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Chronic obstructive pulmonary disease patient journey: hospitalizations as window of opportunity for extra-pulmonary intervention

Mitja Lainscak^{a,b}, Harry R. Gosker^c, and Annemie M.W.J. Schols^c

Purpose of review

Hospitalizations due to exacerbation of chronic obstructive pulmonary disease (COPD) are a major burden for patient and healthcare system. Extra-pulmonary needs and resulting interventions are poorly investigated.

Recent findings

COPD induces nutritional issues, body composition changes and limits patient exercise capacity. The COPD patient journey can be accelerated through exacerbations during which disease-related detrimental factors such as systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify, which acutely and often irreversibly worsens patient condition. Specific needs during exacerbations reach beyond the respiratory system, thus clinicians should comprehensively evaluate patients and identify potent and feasible metabolic and anabolic intervention targets. General and specific nutritional support appear feasible and with potential to cover for the changed bodily requirements during exacerbation. Adjunctive physical exercise or neuromuscular electrical stimulation may prevent the muscle loss.

Summary

Hospitalizations should be considered as a window of opportunity for detailed patient assessment and implementation of tailored extra-pulmonary adjunctive strategies with long-term implications. Nutritional assessment and support as well as physical exercise appear promising but should be investigated in adequately designed and conducted trials.

Keywords

body composition, chronic obstructive pulmonary disease, exercise, hospitalization, nutrition, skeletal muscle

INTRODUCTION

Global burden of disease will change in decades to follow and chronic obstructive pulmonary disease (COPD) will be a major player around the globe [1]. In addition to disease-associated mortality, COPD patients take a journey of frequent exacerbations (Fig. 1) leading to disease deterioration when systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify, commonly causing hospitalizations [2^a] that are main drivers of COPD-related costs [3]. Determinants of vulnerable patient phenotypes and pathophysiological mechanisms behind the clinical presentation are not well studied and remain largely unknown [4]. A number of defense mechanisms are induced that are generally phylogenetically old and serve primarily for a swift response to resolve the acute situations, but few effective drugs and procedures are available [5,6] to counteract the

deleterious mechanisms that remain chronically (over)activated. Once at this stage, patients enter a disability spiral [7^a] with devastating implications for body composition, skeletal muscle function, physical performance, quality of life, and mortality, all being highly clinically relevant [8].

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KEY POINTS

- Hospitalizations are window of opportunity for comprehensive patient assessment to identify specific needs and therapeutic targets.
- Malnutrition, risk of malnutrition, and specific deficiencies are common in COPD and need to be treated adequately.
- COPD exacerbations mimic hypoxic inactivity, thus sufficient anabolic drive through adjunctive interventions is necessary.

Whilst for clinically stable patients evidence and resulting guidelines from well conducted studies exist [9[■],10], the applications during acute exacerbations remain scarce. This review therefore aims to briefly summarize the available knowledge about pathophysiological processes and their consequences for COPD patients during acute exacerbations. We also discuss the potential therapeutic targets during hospitalizations and ongoing research that could, in light of few respiratory treatments with prognostic implications, delay or even reverse the COPD continuum.

DEPARTURE: THE EXACERBATION-RELATED HOSPITALIZATION AND ITS CONSEQUENCES

Particularly during exacerbations, COPD-related detrimental factors such as systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify [11]. Skeletal muscle is

particularly prone to damage; atrophy, and a decreased oxidative phenotype develop early and soon reach irreversible stages [12[■],13]. A number of mechanisms are involved and most of them can interfere simultaneously with metabolic function, muscle mass, and performance [14]. It is important to note the complexity and interrelation of regulatory processes involved induced by various triggers including inflammation, renin-angiotensin-aldosterone, and sympathetic system induction [15[■],16[■]]. Finally, we need to be aware of other organs and systems that are usually neglected, but have a major role in maintaining a metabolic balance in the body. While initially being considered as merely an energy depot, fat tissue, for instance, has recently emerged at the crossroads of many pathophysiological processes with major implications for energy turnover and anabolic/catabolic processes and an important source of persistent systemic inflammation [17]. Implications for COPD patients are numerous and reach beyond the recently described obesity paradox phenomenon [18[■]]. In this context, it is important to evaluate not only whole body fat content (generally protective in chronic disease), but also its distribution throughout the body. In clinically stable COPD, abdominal visceral fat contributes to systemic inflammation independent of BMI and total fat mass [19[■]], with potentially detrimental effects on skeletal muscle oxidative phenotype [20]. Most recent insight regarding molecular pathways indicates that during acute pulmonary inflammation, TNF- α -induced NF- κ B activation is required for the transition to systemic inflammation and muscle atrophy [21]. This animal model study furthermore elegantly

