The Cachexia Associated With COPD

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Research during the past 2 decades consistently has shown that chronic obstructive pulmonary disease (COPD) is not only a chronic inflammatory lung disease but also a metabolic disorder affecting multiorgan systems. Weight loss, skeletal muscle wasting, and a decreased muscle oxidative phenotype are well documented in advanced COPD and a target for multimodal intervention strategies. Existing strategies have obtained promising results from exercise and nutritional supplementation with or without anabolic agents. Furthermore, experimental research rapidly advances an understanding of the molecular mechanisms of altered muscle plasticity in COPD progression, providing new leads for nutritional intervention.

Whole Body and Cellular Energy Metabolism

In comparison with other chronic wasting conditions, part of the weight-losing COPD patients are characterized by elevated activity-induced and daily energy expenditure.[1-3] Without a corresponding increase in caloric intake, patients inevitably lose weight.[1] A recent randomized controlled trial (RCT) reported the effect of dietary counselling and food fortification in COPD outpatients. While the treated group gained weight during the nutritional intervention period of 6 months and maintained weight during the 6 months follow-up, the control group progressively lost weight.[4]

It is postulated that pulmonary pathology increases the work of breathing and thus daily energy expenditure.[5-8] In addition, impaired cellular and whole-body energy metabolism could result from intrinsic muscle abnormalities. Disturbed levels of energy-rich phosphates, such as adenosine triphosphate (ATP) and creatine phosphate, are reported in rest, as well in response to an exercise bout, indicative of impaired oxidative energy metabolism.[9-12] Consequently, the affected muscles rely more on anaerobic energy metabolism to produce ATP, which is far less efficient.

The most prominent intrinsic muscular abnormality in COPD that is likely to cause the previously mentioned impairment in cellular energy metabolism is the loss of muscle oxidative phenotype because of a fiber type I→II shift in lower limb skeletal muscle and in parallel, reduced activities of enzymes involved in muscle oxidative metabolism.[14-17] It seems that these alterations are more pronounced in emphysematous patients who, strikingly, also are more prone to weight loss.[16] Accordingly, loss of muscle oxidative phenotype also is reflected by decreased mitochondrial mass and mitochondrial function, which was more pronounced in patients with low body mass index.[18-21]

These data suggest that the regulation of muscle oxidative phenotype and specifically mitochondrial biogenesis is altered in cachectic COPD patients. The transcription factors peroxisome proliferators-activated receptor (PPAR) α and β/δ and in particular their

coactivator PPAR coactivator-1α (PGC-1α) are considered as key regulators of muscle oxidative phenotype.

Recently decreased expression levels of these regulators were reported in muscle biopsies of patients with COPD and were more pronounced in the cachectic patients, again suggesting that loss of muscle oxidative phenotype and muscle mass are somehow interrelated.[22] Enhanced daily energy expenditure could originate from the loss of muscle oxidative phenotype because of less efficient energy metabolism. Alternatively, elevated muscle oxidative stress, which is consistently demonstrated for COPD, has likely involvement in muscle protein breakdown. Oxidative stress occurs when the production of oxidants exceeds the capacity of the antioxidant defense system.

Evidence shows that the antioxidant system is impaired in COPD; basal muscular levels of the antioxidant glutathione were reduced in emphysema patients, who also adapted less well to exercise training because their muscular antioxidant defense system did not improve as it did in healthy controls.[23,24] On the other side of the balance, enhanced muscular reactive oxygen species (ROS) production was reported for COPD as well, and it is likely that the impaired muscle oxidative capacity itself is the source of enhanced ROS production.[25-27] Moreover, it was shown that muscle-derived mitochondria from COPD patients produce more ROS as compared to healthy controls.[20]

Muscle Maintenance and Protein Balance

Atrophy of skeletal muscles in COPD appears to selectively affect glycolytic type IIA/IIX fibers.[28] Whether fiber type II atrophy is causally linked to the I→II fiber type shift still is undetermined.

Insulin-like growth factor-I (IGF-I) is an important mediator of anabolic pathways in skeletal muscle cells. While improvements in molecular signatures of muscle anabolism are described after exercise or pharmacological modulation in nonwasted COPD patients,[29-31] no studies are available on the muscle protein anabolic response in skeletal muscle of cachectic COPD patients. However, several studies consistently showed that protein/carbohydrate-rich supplements as an integrated part of a pulmonary rehabilitation program are effective in inducing (muscle) weight gain and improving physical performance.[32,33] Optimizing protein intake and essential amino acid intake may not only stimulate protein synthesis per se, but also enhance efficacy of anabolic pharmacological agents. However, no clinical data are available regarding the response to anabolics in cachexia during normal and high-protein intake (0.8-1.0 g/kg vs >1.5 g/kg body weight, respectively).

In cachectic patients with COPD, consistently reduced plasma levels of branched chain amino acids (BCAAs) are reported.[34-36] Some indications show that low-plasma BCAAs in COPD patients are because of specific alterations in leucine metabolism, an amino acid that has received much attention recently for its potential to modulate muscle anabolic signalling.[37] However, only limited studies have compared muscle anabolic effects of selective proteins or specific amino acids in patients at risk or suffering from cachexia. In a

short-term tracer experiment, supplementation of BCAA to a soy-protein meal resulted in a significant acute increase in whole-body protein synthesis in weight-stable COPD patients with borderline muscle mass but not in age-matched healthy controls.[38]

While short-term RCTs consistently showed the anabolic potential of multimodal interventions, muscle rapidly wasted away when this stimulus stopped.[39] This is not surprising because experimental research shows that maintenance of muscle mass by insulin/IGF-I signalling also involves suppression of protein degradation. Doucet et al[40] recently reported increased expression of atrogin-1 and MuRF1 in skeletal muscle biopsies of COPD patients with muscle atrophy. Inflammation is the most explored trigger for impaired muscle maintenance in cachexia. However, despite abundant and elegant experimental evidence for a role for tumor necrosis factor (TNF)-α in muscle wasting, much controversy still exists regarding its role in COPD.

