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Nutritional modulation as part of the integrated management of chronic obstructive pulmonary disease

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Weight loss is a frequent complication in patients with chronic obstructive pulmonary disease (COPD) and is a determining factor for functional capacity, health status and mortality. Weight loss in COPD is a consequence of an inbalance between increased energy requirements and dietary intake. Both metabolic and mechanical inefficiency may contribute to elevated energy expenditure during physical activity, while systemic inflammation has been associated with hypermetabolism at rest. Disease-specific symptoms and systemic inflammation may impair appetite and dietary intake. Altered intermediary metabolism may cause disproportionate wasting of fat-free mass in some patients. A combination of nutritional support and exercise as an anabolic stimulus appears to be the best approach to obtaining marked functional improvement. Patients responding to this treatment even demonstrated a decreased mortality. The effectiveness of anti-catabolic modulation requires further investigation.

Chronic obstructive pulmonary disease: Weight loss: Energy expenditure: Fat-free mass

The association between weight loss and chronic obstructive pulmonary disease (COPD) has been recognized since the late 19th century. In the 1960s several studies reported that a low body weight and weight loss are negatively associated with survival in COPD (Vandenbergh *et al*. 1967). Nevertheless, therapeutic management of weight loss and muscle wasting in patients with COPD has gained interest only recently, since it was generally considered as a terminal progression in the disease process and therefore inevitable and irreversible. Recent clinical and population studies have challenged this attitude and shown that weight loss and a low body weight are associated with poor prognosis independent of, or at least not closely correlated with, the extent of lung function impairment (Wilson *et al*. 1989; Landbo *et al*. 1999). Moreover, weight gain in patients with a BMI of $< 25\,kg/m^2$ was even associated with decreased mortality (Schols *et al*. 1998; Prescott *et al*. 2002).

The renewed interest in nutritional support as therapy in COPD runs parallel to changing concepts in the disease management, not only predominantly aimed at the primary organ failure, but also at the systemic manifestations.

Rationale for nutritional support

The most prominent symptoms of COPD are dyspnoea and an impaired exercise capacity. In addition to airflow obstruction and loss of alveolar structure, skeletal muscle weakness is an important determinant of these symptoms (Prescott *et al*. 2002). Peripheral skeletal muscle strength is predominantly determined by the amount of skeletal muscle mass (Bernard *et al*. 1998; Engelen *et al*. 1999). Several studies have also shown that, in addition to effects on peripheral skeletal muscle strength, body weight and fat-free mass (FFM), a measure of muscle mass, are important determinants of exercise capacity and exercise response (Palange *et al*. 1995, 1998; Baarends *et al*. 1997*b*). Patients with a depleted FFM were characterized by a lower peak O_2 consumption and peak work rate, and early onset of lactic acid compared with non-depleted patients (Baarends *et al*. 1997*b*). These findings suggest that the functional consequences of nutritional depletion not only relate to muscle wasting *per se*, but also to alterations in muscle morphology and metabolism. Indeed, experimental studies and studies of other wasting conditions have shown that nutritional depletion causes generalized fibre atrophy, specifically decreases in muscle fibre type II cross-sectional area (Russell *et al*. 1984). Furthermore, altered levels of glycolytic and oxidative enzymes (Layman *et al*. 1981; Russell *et al*. 1984) and depletion of energy-rich substrates such as phosphocreatine and glycogen (Pichard *et al*. 1988; Bissonnette *et al*. 1997) have been described after nutritional depletion. It has also been clearly shown that nutritional

Abbreviations: COPD, chronic obstructive pulmonary disease; FFM, fat-free mass; GLU, glutamate; PUFA, polyunsaturated fatty acids; REE, resting energy expenditure; TEE, total energy expenditure; TNF, tumour necrosis factor.

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depletion not only decreases peripheral muscle function, but also affects respiratory muscle mass and strength (Rochester & Braun, 1985).

