Collegium Ramazzini

A New Approach to the Control of Chronic Obstructive Pulmonary Disease (COPD)

The Collegium Ramazzini, an international academic society that examines critical issues in occupational and environmental medicine, is dedicated to the prevention of disease and the promotion of health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the early 1700s. Currently, 180 renowned clinicians and scientists from around the world, each of whom has been elected to membership, comprise the Collegium. It is independent of commercial interests.

Summary

Chronic Obstructive Pulmonary Disease (COPD) is a major and growing disease world-wide that is not well-recognized and is thus under-diagnosed. It is caused by exposures to a multitude of vapors, gasses, dusts and fumes known collectively as VGDF. Cigarette smoke, which contains high concentrations of VGDF, is the most significant cause of COPD, but COPD has a significant occupational and environmental risk component. Many VGDF exposures found in the workplace and in the environment are not recognized as serious risks and are often unregulated. The Collegium Ramazzini calls on the international community of occupational and environmental safety and health professionals to adopt a new paradigm towards the recognition and prevention of occupational and non-occupational exposures to VGDFs that cause COPD. Historically this community has understated the significance of VGDF exposures other than smoking. Moreover, a paradigm has been followed which addresses VGDF risk factors on an agent-by-agent basis. We propose a new professional paradigm to reduce occupational and non-occupational VGDF exposures that cause COPD and which recognizes that in the real world most people are exposed to a mixture of VGDFs. To successfully implement the proposed paradigm, we will need to have in place more scientific data, better standards, and better surveillance/monitoring. We recommend a number of actions to prevent exposures to VGDFs, improve medical care for individuals with COPD, and compensate for COPD as an occupational disease.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is important worldwide, causing significant morbidity and mortality. The recent update of the Global Burden of Disease (GBD) estimated that 328 million people have COPD worldwide [1, 2]. Yet, even though COPD ranks within the top three causes of mortality in the global burden of disease, a significant proportion of cases are undiagnosed [3], and the occupational causes have not been addressed globally. New research findings give the public health community the impetus to prevent or ameliorate COPD through occupational and environmental exposure reduction, smoking cessation and early detection.

2. Prevalence of COPD

Estimating the prevalence of COPD can be challenging. Prevalence will vary based on use of self-reports or spirometry, the spirometric criteria used for defining COPD, and the age group analyzed (e.g., 18 years and older, or 40 years and older), and whether pre-bronchodilator or

post-bronchodilator spirometry results are used. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria use a fixed post bronchodilator cutoff for the FEV1/FVC ratio which is simpler to use in daily clinical practice [4, 5], but which over-diagnoses COPD in older age groups [6, 7]. The American Thoracic Society /European Respiratory Society guidelines use age-specific lower limits of normal (LLN) reference ranges for the FEV1/FVC ratio, so their use requires appropriate, population-based, reference equations for the interpretation of pulmonary function tests [8]. Given these differences in case definition, it is difficult to assess world-wide prevalence and trends, but several recent reviews provide some guidance.

Most of what we know about patterns of COPD is from epidemiology in high income countries. In the USA, using a self-reported physician diagnosis of emphysema or chronic bronchitis, prevalence was between 5.5% and 6.5% during the period 1980–2000 [9]. The 2011 US Behavioral Risk Factor Surveillance System Data yields a 6.3% overall estimate among adults 18 years of age and older [10]. Using spirometry among a representative sample of U.S. adults 25 years of age and older, the overall COPD prevalence among US adults aged 40–79 years for the period 2007-2010 varied from 10.2% to 20.9% based on which diagnostic criterion was applied[11].

3. Pathobiology of Particulates and COPD

3.1 Clinical Understanding of COPD

The current understanding of the pathophysiology of COPD/emphysema is based on four interrelated events: (1) chronic exposure to certain types of particulates or gasses (as found in cigarette smoke, occupational exposures, or other particulate or oxidative stress) leads to inflammatory and immune cell recruitment within the terminal air spaces of the lung; (2) these inflammatory cells release proteinases that damage the extracellular matrix of the lung; (3) endothelial cells undergo apoptosis due to oxidant stress and loss of cellular attachment to the lung matrix; and (4) ineffective repair of elastin and other extracellular matrix components leads to airspace enlargement [12]. These mechanisms collectively cause pathological changes in the airways, lung parenchyma, and pulmonary vessels and include chronic inflammation, increased numbers of goblet cells, mucus gland hyperplasia, fibrosis, narrowing and reduction in the number of small airways, and airway collapse due to the loss of tethering caused by alveolar wall destruction in emphysema. These clinically manifest as emphysema, mucus hypersecretion, ciliary dysfunction, airflow limitation, hyperinflation, abnormal gas exchange, pulmonary hypertension, and various systemic effects (e.g., limb muscle weakness) [13].

