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Review

The 2014 ESPEN Arvid Wretlind Lecture: Metabolism & nutrition: Shifting paradigms in COPD management

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SUMMARY

COPD is a chronic disease of the lungs, but heterogeneous with respect to clinical manifestations and disease progression. This has consequences for health risk assessment, stratification and management. Heterogeneity can be driven by pulmonary events but also by systemic consequences (e.g. cachexia and muscle weakness) and co-morbidity (e.g. osteoporosis, diabetes and cardiovascular disease). This paper shows how a metabolic perspective on COPD has contributed significantly to understanding clinical heterogeneity and the need for a paradigm shift from reactive medicine towards predictive, preventive, personalized and participatory medicine. These insights have also lead to a paradigm shift in nutritional therapy for COPD from initial ignorance or focusing on putative adverse effects of carbohydrate overload on the ventilatory system to beneficial effects of nutritional intervention on body composition and physical functioning as integral part of disease management. The wider implications beyond COPD as disease have been as clinical model for translational cachexia research.

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1. Introduction

COPD is a chronic disease of the lungs characterized by persistent airflow obstruction resulting from inflammation and remodeling of the airways, and may include development of emphysema [1]. The disease is a growing global health problem particularly in the third world and it has been predicted that COPD will become the third most common cause of mortality in 2020. Furthermore, the disease causes enormous distress to patients and their families and generates immense costs worldwide. The 2013 Global Burden Disease study shows that COPD is the 8th leading cause of global years lived with disability [2]. Nevertheless, despite these statistics the societal impact of COPD is still undervalued when compared to other chronic diseases and to cancer. This might be due to the fact that COPD has long been considered as *"self-inflicted"* but also attributable to patient's unawareness as already reported in 1898 in the book "Diseases of the lungs" [3]: "*Patients are often ignorant of their disease and accept the accompanying dyspnea until an intercurrent attack of bronchitis leads to examination of the chest and diagnosis*". The recent Burden of Obstructive Lung Disease (BOLD) initiative (ww.boldstudy.org) that collects country-specific data on

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prevalence, risk factors and social and economic burden of COPD indeed confirms a discrepancy between spirometry-based and doctor-diagnosed COPD.

The past decades it has also become clear that COPD is heterogeneous with respect to clinical manifestations and disease progression. This has consequences for health risk assessment, stratification and management. Heterogeneity can be driven by pulmonary events but also by systemic consequences (e.g. cachexia and muscle weakness) and co-morbidity (e.g. osteoporosis, diabetes and cardiovascular disease). In this paper I will show how a metabolic perspective on COPD has contributed significantly to understanding clinical heterogeneity and the need for personalized disease management. These insights have also lead to a paradigm shift in nutritional therapy for COPD from initial ignorance, to focusing on putative adverse effects of carbohydrate overload on the ventilatory system to beneficial effects of nutritional supplementation on quality of life as integral part of disease management. The wider scientific implications beyond COPD management have been as clinical model for translational cachexia research.

2. Old paradigms

In 1898 Fowler & Godlee [3] already described the emaciated and withered appearance of patients with emphysema. Dietary recommendations however were not directed to prevent or treat weight loss which was considered as an epiphenomenon of end stage disease, but to "*prevention of the bowels to be confined as in addition to gastrointestinal derangements likely to ensue, much harm can be done by straining efforts of defecation*" [3]. In contrast to current guidelines proposing a physically active lifestyle to reduce adverse consequences of sedentary behavior on disease progression, it was at that time recommended to avoid exercise when causing dyspnea. Interestingly, although not evidence based, nutritional supplementation advices consisted of *cod liver oil and iron in combination with spirits of chloroform* and could be considered as nutraceuticals 'avant la lettre' as some of these constituents (e.g. omega-3 fatty acids, vitamin A, vitamin D, iron) are nowadays proposed as potent metabolic modulators in COPD [4].

In 1968 Filley et al. [5] described two contrasting clinical phenotypes of patients with chronic airflow obstruction: the emphysematous type (referred to as pink puffer) and the bronchial type (referred to as blue bloater). Pink puffers had larger lungs as they were hyperinflated both at rest and during exercise. This landmark paper focused on oxygen transport and proposed a lower tissue oxygenation in pink puffers compared to blue bloaters as cause of cachexia. Interestingly this hypothesis has recently been revived in a study focusing on skeletal muscle pathology in COPD using a network biology approach to investigate the relationship between muscle molecular and physiological response to exercise training [6].