Nevertheless, two recent RCTs investigated the effect of nutritional anti-inflammatory modulation on muscle maintenance in COPD. Matsuyama et al investigated the effects of a dietary supplement containing n-3 polyunsaturated fatty acid (PUFA) during 2 years and reported a significant decrease in leukotriene B4 levels in serum and sputum and in TNF-α and interleukin-8 (IL-8) in sputum, while no effect was observed in the control group receiving a nutritional supplement enriched with n-6 PUFA.

Broekhuizen et al[42] investigated the effect of PUFAs as adjunct to exercise training in COPD patients eligible for pulmonary rehabilitation. No effects were (yet) seen on systemic inflammatory profile, but PUFAs significantly enhanced improvement in cycle endurance time and peak workload. Experimental research indicates that inflammation may not only modulate muscle mass but could also affect muscle oxidative phenotype by downregulation of the PPARs. A bidirectional antagonism, described between the PPAR and NF-κB signalling pathway, is a possible explanation for the effects of anti-inflammatory modulation on exercise capacity.[43] Indeed, increased NF-κB activation and decreased muscle messenger ribonucleic acid (mRNA) PPARα expression are demonstrated in underweight COPD patients, and are inversely associated with systemic inflammation.[22]

Conclusion

Recent approaches to translation research clearly have advanced our understanding of the pathophysiology of cachexia in COPD. A cure for this complex clinical syndrome may perhaps not yet exist, but would certainly benefit from a multidimensional intervention approach. In addition to further mechanistic insight into the interaction between oxidative phenotype and muscle maintenance regulation, longitudinal COPD studies are needed to unravel genetic and environmental factors underlying cachexia susceptibility, what initiates the cachexia process, and what the sequential molecular steps are.

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Q & A

Q: In the study with the nutritional intervention, what were the supplements and how many calories did they have?

Dr Schols: Supplements were given three times daily, 125 mL. That is because in previous studies, we showed that we can improve the efficiency of nutritional intervention in these patients by providing them with smaller portions spread out during the day. It was 30% protein and 60% carbohydrate, and in total they were given nearly 600 kcal daily.

Q: Did you assess tolerance?

Dr Schols: Yes, we did assess it, and I also have all the data of the mean intake of supplements throughout the maintenance phase, but I thought that was too much detail for this presentation.

Q: I admire the integration of very basic science with elegant clinical studies. One observation that you mentioned briefly in passing is that the TNF link to muscle structure function in patients was based on the TNF expression in the muscles of the patients, suggesting that TNF plays an autocrine-paracrine role. Do you have any idea what the stimulus is for TNF upregulation in muscles of COPD patients? Do you think it is a TNF-induced TNF expression, or is there some other circulating mediator that you think is responsible?

Dr Schols: That is an important question that I cannot answer, but one we are trying to solve. It also still is not clear whether or not there is spillover from the pulmonary compartment to systemic inflammation. We try to address that in experimental models.

Quite some controversy exists in the literature regarding whether or not there is elevated TNF expression in the muscle, but I think that this is partly related to very small-size studies with different patient populations. I think what was nice in our study is that we included a large group of patients.

This analysis shows us that we can not generalize for all COPD patients, because apparently some of the patients may have increased inflammation in the muscles; others do not. We now are analyzing whether or not this is related to systemic inflammation. That could be easy, because then we would have an easy biomarker. But I can not give you the answer yet.

Q: I wonder about the omega-3 PUFA [polyunsaturated fatty acid] studies that you did. Do you think that the baseline levels of the patients have any effect or any influence on the effect? I think that Dutch people usually eat a lot of fish. So, would you expect the effects of omega-3 PUFA supplementation to be better in a population in which people do not eat as much fish?

Dr Schols: Well, they do not eat much fish in Holland. So, that is a misconception. In Holland, we are not the type of people who believe everything; not many people take supplements or capsules. We verified this, and it was not an interfering factor in our study, which was the case in previous cancer cachexia trials.

I think it is also interesting to ask whether genetic TNF polymorphisms are predictive for the response to the intervention. Japanese researchers performed a nutritional intervention trial including omega-3 fatty acids. As in our study, they did not see an enhancing effect of the omega-3 fatty acids on muscle mass and on body weight. This was provided as part of a nutritional supplement. They did show some effects on induced sputum on markers of inflammation. What I like of the concept of the PUFAs is that maybe you have an intervention that not only targets the muscle, but also could benefit the lungs, because we still are dealing with a disease and with a primary impairment.

Q: I know the tissue macrophages respond to hypoxia to produce cytokines. Did you look at oxygenation in the patients? Did you see a pattern showing that the more wasted individuals have hypoxia?

Dr Schols: This is a topic of interest within our group. We certainly are working on this, both in experimental models as well as in human tissue. I cannot give you an answer. Several research groups have shown evidence that tissue hypoxia or hypoxia possibly is related to mitochondrial dysfunction.

It certainly seems logical that this contributes to the abnormalities in muscle metabolism, as well as maybe enhancing the effect of the inflammation. However, we do not have a clear-cut answer yet. It also is very difficult to measure tissue hypoxia in humans.