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PERSPECTIVE

Possible mechanisms underlying the development of cachexia in COPD

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ABSTRACT: About 25% of patients with chronic obstructive pulmonary disease (COPD) will develop cachexia (fat-free body mass index $<$17 kg·m^{-2} (males) or $<$14 kg·m^{-2} (females)). This is associated with ~50% reduction in median survival.

The pathogenetic mechanism has been variously suggested to result from the following: 1) energy imbalance; 2) disuse atrophy; 3) tissue hypoxia from arterial hypoxaemia; 4) systemic inflammation; and 5) anabolic hormonal insufficiency. Genetic polymorphisms implicate inflammatory cytokines, especially interleukin (IL)-1β, but IL-6 and tumour necrosis factor (TNF)-α do not show polymorphisms in these patients. Early reports of elevated TNF-α levels suggested a role for inflammation, but recent studies have not shown elevated levels of either IL-6 or TNF-α. Therapeutic trials of nutritional support, hormonal supplementation, anti-TNF-α immunotherapy, ghrelin and antioxidants have been conducted, but only a few have shown any benefits in muscle structure and function.

Considerably more mechanistic knowledge is needed before therapeutic recommendations can be made. At this time, it is not possible to attribute cachexia in COPD unequivocally to inflammation or any other cause, and much more research is needed.

To date, studies have been predominantly cross-sectional, with measurements made only after cachexia has developed. Future research should target prospective observation, studying patients as cachexia progresses, since once cachexia is established, inflammatory cytokine levels may not be abnormal.

KEYWORDS: Cachexia, chronic obstructive pulmonary disease

There have been several recent reviews of cachexia in chronic obstructive pulmonary disease (COPD; see, for example, [1–6]). They conclude that cachexia in COPD patients who are not regularly taking steroids is multifactorial, based on nutritional insufficiency, increased metabolic rate, hypoxaemia, sympathetic upregulation, inactivity, oxidative stress, inflammation, anabolic hormone insufficiency and altered leptin levels, perhaps all acting on a genetic predisposition in susceptible patients. Why then is another review necessary at this time? The European Respiratory Society Research Seminar on Comorbidities in COPD held in Rome in February 2007 challenged us to examine, amongst other topics, the current standing of inflammation as the cause of cachexia and, after careful reading of both prior reviews and primary research articles, the current author is forced to conclude that there is still no direct evidence for a cause-and-effect relationship between inflammation and cachexia. The circumstantial evidence is, however, tantalising and, ultimately, current views may prove correct. Thus, the message from the present article is to not yet consider the mechanism(s) of cachexia in COPD as well defined. Much more research is needed, as the present review will specify at the end. Much of the ''easy'' correlative research that has informed the above-mentioned reviews has already been carried out. What is now called for is the more difficult, time-consuming and expensive cause-and-effect research to take the present understanding of cachexia mechanisms to a level that will allow subsequent studies to focus the development of the most rational therapeutic approaches to this common and very debilitating problem.

The present article will cover several aspects of cachexia in COPD, beginning with the definition of cachexia, its prevalence and its importance, in

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order to frame the discussion. It will then examine the several potential mechanisms that have been proposed to underlie the development of cachexia, including several genetic polymorphisms that have been suggested as conveying susceptibility to cachexia. Particular attention is given to the possible role of inflammation in its pathogenesis. There have been several therapeutic intervention trials in cachexia with mixed results, and they will also be reviewed. However, the purpose of examining therapies is not to render judgement on how best to manage such patients, but to ask whether these trials shed light on the pathogenesis of cachexia. The present article will end with a list of perceived major research opportunities.

CACHEXIA IN COPD: DEFINITION, PREVALENCE AND SIGNIFICANCE

Definition

Cachexia in any disease refers to a state of severely and pathologically low weight, due principally to the loss of mass of tissues other than fat. While a process of weight loss is implied, in a given patient the time course and degree of weight loss may not be known. Cachexia is a hallmark of certain disease entities, such as various cancers, and some infectious diseases, such as tuberculosis. It is, however, not uncommon in COPD itself. To ascribe cachexia to COPD, one must, of course, be sure that one is not dealing with these other diseases. As all pulmonologists know, COPD is associated with lung cancer through their common aetiology, namely tobacco.

Cachexia was, until recently, measured using body mass index (BMI), which is body weight in kilogrammes divided by the square of body height in metres. Normal values are in the low-to-mid 20s ($kg \cdot m^{-2}$). Using BMI, cachexia in COPD is acknowledged to exist when BMI is <21 $kg \cdot m^{-2}$ [7]. The problem with using BMI is that this parameter does not distinguish between two people of similar BMI but different body composition. Specifically, different fat *versus* nonfat contributions to total weight may exist in patients with the same BMI [8]. Thus, a COPD patient may well have lost considerable lean body mass but may have extra fat stores resulting in an overall normal BMI. Such a patient should be considered as possibly cachectic. Conversely, a COPD patient of the same BMI but with low body fat and well-preserved lean body mass would not be considered cachectic.

