

Chronic Obstructive Pulmonary Disease Emphysema and Chronic Bronchitis

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating lung disease. The disease is characterized by irreversible airflow limitation in the lungs. The umbrella of COPD encompasses the following conditions:

- *Emphysema*, in which the alveoli in the lungs, the tiny sacs where oxygen transfer takes place, are destroyed and enlarged
- *Chronic bronchitis*, or the permanent inflammation of airways, accompanied by a chronic cough

COPD exacts a tremendous toll on society. It affects more than 16 million people in the United States, and by 2020 it is expected to rise from the sixth- to the third-most-common cause of death in the world (Kasper DL et al 2005). Unfortunately, there is no single safe and effective treatment. However, because COPD is an inflammatory disease in which sufferers are subjected to high levels of oxidative stress, high doses of antioxidants and natural anti-inflammatories may be able to slow the disease's progression and reduce the amount of prescription medication needed.

INFLAMMATION AND AIRWAY RESTRICTION

The major cause of COPD in the United States is cigarette smoking, although it has also been linked to other factors, such as hyperresponsive airways, respiratory infections, and exposure to dust and environmental pollutants. The longer and more heavily people smoke, the more likely they are to develop COPD.

COPD is usually a progressive disease that develops slowly, often over the course of decades. In a typical case, a cigarette smoker would experience declining lung function for many years before being diagnosed with COPD and receiving therapy. During those years, while the disease is developing, the lungs are undergoing several changes characteristic of the disease.

The bulk of lung tissue is composed of alveoli, or tiny sacs, where the exchange of oxygen and carbon dioxide takes place. One of the primary factors in COPD is emphysema, which occurs when alveoli enlarge and cluster. This process destroys the very sensitive areas where gases are exchanged across thin walls. Emphysema occurs in stages. First, chronic exposure to an irritant, such as cigarette smoke, causes inflammatory cells (such as macrophages and neutrophils) to gather in the airspaces of the lung. These inflammatory cells release chemicals that damage the extracellular matrix of the lung, that is, the proteins that are responsible for providing structure to the lungs. Finally, the ability of the lung to repair the extracellular matrix is compromised, resulting in the coalescence of alveoli into larger, less efficient air chambers.

People with emphysema also suffer from airway obstruction, especially in airways less than 2 mm in diameter. A number of changes occur in these airways that aggravate the disease, including hypertrophy of smooth muscle cells, the formation of scar tissue in the airway walls (fibrosis), and the infiltration of inflammatory cells.

Underlying all this damage is an inflammatory response mounted by the immune system. In a typical case, cigarette smoke in the lungs would come into contact with macrophages (immune system cells) that normally patrol the airspace. In response to the toxins in the smoke, the macrophages release inflammatory chemicals and begin to recruit more immune-system cells, which in turn release more inflammatory chemicals, as well as enzymes that degrade the extracellular matrix.

These changes in the lung are detectable but incremental. Symptoms appear gradually and may actually have been present for many years before a patient seeks medical treatment. Coughing, sputum production, and breathlessness are the characteristic symptoms associated with COPD. Early in the disease, the patient's physical examination may even be normal. Later in the disease, however, patients sometimes develop the classic "barrel chest" associated with COPD. It occurs because residual air is trapped in the lungs, leading to their hyperinflation. In addition, the increased effort required to exhale can produce wheezing, while pursed lips or grunting respirations may signal the patient's efforts to keep the airways open by increasing pressure at the beginning of expiration (Lim TK 1996).

COPD is a variable condition, with some patients having more symptoms of emphysema, such as breathlessness and "air hunger," while others manifest more symptoms of chronic bronchitis or asthma, such as wheezing and air trapping (Kasper DL et al 2005). The manifestations of COPD are not limited to the lungs. COPD also puts patients at increased risk of atherosclerosis and osteoporosis. Poor lung function and poor nutrition may cause muscle weakness, abnormalities in fluid and electrolyte balance, and depression.

GENETIC CAUSES OF COPD

Although cigarette smoking is the major risk factor for COPD, in recent years researchers have uncovered genetic abnormalities that may make people more susceptible to the disease. Hereditary deficiency of an enzyme called alpha-1 antitrypsin confers significant increased risk (Kasper DL et al 2005). Unlike other forms of COPD, lung damage in alpha-1 antitrypsin deficiency appears relatively early in life (Lee P et al 2002). Patients with alpha-1 antitrypsin deficiency also may have liver disease and other organ system damage, and they are more vulnerable to the damaging effects of cigarette smoke (US National Library of Medicine 2005).

