Extra pulmonary manifestations of COPD Implications in management

DM seminar
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Introduction

- COPD is a chronic inflammatory disorder characterized by progressive expiratory airflow limitation that is poorly reversible
- A substantial proportion of COPD patients have extra-pulmonary symptoms and signs
- Common manifestations include skeletal muscle weakness, osteoporosis, cardiac arrhythmias, ischemic heart disease, stroke, depression, and cancer
- The presence of these extra-pulmonary manifestations of COPD increases morbidity and mortality

Inflammatory markers in COPD

- In COPD ↑ levels of inflammatory cytokines, acute phase proteins, and markers of oxidant stress

  (Oudijk EJ, et al. Eur Respir J Suppl 2003;46:5s–13s)

- Cytokines in COPD include TNF-α, TGF-β, interferon-γ, and ILs- 6 and 8

  (Wouters EF et al.Proc AmThorac Soc 2005;:26–33)

- COPD with lowest FEV1 have the highest levels of CRP, fibrinogen, and other systemic inflammatory markers, while those with the highest FEV1 have the lowest values

  (Circulation 2003; 107:1514–1519)

Inflammatory markers in COPD

- ↑cytokines and CRP are associated with SMD, heart disease, and atherosclerosis in patients with COPD

  (van Eeden SF, et al. Proc Am Thorac Soc 2005;:61–7)

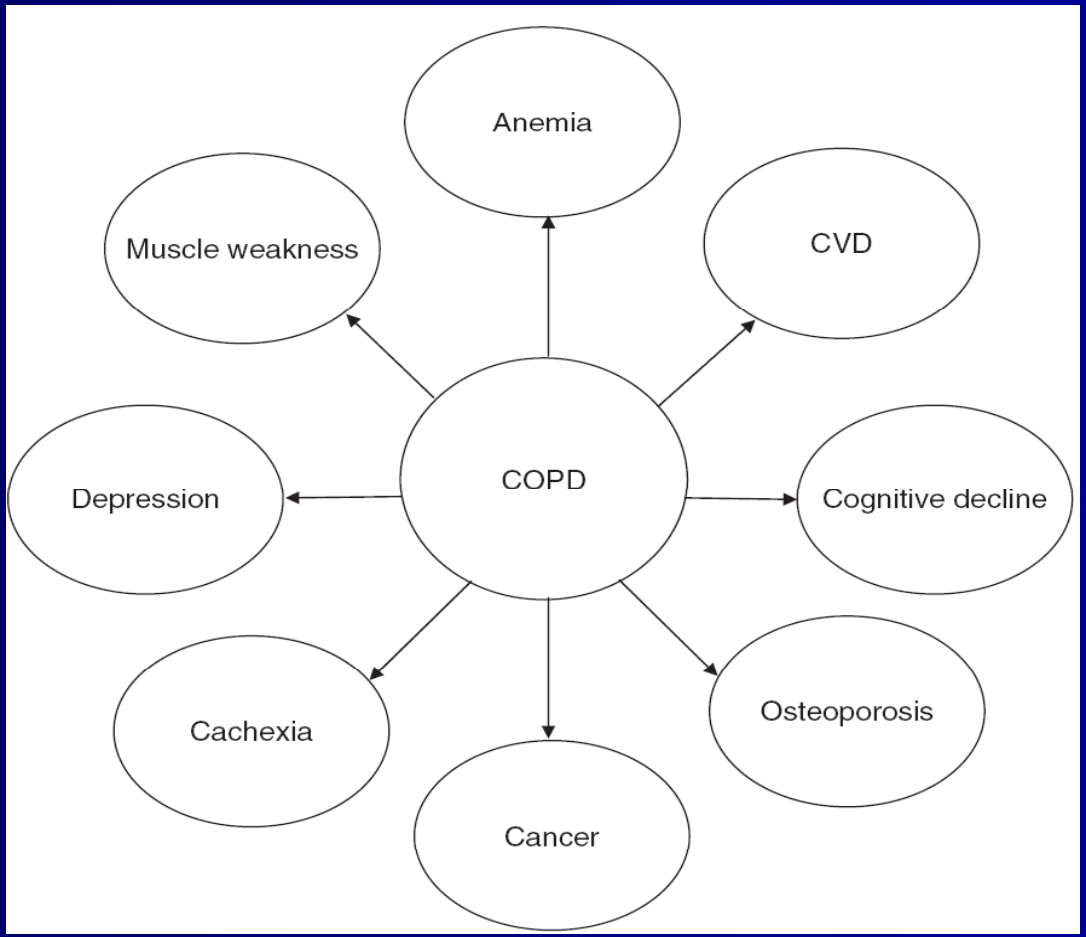
- CRP and fibrinogen, are elevated in smokers, and ↑ fibrinogen levels in smokers are associated with ↓ lung function and ↑ risk for COPD

