Chapter

Chronic Obstructive Pulmonary Disease Related to Wood and Other Biomass Smoke: A Different Phenotype or Specific Diseases?

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Abstract

Around 41% of the world's population continue using solid fuels, including wood and other types of biomass, for cooking or heating their homes. Long-term indoor exposure to wood smoke, and biomass smoke in general, is a risk factor for developing chronic obstructive pulmonary disease (COPD). In some regions of the world, biomass exposure is a more frequent cause of COPD than exposure to cigarette smoke. Recently it has been described notable differences between COPD associated with wood smoke (WS-COPD) and that caused by tobacco smoking (TS-COPD): significantly less emphysema and more airway inflammation in WS-COPD. Recognizing these differences, some authors have suggested that WS-COPD should be considered a new COPD phenotype. This chapter summarizes the differences between WS-COPD and TS-COPD. The information about the characteristics of COPD caused by other types of biomass fuels, different from wood, is very scarce. Accepting that the smoke derived from wood burning and tobacco smoking have some differences (etiology), the inhalation patterns are different (pathogenesis) and the physiopathological mechanisms they induce may also differ, we analyze if the disease caused by indoor chronic exposure to wood smoke should be considered as another COPD phenotype or a distinct nosological entity.

Keywords: chronic obstructive pulmonary disease (COPD), wood smoke, biomass, tobacco, phenotype, emphysema, chronic bronchitis, bronchial anthracofibrosis, indoor air pollution

1. Introduction

Solid and biomass fuels are the most important global environmental risk factor. Around 41% of the world's population, over 2.8 billion people, particularly in developing countries, still use solid fuels, whether coal or biomass (wood, vegetable remains and dung), for cooking or heating their homes [1, 2]. In some countries, these fuels are the main source of energy for over 70% of the rural population. In countries where migration from rural areas to cities is high, the population of urban dwellers over the age of 40 years frequently has a significant history of exposure

to biomass fuels. One example is Colombia, where 39% of the population over 40 years of age living in the five main cities had cooked using wood as fuel for more than 10 years before relocating [3].

Between 1980 and 2010, the population exposed to household air pollution (HAP) increased from 333 million to 646 million in sub-Saharan Africa and from 162 million to 190 million in the eastern Mediterranean. In south-east Asia, it remained stable during the same period at around 1 billion people [1].

Biomass fuels are usually burnt in open fires and inefficient traditional cookstoves, often in poorly ventilated cooking spaces, resulting in indoor high levels of air pollutants including carbon monoxide (CO) and particulate matter (PM). The people most exposed are women who are routinely responsible for cooking and their young children [4].

HAP is responsible for nearly 5% of the global disease burden, making it globally the single most important environmental risk factor [5]. In 2017, it has been estimated that HAP contributed to 1.8 million (95% CI, 1.1–2.7) deaths and 60.9 million (95% CI, 34.6–93.3) disability-adjusted life-years (DALYs) globally [6]. Respiratory disease was the leading cause of these deaths and DALYs attributable to HAP accounting for 38% of all deaths (0.7 million [0.4–1.0]) and 75% of all DALYs (45.7 million [26.8–68.8] [6]. Among the premature deaths related to HAP, 20% are due to chronic obstructive pulmonary disease (COPD) [2].

Biomass fuels and COPD. Several systematic reviews, meta-analyses and reviews of evidence confirm that individuals chronically exposed to solid fuels at home have a higher risk of developing COPD [6–13]. In addition, people chronically exposed to biomass smoke also have a high risk of chronic bronchitis [10, 14, 15]. The pooled analysis of the Pathak's study [7] showed that, globally, exposure to indoor air pollution due to solid biomass fuels increased risk of COPD by 2.65 (95% CI, 2.13–3.31) and chronic bronchitis by 2.89 (95% CI, 2.18–3.82) times more compared to non-biomass fuels. The risk of COPD was higher in Africa region (odds ratio [OR]: 3.19), Asia (OR: 2.88), South America (OR: 2.15), Europe (OR: 2.30) and North America (OR: 2.14). This distribution confirms that although the risk is higher in developing regions [16], the high risk is also present in developed countries, as some studies have shown [17, 18].

In some highly populated countries, like India and China, the exposure to biomass smoke is a significant risk factor for COPD, mainly in women living in rural zones [15, 19–24]. In some areas of India and China, this exposure is the most important risk factor of COPD [20–22, 25–30]. In Latin America, the PREPOCOL [3], the CRONICAS [31] and the PUMA [32] studies have confirmed that the use of biomass fuels, frequently wood, for cooking is a significant and independent risk factor for COPD, stronger in women from rural areas.

Although the risk of COPD from long-term indoor exposure to biomass fuels is particularly high in women [23, 33–36], a population study (n = 5539) showed that, after adjusting for age, smoking, educational level and occupational exposure, men exposed to wood smoke for more than 10 years had a higher risk of COPD (OR: 1.50) [37]. The risk of COPD increases significantly with the length of exposure to wood smoke and with simultaneous exposure to tobacco smoke [37].

This evidence supports that HAP from burning solid fuels, including biomass, is the biggest worldwide risk factor for COPD [38–40]. However, the prevalence of biomass-related COPD has not been precisely defined. The PREPOCOL study found a prevalence of 6.7% in people exposed to wood smoke and not to cigarette smoke compared to 7.8% in people exposed to cigarette smoke and not to wood smoke [37]. In rural Puno, Peru, daily use of biomass fuel for cooking among women was associated with COPD (prevalence ratio: 2.22, 95% CI: 1.02–4.81) and the population attributable risk of COPD due to daily exposure to biomass fuel smoke was 55% [31].