Thus, it has recently been suggested that cachexia should be defined by lean body mass index (LBMI), which is also measured in $kg \cdot m^{-2}$. SCHOLS *et al.* [7] propose that when LBMI is <16 $kg \cdot m^{-2}$ in males and <15 $kg \cdot m^{-2}$ in females, cachexia is present [7]. Since LBMI is a continuously distributed variable, no single criterion value can be theoretically perfect as a cut-off. One principle for defining limits of normal in continuously distributed variables that are reasonably normally distributed is to determine the lower 95% confidence limit, and to use that as a probabilistic cut-off. SCHUTZ *et al.* [9] show that 95% of normal males have an LBMI >17 $kg \cdot m^{-2}$ and that 95% of females have an LBMI >14 $kg \cdot m^{-2}$.

The distinction between BMI and LBMI is not academic. Fundamental to the issue is the understanding that cachexia is really best defined by loss of lean body mass. This in turn implies a pathological process of excessive protein breakdown, not simply a burning of stored fat.

Prevalence

The prevalence of cachexia is variously presented as 20–40% of the COPD population [10, 11], and is probably closer to the lower end of this range. Note that in the article by CONGLETON [10], prevalence was defined on the basis of ideal body weight being <90% of the predicted, while in the article by SCHOLS [11] it was based on reduced fat-free mass. These two studies reported prevalence values of 36 and 20%, respectively, in patients described as having ''moderate-to-severe COPD''. It is possible that the higher value in the article by CONGLETON [10] represents at least in part the inclusion of some patients whose weight was diminished by loss of fat rather than of lean body mass. Thus, by taking a value of 25% for the sake of discussion, this means that only one out of four COPD patients are destined to become cachectic, while three out of four will not. The obvious question becomes ''what is it that separates COPD patients into these two very different phenotypic groups?'' In short, the answer is not yet clear. Genetic polymorphisms associated with specific pro-inflammatory cytokines have been found in COPD; however, while this is a promising line of investigation, these studies seem to raise more questions than they answer. They will be discussed below in some detail. It is likely that while genetic susceptibility will be found to be important, environmental factors, such as tobacco dose, regular exercise, dietary elements, hormonal levels and so on, will also play a role. As with most clinical syndromes, the answer to this simple question is likely to be very complex.

Significance

The significance of cachexia in COPD is starkly evident in survival curves, as shown by SCHOLS and co-workers [7, 12]. Using the above LBMI definitions, SCHOLS *et al.* [7] showed that median survival was cut almost in half by cachexia (fig. 1), from just under 4 yrs to just over 2 yrs. The differences in survival are not due to differences in severity of COPD by spirometric criteria, for which adjustments were made between the two groups in figure 1. What is not known is whether cachexia can be prevented, or even reversed, once developed, and how this will affect survival.

The other obvious consequence of cachexia relates to impaired quality of life. With fatigue and weakness being even greater than for noncachectic COPD patients, cachexia worsens the quality of life considerably.

GENETIC SUSCEPTIBILITY TO CACHEXIA IN COPD

The finding that only one out of about four patients with COPD develops cachexia has prompted studies looking for genetic polymorphisms that may underlie differential susceptibility [13]. It is very early in the search for such altered genes and, even though some associations have surfaced, cause and effect remains to be established in each case. The favourite targets for these studies have been genes encoding pro-inflammatory molecules, such as tumour necrosis factor (TNF)-α, some of the interleukins (ILs), and bradykinin. This is because most people have approached cachexia on the hypothesis that it is based on continued systemic inflammation (as will be discussed hereafter).

The most striking polymorphism finding to date is shown in figure 2, where BROEKHUIZEN *et al.* [14] found that a -511 polymorphism in the IL-1β gene correlated strongly with

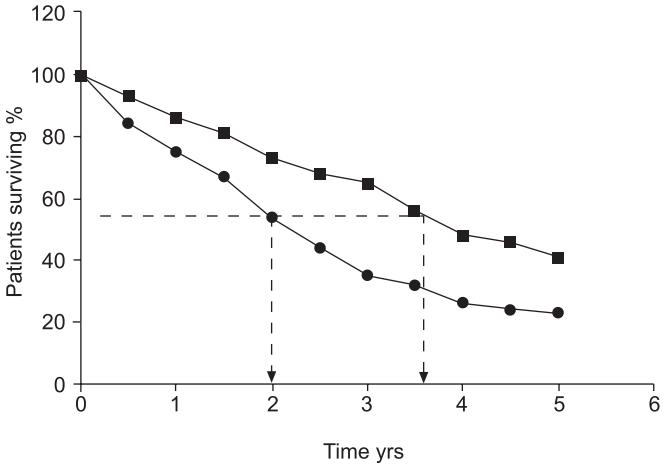

FIGURE 1. Survival in patients with chronic obstructive pulmonary disease according to the presence of cachexia. Median survival is almost twice as short in cachectic patients (●) as in noncachectic patients (■). Cachexia was considered to be a fat-free mass index <16 kg·m^{-2} in males and <15 kg·m^{-2} in females. Reproduced from [7], with permission from the publisher.