  (Dahl M,et al. AJRCCM 2001;164(6):1008–11)

- ↑ CRP is an independent risk factor for CAD, myocardial infarction and stroke

  *(PRIME Study. 2003; **23**: 1255–61)*

Systemic effects



Skeletal Muscle Dysfunction in COPD

- MA is associated with ↑ mortality risk independent of disease staging based on severity of airflow obstruction

  (Am J Respir Crit Care Med 2002;166:787–9)

- SMD in COPD is characterized by a ↓ in strength and endurance of the muscle

- Skeletal MA in COPD selectively affects the predominant glycolytic type IIA/IIX fibers

  (Eur Respir J 2003;46(Suppl):52s–63s)

Skeletal Muscle Dysfunction in COPD

- In COPD, shift of muscle fiber type I to type II, Type I fibers - resistant to fatigue, Type II fibers - more fatigable

  (Am J Respir Crit Care Med 2002;166:787–9)

- In COPD Muscle glycogen content lower, and lactate concentrations are higher

  (Am J Respir Crit Care Med 1996;153:288–93)

- Elevated levels of inflammatory mediators, such as TNF-α and IL-6, cause skeletal muscle to atrophy

Mechanism of skeletal muscle weakness

- Deconditioning is a major contributor to the muscle dysfunction in COPD patients
- Inflammatory mediators in COPD may be responsible for weight loss and muscle wasting.
- Reduced levels of circulating hormone(GH, Test,) in COPD patients
- Chronic steroid myopathy after prolonged administration of lower doses of corticosteroids
- Chronic hypoxemia or hypercapnia or the effects of cigarette smoking cause muscles damage

Evidence of skeletal Muscle Dysfunction in COPD

- Muscle atrophy
- Weakness
- Morphology changes
  * proportion of type I fibers
  * proportion of type IIb fibers
  * Capillarization
- Altered metabolic capacity
  * ↓ Intramuscular pH
  * ↓ ATP concentration
  * ↑ Muscle lactate concentration
  * ↑Iononine monophosphate
  * ↓Mitochondrial enzyme activities

(Maltais, F, et al. Clinics in Chest Medicine, 21:665-685, 2000)

Structural alterations of SM in COPD

- Muscle mass- ↓ Fat free mass
- Muscle fiber types and sizes- ↑ Type IIb fibers and atrophy of Type I and IIa fibers
- Numbers of capillaries per unit surface area in the vastus lateralis is 53% lower than normal subjects
- Lower oxidative enzymes capacities in the vastus lateralis

A Statement of the American Thoracic Society and European Respiratory Society

Etiology of skeletal muscle dysfunction

- Related to COPD-Hypoxia and hypercapnia, inflammation and chronic malnutrition
- Related to comorbid condition- electrolyte disturbances, cardiac failure, deconditioning, diabetes, and hypertension
- Related to therapy- corticosteroids, β2 agonist

Skeletal muscle atrophy

Impacts on clinical outcomes

- Muscle weakness
- Decreased quality of life
- Lower functional capacity
- Increased mortality risk
- Accentuated inflammation and ROS production after exercise

(Respir Med, 94:859-67; 2000)