Some populational studies, however, found no association between exposure to biomass fuels and COPD [41, 42]. Most of the people evaluated in these studies lived near sea level, where cooking is usually done outdoors or with better ventilation. In contrast, many of the studies which document this association have included areas situated at high or intermediary altitudes, where, due to low temperatures, cooking is done all year round inside poorly ventilated homes as it occurs in winter in regions that have seasons. There is lack of standardization of questionnaires or other tools for evaluating the exposure to biomass smoke derived from cooking or heating. A recent study, from Kyrgyzstan, evaluated the prevalence of COPD associated with indoor contamination at different altitudes and found a higher prevalence of COPD at high altitude versus at low altitude (36.7% vs. 10.4%; $p < 0.001$) associated with exposure to a greater indoor contamination at high altitude [43].

2. Differences between WS-COPD and TS-COPD

Although the risk of COPD has been proven for all types of biomass fuels, studies which best characterize COPD due to this type of exposure have focused on COPD caused by inhalation of wood smoke (WS-COPD). Therefore, this chapter also focuses on the differences of WS-COPD and TS-COPD.

Core differences. A growing body of evidence supports that WS-COPD, unlike TS-COPD, is predominantly and markedly a disease of the airways with mild or minimum emphysema [44–54]. Although recent publications have focused on the compromise of the small airways in biomass COPD [46, 50, 52], different from TS-COPD, in WS-COPD there is also a notorious compromise of the central airway due to carbon deposition (bronchial anthracofibrosis) with plaque formation and reduction in the caliber of the lobar bronchi [55–57]. In addition to this fundamental pathological difference between WS-COPD and TS-COPD, there are many other differences that we summarize in **Table 1** and review it below.

Demographic differences. Women and their children are the most exposed population to indoor air pollution from biomass fuels because of women are usually responsible for cooking meals, particularly in developing countries, spending several hours a day in frequently poor ventilated kitchens, and keeping their children close to them [4, 16, 23, 30, 58, 59].

Most of the studies show that women with WS-COPD are consistently shorter in height and have higher body mass index (BMI) than women with TS-COPD [37, 44, 49, 54, 60–66]. There is not a clear explanation for this difference. In general, women with WS-COPD were born and have lived in rural areas as their ancestry, while women with TS-COPD have lived in urban areas for many years and many of them have urban ancestry. Therefore, it is possible that some ethnic, nutritional and socioeconomics conditions could be part of the explanation of the difference, but there is not consistent information about this.

Moreover, women with WS-COPD are older, suggesting that patients with this type of exposure need more time to develop the disease or are diagnosed later [30, 37, 44, 51, 61, 63–65, 67].

Clinical differences. Several studies have shown a high frequency of respiratory symptoms (cough, expectoration, and dyspnea) and chronic bronchitis in subjects exposed to biomass smoke [9, 10, 14, 61]. However, comparative studies between WS-COPD and TS-COPD have found no consistent differences. Some studies show that symptoms, not only cough and phlegm but dyspnea, are more frequent or have more impact in WS-COPD than TS-COPD [48, 61, 68, 69] but other not [63, 65, 70]. Rhonchus and wheezing are more frequent in WS-COPD [68]. The

Characteristics	WS-COPD	TS-COPD
Demographic data		
Sex	Predominantly women	Predominantly men
Age	Higher	Lower
Height	Lower	Higher
BMI	Higher	Lower
Clinical characteristics		
Cough and expectoration	Very common	Common
Chronic bronchitis	Common	Common
Rhonchus and wheezing	Common	Less common
Lung function tests		
$PaCO_2$	Higher (some studies)	Less high
PaO_2 and SaO_2	Lower	Less low
Obstruction (FEV_1/FVC reduced)	Mild	More severe
Reduced FEV_1	Lower	Higher
Bronchial hyperresponsiveness	Higher	Lower
DLco and DLco/VA	Normal or mildly reduced	More reduced
Radiography-tomography		
Emphysema	Uncommon and mild	Common and more severe
Bronchial thickening	Common	Less common
Bronchiectasis	Common	Uncommon
Atelectasis	Common	Uncommon
Histology		
Emphysema	Mild	More severe
Anthracosis	Common	Less common
Airway fibrosis	Common	Less common
Thickening of arteriole intima	Common	Less common
Outcomes and clinical phenotypes		
Pulmonary hypertension	More common	Less common
Quality of life	Symptoms and activities more compromised or similar	Similar or symptoms and activities less compromised
Survival	Similar after adjusting for age. Less after adjusting for age	Similar
Exacerbator phenotype	Similar	Similar
Asthma-COPD overlap phenotype	More common	Less common
Emphysema phenotype	Uncommon	More common

WS: wood smoke; TS: tobacco smoke; BMI: body mass index; DL_{CO}: carbon monoxide diffusing capacity; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $PaCO_2$: carbon dioxide arterial pressure; PaO_2: oxygen arterial pressure; SaO_2: oxygen saturation; VA: alveolar volume.

