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Why act early in COPD?

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a debilitating multi-component disease resulting in progressive airflow obstruction, systemic manifestations and exacerbations.

The current working definition of COPD, as provided by the Global Initiative for Chronic Obstructive Long Disease [1] is: *a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases*.

The earliest manifestations of the disease are either symptoms of cough, production of sputum and/or dyspnoea related to physical exercise or evidence of airflow obstruction in patients without symptoms. Unfortunately, many cases remain undiagnosed until late in the course of the disease [2, 3].

In the majority of patients smoking is the most important cause of COPD. Strikingly, only an estimated 15 to 30% of smokers develop COPD [4, 5].

The career of a typical patient spans several decades, starting from mild symptoms or abnormalities and ranging to severe disability including gas exchange abnormalities and *cor pulmonale*. Not in all patients does the disease follow the same course. In some smokers, clinically meaningful airflow obstruction, can already be found in the 4th or 5th decades of life, which is usually thought to progress in years to come, whereas in others only mild airflow obstruction persists in old age. Unfortunately, the GOLD staging does not take age into account [1].

Since most patients are detected only at an advanced stage, information on the actual course of the disease from the very beginning must come from cohort-studies that follow healthy smokers for many years. Such studies are currently underway.

Management of patients starts with smoking cessation interventions at the earliest possible stage [6], since benefits of quitting smoking in susceptible smokers are believed to be largest before extensive damage to the respiratory system has occurred [7, 8]. Currently, it is debated whether case-finding of early-stage COPD patients is justified [9]. Many believe this to be unnecessary, since maximal efforts at smoking cessation are indicated in all smokers. Others recommend performing spirometry in asymptomatic smokers in an attempt to identify subjects at risk for developing COPD, in order to intensify efforts to help smokers stop [10, 11]. It has to be taken into account that widespread spirometric testing is likely to label a large number of individuals (many of whom report no respiratory symptoms) with disease and may result in considerable testing and treatment costs, potentially unjustified anxiety and health-care resource utilization [12]. Also, the absence of lung function abnormalities may prompt smokers to continue doing so.

In this review we argue that early COPD differs from mild COPD and that early detection and case finding is necessary, not only to help smoking cessation efforts, but also because many manifestations, other than airflow obstruction, develop in the course of the disease that may be targets for early intervention.

Epidemiology of COPD

Typically, COPD is believed to be a disease affecting smokers in their 6th or 7th decade but this has changed in recent years. Airflow obstruction can be found in much younger smokers, even in the absence of a history of asthma [13]. Recent reports indicate that over 40% of patients with mild COPD and nearly 33% of patients with moderate disease are between 25 and 55 years of age [5, 13-16]. Obviously, the presence of airflow obstruction, even when mild and perhaps even characterised by an forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) ratio > 70%, but below the patients personal predicted values, that is below minus 2 times the SD, is much more important in a smoker under the age of 40 than it is in elderly subjects. Patients with moderate-to-severe COPD are not necessarily much older than smokers with normal spirometry or only mild airflow obstruction [17]. It is currently believed that bronchial hyperresponsiveness is a risk factor for the development of COPD (and asthma) in asymptomatic individuals, particularly when it occurs together with cigarette smoke induced airway inflammation [18, 19].

COPD used to be more prevalent in men but the prevalence in women has increased over recent years. Currently, men and women are reported to be affected equally. The mortality rate is increasing more rapidly in women than in men [20, 21]. The risk of death is increased in all categories of disease severity [22].

The true prevalence of COPD is uncertain and depends on the definitions and the methods of surveys. Epidemiological studies suggest that the prevalence varies from a minimum of 3% in whole populations to a maximum of 18% in subjects over 40 years of age [1]. With increasing age, up to 40% of smokers may eventually develop clinically meaningful airflow obstruction [13].

Currently, COPD is the fourth leading cause of morbidity and mortality in the United States and it is believed that by 2020 it will rank fifth as a world-wide burden of disease [1]. Although in recent years much more information on the importance of COPD has become available, the public interest and the sense of urgency do not reflect this impact on society. On top of that, co-morbidity is an issue of increasing importance [23]. Eventually, patients, especially those who fail to stop smoking may proceed to more severe disease, although exact epidemiological data are currently lacking, justifying an early and aggressive intervention in high-risk patients.

Early diagnosis in COPD

Identifying subjects with COPD starts with considering the diagnosis in smokers. It has been shown that only a few questions in combination with spirometry will allow establishing a diagnosis in just minutes and at low cost [13].