Management of SMD

Pulmonary Rehabilitation

- Exercise training
  - – Upper and lower extremity endurance training, respiratory muscle training, strength training
- Education
  - – Self-management strategies
- Psychological and behavioral intervention
  - – Support groups for stress management

American Thoracic Society, *Am J Respir Crit Care Med.* 1999; 159:1666-1682
Ries AL et al, *Am J Respir Crit Care Med.* 2003; 167: 880-888
ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel, *Chest*, 1997; 112:1363-1396

Oxygen therapy

- LTOT in patients with COPD,improvement in skeletal muscle energy metabolism

  (Jakobsson P et al. Respir Med 1995, 89:471-476)

- During exercise, supplemental oxygen to hypoxemic patients with COPD improved aerobic metabolism

  (Respir Med 1995, 89:471-476)

- LTOT could also help by allowing patients to be more active, thereby reducing the effects of deconditioning.

Anabolic hormones

- GH exerts its effects primarily by ↑ levels of IGF
- GH-deficient adults, administration of GH ↑ muscle mass and strength, and improves exercise performance

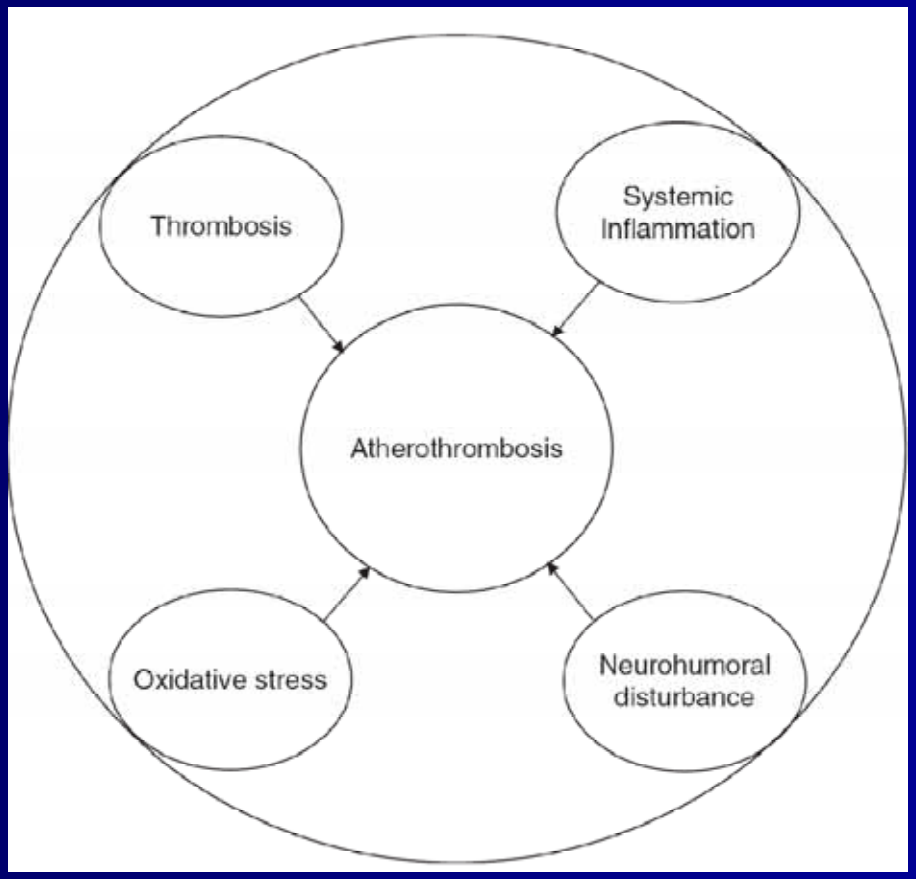
  (J Appl Physiol 1991, 70:688-694)
- Patients received GH plus exercise training increased lean body mass, whereas the group that received exercise training alone did not

  (Am J Respir Crit Care Med 1997, 155:A498)
- Significant increase in weight and lean body weight with anabolic steroids as compared with a control group