Table 1.
Differences between wood smoke COPD and tobacco smoke COPD.

greater bronchial compromise in WS-COPD documented in several publications which use functional and tomographic evaluations supports the studies which show more frequent cough, expectoration, rhonchus and wheezing in WS-COPD.

Differences in quality of life. Using the Saint George's Hospital Questionnaire, Camp *et al*. found worse symptoms and more impaired activity indices in women with WS-COPD [48]. González-Garcia *et al.*, in 138 women with COPD, showed that, at the same degree of obstruction, women with WS-COPD had a worse health status (poorer quality of life and worse dyspnea) than those with TS-COPD, without differences in comorbidities (**Figure 1**) [68]. Some studies have not shown differences in quality of life between these two groups of patients [65].

Differences in lung function. Airflow obstruction, both overall and adjusted by age, is milder [37, 48, 54, 60–63, 65] and the FEV_1 decline is slower and more homogeneous in WS-COPD [54, 62] than in TS-COPD. Ocakli *et al.* described a more significant compromise of FVC with higher FEV1/FVC ratio in people with COPD related to biomass smoke suggesting restrictive ventilatory alteration, but lung volumes were not measured [71]. The chronic airflow limitation in patients with WS-COPD is possibly due not only to the small airways compromise [46, 50, 52, 54], but to anthracofibrosis of the large airways [55–57].

A recent study, aimed to evaluate the lung volumes and the resistance and conductance of the airways using plethysmograhy, showed that residual volumes (RV),

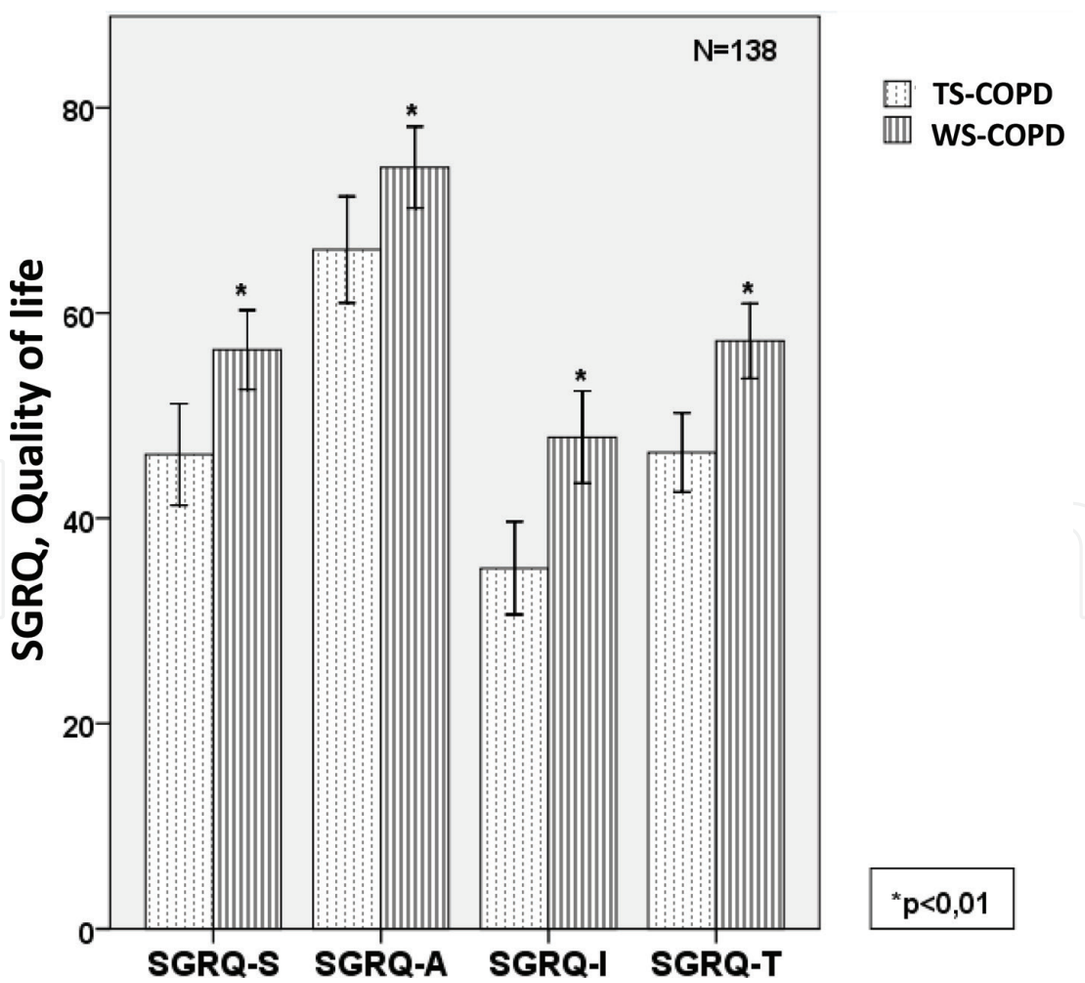

Figure 1.
Quality of life. Comparison between WS-COPD and TS-COPD*. WS-COPD: wood-smoke COPD; TS-COPD: tobacco smoke COPD. SGRQ: Saint George Respiratory Questionnaire. S: Symptoms; A: Activity; I: Impact; T: Total. From: González-García M, et al. Arch Bronconeumol. 2014; 50 (ALAT congress): 59 (ref. 68).*

total lung capacities (TLC) and RV/TLC ratios were significantly increased among both TS-COPD and non-smoking COPD (including biomass smoke COPD) subjects compared to healthy subjects ($p < 0.0001$), with no differences between the two COPD groups [54]. The same study showed that patients with COPD related to biomass smoke had significantly higher airway resistance (sRaw values) than TS-COPD patients ($p = 0.005$) and significantly lower conductance (sGaw values) in biomass COPD than in TS-COPD ($p = 0.010$) [54].