Currently, the FEV_1 as a percentage of the predicted value (corrected for age, body height, gender and race) is used to categorize disease severity [1]:

GOLD 0: at risk. Normal spirometry with chronic symptoms

GOLD 1: mid COPD. $FEV_1/FVC < 70\%$; $FEV_1 \geq 80\%$ of predicted with or without symptoms

GOLD 2: moderate COPD: $FEV_1/FVC < 70\%$; $50\% \leq FEV_1 < 80\%$ of predicted, with or without symptoms

GOLD 3: severe COPD: $FEV_1/FVC < 70\%$; $30\% \leq FEV_1 < 50\%$ of predicted, with or without symptoms

GOLD 4: very severe COPD: $FEV_1/FVC < 70\%$; $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ of predicted plus chronic respiratory failure

Early diagnosis implicates a proactive role from the patient's caregiver in order to timely identify smokers at risk of developing clinically meaningful airflow obstruction. With this in mind COPD case-finding is far more appropriate in smokers in the fourth and fifth decade of their life than in the elderly. An FEV_1 of 85% of predicted in a smoker aged 40 may be a first sign of what may well become moderate to severe COPD later on life. An FEV_1 on 85% of predicted in a smoker aged 75 probably means that this smoker will perhaps not even develop GOLD 1 COPD. Also, GOLD 0 COPD (at risk as it is called in the GOLD document) may be appropriate in young smokers, but to our belief is a misnomer in patients over 60 to 70 years of age. In figure 1 the difference between early airflow obstruction at age 40, evidence

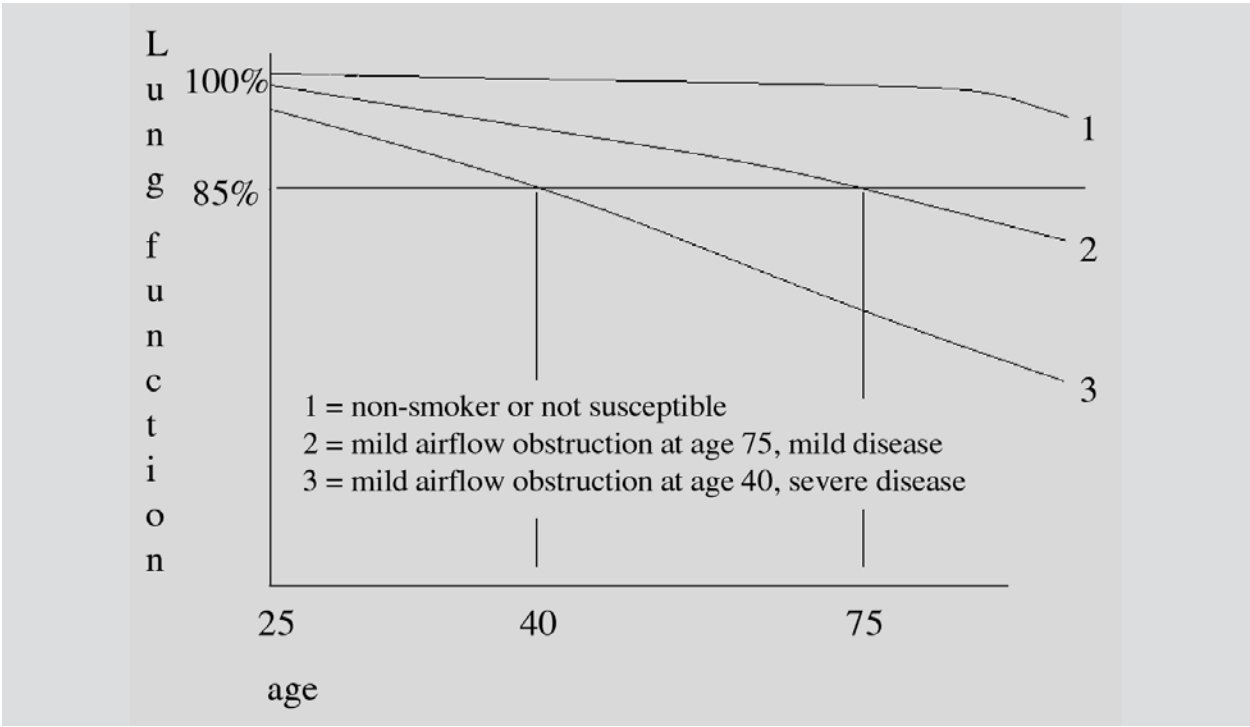

Fig. 1. - Decline in lung function with age of non-smokers or smokers not susceptible to cigarette smoke [1], of smokers with mild airflow obstruction in GOLD 1 COPD [2] and of smokers with mild airflow obstruction as early evidence of potentially severe disease [3].

of potentially severe disease and mild airflow obstruction at age 75 as evidence of GOLD 1 COPD is depicted.

