Eur Respir J 2008; 31: 204–212
DOI: 10.1183/09031936.00114307

SERIES "COMPREHENSIVE MANAGEMENT OF END-STAGE COPD"
Edited by N. Ambrosino and R. Goldstein
Number 2 in this Series

Complex chronic comorbidities of COPD

L.M. Fabbri*, F. Luppi*, B. Beghé* and K.F. Rabe#

ABSTRACT: Chronic obstructive pulmonary disease (COPD) is defined by fixed airflow limitation associated with an abnormal pulmonary and systemic inflammatory response of the lungs to cigarette smoke.

The systemic inflammation induced by smoking may also cause chronic heart failure, metabolic syndrome and other chronic diseases, which may contribute to the clinical manifestations and natural history of COPD. Thus COPD can no longer be considered a disease only of the lungs, as it is often associated with a wide variety of systemic consequences.

A better understanding of the origin and consequences of systemic inflammation, and of potential therapies, will most likely lead to better care of patients with COPD. Medical textbooks and clinical guidelines still largely ignore the fact that COPD seldom occurs in isolation.

As the diagnosis and assessment of severity of COPD may be greatly affected by the presence of comorbid conditions, the current authors believe that lung function measurement, noninvasive assessment of cardiovascular and metabolic functions, and circulating inflammatory markers (*e.g.* C-reactive protein) might help to better characterise these patients. Similarly, preventive and therapeutic interventions should address the patient in their complexity.

KEYWORDS: Bronchitis, chronic diseases, chronic heart failure, emphysema, inflammation, metabolic syndrome

Ageing is commonly characterised as a progressive, generalised impairment of function resulting in an increasing vulnerability to environmental challenge and a growing risk of disease. Ageing is highly complex, involving multiple mechanisms at different levels. Current theoretical understanding suggests that cells tend to accumulate damage as they age. Such damage is intrinsically random in nature, but its rate of accumulation is regulated by genetic mechanisms for maintenance and repair. As cell defects accumulate, the effects on the body as a whole are eventually revealed as age-related frailty, disability and disease [1, 2].

Therefore, ageing of the population increases the prevalence of chronic diseases, which represent a huge proportion of human illness. They include cardiovascular disease (30% of projected total worldwide deaths in 2005), cancer (13%), diabetes (2%) and chronic respiratory diseases (7%), mainly chronic obstructive pulmonary disease (COPD) [3].

COPD is a disease state characterised by poorly reversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke [4]. COPD should be considered in any smoker aged >40 yrs with symptoms of cough, sputum production or dyspnoea, and spirometry should be used to evaluate the degree of airflow limitation [4]. However, because there is increasing evidence that COPD is a more complex systemic disease than an airway and lung disease, a comprehensive approach including imaging [5], exercise tolerance and body mass index [6] may be required for an earlier diagnosis and better assessment of the disease.

Cigarette smoking is the major risk factor of COPD and is also one of the major risk factors of all chronic diseases and cancer [7, 8]. Cigarette smoke causes lung and systemic inflammation, systemic oxidative stress, marked changes of vasomotor and endothelial function and

AFFILIATIONS
*Dept of Oncology, Haematology and Respiratory Diseases, University of Modena and Reggio Emilia, Modena, and
#Dept of Pulmonology, Leiden University Medical Center, The Netherlands.

CORRESPONDENCE
L.M. Fabbri
Dept of Oncology
Haematology and Respiratory Diseases
University of Modena and Reggio Emilia
Via del Pozzo 71
41100 Modena
Italy
Fax: 39 0594224231
E-mail: fabbri.leonardo@unimore.it

Received:
August 31 2007
Accepted after revision:
September 11 2007

SUPPORT STATEMENT
This study was supported by the Associazione per la Ricerca e la Cura dell'Asma (Padua, Italy), the Consorzio Ferrara Ricerche (Ferrara, Italy) and the Associazione per lo Studio dei Tumori e delle Malattie Polmonari (Padova, Italy).

STATEMENT OF INTEREST
Statements of interest for L.M. Fabbri and K.F. Rabe can be found at www.erj.ersjournals.co.uk/misc/statements.shtml

Previous articles in this series: No. 1: Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007; 30: 993–1013.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

enhanced circulating concentrations of several pro-coagulant factors [9–11]. The systemic effects of smoking may significantly contribute not only to respiratory abnormalities, symptoms and functional impairment (*e.g.* exercise intolerance) associated with COPD [12–15] but also to its chronic comorbidities [12, 16–19]. In particular, cachexia [20], skeletal muscle abnormalities [15, 21, 22], hypertension [23, 24], diabetes [25], coronary artery disease [26–28], heart failure [29], pulmonary infections [30–34], cancer [35, 36] and pulmonary vascular disease [37] are the most common comorbidities responsible for the clinical manifestations and natural history of COPD [17, 18]. In addition to smoking, the other major risk factor for cardiovascular and other chronic comorbid conditions is obesity [38, 39]. Although obesity by itself may profoundly affect lung function [40], its relationship with COPD has been poorly investigated and is still unclear [41]. Smoking and obesity are the major risk factors for the complex chronic comorbidities seen throughout the world [42–44]. Obese individuals who smoke have a markedly reduced life expectancy [38, 45]. The two risk factors may interact synergistically, since both obesity and smoking are associated with insulin resistance, oxidative stress and increased concentrations of various (adipo)cytokines and inflammatory markers, all of which ultimately lead to endothelial dysfunction and cardiovascular diseases [46].

