi, India  
E-mail: a.agrawal@igib.in*

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