Variations in other genes may explain some of the variability in severity and age at onset of COPD, and researchers hope to identify markers of these genes that will permit early identification of people at the greatest risk (US National Library of Medicine 2005; Meyers DA et al 2004).

DIAGNOSIS AND CONVENTIONAL TREATMENT

COPD should be considered in any individual with a chronic cough, sputum production, shortness of breath, or risk factors such as tobacco use, alpha-1 antitrypsin deficiency, or occupational exposure to dust and chemicals. Diagnostic testing should include pulmonary function tests (PFTs). PFTs determine lung volume and capacity and take dynamic measurements, such as the amount of air the patient can force out of the lungs during a given time interval. The results of PFTs are used to determine the severity of COPD, which in turn can establish the likely prognosis and may help guide treatment (Pierson DJ 2006). Other tests, such as x-rays, computed tomography, and magnetic resonance imaging, may be performed if complications such as pneumonia are suspected.

COPD cannot be cured, in part because it usually is the result of years of development. According to the Global Initiative for Chronic Obstructive Lung Disease, effective COPD management has the following goals (Global Strategy 2004):

- Preventing disease progression
- Relieving symptoms
- Improving exercise tolerance and health status
- Preventing and treating complications and exacerbations
- Reducing mortality

Among the most important steps for smokers is to quit smoking immediately. Studies have shown that if smoking is ceased early in the disease, the rate of lung decline might be slowed to that of a normal nonsmoker (Kasper DL et al 2005).

Bronchodilators are first-line therapy for COPD (Sutherland ER 2004). This large group of drugs includes the following (Weder MM 2005):

- *Beta agonists*, or agents derived from adrenaline (such as albuterol)
- *Anticholinergics*, or agents related to atropine (such as ipratropium)
- *Methylxanthines*, or agents related to caffeine (such as theophylline)

All three categories have some effectiveness, but all three also produce significant side effects, such as increased heart rate and blood pressure, trembling, and cardiac arrhythmias. The anticholinergics, particularly some of the more recent long-acting agents such as tiotropium, may provide the best combination of tolerability and duration of action (Koumis T 2005). Side effects of these drugs include chest pain, blurred vision, and more. Theophylline has fallen out of use in the industrialized world because of better alternatives, but its low cost and wide availability make it a still-useful agent in less-developed countries (Weder MM 2005).

Patients who cannot be maintained on bronchodilators may need to start an inhaled steroid medication. At low doses, these medications are safe, and they have been shown to contribute to an improvement in quality of life for patients suffering from COPD (Calverley PM 2004).

When COPD patients experience an exacerbation of their disease, more aggressive medical therapy may be required. The most commonly used medications in this situation are the short-acting bronchodilators, which are sometimes used on an as-needed basis to relieve acute symptoms (Chorostowska-Wynimko J 2005; Urbano FL 2005). Inhaled and occasionally oral steroid medications may be added as well. If the acute exacerbation is caused by a bacterial infection, antibiotics may be prescribed.

The most severe exacerbations of COPD require hospitalization, often with mechanical ventilation in an intensive care unit. Unfortunately, ventilatory management of COPD patients is complex and has many pitfalls. This has led to increased use of home, noninvasive, positive-pressure ventilation systems that may stave off the need for more-aggressive treatment (Brochard L 2003;

New drugs. About 70 therapeutic drugs are in development for related COPD needs. The newest class of drugs is phosphodiesterase-4 inhibitors; two of these, roflumilast and cilomilast, may be available in the near future (Business Wire 2004). Phosphodiesterase-4 inhibitors produce bronchial smooth muscle relaxation by taking away the intracellular stimulus that maintains contraction. This effect is similar to that of the other bronchodilators, though it is produced by a different and more targeted mechanism and produces fewer side effects. These drugs have been shown to reduce inflammation, improve lung function, decrease exacerbations, and improve quality of life (Vignola AM 2004).

Researchers are also reporting amazing results with retinoic acid, a biologically active form of vitamin A. In a mouse model of emphysema, retinoic acid was able to completely restore lung architecture and alveolar function (Hind M et al 2004; Maden M et al 2004). Human studies have been similarly encouraging. In one randomized, double-blind, placebo-controlled study, all-trans-retinoic acid was administered in low doses to 20 patients with severe emphysema. The drug was well tolerated, with few side effects, and the researchers called for longer studies with higher doses (Mao JT et al 2002). The same group of investigators also found that retinoic acid restores the balance of important enzymes called matrix metalloproteinases that are thought to contribute to alveolar breakdown (Mao JT et al 2003).