Comorbidities markedly affect health outcomes in COPD [16]; in fact, patients with COPD mainly die of nonrespiratory diseases [47–50], such as cardiovascular diseases (~25%), cancer (mainly lung cancer, 20–33%) and other causes (30%). Respiratory diseases, mainly respiratory failure due to COPD exacerbations, account for 4–35% of deaths, primarily in patients with severe COPD. The wide range of deaths attributable to respiratory diseases may be due to: different criteria used in different populations; the severity of COPD in the population examined [48, 50, 51]; or to under-reporting of respiratory conditions on the death certificate [51, 52].

Considering that the pharmacological treatment of COPD to date is primarily symptomatic, a more comprehensive approach to comorbidities may provide an opportunity to modify the natural history of patients with COPD and to identify novel targets for treatment. This is particularly relevant for those conditions that appear more preventable and treatable than COPD, such as cardiovascular and metabolic disorders.

COMPLEX CHRONIC COMORBIDITIES

Chronic diseases, including cardiovascular disease, cancer, chronic respiratory diseases and metabolic syndrome (hypertension, diabetes, dyslipidaemia) [3, 43], are increasing in the developed countries and result in a substantial economic and social burden [3, 42, 43]. The cost of individual chronic diseases increases exponentially in patients with two or more comorbid chronic diseases [53]; almost half of all elderly people (≥65 yrs) have at least three chronic medical conditions, and one fifth have five or more [54]. Patients with two or more chronic diseases account for only 26% of the population but for >50% of the overall costs [53].

The most frequent chronic diseases often develop together [13, 16, 24, 27, 48, 54–59]. COPD is associated with chronic heart failure (CHF) in ≥20% of patients [29, 60]; there is overwhelming evidence from large-scale epidemiological studies demonstrating that impaired forced expiratory volume in one second is a powerful marker of morbidity and mortality [61] and, particularly, of cardiovascular mortality [62]. Interestingly, increased arterial stiffness is also related to the severity of airflow obstruction and may be a factor in the excess risk for cardiovascular disease in COPD [63]. Patients with severe COPD have elevated circulating levels of C-reactive protein (CRP) [64]. A working hypothesis to account for the high prevalence of left ventricular systolic dysfunction in patients with COPD is that low-grade systemic inflammation accelerates progression of coronary atherosclerosis, which ultimately results in ischemic cardiomyopathy. Such a hypothesis fits the clinical observation of a high incidence of left ventricular wall motion abnormalities noted in patients with COPD and left ventricular dysfunction [64].

Metabolic syndrome is a complex disorder and an emerging clinical challenge, recognised clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidaemia, elevated blood pressure, high blood glucose and/or insulin resistance [65]. Metabolic syndrome is also associated with a pro-thrombotic state and a pro-inflammatory state. Central pathophysiological features of metabolic syndrome include: 1) insulin resistance; 2) atherogenic dyslipidaemia; 3) arterial hypertension, which occurs frequently in individuals with insulin resistance; 4) a pro-inflammatory state, with increases in acute-phase reactants (*e.g.* CRP); and 5) a pro-thrombotic state, with increases in plasminogen activator inhibitor and fibrinogen [65]. Patients with COPD often have one or more component of the metabolic syndrome [66] and osteoporosis (≤70% of patients) which are at least, in part, independent of treatment with steroids and/or decreased physical activity [63, 67]. Even when a specific single chronic comorbidity cannot be diagnosed according to the current criteria, COPD is often associated with a marker of chronic diseases, *e.g.* decreased tolerance to glucose, hypertension or decreased bone density [63, 68].

Type 2 diabetes is associated with hypertension in >70% of patients, and with cardiovascular diseases and obesity in >80% [69]. Diabetes is independently associated with reduced lung function [70, 71], which, together with obesity, may further worsen the severity of COPD [41].

UNDERLYING MECHANISMS AND CONSEQUENCES FOR TREATMENT OF COMPLEX CHRONIC COMORBIDITIES

COPD can no longer be considered a disease only of the lungs [17, 18, 72]. It is associated with a wide variety of systemic consequences, most notably systemic inflammation (fig. 1). A better understanding of its origin, consequences and potential therapy will most likely prove to be of great relevance and lead to better care of patients with COPD. The origin of systemic inflammation in COPD is unresolved, although several potential mechanisms have been proposed [12].

Since smoking remains the major risk factor for the development of COPD and of the associated systemic inflammation [72], the study of the effects of smoking represents the best model for unravelling the underlying mechanisms of COPD