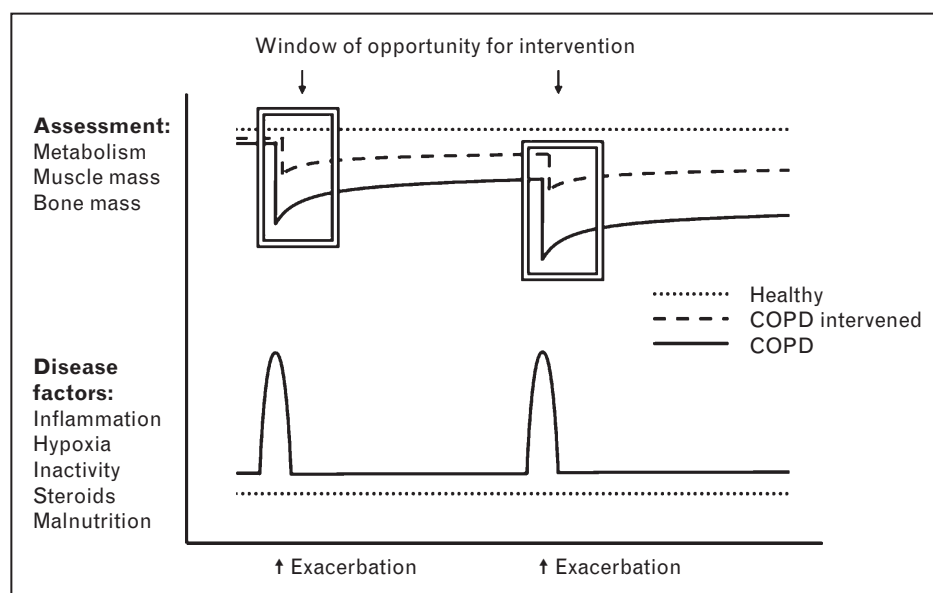


FIGURE 1. Exacerbation related hospitalizations: a window of opportunity for intervention.

demonstrated the importance of malnutrition to act hand in hand with inflammation, causing body wasting and finally an irreversible state of cachexia, out of reach of any known remedies available to date.

Acute exacerbations and commonly administered high-dose glucocorticosteroids induce insulin resistance, and decreased insulin sensitivity associated with a decreased muscle oxidative phenotype has also been shown in the clinically stable condition [12[•]]. Some nutritional interventions could have potential to reverse inflammatory mechanisms that induce insulin resistance, but the field is not explored yet in COPD [22]. Along with activated renin-angiotensin-aldosterone system and evidence for activated peroxisome proliferator-activated receptors [23], angiotensin receptor blockers or sartanes appear to be more attractive interventions to improve the insulin resistance. Although studies in patients with COPD are scarce, Andreas *et al.* [24] demonstrated that irbesartan was well tolerated, safe, and associated with some ancillary benefits in terms of haematocrite and total lung capacity, thus setting the stage for further trials. More data are available for patients with heart failure; the analysis of large-scale Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity program ($N=6933$) demonstrated that weight loss and being lean, particularly when combined, were important predictors for poor prognosis. The weight loss under candesartan therapy, however, was significantly less common when compared to placebo [25]. Combining this with observed pleiotropic effects through peroxisome proliferator-activated receptor activation mediated reduction of insulin resistance could deliver several benefits for the patients [26]. Indeed, in a recent placebo-controlled double-blind trial, 36 patients were treated with irbesartan or matching placebo [27]. After 4 months of treatment, insulin resistance decreased in the irbesartan (by 26%) but not the placebo group (treatment effect $P=0.0026$). Translating the knowledge from patients with heart failure gives us reasonable ground to consider such treatment in COPD, as suggested previously [28].