The absence of reversibility to an inhaled bronchodilator helps differentiating COPD from asthma.

Other abnormalities may be present at an early stage of the disease. Although not easily measured on a large scale, bronchial hyperresponsiveness may be of prognostic importance, because it may predict which smokers will develop airflow obstruction [18, 19, 24]. In contrast, symptoms of chronic bronchitis do not increase the risk for progression of COPD in patients without evidence of airflow limitation [25]. Normal spirometric findings therefore probably exclude future COPD in smokers with chronic bronchitis.

Serum-levels of C-reactive protein (CRP) are raised in many patients with COPD(26). There is evidence that increased CRP levels are associated with systemic inflammation. Recently, it has been shown that in advanced COPD CRP is associated with impaired energy metabolism, functional capacity and distress due to respiratory symptoms [27]. Although longitudinal data on systemic inflammation and CRP in COPD are currently lacking, the presence of increased levels of CRP in early COPD may be of prognostic significance.

Clinical picture and natural history of COPD

Many patients with COPD have symptoms such as cough, increased sputum production or dyspnoea during exercise but airflow obstruction may be present in patients without symptoms.

As stated earlier, COPD is characterised in the GOLD document by airflow obstruction that is often progressive even when exposure to cigarette smoke stops [1]. In many patients evidence of abnormalities of the respiratory system include a decrease in FEV_1 and a reduction in the FEV_1 to FVC ratio (an $FEV_1/FVC < 70\%$ is considered diagnostic for airflow obstruction) and a failure to exhale fully (hyperinflation).

Spirometry, in addition to clinical examination, improves COPD diagnostic accuracy compared to clinical examination alone and it is a useful diagnostic tool in individuals with symptoms suggestive of possible COPD [28]. The primary benefit of spirometry is to identify individuals who might benefit from pharmacologic treatment in order to improve exacerbations. These include adults with symptomatic, severe to very severe airflow obstruction. Spirometry for case finding among all adults with persistent respiratory symptoms or those with a history of exposure to pulmonary risk factors as well as for monitoring individuals or adjusting treatment is currently under debate [9]. Recently it has been suggested that the finding of airflow obstruction results in smokers being more likely to quit smoking [29].

Hyperinflation can occur in patients with less severe disease. Recently, we have found that up to 45% of patients with moderate severe COPD (FEV_1 between 50 and 80% of predicted, GOLD 2) have hyperinflation, as defined by a residual volume (RV) in excess of 150% of predicted [30]. This finding may explain symptoms of dyspnoea and exercise intolerance in those patients who have only moderate airflow obstruction and can be a justification for the use of high doses of inhaled bronchodilators even in patients with less severe airflow obstruction

In COPD both bronchial and parenchymal damage may develop, in the shape of chronic (obstructive) bronchitis and emphysema respectively. Many patients show evidence of both. Apart from damage to the respiratory system, extrapulmonary manifestations may be present, such as unexplained weight loss, depletion of muscle mass and peripheral muscle weakness [31], abnormalities in bone mineralization resulting in clinically important osteoporosis [32], and psychosocial dysfunctions [33, 34].

Not all manifestations develop in all patients and not all manifestations follow the same time-course. Most studies describing the natural history of COPD have focussed on a single biomarker of disease and disease severity, namely FEV_1. The natural history of symptoms, other lung function parameters such as hyperinflation and bronchial hyperresponsiveness, local and systemic inflammation, psychosocial issues and quality of life etcetera and other phenotypic elements have not been extensively studied. The course of different aspects of COPD may vary enormously between patients. For instance, underweight and depletion of fat-free mass can sometimes be found in subjects with only mild airflow obstruction [35]. Other patients remain weight-stable until the final stages of COPD. Body weight, often expressed as Body Mass Index (BMI, body weight in kg divided by body height in m^2) is an independent risk factor in COPD [36]). Decreasing body mass is associated with increased mortality. This association has been found in patients with severe COPD in clinical care as well as in a population sample of patients with less severe disease [36]. The risk increases with further weight loss and observational data suggest that the risk decreases with weight gain [37]. Loss of lean body mass is thought to be more important than loss of body weight *per se*. Epidemiological observations from population samples show that there is both a direct relationship between fat mass and mortality and between fat free mass and mortality [19]. In many patients with COPD a loss of fat free mass is seen. Fat free mass is directly related to muscle mass, as can be measured by bioelectrical impedance measurements and visualized by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) [38]. Mid-thigh muscle cross-sectional area is found to be a better predictor of mortality than BMI [39]. Depending on criteria chosen for lower threshold of low fat free mass, up to 30% of patients with GOLD 1 COPD followed in the Copenhagen City Heart Study were found to have low fat free mass, more so in female patients [37]. In view of the observed inverse relation between fat free mass and mortality, the finding of a low fat free mass in ear-