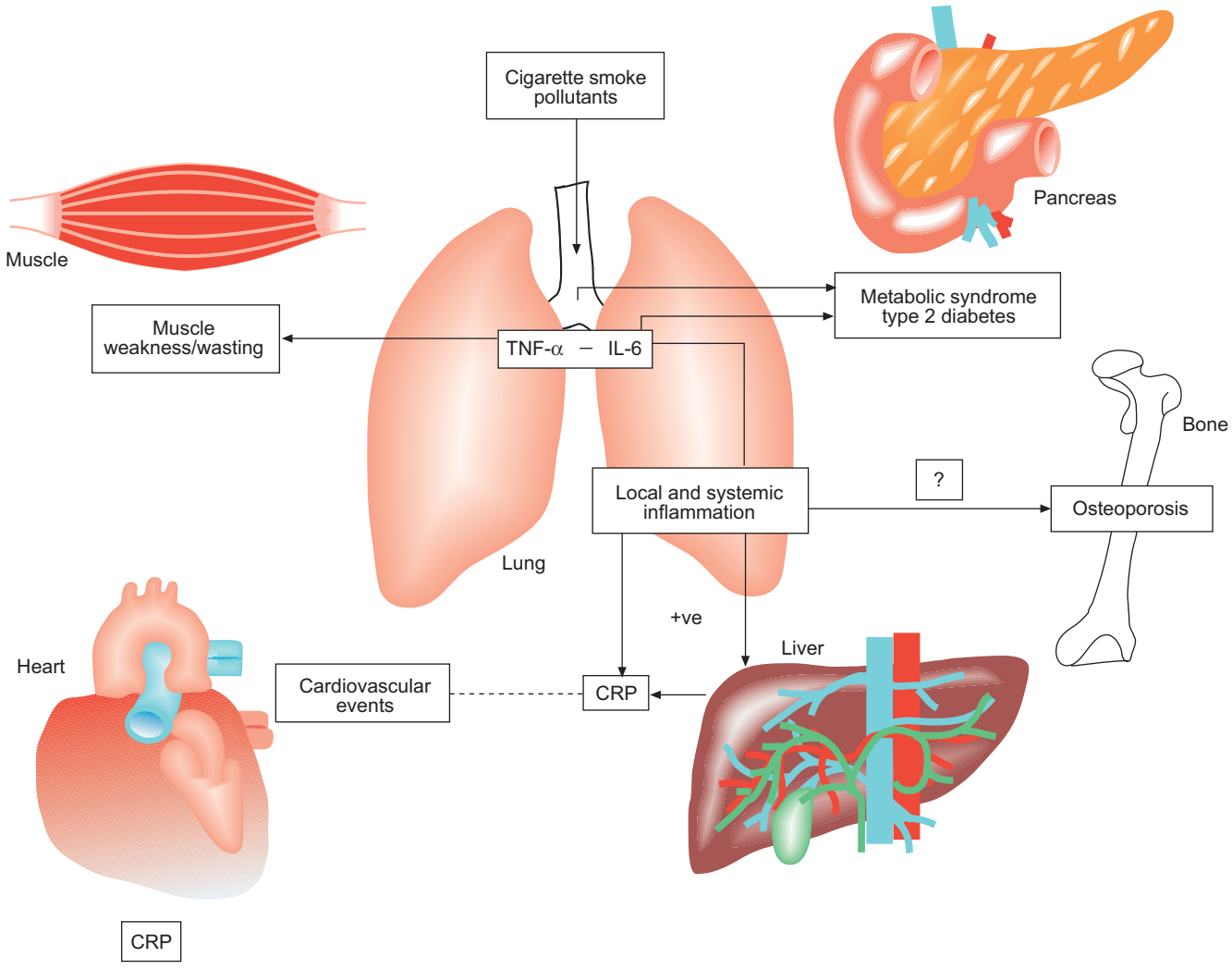

FIGURE 1. The central role of inflammation in comorbidity is associated with chronic obstructive pulmonary disease (COPD). Inflammation appears to play a central role in the pathogenesis of COPD and other conditions that are increasingly being recognised as systemic inflammatory diseases. As part of the chronic inflammatory process, tumour necrosis factor (TNF)-α receptor polymorphisms are associated with increased severity of disease, possibly due to enhanced TNF-α effects. Also, C-reactive protein (CRP) levels can be increased directly by TNF-α and other cytokines. Elevated CRP and fibrinogen may be crucial in the pathogenesis of cardiovascular disease. Reactive oxygen species released as a result of COPD may enhance the likelihood of a patient developing cardiovascular disease, diabetes and osteoporosis. IL: interleukin; ?: unknown; +ve: positive.

and the consequences of systemic inflammation induced by smoking. In fact, cigarette smoke may cause systemic inflammation irrespective of COPD [73], and systemic inflammation in smokers may contribute significantly to the development of cardiovascular diseases, particularly atherosclerosis [74].

Smoking and acute exacerbations of COPD have a marked influence on redox status [75] by increasing levels of lipid peroxidation products and other markers [76]. The increase in oxidative stress results in the inactivation of antiproteases, airspace epithelial damage, mucus hypersecretion, increased influx of neutrophils into lung tissue and the expression of pro-inflammatory mediators [77, 78]. Inflammatory cells are also increased in peripheral blood, including neutrophils and lymphocytes [79]. Furthermore, patients with COPD have increased numbers of neutrophils in the lungs, increased activation of neutrophils in peripheral blood and an increase in tumour necrosis factor (TNF)-α and soluble TNF receptor. Activated T-cells in emphysematous lungs predominantly express a T-helper cell type-1 phenotype and control the release of matrix metalloproteases *via* chemokines. Recent evidence, obtained through *ex vivo* experiments with T-cells from COPD patients, suggests that exposure to cigarette smoke induces secretion of proteolytic enzymes from cells of the innate immune system, which in turn liberate lung elastin fragments [80]. In susceptible individuals, T- and B-cell-mediated immunity against elastin is initiated. Elastin is also abundant in tissues other than the lung, especially in arteries, arterioles and the skin; its fragments are chemotactic and cause pathology in mouse models of emphysema. These novel findings of anti-elastin autoimmunity in emphysema, together with earlier observations [81–84], suggest a broader, systemic autoimmune process involving the major elastin-bearing organs, such as the (coronary) vasculature and the skin.

To understand the relationship between pulmonary inflammation and systemic disease, common inflammatory pathways have been proposed [19]. It is unclear why some patients with COPD have higher baseline concentrations of circulating inflammatory markers [85]; whether this systemic inflammation is a primary or secondary phenomenon is a matter of debate. Some patients with COPD who exhibit increased resting energy expenditure and decreased fat-free mass have marked elevation of CRP and lipopolysaccharide-binding protein [86]. Systemic inflammation may lead to a lack of response to nutritional supplementation [87], further contributing to the development of cachexia.