The functional consequences of underweight, and particularly of depletion of FFM, are also reflected in a decreased health status, as measured by the disease-specific St George's Respiratory Questionnaire (Schoup *et al*. 1997). Depletion of FFM is not only associated with weight loss, but may also occur in normal-weight patients with a relatively increased fat mass (Schols *et al*. 1993). Patients with depletion of FFM, irrespective of body weight, showed greater impairment in health status in comparison with weight-depleted patients with a relative preservation of FFM (Mostert *et al*. 2000).

Several studies using different COPD populations have now convincingly shown that weight loss and a low BMI are associated with an increased mortality risk (Wilson *et al*. 1989; Schols *et al*. 1998). Remarkably, overweight patients with moderate to severe COPD even have a lower mortality risk than normal-weight patients (Wilson *et al*. 1989; Schols *et al*. 1998). After adjustment for the effect of age, gender, lung function, smoking and resting lung function, increased mortality risk was found in patients with a BMI of $< 25\,kg/m^2$ (Schols *et al*. 1998). This finding could be related to the functional consequences of selective depletion of FFM in some of the patients, but also to adverse effects of recent weight loss on other outcome measures. In this context it is of interest to note that recent weight loss is an important factor for the outcome of acute exacerbations, as indicated by non-elective hospital readmission (Pouw *et al*. 2000) and the need for, and the outcome of, mechanical ventilation (Vitacca *et al*. 1996).

Nutritional assessment

Based on the relationship between nutritional status and outcome, the following screening measures of nutritional status are recommended.

Weight indices

Based on BMI, patients can be characterized as underweight, normal weight and overweight. Underweight is normally defined as a BMI of $< 21\,kg/m^2$. In Caucasian subjects this value corresponds to 90 % of the ideal body weight, based on the Metropolitan Life Insurance Tables (1983). However, this value is rather arbitrary, and according to recent recommendations this cut-off point in elderly hospitalized patients should be extended to $24\,kg/m^2$ (Beck & Ovesen, 1998). Interestingly, this value corresponds strikingly to the increased mortality risk that was reported for patients with COPD and a BMI of $< 25\,kg/m^2$.

Weight loss

There are limitations to weight-for-height indices. Underweight patients are not necessarily in a poor nutritional status. This situation was illustrated by the fact that underweight patients with a relative preservation of FFM had a comparable muscle strength and exercise performance to that of normal-weight subjects with a normal FFM (Schols *et al*. 1993). The adverse effects of involuntary weight loss, however, have been well described and progressive weight loss will ultimately lead to underweight and depletion of FFM. Thus, recent involuntary weight loss should be considered in nutritional screening and follow-up. Commonly-used criteria are weight loss of > 10 % of the usual body weight in the past 6 months or > 5 % in the past month.

Body composition

Weight is a rather global measure of nutritional depletion since it does not take body composition into consideration. In basic terms weight can be divided into fat mass and FFM. The FFM consists of water (approximately 73 %), protein and minerals. Water is distributed intracellularly in the body cell mass and extracellularly. The largest single tissue within the body cell mass is muscle. In the absence of shifts between the water compartments, FFM is a useful measure of the body cell mass and thus of muscle mass. Depletion of FFM in COPD is defined as a FFM of $< 16\,kg/m^2$ (males) and $< 15\,kg/m^2$ (females). These values are based on a linear gender-specific relationship between FFM and body weight (in the absence of obesity) using a cut-off point for the BMI of $21\,kg/m^2$. Based on measurement of body weight and FFM, four groups of patients can be differentiated: (1) underweight and depletion of FFM; (2) underweight and relative preservation of FFM; (3) normal weight and depletion of FFM; (4) normal weight and normal FFM.

^2H dilution and bioelectrical impedance analysis are relatively easy non-invasive methods for assessing FFM, and they have been used and validated extensively in COPD (Schols *et al*. 1991*a*; Baarends *et al*. 1997*d*). Dual-energy x-ray absorptiometry allows measurement of lean tissue mass, bone and fat mass not only at the whole-body level, but also for the various regions of the body (trunk, arm, leg; Engelen *et al*. 1998).