Cigarette smoke, workplace exposures and environmental exposures such as indoor cooking over open flames are to a large degree analogous, since they all involve complex mixtures of gases and particulates.

3.2 Experimental Evidence

Research on the health effects of particulate exposure from ambient air pollution and biomass fuel exposures informs our understanding on the pathophysiology of occupational COPD [14-16]. Exposure of mice to particulate matter from biomass combustion leads to a neutrophilic inflammatory response in the airways within 24 hours of exposure, along with the appearance of pro-inflammatory mediators in bronchial alveolar fluid [17], including both neutrophil and

macrophage chemokines. Chronic exposure to wood smoke in guinea pigs caused up-regulation of proteins thought to be involved in the development of emphysema, matrix metalloproteinases (MMP9 and MMP12). Chronic exposure in rats led to peribronchiolar fibrosis. Human epithelial cells exposed to particulates express inflammatory cytokines, and alveolar macrophages release TNF alpha and IL-1 after exposure [13].

4. Epidemiology of COPD

4.1 Population Attributable Risk for Smoking

In 1984, the US Surgeon General concluded that 80–90% of COPD in the United States was attributable to smoking; this estimate is still widely quoted. A recent review from the American Thoracic Society concluded that the estimated fraction of COPD mortality attributable to smoking worldwide is substantially lower than 80%: 54% for men 30–69 years of age, and 52% for men 70 years of age or older [18]. The corresponding attributable fractions for women were 24% and 19%, respectively. The range of attributable fractions varies across studies, and in general, the population-attributable fractions have been lower among younger populations, females, and in developing countries.

4.2 COPD Risks in Occupational Settings

Epidemiological and biological research over the past two decades has demonstrated that occupational exposure to specific exposures such as silica, as well as to mixtures of various vapors, gases, dusts and fumes (VGDF), causes COPD. The VGDF exposure metric is a summary measure of exposures to gases and vapors as well as particulates (dusts and fumes). Increased COPD risk and increased COPD mortality have been observed among workers exposed to VGDF [19-35]. In 2004, the American Thoracic Society estimated that occupational exposures were responsible for 15-20% of COPD; since that statement was published, multiple additional articles also support that occupational exposures are an important contribution to COPD, controlling for the relative contributions of occupation and smoking [18, 28, 32, 36 37, 38 25].

In many occupational environments, low toxicity dusts which are largely insoluble make up a significant component of all VGDF exposures; these are referred to as ‘particulates not otherwise regulated’ (PNOR) and include all mineral and inorganic dusts without specific individual U.S. Occupational Safety and Health Administration Permissible Exposure Limits (PEL) [39, 40]. These dusts are referred to as ‘dusts not otherwise specified’ (Dusts NOS) in Australia and have been classified as ‘inert or nuisance dusts’ in the past [41]. However, there is growing recognition that exposures to low toxicity, insoluble particles are associated with health risks, including COPD [32, 42-47].

While COPD risk is associated with exposures to all VGDF, increased risk is associated with specific occupational exposure agents, including: coal mine dust [20, 48-51]; asbestos [32, 52-55]; silica [32, 54, 56-59]; welding and cutting gases and fumes [22, 32, 54, 60-64]; cement dust [32, 54, 65-68]; diesel exhausts [27, 32, 69-72]; spray painting [60, 73-75]; organic solvents [76-81], and possibly man-made mineral fibers [61, 82-85]. Increased risk of chronic bronchitis/COPD has been observed among populations exposed to pesticides/herbicides and grain dusts [32, 46, 81, 86-93].

Relatively few occupational studies have had sufficient quantitative dust exposure measurement

data to allow exposure-response analyses, especially for longitudinal loss of lung function. Asbestos and silica have been studied more extensively than low toxicity, poorly soluble particles and detailed reviews have concluded that exposure to asbestos and silica increases the risk of COPD [52, 57]. Among white South African gold miners without radiological evidence of silicosis, FEV_1, adjusted for age, height, and tobacco smoking, decreased with increasing cumulative respirable dust exposure, in both smokers and non-smokers [94]. This study estimated that 50-year-old miner exposed for 24 years to an average respirable dust concentration of 0.6 mg/m^3 would experience an average excess FEV_1 loss of 236 ml, or about 10 ml per year. In a longitudinal study of asbestos-cement workers, increasing levels of cumulative exposure were associated with lower levels of FEV_1 in a dose-dependent manner [95]. Among foundry workers longitudinal analyses of FVC and FEV_1 measurements demonstrated a 1.6 mL/yr and 1.1 mL/yr, respectively, decline per mg/m^3 mean silica exposure ($p = 0.011$ and $p = 0.001$, respectively) [96].