CHANGE OF DIRECTION: METABOLIC NEEDS AND NUTRITIONAL SUPPORT

COPD patients have higher energy needs due to increased resting metabolic rate and whole body protein turnover, which can eventually lead to body wasting and cachexia [29]. Nutritional support has the potential to improve patient energy intake and performance [9[•],30[•]]. During an exacerbation, the energy and nutrient-specific needs exceed those in

stable state [31]. The subjective perception for food intake is modified (e.g. loss of appetite due to the illness) and patients may not be willing to adjust their nutritional pattern during exacerbation [32]. To investigate potential for nutritional support during hospitalization for exacerbation of COPD, a double-blind study randomized 56 nutritionally depleted patients to 3×125 ml (2.38 MJ/day) of energy and protein-rich fluid vs. matching non-caloric placebo [33]. This intervention was feasible and increased daily energy (15%) and protein (38%) intake. Considering that 14–22% of hospitalized COPD patients are malnourished or underweight, and a further 55% are at risk of malnutrition [34,35[•],36], the hospitalization should be considered as a window of opportunity to intervene, this time in a physiological manner in terms of feeding and nutritional support. We should learn from space medicine [37] and from top-level athletes [38,39] where many novel applications or nutritional compounds were tested and proved efficacious. In a stable disease, general nutritional support as part of COPD management is validated [40] in wasted COPD patients and cost-effective due to reduced hospitalizations, thus transfer to acute setting with potential extension in stable phase is warranted.

In addition to calories and proteins, a balanced daily diet should cover the daily requirements of micronutrients, vitamins, and minerals. In chronic disease, various causes increase the daily needs and those patients, including COPD, frequently present specific malnutritions, or deficiencies. The literature about these issues is generally scarce, with some recent exceptions presented but not limited to this review. Research about vitamin D has moved our interest beyond calcium and bone homeostasis to enter the field of pulmonary function with inflammation as a linking element [41]. The findings from randomized trials were eagerly expected yet the bar was apparently set too high. According to trial by Lehouck *et al.* [42[•]], 100 000 IU of vitamin D supplementation every 4 weeks for 1 year in 182 patients with moderate to very severe COPD and a history of recent exacerbations generally had no effect vs. placebo on time-to-first exacerbation. Careful subgroup analysis indicates potential benefit in patients with severe vitamin D deficiency [rate of exacerbation ratio 0.57, 95% confidence interval (CI) 0.33–0.98]. Critically ill patients in need of mechanical ventilation have reduced serum levels of trace elements (selenium, manganese, zinc) and supplementation has the potential to shorten time spent with mechanical ventilation support [43]. Some confirmatory data for exacerbated COPD due to upper respiratory tract infection were published

recently. In a randomized, double-blind, placebo-controlled trial, supplementation with *Echinacea purpurea* along with zinc, selenium, and ascorbic acid for 14 days but not with *Echinacea purpurea* alone or with placebo resulted in significantly less severe and shorter exacerbation episode [44]. Importantly, intervention was safe and well tolerated with sleeping disorders occurring as most frequent adverse events. The field of micronutrient supplements appears promising with significant potential for interventional trials.

GOING THE RIGHT DIRECTION: ANABOLIC AGENTS AND PHYSICAL EXERCISE

Complementary to nutritional support are anabolic interventions, which are already implemented for patients with chronic respiratory failure [45]. Indeed, nutrients when only delivered as diet can follow different metabolic pathways according to current bodily needs. Anabolic steroids specifically induce fat free mass gain, improve exercise capacity and can restore response to rehabilitation program, blunted by the low-dose oral steroids as maintenance therapy [46]. Recent experimental evidence for synergistic effects of anabolic steroids and glucocorticoids on muscle recovery may be particularly relevant in the recovery phase from an acute exacerbation [47].

Several other modalities or nutrients have shown promising results in nonacute conditions. Amino acids as main protein components are a physiologically plausible target [48]. In COPD, the splanchnic protein extraction is reduced when compared to healthy age-matched controls. With milk protein (high branched-chain amino-acid content) supplementation, an enhanced anabolic response was observed [49] which could be relevant in acute situations when protein needs are increased. Substituting whey with casein proteins further enhances the effects in terms of protein anabolism, both in postprandial and exercise states [50].