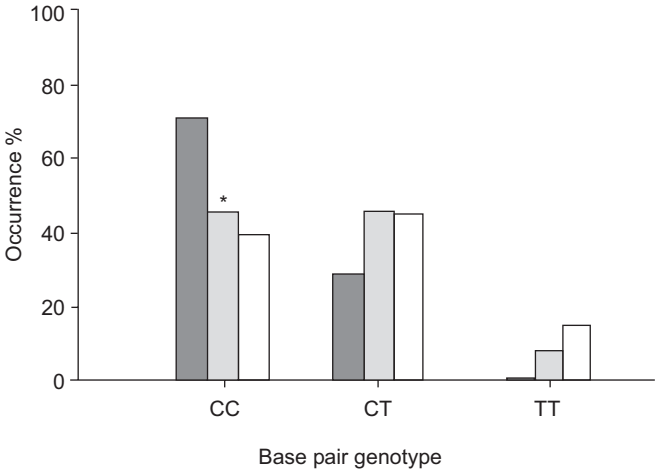

FIGURE 2. Association of the -511 CC polymorphism with cachexia in patients with chronic obstructive pulmonary disease (COPD). While the CC variant is not necessary for cachexia to develop, the TT genotype appears protective. ■: cachectic patients with COPD; ■: noncachectic patients with COPD; □: normal subjects. *: $p<0.05$.

cachexia. As figure 2 shows, the CC genotype at this position in the gene was associated with frequent cachexia, while the TT genotype was not associated with cachexia. The heterozygous CT genotype had an intermediate association with cachexia. Of interest, the authors found that circulating IL-1β was undetectable in all three genotypes, casting doubt on the functional significance of the genetic outcome. However, is this interpretation of the data correct? By definition, cachexia was already present when the studies were done. It is quite reasonable to hypothesise that IL-1β may be key, but had its effects much earlier in the process. It would take an expensive, long-term, prospective cohort study to address this notion. It may also be that circulating IL-1β is not the relevant variable, and that IL-1β levels in muscle may be more important. It is possible that the differences still exist there, even while circulating levels are not different among groups; this was not addressed by direct sampling. At this point in time, no clear message emerges: the association with IL-1β is tantalising, and may reflect a cause-and-effect relationship, but this is presently not known.

Another polymorphism that associates with cachexia is in the bradykinin receptor, as shown by HOPKINSON *et al.* [15] in figure 3. The effects are modest, but suggest that the +9/+9 insertion polymorphism is more prevalent in patients with low LBMI. However, the difference between these patients and those without the insertion (-9/-9) in LBMI is not significant *per se* (fig. 3). Furthermore, that heterozygotes had a higher LBMI than the (-9/-9) patients was unexpected. It is noteworthy in figure 3 that, while LBMI may have slightly differed between (+9/+9) and heterozygotes, BMI itself was not different, and those with low LBMI therefore must have had relatively large fat stores. Most cachectic patients do have low BMI, not just low LBMI, although the distinction may not always hold, as mentioned earlier. HOPKINSON *et al.* [16] and GOSKER *et al.* [17] also examined the ACE gene and found a polymorphism-based association with muscle strength in COPD.

Other cytokines that have been examined for cachexia-related polymorphisms include TNF-α and IL-6. In both cases, no polymorphisms have been found [14]. This is disappointing in that both of these pro-inflammatory molecules have long been regarded as prime candidates in the development of cachexia. Moreover, LANGEN *et al.* [18] studied transgenic mice engineered to overexpress TNF-α (in the lungs only) and found loss of muscle mass as a result. This can be taken as a ''proof of concept'' that TNF-α coming from the lungs is capable of inducing reduction in LBMI. Whether this allows one to implicate TNF-α in human cachexia is debatable and will be further discussed below.

POTENTIAL MECHANISMS OF CACHEXIA IN COPD

With the possibility that patients with COPD being susceptible to cachexia is determined by their genes, the actual mechanisms proposed to explain loss of lean body mass can now be discussed. The mechanisms are listed in table 1, and will be addressed in sequence.