Some studies have showed that carbon dioxide arterial pressure ($PaCO_2$) is higher (lower ventilation) and oxygen arterial pressure (PaO_2) and oxygen hemoglobin saturation (SaO_2) are lower in WS-COPD than in TS-COPD [48, 61, 62, 65, 69]. Interestingly, Olloquequi *et al*. described that COPD patients who have had mixed exposure to tobacco smoke as well as biomass smoke had lower oxygen saturation than those who were exposed only to cigarette smoke or biomass smoke [72]. The lower oxygenation rates observed in WS-COPD may be explained by the compromise of the small airways and/or by hypoventilation. It remains to be determined if the higher BMI in these patients, most of whom are women over 50 years of age, is involved in this behavior.

One of most consistent differences between WS-COPD and TS-COPD is the significantly lower compromise of the diffusion capacity (DL_{CO}) in WS-COPD. DL_{CO} and DL_{CO}/alveolar volume (DL_{CO}/VA) ratio are normal or mildly altered in WS-COPD patients compared to TS-COPD patients, in who these parameters are significantly reduced [49, 60, 61], and occurs at all levels of COPD severity (**Figure 2A** and **B**) [61]. This finding correlates well with the lower grade of emphysema found on computed tomography (CT) in patients with WS-COPD in comparison with TS-COPD [48, 49, 54, 73]. The mildly reduced DL_{CO} with normal DL_{CO}/VA found in women with WS-COPD has been described in patients with significantly compromised small airways with little emphysema (pseudophysiological emphysema) [74]. The correlation between the level of decrease of FEV_1 and the level of DL_{CO} reduction is significantly better in women with TS-COPD than in those with WS-COPD, highlighting the greater contribution of emphysema to airflow obstruction in TS-COPD (**Figure 3**) [61].

Differences in bronchial hyperresponsiveness. Women with WS-COPD have greater bronchial hyperresponsiveness than women with TS-COPD (**Figure 4**) [64].

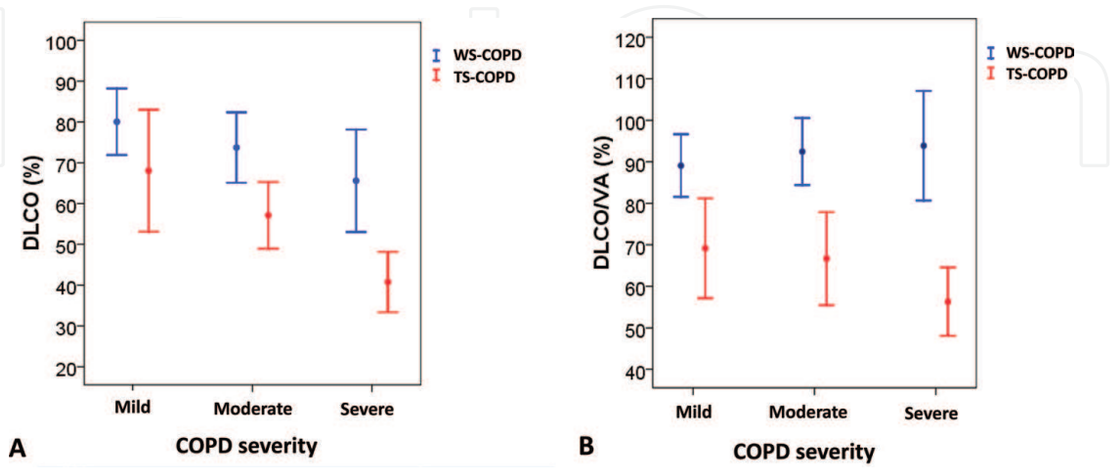

Figure 2.
Comparison of diffusion capacity between WS-COPD and TS-COPD according to degree of obstruction. *A. DL_{CO} (%) and B. DL_{CO}/VA (%). In TS-COPD, DL_{CO} and DL_{CO}/VA are more significantly compromised than in WS-COPD. DL_{CO}/VA is normal in WS-COPD at all levels of severity. WS: wood smoke; TS: tobacco smoke; DL_{CO}: carbon monoxide diffusing capacity; VA: alveolar volume.From: González-García M, et al. Acta Med Colomb. 2004; 29: 17–25 (Ref. 61).*