Systemic inflammation may also explain why patients with COPD have an increased risk of developing type 2 diabetes [88]. Some aspects of inflammation can predict the development of diabetes and glucose disorders [89, 90], while fibrinogen, circulating white blood cell count and lower serum albumin predict the development of type 2 diabetes [89]. Furthermore, patients with noninsulin-dependent diabetes mellitus have increased circulating levels of TNF-α, interleukin (IL)-6 and CRP [91], which are also risk factors for cardiovascular events in males and females [92, 93]. Diabetes is independently associated with reduced lung function, which together with obesity could further worsen the severity of COPD [41]. The complex interaction between smoking and obesity in the development of chronic comorbidities has been recently reviewed (fig. 2) [46].

Patients with COPD have an increased risk of developing osteoporosis even in the absence of steroid use; vertebral fractures are present in $\leqslant$50% of steroid-naïve males with COPD [94]. Post-menopausal osteoporosis is related to high serum levels of TNF-α and IL-6 [95], and osteopenia found in COPD is also associated with an increase in circulating TNF-α [96]. Increased levels of TNF-α (and IL-1) stimulate the differentiation of macrophages into osteoclasts *via* mesenchymal cells releasing receptor activator of nuclear factor-κB ligand, a member of the TNF-α superfamily [97].

The development of inflammatory processes associated with COPD is commonly believed to be initiated and maintained in the lung (parenchyma) [98] and to affect peripheral organs as the disease progresses. This concept is not proven and is probably rather naïvely related to the fact that the major risk factors for COPD enter the body by inhalation. To date, the limited data published on the contribution of the systemic circulation to the priming and activation of inflammatory cells in their transit through the pulmonary circulation [99, 100] have been negative, because the concentrations of inflammatory markers in induced sputum (presumably reflecting local inflammation) and plasma (reflecting systemic inflammation) in patients with moderate COPD are not correlated.

Alternatively, some of the nonpulmonary manifestations of COPD may occur early in the course of the disease and affect pulmonary inflammation. For example, inhibition of vascular endothelial growth factor (VEGF) receptors causes lung cell apoptosis and emphysema [101, 102]. Furthermore, endothelial cell death and decreased expression of VEGF and the VEGF receptor KDR/FLK-1 occur in patients with smoking-induced emphysema [103]. In summary, systemic oxidative stress [75] and the increased levels of pro-inflammatory cytokines could contribute to the pathogenesis of lung damage in COPD early in the course of the disease.

Tissue hypoxia is another mechanism that can contribute to systemic inflammation in COPD. In a recent clinical study [104] it was shown that TNF-α and receptor levels were significantly higher in patients with COPD, but were significantly correlated with the severity of arterial hypoxaemia. These results suggest that arterial hypoxaemia in COPD is associated with activation of the TNF-α system *in vivo*. If confirmed, this might indeed change the whole view on long-term oxygen therapy. Prolonged survival in patients receiving domiciliary oxygen therapy, as described many years ago [105, 106], might be attributable to an effect on systemic inflammation. This hypothesis could be tested in randomised trials.

Skeletal muscle itself can contribute to systemic inflammation. In particular, this has been demonstrated in patients with COPD during exercise [107, 108]. Physical exercise specifically increases plasma TNF-α levels in COPD [109]. TNF-α has a variety of effects that could lead to muscle wasting [110]. TNF-α effects are mediated by the transcription factor nuclear factor (NF)-κB, which is normally inactive but can be activated by inflammatory cytokines such as TNF-α [96]. Different mechanisms by which TNF-α could induce muscle loss have been described previously, including direct stimulation of protein loss, apoptosis of muscle cells and oxidative stress-induced alteration in TNF-α/NF-κB signalling [111]. Inflammation and oxidative stress, characteristic of COPD [112], have synergistic effects on muscle breakdown [113].

Under conditions of nutritional imbalance, resting energy requirements are normally reduced [114]. This is in contrast to the increased resting energy expenditure that is characteristic of some patients with COPD; the discrepancy is believed to be linked to systemic inflammation [86, 115]. Increased oxygen consumption by respiratory muscles seems an incomplete explanation on its own [100], and as nutritional intake in stable disease is, on the whole, sufficient, generally accelerated loss of skeletal muscle in the context of a chronic inflammatory response is the most likely explanation [116]. This loss of muscle is not specific to COPD but is generally found in states of cachexia with enhanced protein degradation [117] and poor responsiveness to nutritional interventions [118, 119]; it also displays similarities to CHF, renal failure, AIDS and cancer.

Finally, bone marrow is an obvious site of production of systemic inflammation, although knowledge of its role in patients with COPD is sparse. Smoking causes leukocytosis with increased numbers of band cells, a higher content of myeloperoxidase and enhanced surface expression of L-selectin [73]. Furthermore, these sequestrated polymorphonuclear leukocytes can be found in lung microvessels [120], supporting the concept that the bone marrow may directly contribute to smoking-induced lung inflammation.