Energy imbalance

Historically, the first mechanism to be discussed was energy imbalance, but this theory has lost some favour as the primary cause of cachexia. It was postulated that due to airways obstruction, the work of breathing was increased, 24 h a day, 7 days a week. Whether work of breathing explains the results or not, hypermetabolism has been noted, for example, by SERGI *et al.* [19], where resting energy expenditure was found to be 10% higher in COPD patients than in normal subjects of a similar age, height and weight. The oxygen cost of exercise has also been found to be higher than in normal subjects [20]. Without a corresponding increase in caloric intake, patients would inexorably lose weight because obstruction was irreversible. Supporting this idea, use of noninvasive positive pressure ventilation has been shown to increase free-fat mass index (FFMI) [21]. In addition to this concept, it is known that there is some fibre-type shift in skeletal muscle in COPD away

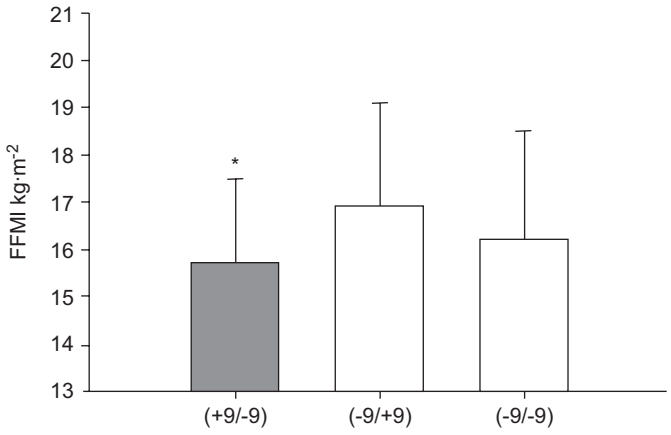

FIGURE 3. Fat-free body mass in patients with chronic obstructive pulmonary disease in 110 patients according to bradykinin insertion genotype. The (+9/+9) insertion variants have cachexia, heterozygotes and normal subjects do not. It is not clear why normal subjects have a lower fat-free mass index (FFMI) than heterozygotes (*c.f.* -9/+9 and -9/-9 variants). ■: body mass index (BMI) 23.5 kg·m^{-2}; □: BMI 24.1 kg·m^{-2}. Reproduced from [15], with permission from the publisher.

TABLE 1 Potential mechanisms of cachexia

Energy imbalance
Increased work of breathing
Inefficient metabolism (fibre type conversion to type II)
Anorexia
Disuse atrophy of muscles
Hypoxaemia
Systemic inflammation
Tumour necrosis factor-α
Interleukin-1β and -6
C-reactive protein
Reactive oxygen species
Hormonal insufficiency
Growth hormone
Testosterone
Insulin-like growth factor
Leptin
Sympathetic activation (pro-inflammatory)
Accelerated ageing

from type I and towards type II. It is also known that type II muscle uses more oxygen per unit work output than type I, thus, there is an extra metabolic load due to oxygen-inefficient muscle usage. Another factor is that cachexia itself leads to anorexia [22], and this must create a vicious circle, such that the more weight lost, the less food is taken in. Aggressive nutritional augmentation and appetite stimulation have not solved the problem [10, 23, 24], casting some doubt on the centrality of this mechanism. CREUTZBERG *et al.* [25] found that poor responders to nutritional therapy were somewhat older, had less appetite and evidence of more inflammation. The statistical contribution of inflammation, parameterised by the concentration of soluble TNF-α receptor 55, was small (0.1 in a total R^2 of 0.8) and the receptor levels were identical between patients who gained <2% body weight and those who gained 2–5% body weight. Furthermore, it is impossible to know from such studies whether the correlation with inflammation is causative. Consequently, their findings cannot be concluded as proving a role for inflammation in the poor response to nutritional therapy. However, their data do provide the basis for future research on the causative role of inflammation in cachexia. Despite these uncertainties, nobody would advocate anything other than assuring optimal nutrition in all COPD patients.

Disuse atrophy of the muscles

When a normal subject has a fractured limb placed in a cast for several weeks, there is very evident loss of muscle mass as fibres atrophy from disuse. Patients with severe COPD are very inactive, and are likely to be more so than healthy people of the same, usually advanced, age (even those healthy subjects who do not undertake regular exercise). Thus, extreme inactivity may play a role in cachexia. This would not seem to fit with the prevalence (one out of four COPD patients suffering from cachexia, as mentioned above) in that disuse atrophy should affect all individuals, not just one out of four, and thus it is not likely to be the only factor involved in cachexia. As with nutritional guidance, instituting a regimen of regular exercise does not cure cachexia *per se*, but just as with nutrition, physical activity is always encouraged (but see below regarding exercise and oxidative stress). Several studies have found that cachectic COPD patients have increased activity of their protein breakdown pathways, in particular the nuclear factor (NF)-κB-activated ubiquitin/proteasomal pathway and apoptosis [26–29]. As stated in an editorial by LEWIS [30], these pathways may be stimulated by inflammatory processes producing increased levels of reactive oxygen species (ROS) and cytokines, such as TNF-α. The key question would seem to be ''what turns on these pathways for increased protein breakdown in some patients and not others?''