ly COPD should prompt attempts to prevent further weight loss and correct this at an early stage. Low body weight appears to be related to hospital (re)admissions and reduced survival rates [40].

Many patients, not only those with severe disease have exacerbations, usually as a result of viral or bacterial infections, that come with huge costs, both in terms of costs and in terms of morbidity and mortality. Exacerbations are temporary increases in disease severity, either characterized by an increase in symptoms of dyspnoea and/or cough or by an increase in need for care or medications. Many exacerbations are not reported to care-givers and therefore, the number of exacerbations tends to be underestimated, especially in less severe patients [41].

Some patients rarely if ever experience exacerbations, others have many. Two to three exacerbations per year is considered normal, reflecting the number of upper airway infections occurring in the general population. In a Spanish survey the median number of exacerbations seen in primary care was two per year, with 31% of patients suffering three or more exacerbations in 1 year [42]. Findings from a General Practice Research Database in the UK are an average of 4,0 GP visits related to chronic bronchitis and acute exacerbations in the 45 to 54 age range, 4,5 visits in the 55 to 64 age range and 3,6 per year in the 65 to 74 age range, with numbers dropping in the older age groups [43]. Frequent exacerbations are associated with the decline in lung function (FEV_1) that comes with COPD, especially in patients who continue smoking and with a poorer quality of life, and higher inflammatory markers in a stable phase of the disease [44].

Mortality in COPD is significantly related to the frequency of severe exacerbations requiring hospital care, independently of age, co-morbidity, severity of airflow obstruction (FEV_1), body mass index or long term treatment with oxygen [44]. Taken together a large number of potentially treatable disease characteristics have prognostic implications and should be considered carefully as soon as evidence of developing COPD is found.

Management of COPD

Treatment goals in COPD are well defined: slow progression of the disease, improve functional status and quality of life, prevent the development of complications and reduce the frequency and severity of exacerbations [1]. These goals apply to all stages of the disease, but effects of interventions may well differ between stages. Therapies to reduce inflammation can be expected to slow or even stop progression of the disease.

Therefore, management of COPD starts with attempts to quit smoking. Irrespective of age, severity of airflow obstruction and number of pack-years, successful attempts are associated with reduced symptoms and slowing down the progression of airflow obstruction as has been shown in a number of studies [7, 46]. In patients with COPD smoking cessation is associated with a 40% reduction in hospital admissions [47]. This effect was not seen with merely reducing the number of cigarettes that are smoked.

Generally it is believed that screening with spirometry to identify airflow obstruction in asymptomatic smokers does not influence the outcome of smoking cessation attempts [9], but confronting smokers with the results of spirometry as part of multifaceted strategies may be of help [10].

Many methods to support smoking cessation attempts are available, including intensive counselling using various methods such as motivational interviewing, nicotine replacement drugs like chewing gums and skin adhesives and antidepressants like bupropion and nortryptilin [48]. Typically, most attempts to stop smoking fail, even with intensive non-pharmacological and pharmacological support, but this should not stop nor discourage smokers or their healthcare providers. Sometimes repeated attempts succeed where previous, similar attempts failed. Recently, Stratelis *et al.* have demonstrated that smoking cessation advice combined with spirometry repeated over a period of three years increased the cessation rate in smokers with airflow obstruction but not in smokers with a normal lung function [49]. The motivation to stop appears to be enhanced when symptoms are present that can be linked with the smoking habits. There is evidence that smokers with COPD differ from smokers without airflow obstruction in terms of smoking behaviour and inhalation habits [50]. Smokers with airflow obstruction smoke more, are more dependent on nicotine and have higher concentrations of CO in exhaled air. Also, in view of the dose-response pattern that is seen with smoking and airflow obstruction, smoking COPD patients are believed to be more heavily addicted. Smoking cessation strategies therefore should be adapted and tailored to the specific needs of COPD patients. Whether the motivation to stop smoking can be enhanced by confronting smokers with lung function abnormalities is still the subject of debate and research [10, 29].