In clinically-stable patients with moderate to severe COPD depletion of FFM has been reported in 20 % of the outpatients with COPD (Engelen *et al*. 1994) and in 35 % of those eligible for pulmonary rehabilitation (Schols *et al*. 1993). Limited data are available on the prevalence of nutritional depletion in representative groups with mild COPD as well as in patients suffering from acute respiratory failure, although in the latter group values ≤ 70 % have been reported (Fiaccadori *et al*. 1988). There is no clear relationship between measures of nutritional status and airflow obstruction, but weight loss and underweight are associated with decreased diffusing capacity and observed more frequently in patients with emphysema than in patients with chronic bronchitis (Engelen *et al*. 1999). The difference in body weight between the two COPD subtypes is merely a difference in fat mass. Depletion of FFM, even despite a relative preservation of fat mass, also occurs in chronic bronchitis (Engelen *et al*. 1999).

Causes of weight loss and muscle wasting

In order to be able to assess the need for, and the effectiveness of, nutritional therapy as well as the optimal

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nutritional support strategy, insight is needed into the underlying mechanisms and contributing factors of overall weight loss and specific tissue wasting in COPD. Weight loss, particularly loss of fat mass, occurs if energy expenditure exceeds dietary intake. More specifically, muscle wasting is a consequence of an inbalance between protein synthesis and protein breakdown. Alterations in both aspects of the energy balance have been reported in COPD.

Energy expenditure

Total energy expenditure (TEE) can be divided into several components, of which BMR is usually the largest and physical activity-induced thermogenesis can vary substantially between different individuals. Other components of TEE include diet-induced thermogenesis and drug-induced thermogenesis. Gas-exchange measurement of patients in awake relaxed conditions after an overnight fast is a convenient technique for measuring resting energy expenditure (REE), i.e. the sleeping BMR and the energy cost of arousal.

Based on the assumption that REE is the major component of TEE in sedentary subjects, several studies have measured REE in COPD. After adjustment for the metabolically-active FFM, REE was found to be elevated in COPD (Fitting *et al*. 1990). While in healthy control subjects FFM could explain ≤ 84 % of the individual variation in REE, in patients with COPD it was only 43 % (Schols *et al*. 1991*b*). Thus, other factors have been considered, such as the contribution of breathing, hormone levels, drug therapy and inflammation. A likely cause of the increased metabolic rate in patients with COPD is increased work performed by respiratory muscle, since the energy cost of increasing ventilation is higher in patients with advanced disease than in healthy controls of comparable age and gender. REE, however, correlates only weakly, if at all, with individual or combinations of comprehensive lung function tests and blood gas values (Schols *et al*. 1991*b*). Thus, patients with the worst lung function, and in whom the work associated with breathing would be expected to be the highest, are not necessarily hypermetabolic. Nasal intermittent positive-pressure ventilation, which eliminates diaphragmatic and intercostal activity, did not reduce REE to normal in a group of hypermetabolic patients (Hugli *et al*. 1995). Furthermore, in COPD and in chest wall disease airflow obstruction and O_2 cost of breathing were mutually related, but no correlation was found between O_2 cost of breathing and REE (Sriddhar *et al*. 1995).

Maintenance broncho-dilating treatment for many patients consists of inhaled β_2-agonists. Treatment with salbutamol for 2 weeks increased REE by < 8 % in healthy males (Wilson *et al*. 1993), whereas acute inhalation of clinical doses of salbutamol has been shown to increase REE by ≤ 20 % in a dose-dependent manner (Amoroso *et al*. 1993). High doses of nebulized salbutamol are commonly administered during acute disease exacerbations. Nevertheless, no significant acute metabolic effects of this treatment were found in elderly patients with COPD in comparison with an age-matched control group (Creutzberg *et al*. 1998).