Arterial hypoxaemia

It has been suggested that the hypoxaemia of COPD is a causative factor in cachexia. Hypoxaemia may increase the generation of ROS and TNF-α [31], which may in turn give rise to inflammatory changes leading to cachexia. However, the degree of hypoxaemia in COPD is often mild, with arterial oxygen tension (P_{a,O_2}) in the range of 8–9 kPa (60–70 mmHg). Normal individuals residing at modest altitudes of 1,500–3,000 m have similar P_{a,O_2} values, yet do not become cachexic. Many COPD patients with similar degrees of hypoxaemia do not become cachectic, and patients with far lower P_{a,O_2} values, such as in cyanotic congenital heart disease, are not generally cachectic (absent evident cardiac failure). That said, it is well known in climbing circles that even short sojourns by healthy, fit, young subjects to altitudes above about 5,000 m result in inexorable loss of lean body mass. It is also known that arterial hypoxaemia appears to stimulate cytochrome oxidase in patients with COPD in a dose-dependent manner [32]. This suggests that the muscles are responsive to hypoxaemia, at least in terms of this enzyme, and could possibly respond more generally to hypoxia. Finally, hypoxaemia may stimulate the sympathetic nervous system, and this itself has been shown to produce systemic inflammation [33]. Thus, the importance of hypoxaemia as a factor leading to cachexia remains in

question. There are clues to the importance of hypoxaemia, but several findings, as just mentioned, prevent assignment of a clear cause-and-effect relationship between hypoxaemia and cachexia.

Systemic inflammation/oxidative stress

Systemic inflammation has become the primary focus of research into the genesis of cachexia in COPD. There is considerable evidence that this may be important, but there are many gaps in present knowledge that stand in the way of making any definitive statements about the role of inflammation. The molecules receiving the greatest amount of attention are TNF-α, IL-1β, IL-6, C-reactive protein, and ROS and reactive nitrogen species (RNS). There may also be a link between inflammation and low leptin levels [34, 35].

TNF-α is a molecule that has among its effects the upregulation of the transcription factor NF-κB, which in turn upregulates the protein breakdown machinery in cells, providing a molecular mechanism for muscle loss. TNF-α has been measured in circulating plasma of cachectic patients, and the data are shown in table 2. As can be seen, an interesting temporal pattern in TNF-α levels is reported. In 1994, DI FRANCIA *et al.* [36] found large differences between cachectic and noncachectic COPD patients, with very high levels in the former. Five years later, in 1999, TAKABATAKE *et al.* [34] found 10-fold smaller values and only slight differences, as did EID *et al.* [37] in 2001 and also ITOH *et al.* [38] in 2004. Even more recently, reported absolute TNF-α levels appear even lower, and differences between patient groups cannot be seen [14, 39]. The high absolute levels from early studies that fall systematically over time suggest a degree of nonspecificity in the assay in past years. It seems reasonable to suggest that the low levels currently found are likely to be due to improving test specificity. The outcome is that recent studies show no difference in TNF-α levels across cachectic and noncachectic groups of COPD patients. Furthermore, TNF-α polymorphisms have not been identified, despite a search [14]. Finally, a recent clinical trial of short-term anti-TNF-α treatment in general patients with COPD (not limited to cachectic patients) found no effect [40].

TABLE 2 Tumour necrosis factor (TNF)-α blood levels in chronic obstructive pulmonary disease (COPD)

First author [Ref.]	Group	BMI/FFMI	TNF-α pg·mL^{-1}	p-value
DI FRANCIA [36]	COPD	BMI 18.1	70.2	<0.001
	COPD	BMI 26.2	6.7	
TAKABATAKE [34]	COPD	BMI 18.1	6.59	<0.05
	Healthy	BMI 22.8	5.41	
EID [37]	COPD	BMI 21.2	3.2	<0.04
	COPD	BMI 24.4	2.4	
ITOH [38]	COPD	BMI 18.0	6.8	<0.01
	COPD	BMI 24.2	4.3	
BROEKHUIZEN [14]#	COPD	FFMI 14.2	1.35	
	COPD	FFMI 16.9	1.22	
	Healthy	FFMI 20.2	1.23	
	COPD	FFMI 14.5	0.39	
VAN HELVOORT [39]	COPD	FFMI 18.6	0.46	
	Healthy	FFMI 19.7	0.70	

BMI: body mass index; FFMI: free-fat mass index. #: no TNF-α polymorphisms found.