  (Chest 1998, 114:19-28)

Cardiovascular disease in COPD

Mechanisms of Increased Risk of CVD in COPD



Cardiovascular disease in COPD

- Why COPD would predispose to cardiovascular events is largely a mystery
- COPD and CHD have shared risk factors including advancing age, cigarette smoking, and environmental air pollution
- However, even among relatively young nonsmokers, COPD is an independent risk factor for incident cardiovascular disease suggesting other mechanisms

Cardiovascular disease in COPD

- In COPD, persistent pulmonary inflammation promotes the release of pro-inflammatory chemokines and cytokines into the circulation
- The systemic inflammation in turn adversely impacts the blood vessels, contributing to plaque formation and, to plaque instability and rupture

  (Sin et al. Chest 127: 1952–1959.2005)
- Hemostasis and thrombotic pathways may also play relevant roles in COPD and ischemic heart disease

  (Wu and Thiagarajan, 1996)

Cardiovascular disease

- FEV1 >50% of predicted, CVD account for approximately 50% of all hospitalizations and nearly a third of all deaths

  (Anthonisen et al.1994 Jama 272: 1497–1505)

- In more advanced disease, cardiovascular events account for 20–25% of all deaths in COPD

  (Sin et al. 2006Eur Respir J 28: 1245–1257)

- A RR of 2.74 for women and 1.42 for men who were in the lowest FEV1 compared to those in the highest

  (Speizer et al. 1989Am Rev Respir Dis 140: S49–55.)

Cardiovascular disease

- The AR of ischemic cardiac deaths from reduced FEV1 is 26% in men and 24% in women, independent of the effects of cigarette smoking

  (Hole et al. 1996 Bmj 313: 711–715)

- Patients had both COPD and arrhythmias at baseline, the risk of coronary events increased by over two fold compared with subjects without COPD

  (Engstrom et al. Circulation 103: 3086–3091. 2001)

- For every 10% ↓ in FEV1, all cause mortality ↑ by 14%, cardiovascular mortality ↑ by 28%, and nonfatal coronary event ↑ by almost 20%

  (Anthonisen et al. Jama 272: 1497–1505 1994)

Arrhythmias in COPD

- Stable COPD patients: 72 % of arrhythmias were ventricular in origin, while 52 % were supraventricular

  (Kleiger, RE et al. Chest 1974; 65:483)

- Reduced FEV1 is an independent predictor of new onset atrial fibrillation in patients with stable COPD

  (Eur.Respi.J 2003;21.1012)

- Atrial fibrillation and ventricular arrhythmia were independent predictors of death

- In patients with acute respiratory failure, the presence of arrhythmia may be associated with increased mortality

Therapeutic Interventions and Modification Of Cardiovascular Risk In COPD

- ICS is a mainstay of COPD therapy for many years and there is some evidence showing they ↓ exacerbation
- ↓ plasma CRP levels of COPD patients in response to ICS, suggesting that ICS may act to reduce systemic inflammation, an important element of cardiovascular pathophysiology

(Man SF et al.Thorax 2006; 61: 849–53)

- EUROSCOP study use of budesonide in mild COPD found a reduction in cardiovascular adverse events in the treatment arm

Therapeutic Interventions and Modification Of Cardiovascular Risk In COPD

- TORCH study, a RCT which investigated whether combined ICS and LABA therapy improved mortality compared with LABA or ICS alone, or placebo, showed no significant difference in all-cause or disease-specific mortality with active treatment.
- HMG CoA reductase inhibitors in primary and secondary prevention of coronary heart disease
- A retrospective Norwegian study showed a reduction of all-cause mortality in COPD patients on statin therapy who have had a recent exacerbation

(Soyseth V et al. Eur.Respir. J. 2007; 29: 279–83)

Therapeutic Interventions and Modification Of Cardiovascular Risk In COPD

- COPD had improved cardiac, pulmonary and all-cause mortality when receiving either statin therapy, ACEI,ARB either alone or in combination