Flu vaccines. Flu vaccines can reduce COPD exacerbations, serious illness, and death by 50 percent. They are given in the fall or twice a year, in fall and winter. Vaccines that prevent infection with the bacterial organism *pneumococcus* can reduce complications such as pneumonia and may reduce the rate of exacerbations of the disease. (Alfageme I et al 2006; Ansal di F et al 2005).

NUTRITIONAL THERAPY

Medications and surgery can be effective in treating symptoms, but they do little to prevent disease progression. Mortality rates from COPD are still high, and quality of life is often severely impaired.

Nutritional supplementation aimed at increasing antioxidant capacity and reducing inflammation may offer significant added value (Schols A 2003; Romieu I et al 2001). In addition, people with COPD have increased energy requirements because it is harder for them to breathe. Difficulty breathing may affect eating, potentially resulting in malnutrition. Proper nutrition through a balanced diet and appropriate supplementation is important in COPD management.

Because of the role of oxidant stress in causing and perpetuating COPD (Drost EM et al 2005) and the low levels of natural antioxidants in patients' tissues (Kluchova Z et al 2006; Rahman I et al 2006; Nadeem A et al 2005), antioxidant supplementation may be helpful (Kelly FJ 2005; Spurzem JR et al 2005; Romieu I et al 2001).

Vitamins A, C, and E. Levels of vitamins A and E are significantly lower during exacerbations of COPD than they are in stable COPD, suggesting that antioxidants should be used during exacerbations (Tug T et al 2005). Although vitamins A, C, and E are beneficial, vitamin A may be most important because it catalyzes removal of the most reactive form of oxygen radical (Tug T et al 2005). Serum levels of vitamin A are lower in those with moderate or severe COPD. Vitamin A supplements for 30 days improved performance on PFTs in one small study (Paiva SA et al 1996).

Vitamin E levels are low in smokers, increasing their susceptibility to injury from free radicals. Vitamin E supplementation can reduce the risk of COPD in smokers (Daga MK et al 2003). Serum vitamin C levels are also frequently reduced in COPD (Tug T et al 2005). High-dose vitamin C may prevent oxidant-mediated lung injury during inflammation. Vitamin C also reactivates vitamin E that has been depleted by oxidant molecules.

Coenzyme Q10. When coenzyme Q10 (CoQ10) was given to eight COPD patients with low levels of the nutrient, they experienced improved oxygenation of blood without a change in lung function. Oxygen pressure significantly improves, and heart rate decreases. Exercise performance increases. CoQ10 affects muscular energy metabolism in chronic lung diseases (Fujimoto S et al 1993).

N-acetylcysteine. N-acetylcysteine (NAC) is a powerful antioxidant that protects against toxins, including acrolein, found in cigarette smoke. NAC is a selective immune-system enhancer, improving symptoms by breaking down mucus and preventing recurrence of lung illness such as chronic bronchitis. Supplementation with NAC reduces exacerbation and improves chronic bronchitis (Stey C et al 2000).

L-carnitine. Respiratory infections increase the frequency and severity of exacerbations. L-carnitine may boost immune function, enhance fatty acid and glucose energy metabolism, and prevent wasting syndrome. In one very recent human trial, carnitine improved exercise tolerance and the strength of respiratory muscles in COPD patients; levels of the metabolic by-product lactate, which causes fatigue, were also reduced (Borghini-Silva A et al 2006).

Bromelain. Bromelain, which is present in the pineapple fruit, can benefit stable COPD patients and decrease exacerbations by

reducing mucin production (Bernkop-Schnurch A et al 2000). Individuals allergic to pineapple may be sensitive to bromelain. Gastritis can be aggravated by bromelain (Jaber R et al 2002).

Essential Fatty Acids

Essential fatty acids are those that cannot be produced by the body and must come from dietary or supplemental sources. Omega-3 fatty acids are essential in modulating toxic inflammatory responses. Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) protect against damaging inflammatory reactions and, with vitamin E, build healthy cell membranes and repair tissues (Ergas D et al 2002; Fernandes G et al 1996).

The destructive effects of chronic inflammation on cellular structures can be reduced by supplementing with EPA and DHA, which repair both cell and mitochondrial membranes (Chapkin RS et al 2002). Mitochondrial membranes, because of their involvement in energy production, are especially susceptible to oxidant damage.

Supplementing with omega-3 fatty acids improves oxygen transfer in adult respiratory distress syndrome, a condition in which oxidant damage and inflammation cause impaired lung function. Omega-3 supplements have been shown to be beneficial in patients with COPD. One study showed a significant improvement in dyspnea and pulse oximetry levels and a decrease in inflammatory markers in serum and sputum in a group of patients receiving supplementation, compared with controls (Matsuyama W et al 2005). Higher dietary levels of omega-3 fatty acids may protect smokers against COPD (Shahar E et al 1994).