Another contributing factor to hypermetabolism may be related to inflammation. The polypeptide cytokine tumour necrosis factor (TNF) is a proinflammatory mediator produced by several cell types. TNF inhibits lipoprotein lipase activity and is pyrogenic. It also triggers the release of other cytokines, which themselves mediate an increase in energy expenditure, as well as mobilization of amino acids and muscle protein catabolism. Using different markers several studies have provided evidence for the involvement of TNF-α-related systemic inflammation in the pathogenesis of tissue depletion. Elevated levels of TNF-α in (stimulated) plasma and soluble TNF receptors were found in patients with COPD (Di Francia *et al*. 1994; De Godoy 1996; Takabatake *et al*. 1999), particularly those suffering from weight loss. Furthermore, several studies showed a relationship between TNF-α-related inflammation and resting metabolic rate (Schols *et al*. 1996). Since diet-induced thermogenesis accounts for only 10 % of the daily TEE, the effect of a possible increase in diet-induced thermogenesis on daily TEE will be small. Normal and increased diet-induced thermogenesis have been described in patients with COPD (Hugli *et al*. 1993). Despite the methodological difficulties in measuring daily TEE, recent studies have investigated activity-related energy expenditure in patients with COPD. Using the doubly-labelled water ($^2H_2O^{18}$) technique to measure TEE it was demonstrated that patients with COPD had a significantly higher TEE than healthy subjects (Baarends *et al*. 1997*c*). Remarkably, the non-resting component of TEE was significantly higher ($P < 0{\cdot}05$) in the patients with COPD than in the healthy subjects, resulting in a TEE:REE of 1·7 in patients with COPD and 1·4 in normal subjects. On the other hand, when TEE was measured in patients with COPD and healthy subjects, using a respiration chamber, no differences in TEE were found between the two groups, possibly as a result of the limitation on activities in the respiration chamber (Hugli *et al*. 1996). There was no difference in TEE between hypermetabolic and normo-metabolic patients with COPD, and REE was not significantly ($P > 0{\cdot}05$) correlated with daily TEE when FFM was taken into account (Baarends *et al*. 1997*e*). The cause of an increased activity-related TEE has not been elucidated. It could be related to the observed decrease in mechanical efficiency during leg exercise (Baarends *et al*. 1997*a*). Part of this increased O_2 consumption during exercise can be explained by inefficient ventilation in a situation of increased ventilatory demand, especially under conditions of dynamic hyperinflation. Furthermore, the results of some studies suggest severely impaired oxidative phosphorylation during exercise in COPD, accompanied by an increased and highly anaerobic metabolism involving both energy release from high-energy phosphate compounds as well as enhanced glycolysis (Wuyam *et al*. 1992). Anaerobic metabolism is less efficient than aerobic metabolism.

Cellular energy metabolism

In addition to impaired oxidative phosphorylation during exercise, recent studies have shown alterations in resting cellular energy metabolism in peripheral muscle. A decrease

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in the activity of citrate synthase (Maltais *et al*. 1996), an increase in the glycolytic enzyme phosphofructokinase (Jakobsson *et al*. 1995) and (in hypoxaemic patients) an increase in the activity and expression of cytochrome oxidase have been reported (Sauleda *et al*. 1998). These enzymic adaptations could indicate a shift towards a more glycolytic metabolism. The functional consequences of these changes were reflected in alterations in adenosine nucleotide metabolism, as reflected by decreased phosphocreatine:creatine and detectable levels of inosine monophosphate, indicative for an imbalance between the utilization and resynthesis of ATP in resting muscle of patients with COPD (Pouw *et al*. 1998). It could be speculated that the observed changes in intracellular metabolites result in an increased overall energy metabolism.

Dietary intake

Hypermetabolism can explain why some patients with COPD lose weight despite an apparent normal or even high dietary intake (Hunter *et al*. 1981). Nevertheless, it has been shown that dietary intake in patients losing weight is lower than that in weight-stable patients, both in absolute terms and in relation to measured REE (Schols *et al*. 1991*d*). This finding is quite remarkable because the normal adaptation to an increase in energy requirements in healthy men is an increase in dietary intake. The reasons for a relatively low dietary intake of patients with COPD are not completely understood. It has been suggested that patients with COPD eat suboptimally because chewing and swallowing change the breathing pattern and decrease arterial O_2 saturation. Furthermore, gastric filling in these patients may reduce the functional residual capacity and lead to an increase in dyspnoea. Of particular interest is the role of leptin in energy homeostasis. This adipocyte-derived hormone represents the afferent hormonal signal to the brain in a feedback mechanism regulating fat mass. Leptin also has a regulating role in lipid metabolism and glucose homeostasis, and increases thermogenesis, as well as affecting T-cell-mediated immunity. Few data have been reported on leptin metabolism in COPD. Circulating leptin levels correlate well with BMI and percentage fat, as expected, but lower values were observed in patients with COPD compared with healthy subjects (Takabatake *et al*. 1999). In experimental studies administration of endotoxins or cytokines produced a rapid increase in serum leptin levels (Grunfeld *et al*. 1996). In COPD a relationship was found between leptin and soluble TNF-receptor 55, particularly in the emphysema subtype. Leptin, as well as soluble TNF-receptor 55, were in turn inversely related to dietary intake in absolute terms as well as when adjusted for REE (Schols *et al*. 1999). The precise mechanism for the regulation of leptin in COPD needs further investigation.