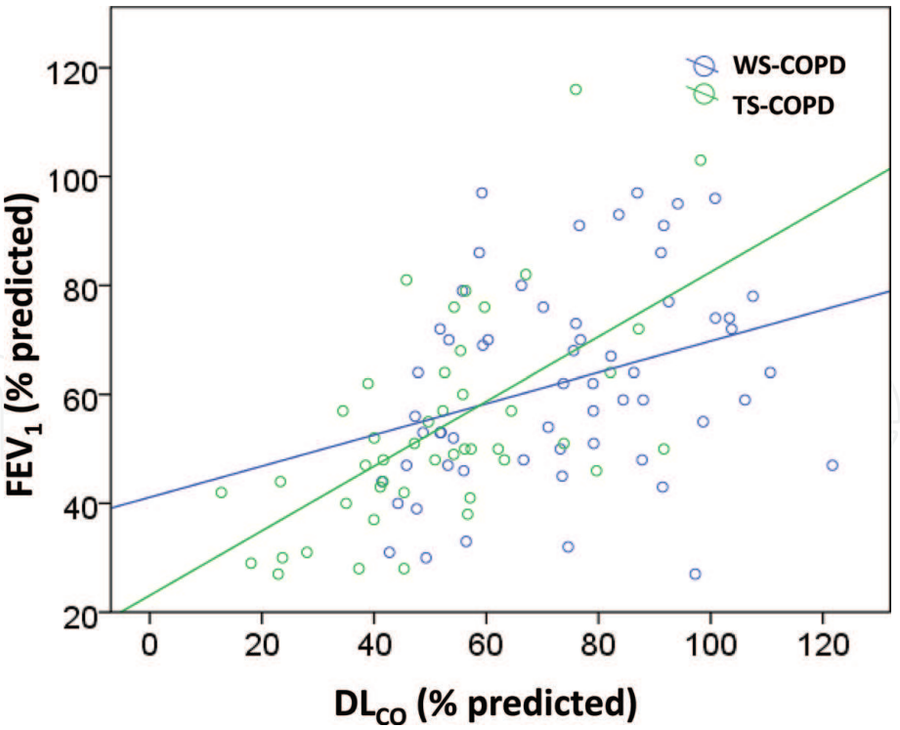

Figure 3.
Correlation between FEV$_1$ (%) and DL$_{CO}$ by exposure. *Greater correlation is observed between FEV$_1$ and DL$_{CO}$ in TS-COPD (P < .001, r = 0.599) than in WS-COPD (P = .014, r = 0.320). WS: Wood smoke; TS: Tobacco smoke; DL$_{CO}$: carbon monoxide diffusing capacity; FEV$_1$: forced expiratory volume in 1 s.From: González-García M, et al. Acta Med Colomb. 2004; 29: 17–25 (ref. 61).*

This finding could be correlated to the higher frequency of the asthma-COPD overlap phenotype described in biomass-related COPD [63].

Differences in exercise tolerance. Some studies which included the 6-minute walking test found no significant differences in distances walked between patients with WS-COPD and TS-COPD [48, 65, 68]. However, the study carried out by Zhao *et al.* found that patients exposed to biomass smoke walked fewer meters in the 6-minute walk than those with TS-COPD [46].

Tomography and histological differences. Patients with WS-COPD have consistently less emphysema and more airway changes (bronchial and peribronchial thickening and fibrosis, bronchiectasis, segmental and laminar subsegmental atelectasis, mosaic perfusion pattern, parenchymal bands) than patients with TS-COPD on both chest tomography and histological studies [48–50, 52, 60, 69, 73] (**Figure 5**). Bronchial and lung biopsies from patients with WS-COPD show significant inflammation and thickening of the bronchial wall, mainly of its basal membrane, squamous cell metaplasia with a remarkable anthracotic pigment deposition in the bronchi and pulmonary interstitium [60, 75–77].

Differences in the distribution of clinical phenotypes. Golpe *et al.* evaluated the frequency of clinical phenotypes defined by the 2014 Spanish COPD guidelines [78] in patients with COPD caused by biomass or tobacco smoke. They found a greater frequency of emphysema phenotype in TS-COPD and a more common asthma-COPD overlap phenotype in biomass COPD, but the difference disappeared after adjusting for sex [63]. These differences fit perfectly with the findings of the studies reported so far in this chapter. No difference was found in the frequencies of chronic bronchitis or exacerbator phenotypes [63].

Differences in pulmonary hypertension. Sertogullarindan *et al.* found that pulmonary hypertension (PH) on echocardiography was more common in WS-COPD than in TS-COPD patients [79]. In previous studies, our group, based