NONDRUG STRATEGIES

Smoking cessation and patient education. The major cause of COPD is cigarette smoking. Comprehensive smoking cessation programs include counseling, organized “quit” plans, and when necessary, nicotine replacement therapy (such as gum, inhalers, skin patches, and other methods). Drugs such as bupropion (Wellbutrin®) are also effective when taken under a doctor’s care (Cornuz J 2006). Both hypnosis and acupuncture may be helpful in quitting smoking (Zwick H 2005). The National Network of Tobacco Cessation Quitlines at 1-800-QUITNOW (1-800-784-8669) can provide information on finding a quitline in any geographical area in the United States.

Exercise programs. Because air passage is obstructed in COPD, the lungs and heart work harder to carry oxygen throughout the body. Exercise programs strengthen chest muscles and facilitate breathing. Multidisciplinary pulmonary rehabilitation programs provide well-monitored exercise programs.

Breathing exercises. Breathing exercises induce relaxation and make breathing easier. Pursed-lip breathing stimulates relaxation, increasing oxygen intake and preventing shortness of breath. It has been shown to increase exercise tolerance and shorten recovery times (Garrod R et al 2005). Breathing exercise regimens are an important part of a COPD rehabilitation program. Respiratory therapists working closely with physicians can specify the best regimen for each individual (Beckerman M et al 2005).

Oxygen. Oxygen therapy alleviates a lack of oxygen but increases oxidative stress, potentially increasing damage to airways. Patients with COPD are known to have reduced antioxidant capacity (Kluchova Z et al 2006; Rahman I et al 2006), which may be further diminished by oxygen therapy (Nadeem A et al 2005). A recent study, however, demonstrated that supplemental oxygen actually reduced levels of oxidant molecules and inflammatory cytokines in exercising patients with COPD, presumably by supporting normal metabolism and preventing stress-induced oxidant species from being produced (van Helvoort HA et al 2006).

Surgery. Surgical interventions are becoming more important in COPD as techniques improve (Kasper DL et al 2005). When alveoli coalesce in emphysema, they can form large blebs, or bullae; surgical removal of these bullae can help restore lung volume and allow remaining healthy parts of the lung to function better. Similarly, lung volume reduction surgery has been used successfully to improve lung function and quality of life. Lung transplantation is also a consideration for COPD sufferers.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Any patients with COPD, emphysema, or bronchitis are urged to stop smoking and to limit their exposure to environmental toxins whenever practical. Additionally, exercise, breathing exercises, and oxygen therapy may be helpful, as well as the use of steam and hot-mist vaporizers. If the breathing difficulty results in trouble eating, a strong multivitamin that includes magnesium is recommended to prevent malnutrition and restore energy to damaged cells.

Studies have shown that retinoic acid has a remarkable ability to restore alveolar architecture. Retinoic acid is available as Vesanoid (tretinoin) for the treatment of leukemia, but it can be prescribed for COPD.

In addition, the following nutrients have been shown to restore antioxidant capacity and help reduce inflammation:

- **Vitamin A**—25,000 international units (IU) daily
- **Vitamin C**—3000 milligrams (mg) daily
- **Vitamin E**—400 IU daily (with at least 200 mg gamma tocopherol)
- **NAC**—600 mg, three times daily
- **CoQ10**—200 to 400 mg daily
- **Omega-3 fatty acids**—1000 mg DHA and 1400 mg EPA daily
- **Gamma-linolenic acid**—900 to 1800 mg daily
- **L-Carnitine**—2000 to 3000 mg daily
- **Bromelain**—500 mg several times daily on an empty stomach

PRODUCT AVAILABILITY

All the nutrients and supplements discussed in this section are available through the Life Extension Foundation Buyers Club, Inc. For ordering information, call anytime toll-free 1-800-544-4440, or visit us online at www.LifeExtension.com.

The blood tests discussed in this section are available through Life Extension National Diagnostics, Inc. For ordering information, call anytime toll-free 1-800-208-3444, or visit us online at www.LifeExtension.com.

COPD SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

Bromelain

- Consult your doctor before taking bromelain if you are taking anticoagulants or antithrombotic agents. Bromelain can thin the blood.
- Bromelain can cause gastrointestinal symptoms such as nausea and diarrhea.
- Bromelain can cause bleeding from the uterus between menstrual periods (metrorrhagia) and excessive uterine bleeding during menstruation (menorrhagia).

Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 level.

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

L-Carnitine

- L-Carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

NAC

- NAC clearance is reduced in people who have chronic liver disease.

- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Vitamin A

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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