Another factor of interest in evaluating dietary intake is the influence of psychological dysfunction, such as anxiety, depression and appetite. Although no data from systematic studies are available, limited physical abilities, financial constraints and lack of supportive care should also be considered as factors that may interfere with dietary intake.

Outcome of nutritional intervention

Oral nutritional supplements

The first clinical trials that investigated the effectiveness of nutritional intervention involved nutritional supplementation using oral liquid supplements. All short-term studies (2–3 weeks; Wilson *et al*. 1986; Whittaker *et al*. 1990) showed a significant increase ($P < 0{\cdot}05$) in body weight and respiratory muscle function. This short-term effectiveness is probably related partly to repletion of muscle water and K, as well as changes in the composition of muscle protein-N (Russell *et al*. 1983). One study addressed the immune response to short-term nutritional intervention in nine patients with advanced COPD (Fuenzalida *et al*. 1990). Refeeding and weight gain were associated with a significant increase in absolute lymphocyte count and with an increase in reactivity to skin-test antigens after 21 d of refeeding.

Significant improvements (Efthimiou *et al*. 1988; Rogers *et al*. 1988) in respiratory and peripheral skeletal muscle function, as well as exercise capacity and health-related quality of life, were observed in one inpatient study and one outpatient study after 3 months of oral supplementation with approximately 4200 kJ (1000 kcal)/d. Other outpatient studies, however, despite a similar nutritional supplementation regimen, reported that the average weight gain was $< 1{\cdot}5$ kg in 8 weeks (Lewis *et al*. 1987; Knowles *et al*. 1988; Otte *et al*. 1989). In addition to non-compliance and variation between individuals, the poor treatment response may be attributed, at least partly, to inadequate assessment of energy requirements and to the observation that the patients were taking supplements instead of their regular meals.

Nutrition and exercise

From a functional point of view it is obvious that nutritional support should be combined with exercise if possible. Indeed, a daily nutritional supplement as an integral part of a pulmonary rehabilitation programme resulted in significant weight gain (0·4 kg/week), despite a much lower level of daily supplementation than in most previous outpatient studies (Schols *et al*. 1995). The combination of nutritional support and exercise not only increased body weight but also resulted in a significant improvement in FFM and respiratory muscle strength. The clinical relevance of the response to treatment was shown in a *post-hoc* survival analysis of this study, which demonstrated that weight gain and increased respiratory muscle strength were associated with increased survival rates (Schols *et al*. 1998). On Cox regression analysis weight gain during the rehabilitation period remained a significant predictor of mortality, independent of baseline lung function and other risk factors including age, gender, smoking and resting arterial blood gases. A more recent study also showed beneficial effects of nutritional support as an integral part of a pulmonary rehabilitation programme on skeletal muscle strength, exercise capacity and health status (Creutzberg *et al*. 2003). In view of the ventilatory limitation and the symptoms experienced, exercise in most rehabilitation settings consists

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of general physical training, with emphasis on endurance exercise. However, muscle strength is specifically impaired by nutritional depletion, and studies in elderly subjects without pulmonary disease have shown that strength training with nutritional support is superior to nutritional support alone in achieving an increase in FFM. There are no data available on the effects of nutritional support and strength training in nutritionally-depleted patients with chronic respiratory disease.