That said, a transgenic mouse model of lung-limited TNF-α overexpression has shown a loss of body weight [18]. This suggests that COPD-related inflammation within the lungs has the potential to contribute to cachexia, presumably *via* systemic release of TNF-α. However, the arithmetic is hard to believe when the mouse response is compared with human findings. Thus, even taking into account, for example, the older data of TAKABATAKE *et al.* [34] showing a 20% higher TNF-α level in patients than in controls, those patients had a 25% lower body weight. In the above-mentioned transgenic mouse study [18], the TNF-α levels were 600% higher than in control mice, but the body weight was just 9% less. These numbers imply that, per unit rise in circulating TNF-α, the weight in humans must be 80-fold more sensitive to TNF-α than in mice, which is hard to believe.

As well as TNF-α, IL-1β has been considered for its role in cachexia [14]. As shown in figure 2, there is a striking association between the -511 CC polymorphism and cachexia, but the same authors assessed circulating IL-1β levels in their subjects and were unable to find measurable levels in any group [14]. This negative finding does not support a role for this molecule, at least in established cachexia.

IL-6 levels have been found to be slightly elevated in cachectic COPD patients [39], a finding that also remains an association rather than indication of cause and effect.

Blood leptin levels may be reduced [34], but whether this applies to all COPD patients or only those with cachexia is not clear from the article by TAKABATAKE *et al.* [34]. It is known that reduced leptin levels are generally associated with weight loss, and high levels with weight gain, but this may be mostly attributable to effects of leptin on fat rather than muscle. In keeping with this concept, SCHOLS *et al.* [41] found that leptin levels were reduced in emphysematous patients with low BMI (leptin 2.6 ng·mL^{-1}; BMI 21.6 kg·m^{-2}), compared with chronic bronchitic patients with higher BMI (leptin 5.1 ng·mL^{-1}; BMI 25.1 kg·m^{-2}). However, fat-free mass was the same in the two groups, and it was the amount of fat that explained the weight differences. It is possible, and even likely, that the reduced leptin levels are the consequence rather than the cause of the lower fat mass. It has also been reported that inflammatory cytokines actually stimulate leptin [42, 43]; ordinarily, this would be expected to raise and not lower weight. Thus, taken together, it does not seem likely that reduced leptin is a major mediator of cachexia as defined by fat-free mass reduction. Conversely, leptin may significantly affect fat mass, and thus BMI, in patients with COPD. This emphasises the mechanistic importance of defining cachexia by fat-free mass.

Oxidative stress is greater in COPD patients than in controls, and the oxidised/reduced glutathione ratio is also increased [44, 45]. Furthermore, exercise training appears to accentuate oxidative stress in COPD [46]. Thus, ROS and/or RNS may play a role in cachexia as molecules capable of incurring tissue

damage. However, these authors [46] found that cachectic patients were able to increase their exercise capacity after training, and by relatively the same amount as noncachectic patients and normal subjects. In this context, it should not be forgotten that ROS can also serve as signalling molecules in the process of adaptation to exercise. It remains a puzzle whether exercise, both acute and repeated (training), is pro- or maladaptive in these patients, and thus whether exercise has positive or negative (or no) effect on quality of life and mortality in cachexia. Of course, as part of a comprehensive rehabilitation programme, exercise does enhance the quality of life in the general COPD population.

Limitations of association studies assessing circulating cytokines

All of the studies examining inflammatory mediators and oxidative stress in patients with COPD are, by necessity: 1) observational, 2) mostly limited to circulating plasma level measurements, and 3) conducted long after cachexia has become evident. These are major limitations to the interpretability of these studies.

It is entirely possible that the quoted results are, biologically and not statistically speaking, falsely positive in terms of cause and effect when differences between cachectic and noncachectic patients are found. Similarly, it is entirely possible that the results are biologically falsely negative when no differences are found. This may be for the simple reason that circulating levels may not reflect concentrations in skeletal myocytes, where the cachectic process takes place. It may also be the case that inflammation is important in the pathogenesis of cachexia, but only early on in the process. Thus, by the time cachexia is evident, the major steps in the process are complete, and blood levels of cytokines may no longer have a relationship with the myopathic state. It is also possible that associations found between cytokines and cachexia are not related by cause and effect. However, even if they do turn out to have a cause-and-effect relationship, it may be that cachexia explains the cytokine patterns rather than the possibility that the cytokine levels explain cachexia. It is critical to keep these limitations in mind when evaluating reports of cytokine measurements. The conclusion that must be reached regarding the role of inflammation in causing cachexia in patients with COPD is that it remains unknown. The good news is that there are plenty of tantalising correlations to allow good hypotheses to be advanced; the challenge is to design feasible and ethical studies with which to test cause and effect.