In contrast to being ignored in COPD management, good nutrition was cornerstone in the management of tuberculosis in the absence of effective medications at that time. These patients were referred to sanatoria for a multidisciplinary treatment including fresh air, extensive periods of rest but also tailored exercise training. These sanatoria were seen as revolutionary not only for what they did for patients but also for their impact on twentieth-century medical research, public health and education. As Fowler described [3]: *"For patients wracked with the symptoms of tuberculosis, spending time in a sanatorium was like the chance at a new lease on life. Many had spent their lives residing in smog-streaked urban neighborhoods, struggling through uncaring crowds and working in airless factories. Who wouldn't have wanted to escape to the quiet rural settings offered by most sanatoriums"*. But sanatorium life wasn't an idyllic stay in the country-side. Patients were expected to follow strict rules of rest, behavior and social interaction. The regime as illustrated in Table 1 remarkably resembles what was prescribed in the first guidelines of pulmonary rehabilitation in 2006 [7]. A difference between tuberculosis and COPD is the chronicity of COPD requiring lifelong intervention. The updated pulmonary rehabilitation guidelines of 2013 [8] therefore not only stress a multidisciplinary approach but also discuss in more detail the positioning of pulmonary rehabilitation in chronic disease management as well as the role of health behavior change in optimizing and maintaining benefits.

While in the 1960s awareness increased that smoking and also air pollution likely contributed to emphysema and chronic bronchitis, management of COPD was still rather nihilistic. Already in 1967 Vandenbergh et al. [9] convincingly showed a very poor prognosis in weight-losing patients. At that time treatment however focused on irreversible airflow obstruction whereas weight loss was considered merely an inevitable and irreversible symptom or even as adaptation to decrease ventilatory load. It was not until the 1980's that chronic oxygen therapy was shown as first medical intervention to benefit survival in COPD [10]. Gradually it was recognized that the toll of COPD grew with each passing year and in 1987 a first set of guidelines was released by the American Thoracic Society describing optimal treatment for COPD [11]. The guidelines also called attention for optimal nutrition to prevent adverse effects of malnutrition on respiratory muscle function and ventilatory capacity supported by an excellent state of the art review "Nutrition and chronic lung disease" by Wilson et al. [12].

3. Bridging the gap

Development of new technologies to measure energy metabolism and body composition in a clinical setting in the eighties has contributed largely to understanding why part of patients with COPD are prone to weight loss. By indirect calorimetry, using a ventilated hood system, resting metabolic rate could be assessed even in severely dyspneic COPD patients. The doubly-labeled water technique allowed investigation of energy metabolism in daily circumstances and the combination of the two methods enabled estimation of physical activity-induced thermogenesis. Two elegantly designed physiological studies by Goldstein et al. [13,14] investigated the effect of controlled dietary intervention on energy and protein metabolism in malnourished patients with and without emphysema using low intensity exercise as metabolic stressor. The authors pointed out that compared to other stressed states (eg. infection) clinically stable malnourished patients with emphysema were unusual because, despite being hypermetabolic, they were not hypercatabolic and did not demonstrate preferential

Table 1
Mean features of the treatment from the Nordrach Sanatorium by which it was thought to effect a really permanent cure of pulmonary tuberculosis [3].

1. An absolutely open-air life for every variety of case, whether acute of chronic, accompanied by fever of apyrexial, in all weathers and seasons, by night as by day.
2. A regular course from first to last of over-feeding-stuffing would be a more appropriate term-with a rich and varied diet, including much meat, milk, fatty and farinaceous food, given in large quantities at a time, with long intervals between the meals.
3. A judicious combination of exercise (hill-climbing), carefully regulated and carried out so as always to fall short of producing either dyspnea or fatigue, in order not to interfere with the processes of repair, with the maximum amount of mental and physical rest.
4. Every patient is under de constant personal supervision of the physician- a vital and distinctive factor in the treatment.