Multimodal intervention: why and what is the evidence?

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As in other chronic diseases (1), COPD is characterized by a high prevalence of abnormalities in body composition including sarcopenia, cachexia and in some instances obesity, see ref.(2) for review. Nutritional depletion in patients with COPD patients recapitulates complex genes-environmental insults and biological abnormalities resulting in a poor functional and vital prognosis (3). As nutritional depletion in COPD results from multiple and complex mechanisms, nutritional intervention alone could not address all issues raised by these complex phenotypes. ERS and ATS joined guidelines in 2006 and French speaking society of Pneumology, SPLF in 2010 both recommended nutritional interventions to be implemented in the context of pulmonary rehabilitation to prevent nutritional depletion (4-7) and to achieve better outcomes in all patients with COPD and especially in depleted patients (8, 9).

Nevertheless, nutritional interventions alone, mostly oral supplements, aiming at restoring fat-free mass after decades of scepticism (10) is near to be accepted with a positive 2012 meta-analysis including original data up to 7 January 2010 (11). Since 2006 and especially since 2010, recommendations should move from expert-based to evidence-based guidelines regarding nutritional interventions to be set up in multimodal scheme during pulmonary rehabilitation. In this respect, within the 13 nutritional interventional studies selected for the 2012-meta-analysis, only 3 combined nutritional intervention in a context of pulmonary rehabilitation (6, 12), all 3 resulting in clinically significant improvements in weight and exercise tolerance suggesting a role for multimodal
intervention as compared to the 10 others (11).

Since this meta-analysis, 4 studies (13-17) including respectively 199, 122, 32 and 22 patients with COPD set up in the community brought new convincing evidences in favour of multimodal interventions including besides nutritional intervention, oral androgens substitution in one study (16), self education and pulmonary rehabilitation. INTERCOM trial showed that a 4 month-multimodal intervention and 18 maintenance-months intervention on depleted and non depleted patients with COPD GOLD stages 2 and 3 resulted in improvements in body composition, quality of life and exercise tolerance as compared to standard care (14, 15). IRAD2 study in malnourished patients suffering with chronic respiratory failure mainly due to COPD GOLD stage 4 at home on long term oxygen therapy ± non invasive ventilation achieved similar results, plus a survival advantage in compliant patients to multimodal intervention. A 2010 home Japanese trial resulted in similar outcomes in moderate to severe COPD with cachexia. Finally, a randomized, controlled, double-blind pilot study showed combined effects of dietary supplementation with pressurized whey and exercise training in 22 patients with COPD by week 16 on quality of life and sub maximal endurance time in the combined arm (18).

Besides, exercise training cornerstone of pulmonary rehabilitation to improve nutritional interventions in depleted COPD or at risk of depletion during rehabilitation, there are numerous interventions that could enhance effects of nutritional supplementation: smoking cessation (19), correction of hypoxemia and/or hypercapnia with LTOT and / or non invasive ventilation (20), vitamin D repletion (21), omega-3 addition to the diet with good evidences (13, 22), reduction of static and dynamic hyperinflation by long acting bronchodilatatators (19), androgens substitution with 4 positives studies (12, 16, 23, 24) as in cardiac failure (25), lung volume reduction (26).

A significant number of patients up to 30% do not respond to nutritional rehabilitation rising questions about non-response to intervention where systemic inflammation (27) or epigenetic controls due to hypoxia (28) may play a significant role besides difficulties to implement such interventions in the community.

At the end, developing translational and clinical research in the field of integrated care is difficult, needs significant budgets, long term time frame to assess clinical outcomes and more problematic difficult to publish since reviewers require numerous arms to disentangle specific effects of each component.

Nutrition interventions in COPD should be integrated in pulmonary rehabilitation (8, 19) and more broadly in an integrated perspective in accordance to the chronic care model (29). In this respect, nutritional interventions in patients with COPD are necessarily multimodal and should follow principles of Systems biology and 4P medicine: preventive, predictive, participatory, and personalised (30, 31).

References
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