Hormonal insufficiency

There is evidence that insufficiency of one or more of three hormones may contribute to cachexia. CREUTZBERG and CASABURI [47] provide a succinct overview of endocrine factors in COPD. These hormones are testosterone, growth hormone and insulin-like growth factor. Observational studies in cachectic COPD patients have found diminished circulating levels of these hormones [48, 49]. These hormones may be a rational choice for factors contributing to cachexia but, as stated above, this does not mean that observed associations prove cause and effect. Much more research will be required to establish this association. While increased thyroid activity could lead to weight loss, there is no evidence that this happens systematically in COPD [47].

Ghrelin, a naturally occurring growth hormone-releasing peptide, has been found to be increased in cachectic COPD patients [38], although the relationship is not statistically strong (R^2=0.14). At first sight, high ghrelin levels should promote weight gain, which by definition has not occurred in these patients. Perhaps the elevated levels represent a feedback loop in response to low growth hormone levels, signalling a need which cannot be met and whose components have yet to be identified.

Accelerated ageing as a factor contributing to cachexia in COPD

It is possible that some otherwise normal subjects undergo accelerated ageing. Since ageing is associated with loss of lean body mass [50], it is possible that those subjects with COPD who develop cachexia are those who, in the absence of their disease, would have shown accelerated ageing and loss of lean body mass. Therefore, this hypothesis does not depend on cigarette smoking. However, the prevalence of cachexia (in normal subjects in the 60–75-yr-old age group in which COPD is most commonly studied) as defined by an LBMI <16 kg·m^{-2} in males and <15 kg·m^{-2} in females is likely to be lower that that in COPD. This would suggest that accelerated ageing *per se* (independently of smoking) may not account for much of the cachexia that is seen in COPD patients.

Conversely, several studies have shown that tobacco smoke exposure leads to accelerated senescence of pulmonary fibroblasts [51–54]. While this does not prove that similar effects occur in muscle and are responsible for reduced lean body mass, it does demonstrate mechanisms of accelerated cell senescence in smokers that might eventually be shown to contribute to cachexia. It leaves open the question of why only some patients develop cachexia if cigarette smoke universally accelerates cell senescence.

PATHOGENETIC INSIGHTS FROM THERAPEUTIC INTERVENTIONS

Many different approaches to treating cachexia have been attempted, and are listed in table 3. They are briefly reviewed herein, not for clinical recommendations but rather for the light they shed on pathogenetic mechanisms of cachexia development.

Active nutritional support and appetite stimulation

SCHOLS [23] has long advocated for nutritional support (including vitamins and antioxidants) as part of an integrated approach to the patient with COPD, especially when cachectic. While it is likely that nobody would argue against this, the improvement provided by dietary modification has been somewhat inconsistent. Even when appetite stimulants are used, the net result has been modest [49]. Whether attention to diet would be more effective earlier in the course of disease, before cachexia had developed, remains to be tested. Indeed, this comment applies to all of the treatments listed in table 3.

Exercise training

Exercise training has always been regarded somewhat like nutritional support: an obvious adjunct to therapy in chronic

TABLE 3 Therapeutic interventions

Nutrition
Active nutritional support
Appetite stimulation
Exercise
Oxygen
Anti-inflammatory drugs
Specific cytokine targets
Antioxidants
Inhaled steroids and bronchodilators
Anabolic hormones
Growth hormone (ghrelin)
Insulin-like growth factor
Nandrolone
Oxandrolone
Other treatments (tested or suggested)
Melanocortin-4 antagonists
Angiotensin-converting enzyme inhibitors
β-Blockade
Noninvasive positive pressure ventilation
Creatine
Omega-3 fatty acids
Ubiquitin/proteasome inhibition

diseases of most types, especially those associated with weight loss. However, recent findings have suggested that exercise creates an oxidative stress challenge [45, 46] that COPD patients may not be able to deal with. Markers of oxidative stress are increased by exercise, as are those for lipid peroxidation, indicating cell membrane damage. At the same time, antioxidant state is depressed in these patients, and cytokines such as IL-6 are elevated in the plasma. The implication of these studies is that exercise training may prove disadvantageous in the long term. This must be balanced against the findings that exercise training does in fact lead to a substantial improvement in exercise capacity, even in cachectic patients. The relative magnitude of these gains is similar to that seen from training of normal age-matched subjects. It will be important to determine if training improves or worsens either quality of life or mortality, given the significantly higher mortality rate in cachectic in comparison with noncachectic COPD patients (fig. 1).

Correcting arterial hypoxaemia with supplemental oxygen

Whether preventing arterial hypoxaemia has any influence on either the development or reversal of cachexia is not known, and it will take substantial prospective cohort studies to answer this question. If oxygen were found to be of benefit, it would be a relatively simple and cost-effective approach to treating a disease where supplemental oxygen is already frequently used, albeit mainly to decelerate the development of pulmonary hypertension and cor pulmonale.