  (J. Am. Coll. Cardiol. 2006; 47: 2554–60)

- Infliximab is a mAb that specifically inhibits TNFα, and therefore specifically inhibits inflammation

- TNFα antagonists have been studied in COPD but showed no improvement in morbidity over a short follow-up period, although cardiovascular outcomes were not specifically assessed

  (Am. J.Respir. Crit. Care Med. 2007; 175: 926–34)

Therapeutic Interventions and Modification Of Cardiovascular Risk In COPD

- BRONCUS study treatment with antioxidant NAC showed no improvement of lung function or exacerbation rates compared with placebo

- Use of antioxidant treatment in primary prevention of CVD in the general population showed no improvement in mortality

(*Lancet* 2003; 361: 2017–23)

- MRC LTOT study only showed survival advantage in severe patients with resting pO2 < 7.3 or those with pO2 < 8.0 and evidence of cor pulmonale. Cardiovascular mortality was not specifically assessed

(*Lancet* 1981; 1: 681–6)

Anaemia in COPD

- WHO defines anaemia as a haematocrit level , <39%(13g%) in males and <36%(12g%) in females
- Prevalence of anaemia of 12.6% in males and 8.2% in females

(Chambellan A et al. Chest 2005; 128: 1201–1208)

- Putative mechanisms that are thought to lead to ACD, namely: shortened RBC survival, iron homeostasis dysregulation and impaired bone marrow erythropoietic response

Anemia in COPD

- Other factors, such as nutritional disorders, occult blood loss, treatment with certain drugs (theophylline or angiotensin-converting enzyme inhibitors), and even oxygen therapy causes anemia in COPD

(Similowski T et al. Eur Respir J. 2006;27:390-6)

- Anemic patients had higher levels of EPO than non-anemic COPD patients as well as more ↑values of IL-6 and CRP

(John M et al. Chest. 2005;127:825-9)

Anemia in COPD

- ANTADIR study, COPD receiving domiciliary oxygen therapy, demonstrated reduced hematocrit level was a strong predictor of mortality and was also associated with more frequent hospitalizations and a longer mean hospital stay

  (Chambellan A et al. Chest. 2005;128: 1201-8)

- In the ANTADIR study , haematocrit decreased with age and with the degree of obstruction (FEV1/vital capacity)

- Patients with an average FEV1 of 37±2% predicted, the prevalence of anaemia of 13%.

  (John M et al. Chest 2005; 127: 825–829)

Anemia in COPD

- Multivariate analysis emphasised haematocrit as an independent and major predictor of survival
- BODE prognostic index, haematocrit was significantly higher in the patients who survived (42±5%) compared with those who died (39±5%)

  (Celli BR et al.N Engl J Med 2004; 350: 1005–1012)
- NETT, ↓ hemoglobin to be an independent predictor of mortality together with other variables, such as age, supplemental oxygen use, higher residual volume, and higher BODE score.

COPD and Osteoporosis

COPD and Osteoporosis

- Osteopenia is BMD between 1 and 2.5 SDs and osteoporosis is BMD of 2.5 SDs below the mean for young adults

(Eastell R et al. N Engl J Med 1998; 338:736–746)

- As many as 35 to 72% of patients with COPD have been reported to be osteopenic, and 36 to 60% of patients with COPD have osteoporosis

(Incalzi RA et al Respir Med 2000; 94:1079–1084)

- Patients receiving oral CS (average cumulative dose, 19.5 ± 24.8 g) have been found to have a 1.8-fold (95% CI, 1.08 to 3.07) ↑ incidence of one or more vertebral fractures.