Coal mine dust is a mixture of various minerals, including coal dust and dust from the surrounding geological strata such as clays. Coal mine dust with a low silica content has been suggested as a benchmark for other poorly soluble dusts of low toxicity [97]. Cherrie et al. reviewed evidence for several low-toxicity dusts including coal mine dusts [42]. British coal miners exposed to an average of 3 mg/m^3 for 20 years experienced an average FEV_1 reduction of 70 ml attributable to dust exposure. Likewise, carbon black workers exposed for 40 years at an average of 0.77 mg/m^3 were estimated to have an excess FEV_1 loss of 142 ml. In this same review, workers exposed to polyvinyl chloride (PVC) dust at a level of 0.7 mg/m^3 for 20 years experienced an average excess FEV_1 loss of 52 ml. A recent meta-analysis concerning exposures to biopersistent granular dusts found an average decline of FEV_1 of 1.58 ml per 1 $mg \cdot m^3 \cdot$years of exposure (95% CI: 1.24-1.93) [98].

Increased COPD risk associated with occupational exposures to irritant gases and solvents is supported in the literature. Pulp and paper mill workers exposed to irritant gases (ozone, SO_2 or Cl_2/chlorine dioxide (ClO_2) have been shown to be at increased risk of chronic bronchitis [99-102]

4.3 Management of COPD and Work Exposures

Despite the contribution of work exposure to COPD reported in the medical literature some physicians do not consider work exposures when evaluating a patient with COPD. A review of 6,150 medical records on 54 patients with chronic bronchitis from a Veteran's Administration hospital in California found three patients (5%) where the medical record stated that work exposures potentially contributed to the etiology of the chronic bronchitis and six (10%) where avoidance of workplace exposures was recommended [103].

The consequences from a lack of attention to workplace exposures in patients with COPD has been documented in the Lung Health Study, a longitudinal follow-up of 5,724 individuals with early COPD. One of the conclusions of that study was that "In men with early COPD, each year of continued fume exposure was associated with a 0.25% predicted reduction in post-bronchodilator FEV_1 % predicted" [104].

Statistical models have been developed that predict that COPD could be reduced by 20% by an 8.8% decrease in the prevalence of occupational exposures. In comparison, these models predict the same 20% reduction in COPD with a 5.4% reduction in smoking [105].

4.4 COPD Risks in Non-Occupational Settings

Studies of the health effects of indoor and outdoor air pollution have focused on particulate matter (PM), which is but one component of VDGF. These epidemiology and health effects studies of air pollution are, however, essential to our understanding of the role of VGDF in the occupational setting.[106]

Longitudinal cohort studies have shown that exposure to PM leads to decreased lung function growth in children, and that this effect is reversible when exposure to pollution is reduced. Although there is limited epidemiologic evidence that PM in ambient air is a primary cause of COPD in adults [107-114], it is clear that on a cellular level particulates result in airways stress and pulmonary inflammation, and the inflammatory mediators measured in COPD are very similar to those induced by PM exposure.

The air pollution from indoor combustion of solid fuels for heating and cooking may now be the biggest risk factor for COPD globally [14]. These fuels include coal, wood, crop residues, animal dung (and almost anything else available); the combustion produces a complex mixture of air pollutants, including respirable PM, carbon monoxide, oxides of nitrogen and sulfur, aldehydes, volatile organic compounds, and other agents. PM_{10} concentrations in these kitchens reach peak values of 20 mg/m^3, which can be compared to the US Environmental Protection Agency 24-hour recommended standard for PM_{10} of no more than 150 $\mu g/m^3$.

5. Regulatory Standards for Occupational Exposures

The regulatory framework for VGDFs and low toxicity dusts is confusing and inconsistent. In the United States, OSHA's current PEL for the respirable fraction of dust NOS (or PNOR) for general industry is 5 mg/m^3, while the ACGIH TLV for the respirable fraction of dust NOS is 3 mg/m^3. The UK HSE has set the recommended upper exposure limit at 4 mg/m^3. The Australian Institute of Occupational Hygienists recently recommended 1 mg/ m^3 for the respirable fraction of dust, and the commission in Germany which sets maximum allowable exposures has adopted a TLV for granular persistent dust of 0.3 mg/ m^3 adjusted for density of the dust.