MANAGEMENT OF COPD AS A COMPLEX DISEASE

Although textbooks [121] and guidelines have increasingly recognised the frequency and importance of comorbidities, particularly in the elderly, the fact that chronic diseases seldom occur in isolation is still largely ignore [4, 122, 123]. Thus, clinicians treating chronic diseases lack definitions and a

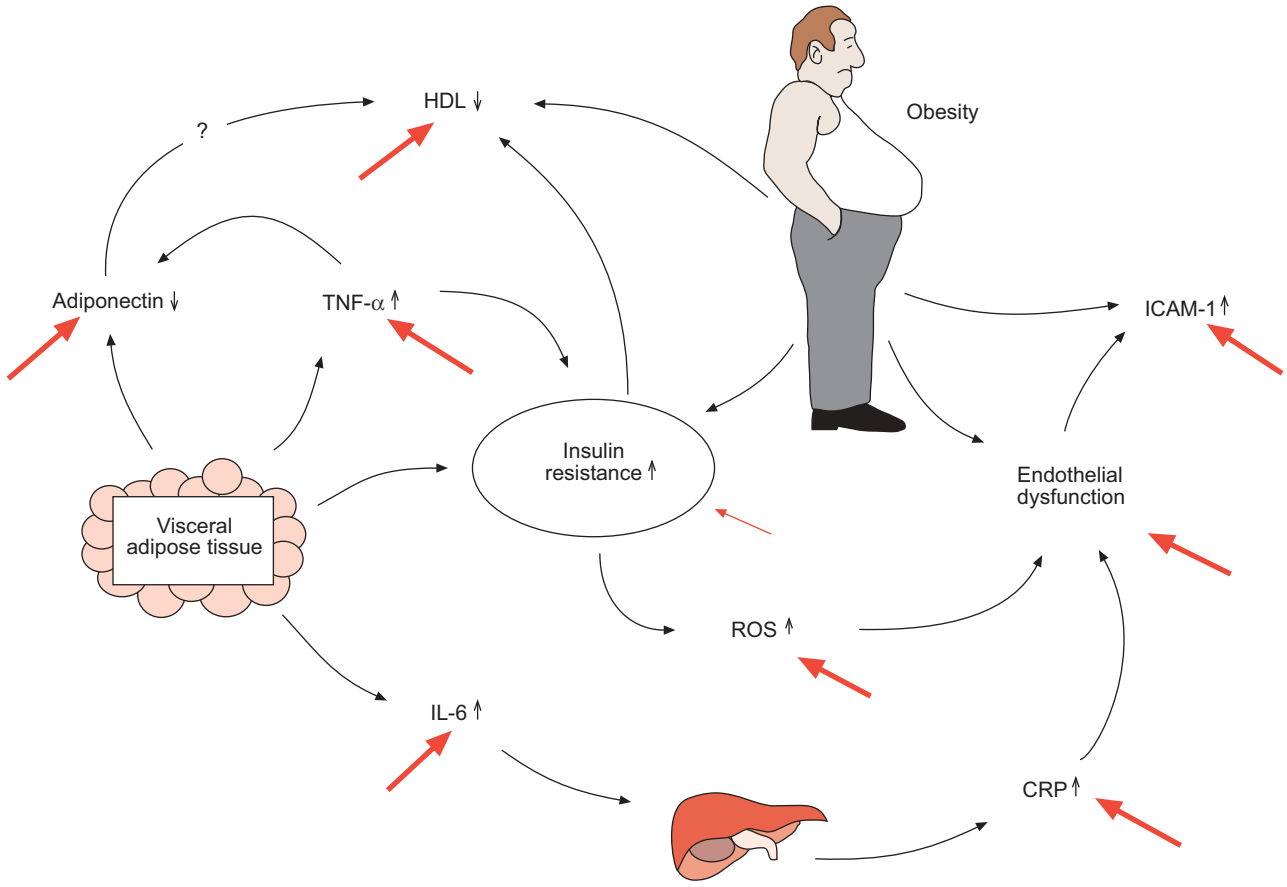

FIGURE 2. Schematic representation of how smoking might add to several mechanisms linking obesity to cardiovascular disease. Red arrows indicate an effect of smoking. HDL: high-density lipoprotein; TNF: tumour necrosis factor; ICAM: intercellular adhesion molecule; ROS: reactive oxygen species; IL: interleukin; CRP: C-reactive protein. Reproduced with permission from [46].

vocabulary to describe a syndrome that reflects real-life bedside medicine, not the medicines that have been taught [121]. Recently, FABBRI and RABE [124] suggested adding the term ''chronic systemic inflammatory syndrome'' to the diagnosis of COPD to reflect the complexity of the problem.

The diagnosis and assessment of severity of COPD may be greatly affected by the presence of a comorbid condition; therefore, lung function measurement, noninvasive assessment of left ventricular function (*e.g.* echocardiography and brain natriuretic peptide) and/or glycaemia, such as CRP serum levels, should be performed in these patients.

Considerations almost identical to those mentioned previously can obviously be applied to preventive and therapeutic interventions. Smoking prevention and cessation, weight control and diet, and exercise and rehabilitation all have the potential to beneficially affect all components of chronic disease.

Pharmacological treatment is more complex, as drugs are usually developed for single diseases or organs. However, glucose control with insulin or oral antidiabetic agents not only controls diabetes but also prevents systemic effects and comorbidities [123]. Likewise, antihypertensive agents not only help control blood pressure but are also associated with dramatic prevention of coronary and cerebrovascular disease, with marked reduction of mortality [125]. More recently, these agents have been found to have unexpected beneficial effects on COPD. Statins, which are used primarily as lipid-lowering agents in the treatment of metabolic syndrome, have potent anti-inflammatory properties that might positively affect comorbidities of metabolic syndrome, *e.g.* COPD, CHF and vascular diseases [126–128]. However, on the negative side, β-blockers, which are considered to be life-saving drugs in CHF, might have some risks in COPD patients who have an asthmatic component [129]. Furthermore, systemic steroids, which are required to treat COPD exacerbations [130], might negatively affect glucose control and cause osteoporosis and hypertension [131]. Even drugs specifically developed and used to treat respiratory diseases, such as inhaled bronchodilators and steroids, may have significant beneficial effects on cardiovascular diseases [132, 133].