Anti-inflammatory drugs

Several approaches using anti-inflammatory drugs have been tried, or at least proposed for formal trial. The antioxidant *N*-acetyl cysteine has been found to reduce oxidative stress markers and, at the same time, to improve exercise endurance time [44]. This study was of quite a short duration did not address weight changes, and longer term trials of this generally benign and promising drug may be warranted.

Reducing proteasomal protein degradation has been suggested as a therapeutic target. A proposal has been advanced to use eicosapentanoic acid to reduce proteolysis inducing factor [55], but no study has been reported yet. Similarly, advocates of the theory of heightened hypoxia-induced sympathetic activation have proposed a study of β-sympathetic blockade [33], but this has also not been reported. Of course, β-blockade is well known to be a concern in diseases of airways obstruction because of the risk of bronchoconstriction.

Finally, it has been proposed to study inhaled steroids and bronchodilators as modulators of inflammation and, thereby, as agents to prevent or reverse cachexia [56].

Anabolic hormones

Treatment with growth hormone and insulin-like growth factor have been studied in COPD patients [57]. The outcomes have been mixed in that while fat-free body mass was increased, no accompanying benefits to skeletal muscle function were detected [57]. In a similar approach, nandrolone [48] and oxandrolone [58] have also been studied, with very similar outcomes: increased fat-free mass but no increase in muscle strength.

In the context of growth hormones, mention should be made of ghrelin, a growth hormone-releasing factor. Ghrelin has been found to increase fat free body mass and increase the distance patients can cover in the 6-min walk test [59, 60].

Ancillary treatments

Noninvasive positive pressure ventilation appears to result in a gain in total body mass [21]. Whether the mechanism is based on reduced work of breathing and, thus, on enhanced energy balance is unclear. The authors also report only on total body mass, and not fat-free mass. Creatine supplementation has been reported to produce increased fat-free mass and also to lead to improved muscle strength [61]. This single report in ~20 patients needs to be repeated by others and confirmed, as

TABLE 4 Major research gaps in the treatment of cachexia

Why do only some patients become cachectic?
What are the genetic and environmental factors underlying cachexia susceptibility?
What initiates the cachexia process?
What are the sequential molecular steps?
What is the role for nutritional enhancement?
What is the role for supplemental oxygen?
Will suppression of inflammation prevent cachexia?
Will suppression of inflammation reverse cachexia?
What is the role for anabolic hormones?
Is exercise training harmful or beneficial?
What roles do comorbidities play in:
Susceptibility to cachexia?
Development of cachexia?
Management of cachexia?

it describes another relatively simple approach with promising preliminary findings. Based on animal studies [62], melanocortin-4 inhibitors have been proposed, but not yet studied. Omega-3 fatty acids have also been proposed but not yet tested [63]. That said, there is some evidence that a diet rich in omega-3 polyunsaturated fatty acids A and B improves skeletal muscle function in COPD [62, 63]. The basis of their action is thought to be in their anti-inflammatory effects, but in the two studies [62, 63], a reduction in cytokine levels was found in one but not the other. It is also noteworthy that while these studies were not designed to address cachexia *per se*, they found no effect on body composition compared with patients treated similarly except for diet. Finally, angiotensin-converting enzyme inhibition has also been suggested as a treatment for cachexia, but remains to be investigated [59].

What all of these therapeutic approaches show is that many different pathways could affect the development of cachexia in COPD. All have been studied or proposed based on a physiological rationale that is generally clear and comes from pilot data or animal studies of possible responsible mechanisms.

Limitations of studies assessing therapeutic responses

Just as with the cautions applied to interpreting human data associating cellular or molecular findings with cachexia, interpreting responses to these many therapies also requires caution. A negative effect may mean that a beneficial approach was attempted too late in the course of disease, in an insufficient dose, for insufficient duration, or as an isolated drug trial without adding in the several other factors that rehabilitation studies have indicated are important to foster, such as education, activity, diet, *etc*. A positive result may look encouraging, and speaking empirically that may be the case. However, the burden of proof falls to the investigator to tie any positive result to the basic mechanism of cachexia in the first place. A given treatment may possibly work by ''supersizing'' a parallel process that is normal, rather than by restoring the primary abnormal process, which may well remain ''broken''. Again, as with all new therapies, long-term negative side-effects cannot be ignored.

MAJOR RESEARCH GAPS

The present brief review has examined research findings concerning mechanisms of cachexia in chronic obstructive pulmonary disease based on a variety of studies. Some have associated biomarkers with cachexia, others have taken a genetics approach, and still others are based on therapeutic responses to experimental treatments. It seems fair to say that today, the full story is still not known and, as a result, there are many important research gaps remaining to be filled; those seen to be most important are summarised in table 4. It is hoped that these questions will be pursued in the coming years and that their answers will lead us to a better understanding and, as a result, management of cachexia in chronic obstructive pulmonary disease.

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