Macronutrient composition of nutritional supplement

Carbohydrate and fat

After optimization of meals and dietary habits, nutritional supplements are added to balance energy expenditure or enhance weight gain. However, meal-related dyspnoea and limited ventilatory reserves may restrict the quantity and composition of nutritional supplements for patients with respiratory disease. Nutrient administration is associated with an obligate increase in ventilation and metabolic rate. The composition of the energy intake can influence CO_2 production and, therefore, ventilatory demand. The RQ for glucose oxidation is 1, while the RQ for fat oxidation is 0·71, indicating a lower ventilatory load by reduced CO_2 production. Excessive CO_2 production by carbohydrate administration was observed in mechanically-ventilated patients (Askanazi *et al*. 1980; Talpers *et al*. 1992). However, these effects only occurred with energy overload. Several studies in clinically-stable patients with COPD have investigated the effects of nutritional supplements on functional capacity in the immediate postprandial period. They reported adverse effects of a high-energy carbohydrate-rich supplement (4044 kJ (920 kcal), 53 % energy as carbohydrate) relative to a fat-rich supplement. These effects included greater increases in minute ventilation (l/min), CO_2 elimination, O_2 con- sumption, RQ, arterial CO_2 tension and fatigue score, together with a greater fall in the distance walked (Frankfort *et al*. 1991; Efthimiou *et al*. 1992). After a more physiological energy load (1050–2100 kJ (250–500 kcal)) there was no difference in postprandial exercise capacity between a high-fat supplement and a low-fat supplement (Akrabawi *et al*. 1996) and there were even positive effects of a carbohydrate-rich supplement on lung function and dyspnoea sensation (Vermeeren *et al*. 2001).

There were also contraindications for a high-fat supplement related to the significant delay in gastric emptying, even compared with moderate-fat supplements (Akrabawi *et al*. 1996). As a result of the disease process itself, such patients already suffer from hyperinflation, a flattened diaphragm and a reduction in abdominal volume, which results in feelings of bloating, abdominal comfort and early satiety. A delay in gastric emptying may lead to an extended period of abdominal distention, impacting on diaphragmatic mobility and thoracic expansion. High-fat diets may also cause bloating, loose stools or diarrhoea and may thus create tolerance problems. Furthermore, meal-related oxyhaemoglobin desaturation may limit energy intake and contribute to meal-related dyspnoea in some patients, primarily in those who are hypoxaemic at rest (Schols *et al*. 1991*c*). The extent of oxyhaemoglobin desaturation appeared to depend on meal type, being significantly higher after a fat-rich warm meal compared with a carbohydrate-rich 'cold' meal (Schols *et al*. 1991*c*).

Protein

The effect of wasting disease on protein metabolism is characterized by net protein catabolism as a result of differences between protein synthesis and breakdown rates. This effect is observed as a negative N balance. The emphasis with regard to protein requirements in disease must be on optimal rather than minimal amounts of dietary proteins. Unfortunately, a clear clinical or physiological end point for the determination of optimal protein requirements is not available. Only studies documenting the effects of dietary protein content on N balance or on protein kinetics in various conditions have been published. The available data suggest that in healthy subjects and in stable disease protein synthesis is optimally stimulated during administration of 1·5 g protein/kg per d. Similarly, although the catabolic effects of acute disease cannot be manipulated merely by nutrition, net protein catabolic rates in these conditions are lowest with administration of 1·5–2·0 g protein/d (Hopkins *et al*. 1983).