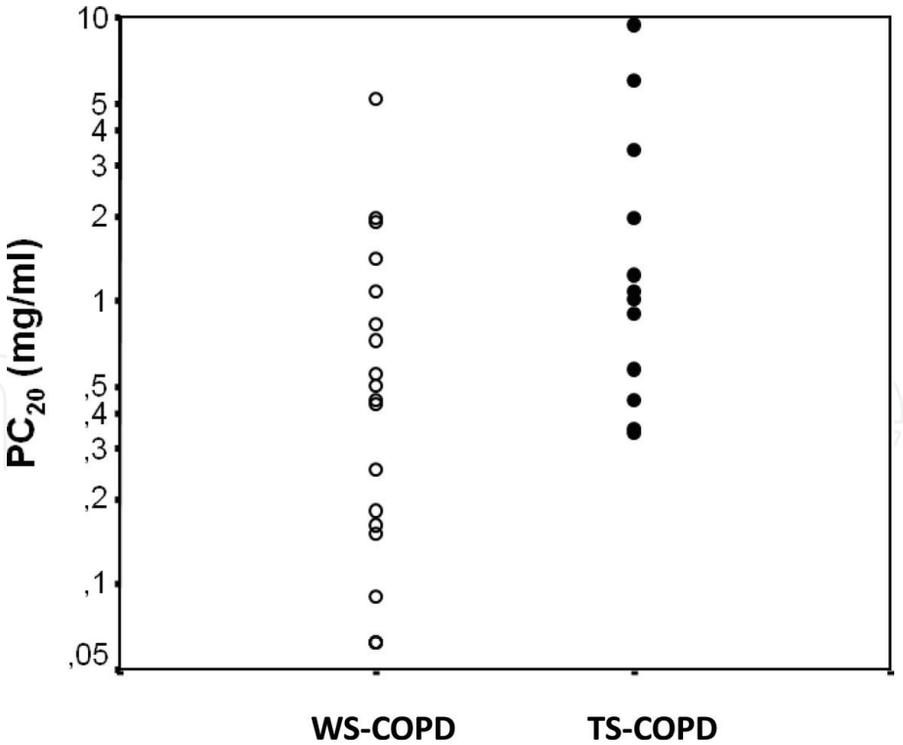

Figure 4.
Bronchial hyperresponsiveness evaluated by PC20 by exposure. *PC20: methacholine concentration causing ≥ 20% reduction in FEV_1. White circles: WS-COPD; black circles: TS-COPD. PC20 geometric mean: WS-COPD versus TS-COPD: 0.39 (0.06–5.13) versus 1.24 (0.34–9.39), P = .028. WS: wood smoke; TS: tobacco smoke. From: Gonzalez-Garcia M, et al. Int J Chron Obstruct Pulmon Dis. 2012; 7: 367–373 (Ref. 64).*

on radiographic evaluation, suggested the same higher frequency of PH in patients with severe WS-COPD [61], and Sandoval *et al*. showed a high rate of PH and cor pulmonale among patients with long-term domestic exposure to wood smoke [80]. It has been posed that the PH observed in WS-COPD could be associated not only to airflow obstruction and hypoxemia, but to a direct inflammatory effect of the inhaled smoke. It has been described that mice exposed to biomass exhibited more perivascular inflammation than those exposed to cigarette smoke [81].

Differences in the frequency of bronchial anthracofibrosis. The incidence of bronchial anthracofibrosis and its severity in individuals exposed to wood smoke or tobacco smoke has not been evaluated in prospective studies, and no differences are known. However, marked anthracofibrosis is commonly encountered in the airway of subjects exposed to wood smoke [16, 55–57], sometimes accompanied by bronchial stenosis, and it seems more frequent and severe than in tobacco smoke exposed. A significant proportion of these patients have chronic airflow limitation and meet the functional criteria of COPD [55] possibly due to the small airways compromise aggravated by anthracofibrotic central airway stenosis. It is currently impossible to ascertain if bronchial anthracofibrosis is another feature of WS-COPD that appears more commonly and in a more severe form than in TS-COPD, or if it is a specific entity accompanied by obstruction.

Differences in survival and frequency of exacerbations. After adjusting for age, sex, and disease severity, no differences have been found in survival between WS-COPD and TS-COPD [65, 82].

Recently, Cho *et al*., among 1033 patients with COPD, have shown that patients with COPD associated with biomass smoke and those with COPD associated with tobacco smoke had a similar risk of exacerbations [67], confirming previous observations [63].