We can look to ambient air standards for comparison because those standards are supported by a detailed assessment of health effects. In the US, the EPA ambient air quality standard for exposure to particulate matter is 12 $\mu g/m^3$ for an annual average exposure to $PM_{2.5}$ [115]. Factoring work ventilation rates and duration of exposure, and adjusting an environmental time frame (24 hrs per day/7 days per week/365 days per year over 70 years) to an occupational setting (8/5/250 over 45 years) yields an occupational equivalent to the EPA $PM_{2.5}$ daily limit of approximately 70 $\mu g/m^3$. This comparison suggests current exposure limits for dust NOS specifically, and for VGDF more generally, are not stringent enough to prevent injurious exposures [43].

6. Recommendations

The Collegium Ramazzini calls call on the international community of occupational and environmental safety and health professionals to adopt a new paradigm for better recognition and prevention of occupational and non-occupational exposures to VGDFs that cause COPD. Historically, this community has understated the significance of VGDF exposures other than smoking. Moreover, a paradigm has been followed which addresses risk factors on an agent-by-agent basis while, in the real world, most people are exposed to a mixture of VGDFs. The risks for COPD can be substantially controlled by the international community adopting the following six action items. We call on the World Health Organization (WHO) to adopt these action items as the core of its policy towards preventing COPD, and to urge its member nations to adopt it as well. Further, the WHO collaborating Centers in Occupational Safety and Health, as well as all international and national professional societies in the fields of occupational and environmental health should harmonize with this their respective existing professional practice guidelines and training curriculae for the recognition and prevention of COPD.

6.1 Preventing Smoking. WHO and its member nations should reinforce and revise the Framework Convention on Tobacco Control adopted in 1999 and the Tobacco Free Initiative adopted in 2003 to:

- 6.1.1 Include clear statements about VGDFs being the causes of COPD which are found in tobacco products, occupational settings and other non-occupational sources as indicated below, and that there are significant interfaces between smoking and non-smoking sources of exposure.
- 6.1.2 Encourage tobacco control practices to recognize and incorporate knowledge about all sources of VGDF exposures in their efforts to prevent COPD and in smoking cessation, counseling and treatment.

6.2 Preventing Occupational Exposures. The global community of occupational safety and health professionals should:

- 6.2.1 Raise awareness about the magnitude of occupational COPD and its causes among stakeholders: workers, employers, insurance companies and social insurance agencies through a social marketing campaign.
- 6.2.2. Identify major tasks contributing to VGDF exposure in specific occupational sectors, with a focus on agriculture, construction, mining, transportation and manufacturing. The process should include focus groups and other input from stakeholders.
- 6.2.3 Reduce exposures through product substitution, engineering controls and work practices. Additional research will be needed to develop strategies for specific industries. Dust control strategies include process control, ventilation, and dust suppression, but many current controls do not sufficiently reduce dust to obviate the concomitant use of personal protective equipment if a lower exposure limit were widely used.

6.3 *Preventing Environmental Exposures.* Public health authorities should promote programs in accordance with national or local conditions:

6.3.1 Encourage reduction of air pollution from indoor cooking by advocating change to cleaner fuels and use of improved stoves recommended by WHO [116].

6.3.2 Reduce reliance on coal-fired electrical power generation.

6.3.3 Reduce reliance on motor vehicles with internal combustion engines (especially those that rely on diesel fuel) and especially in urban or congested areas.

6.3.4 Reduce burning of agricultural biomass.

***6.4 Expanding Medical Surveillanc*e**. Public health authorities should expand their surveillance in order to:

6.4.1 Identify causes of airway obstruction in individuals and populations.

6.4.2 Track change in spirometry over time in exposed populations.

6.5 Conducting Research. Funding for research in the field of occupational and environmental safety and health and pulmonary medicine should be increased and focused in order to:

6.5.1 Better characterize the role of particle size/mass in development of COPD in adults.

6.5.2 Standardize an index of VGDF exposures for future epidemiological studies and risk assessments.

6.5.3 Develop cost-effective PPE relying on positive pressure air supplied technologies as alternatives to current practice of relying on negative pressure breathing masks.

6.6 *Recognizing and Compensating COPD as an Occupational Disease.* The International Social Security Association (ISSA) and International Labor Organization (ILO) should establish international guidelines for the recognition of COPD as a compensable disease for individuals who worked in an occupation with sufficient VDGF exposures to cause this disorder.

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