The most potent physiological anabolic trigger is physical training, in particular, resistance exercise. During exacerbation, patients experience severely limited physical performance, mainly due to dyspnoea or infection. Thus, patients need to maintain a sufficient anabolic drive through adjunctive intervention, and data supporting feasibility and safety of rehabilitation during or immediately after hospitalization are emerging. In a randomized trial comparing low, moderate/high and no exercise during acute exacerbation of COPD, adherence of 80% was demonstrated and exercise was considered safe and feasible [51]. One step further Babu *et al.* [52] randomized 38 patients during acute exacerbation of COPD

to regular physical therapy vs. regular and on-call physical therapy. The addition of on-call sessions increased 6-min walk distance and improved peak expiratory flow. Feasibility, safety, and effects of resistance training were investigated in a randomized trial of 40 patients hospitalized for COPD exacerbation [53]. In addition to routine physiotherapy, the intervention group performed three sets of eight repetitions of quadriceps resistance exercise that improved muscle strength and 6-min walk distance at discharge and promoted more anabolic status in skeletal muscle as investigated in biopsy samples. If the patients are too ill to follow the physiotherapy or if this is beyond available resources, transcutaneous electrical muscle stimulation can be considered. Meglic *et al.* [54] tested the feasibility of this method in 19 patients hospitalized due to COPD exacerbation and demonstrated good tolerability, feasibility, and safety of an average of 15 sessions per patient. Such an intervention improved quadriceps strength, which correlated to stimulation intensity during 14 sessions, without any adverse events [55]. To date, no study has investigated the molecular or histological profile of such an intervention starting at admission to hospital. The best information comes from Abdellaoui *et al.* [56] who performed skeletal muscle biopsies in 15 patients who were randomized to electrical muscle stimulation ($N=9$) or placebo on average 12 days after hospital admission. On top of longer 6-min walk distance, they were able to demonstrate a significant increase in type I fibres proportion in patients receiving electrostimulation.

ARRIVAL: HOSPITALIZATION, THE WINDOW OF OPPORTUNITY FOR TREATMENT

The consensus of the authors is that our understanding of pathophysiological mechanisms and processes during bouts of COPD exacerbations remains insufficient. We also believe that translation from other chronic diseases (that frequently coexist), space medicine, and top-level sport is suboptimal. From physiological perspective, most attractive therapeutic targets would be defense mechanisms (e.g. sympathetic nervous system, renin-angiotensin-aldosterone system, inflammation) that are activated when exposed to acute metabolic stress. Furthermore, it seems plausible to block these systems on a long-term basis to prevent cumulating damage, which makes subclinical changes clinically important and mostly irreversible. In this context, physical activity with all direct and indirect effects appears an attractive target to focus on. Being the most effective anabolic 'remedy', it has important effects beyond physical performance. Through exercise, metabolic

processes, acute defense mechanisms, and anabolic/catabolic equilibrium are balanced to prevent the body wasting and eventually cachexia. Finally, the energy demands increase during deterioration thus nutritional support is deemed as necessary to avoid loss of the bodily reserves and tissues utilization.

CONCLUSION

Available evidence and ongoing research in the field are scarce; we, however, anticipate this will change shortly with the focus on both most feasible and most sophisticated cutting edge interventions. First step in patient assessment during exacerbation/hospitalization should be comprehensive assessment and identification of plausible intervention targets. With evidence at hand, the stage is set for exercise or muscle stimulation as a surrogate for normal daily activity where there already is some guidance about the timing and dose of the intervention. The nutritional strategies to cover for specific needs during exacerbation are less well investigated and simple translation from stable chronic disease may not be optimal. Transition of these strategies into the chronic disease state should be the next step, with particular emphasis on patient self-management. Clinicians should not, however, be too much focused on individual patients only and think more globally. Many of the suggested interventions are public health strategies to prevent and to control chronic disease. With limited funding available, the output and impact are therefore largely dependent upon joint efforts and collaborative projects where awareness about COPD, which appears poor among lay public and patients [57], and all associated consequences may be one of interim goals.

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Conflicts of interest

There are no conflicts of interest.

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