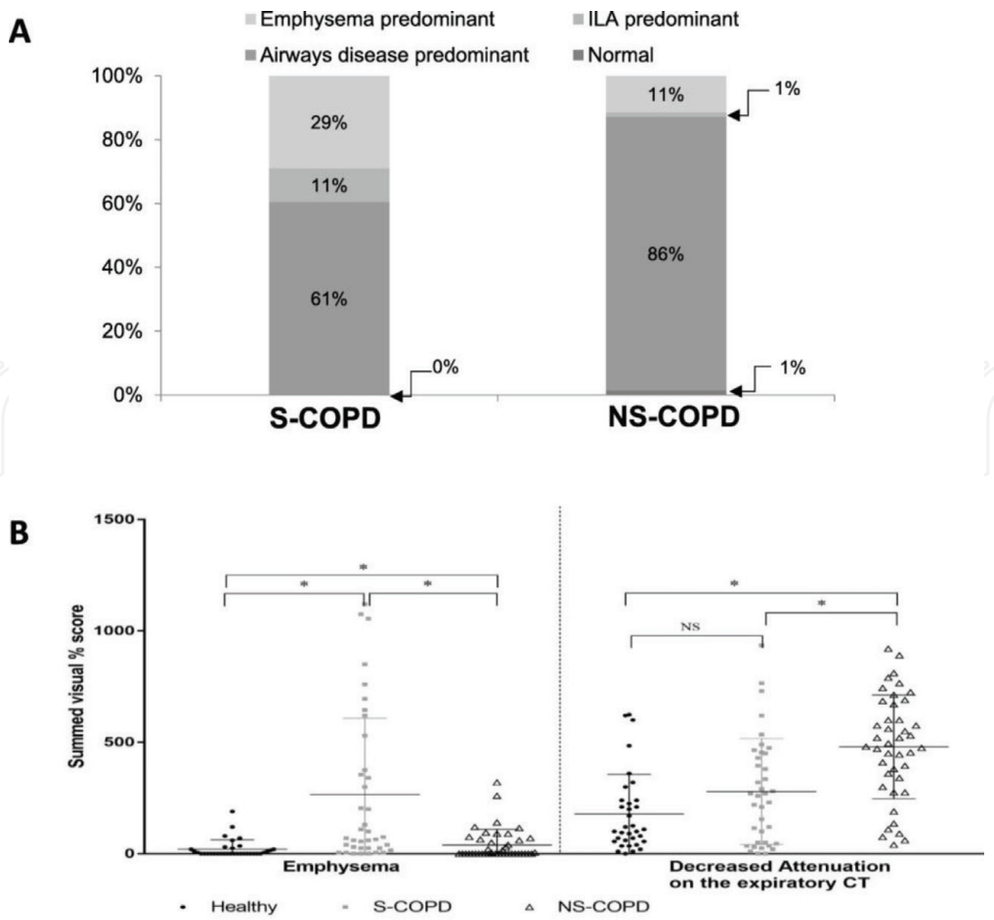

Figure 5.
Tomographic differences between smoking and non-smoking COPD*. Differences between smoker COPD (S-COPD) (n = 38) and non-smoker COPD (NS-COPD) (n = 70) on inspiratory-expiratory high resolution computerized tomography (HRCT) imaging (A) Showing HRCT classification of smoker and non-smoker COPD, including airway disease (black bars), emphysema (open bars) and interstitial lung abnormality (ILA) predominance (gray bars); (B) dot plot for emphysema and decreased attenuation of expiratory CT in S-COPD (■) and NS=COPD (△) compared to healthy subjects (●), where bars indicate median and interquartile rages and * p < 0.05, (C) Representative HRCT images of Smoker-COPD showing extensive centrilobular emphysema in the upper lobes and non-smoker COPD showing generalized decreased attenuation and some bronchial wall thickening. From: Salvi SS, et al. phenotypic comparison between smoking and non-smoking chronic obstructive pulmonary disease. Respiratory Research. 2020; 21: 50 [64].*

Differences in inflammatory profile and pathophysiological ways. It is expected that the greater airway inflammatory involvement and the lower rate of emphysema in biomass COPD, including WS-COPD, compared to TS-COPD have an etiological, pathogenic and physiopathological basis. However, although there is a growing information about the pathogenic mechanisms in COPD due to biomass smoke exposure [83], it is not clear what are the reasons explaining its differences

with TS-COPD. Some studies have focused on looking for differences in the type of inflammation and the proteolytic activity, and recently the gene expression.

The exposure to biomass smoke induces pulmonary macrophages and mononuclear and polynuclear cells to generate numerous inflammatory mediators, including interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 2 (MIP2) and tumoral necrosis factor (TNF) [83, 84]. These can generate a second wave of mediators that include enzymes, such as matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 12 (MMP-12) involved in proteolysis and tissue remodeling typical of COPD. A recent study explored differences in chemokine and cytokine concentrations among biomass-COPD versus TS-COPD and exposed controls without COPD. The author identified CCL27 and CXCL13 as putative, plausibly homeostatic/protective biomarkers for biomass COPD [85].

Golpe *et al*. found that serum IL-6, IL-8, IL-5 were significantly higher in TS-COPD patients than in biomass COPD without differences in serum IL-13, periostin, surfactant protein-P, TNF-α, IgE, erythrocyte sedimentation rate, C-reactive protein and fibrinogen [86]. The level of exhaled nitric oxide (FeNO) was higher in biomass COPD (39.0 ± 14.6 ppb) than in TS-COPD (27.6 ± 16.3 ppb); although the difference did not reach the statistical significance level, it was borderline (p: 0.056) and it could be related to a small sample size [86].

A study by Solleiro-Villavicencio *et al*., done in women with COPD and healthy controls, found that IL-4 and T_H2 cells were significantly higher in biomass COPD than in TS-COPD [87]. Frequency of T_H17 cells in patients with TS-COPD was significantly higher than in patients with biomass COPD. They suggested that a T_H2 cytokine inflammatory profile could predominate in biomass COPD [87]. Although the majority the authors have not found differences in blood eosinophils counts between biomass COPD and TS-COPD, Fernandes *et al*., using a cutoff of ≥3%, found more frequent sputum eosinophilia in biomass COPD than in TS-COPD [88]. In the same way of the responses T_H2, Olloquequi *et al*. found higher levels of total IgE in patients with biomass smoke COPD than in TS-COPD (**Figure 6**) [72].

It seems clear that the development and clinical course of COPD depend on an interaction between genetic and environmental factors. The gene regulation and expression are fundamentally involved in the pathophysiology of COPD and it is known that microRNAs (miRNAs) participate in the control of post-transcriptional regulation in TS-COPD. Recently, Velasco-Torres *et al.* have described the differential role of miR-34a (downregulated) [89] and of the axis miR-22 - histone deacetylase activity (HDAC4) – IL-17 [90]. This axis has been linked to the development of emphysema in rats. Serum miR-22-3p was downregulated in biomass COPD-BS relative to COPD-TS. In contrast, the concentration of HDAC4 was higher in biomass and exhibited a significant positive correlation with DL_{CO}% [90]. This mechanism could be involved in the lower expression of emphysema in WS-COPD.

In summary, inflammation in biomass COPD, including WS-COPD, could be different from that in TS-COPD with a possible predominance of T_H2 profile, and the lower generation of emphysema could be related to a particular and different response to biomass smoke.