SINGLE-DISEASE *VERSUS* PATIENT-ORIENTED GUIDELINES FOR CHRONIC DISEASES

Clinical practice guidelines are being increasingly used as performance indicators, and have been shown to substantially improve the quality of clinical care. However, most guidelines ignore the fact that the majority of individuals with a chronic disease have one or more comorbidities.

COPD, CHF, peripheral artery disease, diabetes or nonlife-threatening cancer can have a major impact on individuals

with a chronic disease, particularly the elderly [14]. Therefore, it is evident that clinical practice guidelines, designed largely by specialty-dominated committees for managing single diseases, provide clinicians with little guidance in caring for patients with multiple chronic diseases. This lack of guidance frequently results in polypharmacia in these patients.

It is not only clinicians who will have to change their approach to treating chronic diseases; it is also the healthcare system in general that must rise to this major challenge.

ACKNOWLEDGEMENTS

The authors would like to thank M. McKenney (Menominee, MI, USA) for scientific assistance with the manuscript, and E. Veratelli (University of Modena and Reggio Emilia, Modena, Italy) for scientific secretarial assistance.

REFERENCES

1 Hadley EC, Lakatta EG, Morrison-Bogorad M, Warner HR, Hodes RJ. The future of aging therapies. *Cell* 2005; 120: 557–567.
2 Kirkwood TB. Understanding the odd science of aging. *Cell* 2005; 120: 437–447.
3 Horton R. The neglected epidemic of chronic disease. *Lancet* 2005; 366: 1514.
4 Rabe KF, Hurd S, Anzueto A, *et al.* Global Strategy for the diagnosis, management, and prevention of COPD: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.
5 Omori H, Nakashima R, Otsuka N, *et al.* Emphysema detected by lung cancer screening with low-dose spiral CT: prevalence, and correlation with smoking habits and pulmonary function in Japanese male subjects. *Respirology* 2006; 11: 205–210.
6 Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
7 Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003; 362: 847–852.
8 Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. *Thorax* 2006; 61: 472–477.
9 MacCallum PK. Markers of hemostasis and systemic inflammation in heart disease and atherosclerosis in smokers. *Proc Am Thorac Soc* 2005; 2: 34–43.
10 MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 50–60.
11 van Eeden SF, Yeung A, Quinlam K, Hogg JC. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 61–67.
12 Agusti A. Thomas A. Neff lecture. Chronic obstructive pulmonary disease: a systemic disease. *Proc Am Thorac Soc* 2006; 3: 478–481.
13 Kriegsman DM, Deeg DJ, Stalman WA. Comorbidity of somatic chronic diseases and decline in physical functioning: the Longitudinal Aging Study Amsterdam. *J Clin Epidemiol* 2004; 57: 55–65.
14 Di Fazio I, Franzoni S, Frisoni GB, *et al.* Predictive role of single diseases and their combination on recovery of balance and gait in disabled elderly patients. *J Am Med Dir Assoc* 2006; 7: 208–211.
15 Balasubramanian VP, Varkey B. Chronic obstructive pulmonary disease: effects beyond the lungs. *Curr Opin Pulm Med* 2006; 12: 106–112.
16 Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.
17 Fabbri LM, Ferrari R. Chronic disease in the elderly: back to the future of internal medicine. *Breathe* 2006; 3: 40–49.
18 Fabbri LM, Rabe KF. Complexity of patients with multiple chronic diseases. Proceedings of an ERS Research Seminar (Rome, February 11–12, 2007). www.ersnet.org/ers/lr/browse/default.aspx?id_dossier=67422 Date last accessed: October 31, 2007.
19 Sevenoaks MJ, Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity–a common inflammatory phenotype? *Respir Res* 2006; 7: 70.
20 Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006; 83: 735–743.
21 Maltais F. Skeletal muscles in chronic airflow obstruction: why bother? *Am J Respir Crit Care Med* 2003; 168: 916–917.
22 Orozco-Levi M. Structure and function of the respiratory muscles in patients with chronic obstructive pulmonary disease: impairment or adaptation? *Eur Respir J* 2003; 22: Suppl. 46, 41s–51s.
23 Taichman DB, Mandel J. Epidemiology of pulmonary arterial hypertension. *Clin Chest Med 2007;28*, 1–22: vii.
24 Wang PS, Avorn J, Brookhart MA, *et al.* Effects of noncardiovascular comorbidities on antihypertensive use in elderly hypertensives. *Hypertension* 2005; 46: 273–279.
25 Blacher J, Safar ME. Large-artery stiffness, hypertension and cardiovascular risk in older patients. *Nat Clin Pract Cardiovasc Med* 2005; 2: 450–455.
26 Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005; 128: 2068–2075.
27 Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005; 128: 2099–2107.
28 Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005; 2: 8–11.
29 Rutten FH, Moons KG, Cramer MJ, *et al.* Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ* 2005; 331: 1379.
30 Veeramachaneni SB, Sethi S. Pathogenesis of bacterial exacerbations of COPD. *COPD* 2006; 3: 109–115.
31 Hogg JC. Infection and COPD. *Exp Lung Res* 2005; 31: Suppl. 1, 72–73.
32 Mallia P, Johnston SL. How viral infections cause exacerbation of airway diseases. *Chest* 2006; 130: 1203–1210.
33 Almirall J, Bolíbar I, Balanzó X, González CA. Risk factors for community-acquired pneumonia in adults: a