Ideally, an attempt at smoking cessation should include assessment of the nicotine dependence and of the motivation to stop, personal and group counselling and face-to-face and telephonic support, preferably using motivational interviewing techniques, and pharmacotherapy with nicotine replacement and/or antidepressants following an ask, advice, assess, assist and arrange strategy [51]. The results of studies with newer pharmacotherapy with vaccination [52] and varenicline [53] are eagerly awaited.

Sadly, the effects of other early interventions in COPD are much less clear. In fact, only one intervention other than smoking cessation has been proven to influence prognosis in COPD at al, being oxygen therapy albeit only in patients with very severe COPD with persistent hypoxemia at rest [54]. Pharmacotherapy has not been shown to really modify the course of the disease, although important effects of both bronchodilators and anti-inflammatory drugs have been noted [1). Progress in COPD is related to the frequency and severity of

exacerbations [44]. Currently, various method to achieve this are available [55]. Unfortunately, these effects haven been found in highly selected patients and usually in those patients with more advanced disease. Inhaled corticosteroids were not found to reduce the decline in FEV_1 in current smokers with mild-to-moderate airflow obstruction [56]. Various bronchodilators reduce symptoms and hyperinflation, albeit probably more so in severe disease, thereby reducing the number of exacerbations [57]. All patients with symptoms of COPD should be offered a trial of drug treatment in an attempt to reduce symptoms, improve exercise tolerance and quality of life and reduce the number and severity of exacerbations. Other than smoking cessation, most treatment options have been shown to be ineffective in slowing down the disease progress in early COPD, but unfortunately, these studies have usually taken the decline in FEV_1 into account. In severe disease inhaled steroids may be effective in reducing the number of exacerbations and in slowing-down the decrease in quality of life that is a characteristic finding in COPD-patients [58]. It is believed that pharmacotherapy may affect the course of the disease and the prognosis in COPD mainly through the reduction of the number and the severity of exacerbations [59]. Again, this is probably the case in more advanced disease but has also been demonstrated at earlier stages. Long-acting bronchodilators such as tiotropium and the long-acting β2-agonists formoterol and salmeterol reduce the number of exacerbations [60]. Inhaled corticosteroids have a small beneficial effect on the frequency and the severity of exacerbations in patients with severe COPD and frequent exacerbations [54]. Inhaled steroids possibly have an effect on systemic inflammation in COPD and through this effect they may eventually reduce long term complications such as weight loss, cachexia, osteoporosis, cardiovascular disease and even cancer [60]. Interestingly, it has recently been shown that statines, used to reduce cholesterol levels may have anti-inflammatory properties in a rat model of emphysema, possibly through a reduction in CRP by reducing IL-6 production [61, 62].

The effects of physical reactivation and rehabilitation have been almost exclusively studied in more advanced stages of COPD, not in patients that have too little physical exercise but do not yet have evidence of muscle mass depletion and the functional abnormalities that eventually develop in many COPD patients. Rehabilitation has been shown to improve the functional status and quality of life, the rate of exacerbations, the risk of hospital (re)admissions, and can be cost-effective [63], but this has not been shown in patients with less severe disease. Changes in behaviour, especially when implemented early, can probably influence the course of the disease, but proof of this is not available. Studies to provide evidence for the effects of early behaviour interventions aimed at preventing and treating the lack of physical exercise that is typical for COPD patients and patients at risk of developing COPD are urgently needed.

Does this imply that early recognition and case-finding in COPD is useless? We believe that is not the case. Early diagnosis and early intervention in smokers at risk of developing COPD is extremely important and there is every reason to assume that this will allow modifying the course of the disease in many patients. Even if effects on smoking habits are limited with case-finding, other issues may be important as well. COPD does not start with severe COPD, COPD starts with early changes in susceptible smokers that can be detected and has with time proceeded to severe disease in all those patients that are now in the GOLD 3 and 4 strata. Many patients develop systemic manifestations of COPD, although it has so far not been possible to predict which patients eventually will. Amongst these are abnormalities in muscle volume, muscle fibre composition and metabolic characteristics of muscle cells. Muscle wasting and dysfunction are common in patients with severe COPD [31]. This may in part be explained by the systemic inflammation that comes with COPD in many patients but inactivity is thought to be a factor as well. Behaviour interventions to cope with the tendency of patients to limit their physical activity in response to dyspnoea may help prevent this [64]. The same applies to the osteopenia and osteoporosis that is found in a large proportion of patients, even with less severe disease [32]. Early preventive measures against osteoporosis, such as exercise and drug therapy can help prevent bone mineralization disorders in COPD. In many patients with COPD unintentional weight loss and underweight with or without depletion of fat free mass is present and reflects a poorer outcome and prognosis [65]. Irrespective of the stage of the disease, underweight is an important, independent risk factor for mortality and even in mild to moderate COPD the best prognosis is found in those patients that have a normal or above normal body-weight [36]. Low body-weight probably takes a long time to develop and may better and more successfully be prevented than treated. Studies on lifestyle modification in early phases of the disease have so far not been performed and are badly needed, but common sense has it that prevention and early intervention are easier and more effective than therapeutic approaches once damage has been done.