Differences in therapeutic interventions. Almost all the studies on pharmacological interventions in COPD supporting clinical guidelines and strategies [91] have been done in developed countries and use the exposure to tobacco smoke as inclusion criteria. So, the derived evidence could not be extrapolated to other causes of COPD. Taking into account the different type of inflammation, higher bronchial hyperresponsiveness and higher frequency of the asthma-COPD overlap phenotype, it is expected a benefit role of inhaled corticosteroids. To our best knowledge, there is only one study in a small sample of patients that showed better results in

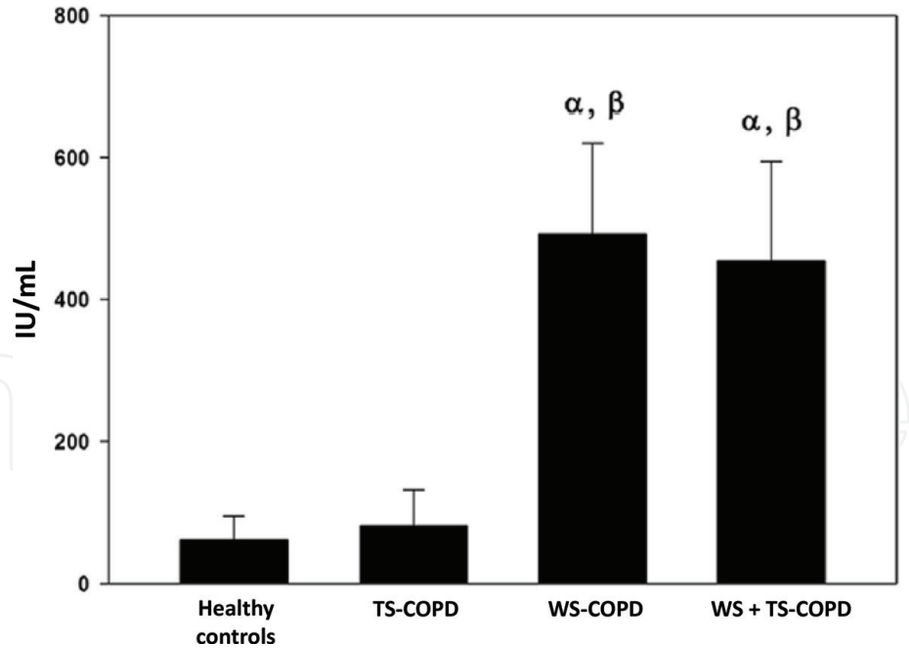

Figure 6.
IgE levels in COPD due to tobacco smoke, wood smoke or both. *α: Different from control subjects (p < 0.05).β: Different from TS COPD group (p < 0.05). TS: Tobacco smoke; WS: Wood smoke. From: Olloquequi J, et al. Respiratory Research (2018) 19:13 [72].*

reducing the exacerbation frequency and improving lung function in patients with WS-COPD with the use of ICS [92]. So, there is a lack of information regarding the efficacy and safety of pharmacological interventions in patients with WS-COPD, particularly on the potential benefits of the use of ICS in these patients.

3. COPD related to biomass fuels different from wood smoke

Biomass fuels used for cooking include mainly wood, charcoal, agricultural residues, and animal dung. The composition of these types of biomass and the smoke derived from burning it significantly differ [93]. There is growing information about the different animal and human responses to the exposures to different kind of the biomass fuels. As we have presented in this chapter, probably the most studied biomass smoke and the responses to its inhalation is wood [94, 95]. Animal manure contains greater diversity and greater quantities of microorganisms and the inflammatory response could be different [81, 96, 97]. Dung biomass smoke [96] activates inflammatory responses in human epithelial cells from airways. Cow dung exposure, but not wood smoke exposure, mediated a measurable increase in non-tipeable *Haemophilus influenzae* adhesion to airway epithelial cells.

Most of the epidemiologic, systematic reviews and meta-analysis group these types of fuels as the generic term "biomass" studies. The distribution of the types of biomass fuels used for cooking differ depending on the country and region. In certain regions, wood or wood and charcoal are the only or most used fuel but in other ones it could predominate animal dung or agricultural residues. One study in Tanzania shows that 99.5% of participants had exposure to biomass: 92.4% used wood, 14.9% used charcoal, 1.5% used crop residues and 0.6% used animal dung for cooking and heating purposes [98].

Studies that have characterized COPD, this means that have described the clinical, functional, radiographic and histopathological characteristics, have been done in wood smoke exposed, and those that have grouped patients under "biomass"

exposed or "non-smokers" have included mainly people exposed to wood smoke. Therefore, it is possible that the COPD related to dung or crop residues be different and it is not recommendable to generalize the observations done in WS-COPD and described in this chapter to other types of biomass fuels.

4. Respiratory disease due to indoor chronic exposure to wood smoke: a different phenotype of COPD or a separable disease?

COPD is defined using a functional criterion and an unspecific exposure. So, under this term can be included a very numerous and heterogenous pathologic conditions. Accepting the weakness of the definition of COPD as a disease (it is more a syndrome), the WS-COPD (it is not sure if all type of biomass COPD) could be accepted as a phenotype of COPD. However, if we assume that etiology is different (wood smoke is not cigarette smoke), the inflammatory responses and the pathophysiologic could be different, and the clinical, functional and histopathologic expression are also different, the chronic respiratory disease due to long-term indoor exposure to wood smoke is better understood as a separate nosology entity. Most importantly the actions for prevention significantly differ and the therapeutic interventions could be also different.

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