population-based case–control study. *Eur Respir J* 1999; 13: 349–355.
34 Farr BM, Woodhead MA, Macfarlane JT, *et al.* Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Respir Med* 2000; 94: 422–427.
35 Brody JS, Spira A. State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006; 3: 535–537.
36 Ben-Zaken Cohen S, Pare PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. *Am J Respir Crit Care Med* 2007; 176: 113–120.
37 Mal H. Prevalence and diagnosis of severe pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2007; 13: 114–119.
38 Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med* 2003; 138: 24–32.
39 Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. *Am J Epidemiol* 2002; 156: 832–841.
40 Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J* 2006; 13: 203–210.
41 Poulain M, Doucet M, Major GC, *et al.* The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. *CMAJ* 2006; 174: 1293–1299.
42 Epping-Jordan JE, Galea G, Tukuitonga C, Beaglehole R. Preventing chronic diseases: taking stepwise action. *Lancet* 2005; 366: 1667–1671.
43 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; 367: 1747–1757.
44 Strong K, Mathers C, Epping-Jordan J, Beaglehole R. Preventing chronic disease: a priority for global health. *Int J Epidemiol* 2006; 35: 492–494.
45 Huttunen R, Laine J, Lumio J, Vuento R, Syrjanen J. Obesity and smoking are factors associated with poor prognosis in patients with bacteraemia. *BMC Infect Dis* 2007; 7: 13.
46 Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; 444: 875–880.
47 Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003; 22: 809–814.
48 Mannino DM, Watt G, Hole D, *et al.* The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27: 627–643.
49 Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med* 2006; 100: 115–122.
50 McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.
51 Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. *Eur Respir J* 2006; 28: 781–785.
52 Goldacre MJ, Duncan M, Cook-Mozaffari P, Griffith M. Mortality rates for common respiratory diseases in an English population 1979–1998: artefact and substantive trends. *J Public Health (Oxf)* 2004; 26: 8–12.
53 Charlson M, Charlson RE, Briggs W, Hollenberg J. Can disease management target patients most likely to generate high costs? The impact of comorbidity. *J Gen Intern Med* 2007; 22: 464–469.
54 Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; 294: 716–724.
55 De Backer G, Ambrosioni E, Borch-Johnsen K, *et al.* European guidelines on cardiovascular disease and prevention in clinical practice. *Atherosclerosis* 2003; 171: 145–155.
56 Schraeder C, Dworak D, Stoll JF, Kucera C, Waldschmidt V, Dworak MP. Managing elders with comorbidities. *J Ambul Care Manage* 2005; 28: 201–209.
57 Dahlstrom U. Frequent non-cardiac comorbidities in patients with chronic heart failure. *Eur J Heart Fail* 2005; 7: 309–316.
58 Braunstein JB, Anderson GF, Gerstenblith G, *et al.* Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; 42: 1226–1233.
59 Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Impact of comorbidity on lung cancer survival. *Int J Cancer* 2003; 103: 792–802.
60 Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail* 2006; 8: 706–711.
61 Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007; 30: 616–622.
62 Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711–715.
63 Sabit R, Bolton CE, Edwards PH, *et al.* Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 1259–1265.
64 Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; 49: 171–180.
65 Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood

Institute Scientific Statement. *Circulation* 2005; 112: 2735–2752.
66 Marquis K, Maltais F, Duguay V, *et al.* The metabolic syndrome in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25: 226–232.
67 Jørgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 2007; 101: 177–185.
68 Hjalmarsen A, Aasebo U, Birkeland K, Sager G, Jorde R. Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. *Diabetes Metab* 1996; 22: 37–42.
69 Walker CG, Zariwala MG, Holness MJ, Sugden MC. Diet, obesity and diabetes: a current update. *Clin Sci (Lond)* 2007; 112: 93–111.
70 Litonjua AA, Lazarus R, Sparrow D, Demolles D, Weiss ST. Lung function in type 2 diabetes: the Normative Aging Study. *Respir Med* 2005; 99: 1583–1590.
71 Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Diabetes Care* 2004; 27: 2966–2970.
72 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
73 van Eeden SF, Hogg JC. The response of human bone marrow to chronic cigarette smoking. *Eur Respir J* 2000; 15: 915–921.
74 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685–1695.
75 Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med* 1996; 154: 1055–1060.
76 Pratico D, Basili S, Vieri M, Cordova C, Violi F, Fitzgerald GA. Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F2α-III, an index of oxidant stress. *Am J Respir Crit Care Med* 1998; 158: 1709–1714.
77 Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. *Am J Respir Crit Care Med* 1997; 156: 341–357.
78 MacNee W, Rahman I. Is oxidative stress central to the pathogenesis of chronic obstructive pulmonary disease? *Trends Mol Med* 2001; 7: 55–62.
79 Sauleda J, Garcia-Palmer FJ, Gonzalez G, Palou A, Agusti AG. The activity of cytochrome oxidase is increased in circulating lymphocytes of patients with chronic obstructive pulmonary disease, asthma, and chronic arthritis. *Am J Respir Crit Care Med* 2000; 161: 32–35.
80 Lee SH, Goswami S, Grudo A, *et al.* Antielastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med* 2007; 13: 567–569.
81 Agusti A, MacNee W, Donaldson K, Cosio M. Hypothesis: does COPD have an autoimmune component? *Thorax* 2003; 58: 832–834.
82 Taraseviciene-Stewart L, Scerbavicius R, Choe KH, *et al.* An animal model of autoimmune emphysema. *Am J Respir Crit Care Med* 2005; 171: 734–742.
83 Sullivan AK, Simonian PL, Falta MT, *et al.* Oligoclonal CD4+ T cells in the lungs of patients with severe emphysema. *Am J Respir Crit Care Med* 2005; 172: 590–596.
84 Barnes P, Cosio M. Characterization of T lymphocytes in chronic obstructive pulmonary disease. *PLoS Med* 2004; 1: 25–27.
85 Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
86 Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51: 819–824.
87 Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 745–752.
88 Rana JS, Mittleman MA, Sheikh J, *et al.* Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27: 2478–2484.
89 Schmidt MI, Duncan BB, Sharrett AR, *et al.* Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet* 1999; 353: 1649–1652.
90 Barzilay JI, Abraham L, Heckbert SR, *et al.* The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 2001; 50: 2384–2389.
91 Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997; 40: 1286–1292.
92 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836–843.
93 Pai JK, Pischon T, Ma J, *et al.* Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004; 351: 2599–2610.
94 McEvoy CE, Ensrud KE, Bender E, *et al.* Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 704–709.
95 Gianni W, Ricci A, Gazzaniga P, *et al.* Raloxifene modulates interleukin-6 and tumor necrosis factor-α synthesis *in vivo*: results from a pilot clinical study. *J Clin Endocrinol Metab* 2004; 89: 6097–6099.
96 Reid MB, Li YP. Tumor necrosis factor-α and muscle wasting: a cellular perspective. *Respir Res* 2001; 2: 269–272.
97 Chambers TJ. Regulation of the differentiation and function of osteoclasts. *J Pathol* 2000; 192: 4–13.
98 Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1998; 53: 129–136.
99 Vernooy JH, Kucukaycan M, Jacobs JA, *et al.* Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. *Am J Respir Crit Care Med* 2002; 166: 1218–1224.