Early lifestyle modification in COPD

Especially with respect to smoking cessation, primary and secondary prevention is of greatest importance. In integrated management of smokers with or without airflow obstruction, all relevant patient characteristics need to be taken into account and the severity of lung function abnormalities, even at an early stage are part of that.

Lifestyle modification can be of importance in other aspect of behaviour as well. Moderate and severe COPD are often associated with nutritional and metabolic abnormalities leading to involuntary weight loos, underweight and depletion of fat-free mass. Nutritional intervention combined with re-

habilitation can result in correction of these abnormalities [66]. Primary and secondary prevention with correction of negative energy balance and possibly ingestion of specific nutrients such as fish-oil may stop developing abnormalities [67]. When it comes to nutritional and metabolic abnormalities prevention may proof easier than treatment. The same probably applies to exercise. In the course of COPD most patients develop exercise-intolerance and dyspnoea on exertion. Early correction of inactivity with strategies aimed at promoting physical exercise should help preventing exercise-intolerance at an early stage of the disease.

Areas of uncertainty related to early COPD

A number of questions related to acting early in COPD need to be answered:

What is the exact prevalence of airflow obstruction and COPD? Percentages vary according to different sources, but is seem more and more likely that prevalence has been underestimated and increases rapidly, especially in the elderly. Are GOLD 0 smokers really at risk? In whom does early airflow obstruction proceed to severe airflow obstruction? Does spirometry and confronting smokers with early evidence of damage, i.e. airflow obstruction improve smoking cessation? Does the effectiveness of smoking cessation interventions differ between subjects with different severities of airflow obstruction or with different GOLD stages? It may well be the case that it is easier to stop with less severe disease and at an earlier stage of nicotine-addiction. Does spirometry affect prognosis related to pulmonary outcomes? Is an increased plasma C-reactive protein as a recently identified marker of systemic inflammation a useful tool for early diagnosis and monitoring of smokers at risk of developing COPD?

Conclusion

COPD is a multi-component disease that usually starts with smoking and ends with severe disabilities. The career of a typical patient spans several decades, in spite of the fact that the disease is often diagnosed at a stage when distinct, irreversible abnormalities are already present. In moderate to severe disease pharmacologic and non-pharmacologic interventions can reduce symptoms, improve quality of life and slow-down disease progression. The effects however are limited and apart from smoking cessation in all patients and long-term oxygen therapy in patients with persistent hypoxemia, no disease modifying options are available. Future research is needed to identify interventions that, when applied early, are of influence on the course of the disease. For the time being prevention may be more effective than treatment and it is our firm belief that early identification of smokers-at-risk, followed by immediately promoting lifestyle modification can help reduce the damage in individual patients and the burden of disease for society. Early identification is possible and preventive measures such as lifestyle modification including smoking cessation should be promoted in all patients. This implicates a huge challenge for primary care teams including general practitioners and practice nurses but also to respiratory specialists in stimulating the introduction of early detection of patients through spirometry and providing expertise.

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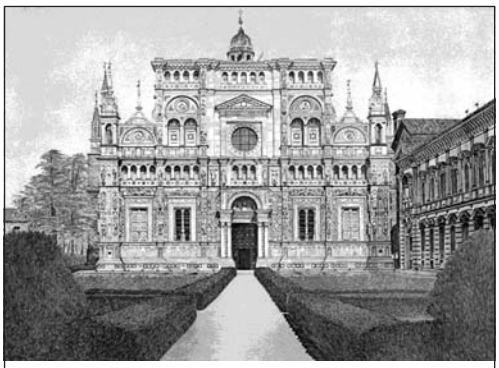

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