Anabolic nutritional modulation

The observed alterations in cellular energy metabolism towards a decreased oxidative metabolism have increased the interest in nutritional modulation to enhance physical performance. Specific attention has been paid to the potential benefit of amino acid modulation, in particular the branched-chain amino acids and glutamate (GLU). The most consistent results have been reported for GLU. Intracellular GLU has various important functions, as it plays an important role in preserving high-energy phosphates in muscle through different metabolic mechanisms. GLU concentration is high in the free amino acid pool of human skeletal muscle. Intracellular GLU is known as an important precursor for the antioxidant glutathione and for glutamine synthesis in the muscle. Certainly, muscle GLU is strongly associated with muscle glutathione, and patients with emphysema suffer from decreased muscular GLU and glutathione levels in lower limb muscle (Engelen *et al*. 2000*a*). Studies have shown that in healthy human muscle the GLU pool functions to generate tricarboxylic acid intermediates during the first minutes of exercise, which is achieved via the alanine aminotransferase reaction (pyruvate + GLU $\rightarrow$ alanine + α-ketoglutarate) at the cost of GLU. Moreover, this reaction can shunt the pyruvate accumulated during exercise towards alanine instead of lactate, suggesting the possible involvement of the intracellular GLU level in the lactate response to exercise. In line with this hypothesis early lactic acidosis during exercise in patients with COPD was found to be associated with a reduction in muscle GLU (Engelen *et al*. 2000*b*). At rest and also during 20 min of submaximal constant cycle exercise a different response in amino acid status was found in skeletal

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muscle and plasma of patients with COPD as compared with healthy age-matched controls (Engelen *et al*. 2001). Marked reductions in most muscle amino acids were observed post-exercise, while some plasma amino acids were increased, suggesting an enhanced amino acid release from muscle during exercise in patients with COPD. The increase in plasma alanine and glutamine was even higher post exercise, suggesting enhanced N efflux. There are no data available from intervention studies of patients with COPD. However, in the frail elderly it has been observed that oral amino acid intake stimulates the transport of amino acids into muscle, and that there is a direct link between amino acid transport and protein synthesis when amino acids are ingested before exercise or some time after exercise.

Anti-catabolic nutritional modulation

Even in a controlled environment such as an inpatient rehabilitation centre, some patients do not respond to nutritional therapy. In addition to non-compliance to therapy, an inadequate energy intake relative to energy requirements and the inability of the patients to ingest the extra energy, inadequate metabolic handling may contribute to poor treatment response. The interaction between nutritional depletion and systemic inflammation as well as an inverse association between systemic inflammation and response to nutritional supplementation (Creutzberg *et al*. 2000) have drawn attention to the potential beneficial effects of anti-catabolic agents in specific modulation of the systemic inflammatory response. The fatty acid composition of inflammatory and immune cells is sensitive to changes in the fatty acid composition of the diet. The *n*-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid and docosahexaenoic acid are found in high proportions in oily fish and fish oils. The *n*-3 PUFA are structurally and functionally distinct from the *n*-6 PUFA. Typically, human inflammatory cells contain high proportions of the *n*-6 PUFA arachidonic acid and low proportions of *n*-3 PUFA. The importance of this difference is that arachidonic acid is the precursor of 2-series prostaglandins and 4-series leukotrienes, which are highly-active mediators of inflammation. Feeding fish oil results in partial replacement of arachidonic acid in inflammatory cell membranes by eicosapentaenoic acid. This change leads to decreased production of arachidonic acid-derived mediators. This response alone is a potentially beneficial anti-inflammatory effect of PUFA. Recent studies have shown that *n*-3 PUFA can down regulate the activity of nuclear factor kappa B, which is a critical mediator of the intracellular signalling events triggered by TNF-α and other inflammatory cytokines, including skeletal muscle-specific gene expression (Calder, 2001). The interaction of *n*-3 PUFA and cytokine biology is, however, complex. In healthy volunteers the sensitivity of an individual to the suppressive effects of *n*-3 PUFA on TNF-α production is linked to the inherent level of production of the cytokines by cells from the individual before supplementation and to genetic variation encoded by, or associated with, the TNF-α −308 and lymphotoxin a +252 single nucleotide polymorphisms (Grimble *et al*. 2002). Therapeutic effects of *n*-3 PUFA in COPD have yet to be determined. In this context it may be relevant to note that TNF-α −308 polymorphism has been associated with the presence of COPD (Sakao *et al*. 2001), and even specifically with the extent of emphysematous changes in these patients (Sakao *et al*. 2002).

Conclusion

In patients with COPD a combination of nutritional support and exercise as an anabolic stimulus appears to be the best approach to obtaining marked functional improvement. Patients responding to this treatment even demonstrated a decreased mortality. The effectiveness of anti-catabolic modulation requires further investigation.

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