100 Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 367–370.
101 Kasahara Y, Tuder RM, Taraseviciene-Stewart L, *et al.* Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. *J Clin Invest* 2000; 106: 1311–1319.
102 Tuder RM, Zhen L, Cho CY, *et al.* Oxidative stress and apoptosis interact and cause emphysema due to vascular endothelial growth factor receptor blockade. *Am J Respir Cell Mol Biol* 2003; 29: 88–97.
103 Kasahara Y, Tuder R, Cool C, Lynch D, Flores S, Voelkel N. Endotelial cell death and decreased expression of VEGF and KDR/FLK-1 in smoking-induced emphysema. *Am J Respir Crit Care Med* 2000; 161: A583.
104 Takabatake N, Nakamura H, Abe S, *et al.* The relationship between chronic hypoxemia and activation of the tumor necrosis factor-α system in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1179–1184.
105 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
106 Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
107 Couillard A, Maltais F, Saey D, *et al.* Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 1664–1669.
108 Koechlin C, Couillard A, Cristol JP, *et al.* Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? *Eur Respir J* 2004; 23: 538–544.
109 Rabinovich RA, Figueras M, Ardite E, *et al.* Increased tumour necrosis factor-α plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J* 2003; 21: 789–794.
110 Stewart CE, Newcomb PV, Holly JM. Multifaceted roles of TNF-α in myoblast destruction: a multitude of signal transduction pathways. *J Cell Physiol* 2004; 198: 237–247.
111 Oudijk E-JD, Lammers J-WJ, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: Suppl. 46, 5s–13s.
112 Barreiro E, de la Puente B, Minguella J, *et al.* Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 1116–1124.
113 Debigare R, Cote CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease. Clinical relevance and mechanisms. *Am J Respir Crit Care Med* 2001; 164: 1712–1717.
114 Schols AMWJ. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J* 2003; 22: Suppl. 46, 81s–86s.
115 Baarends EM, Schols AM, Westerterp KR, Wouters EF. Total daily energy expenditure relative to resting energy expenditure in clinically stable patients with COPD. *Thorax* 1997; 52: 780–785.
116 Kotler DP. Cachexia. *Ann Intern Med* 2000; 133: 622–634.
117 Morrison WL, Gibson JN, Scrimgeour C, Rennie MJ. Muscle wasting in emphysema. *Clin Sci (Lond)* 1988; 75: 415–420.
118 Tisdale MJ. Biology of cachexia. *J Natl Cancer Inst* 1997; 89: 1763–1773.
119 Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med* 1995; 152: 1268–1274.
120 MacNee W, Wiggs B, Belzberg AS, Hogg JC. The effect of cigarette smoking on neutrophil kinetics in human lungs. *N Engl J Med* 1989; 321: 924–928.
121 Kasper DL, Braunwald E, Hauser S, Longo D, Jameson JL, Fauci AS, eds. Harrison's Principles of Internal Medicine. 16th Edn. New York, McGraw-Hill, 2007.
122 Swedberg K, Cleland J, Dargie H, *et al.* Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 1115–1140.
123 Ryden L, Standl E, Bartnik M, *et al.* Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; 28: 88–136.
124 Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370: 797–799.
125 European Society of Hypertension-European Society of Cardiology Guidelines Committee, European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21: 1011–1053.
126 Lee JH, Lee DS, Kim EK, *et al.* Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am J Respir Crit Care Med* 2005; 172: 987–993.
127 Morimoto K, Janssen WJ, Fessler MB, *et al.* Lovastatin enhances clearance of apoptotic cells (efferocytosis) with implications for chronic obstructive pulmonary disease. *J Immunol* 2006; 176: 7657–7665.
128 van der Harst P, Voors A, van Gilst W, Bohm M, van Veldhuisen D. Statins in the treatment of chronic heart failure: biological and clinical considerations. *Cardiovasc Res* 2006; 3: e333.
129 Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; 125: 2309–2321.
130 Niewoehner DE. The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Med* 2002; 1: 243–248.
131 Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 3: CD005374.
132 Sin DD, Man SF. Do chronic inhaled steroids alone or in combination with a bronchodilator prolong life in chronic obstructive pulmonary disease patients? *Curr Opin Pulm Med* 2007; 13: 90–97.
133 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.