(McEvoy C et al. AJRCCM 1998; 157:704–709)

Contributing Factors to Osteoporosis in COPD

- Smoking
- Increased alcohol intake
- Vitamin D levels
- Genetic factors
- Treatment with corticosteroids
- Reduced skeletal muscle mass and strength
- Low BMI and changes in body composition
- Hypogonadism
- Reduced levels of insulin-like growth factors
- Chronic systemic inflammation

COPD and Osteoporosis

- Subjects with severe ↓in PFT requiring ICS (FEV1, 59 ± 3.7%) or OS (FEV1, 50.6 ± 2.8%) had a 9 fold ↑ risk of osteoporosis compared to the control group.
- In a prospective study of 286 patients with COPD who were randomized to inhaled budesonide (800 µg/d) or placebo, reported no significant change in BMD in either group after 3 years

  (N Engl J Med 1999; 340:1948–1953)
- Patients with low dose of prednisone (*ie*, 2.5 to 7.5 mg/d) had a 1.77-fold ↑ risk of fractures, and patients receiving 7.5 mg/d prednisone had a 2.27-fold ↑ risk

  (J Bone Miner Res 2001;16:581–588)

COPD and Osteoporosis

- Slemenda et al. reported that lumbar spine BMD was 12% lower in smokers who have smoked 20 pack-years compared to nonsmokers.

  (J Bone Miner Res 1989; 4:737–741)

- Risk of vertebral fractures increases 2.3 fold among long term smokers

  (Seeman et al. Am J Med 1983; 75:977–983)

- In COPD, BMI was the strongest predictor of osteoporosis, with a BMI ≤ 22 having an odds ratio of 4.18 (95% CI, 1.19 to 14.71)

  (Incalzi RA et al. Respir Med 2000; 94:1079–1084)

Osteoporosis screening tool for COPD patients

Yes = 1 No = 0	Risk Factor Assessment
	≥ 68 years
	≥5 mg daily for >3 months, or ≥1000mg prednisone in 12 months
	Previous fagility fracture
	Smoking history
	Maternal history of hip fracture
	BMI less than 20

Three or more of the risk factors indicate high risk of osteoporosis

Recommendations to Decrease Osteoporosis Risk in COPD

Measure BMD in the following high-risk patients at baseline:

- Those on chronic oral glucocorticoids or high-dose inhaled glucocorticoids
- Postmenopausal women
- Premenopausal women with amenorrhea
- Hypogonadal men
- History of fracture
- BMI <22

(Diane M. et al. CHEST 2002; 121:609–620)

Recommendations to Decrease Osteoporosis Risk in COPD

- Follow BMD every 6–12 mo in those receiving oral glucocorticoids or every 12–24 mo in those not taking oral glucocorticoids
- Give supplements to daily intake of 1,000–1,500 mg calcium and 400–800 IU vitamin D
- Encourage an exercise program to improve strength and balance

(Diane M. et al. CHEST 2002; 121:609–620)

Recommendations to Decrease Osteoporosis Risk in COPD

- Gonadal hormone replacement to all postmenopausal women, premenopausal women with amenorrhea, and hypogonadal men (unless contraindicated)
- Consider bisphosphonates or calcitonin in patients with osteoporosis or in high-risk patients in whom HRT is not effective or indicated

(Diane M. et al. CHEST 2002; 121:609–620)

Cachexia in COPD

- Cachexia is defined as excessive weight loss in the setting of ongoing disease, associated with disproportionate muscle wasting
- Associated with poor functional capacity, reduced health status, and increased mortality
- The prevalence of weight loss in COPD increases with COPD disease progression

Cachexia in COPD

- In mild to moderate COPD, only 10 to 15% and severe COPD, nearly 50% of patients have significant weight loss

(Creutzberg et al. 2003 Eur J Clin Nutr 52: 396–401 *)*

- COPD-related cachexia is an independent risk factor for morbidity and mortality.

- COPD mortality was 2.2-fold higher with FEV1 <50% of predicted, who had a BMI <20 compared with those whose BMI was between 20 and 25 and over seven-fold higher compared with those whose BMI was 30 or greater

(Landbo et al. 1999,Am J Respir Crit Care Med 160: 1856–1861)

Cachexia in COPD

- Cytokines, TNF-α, and INF-γ inhibit mRNA expression for myosin heavy chain, leading to $\downarrow$ muscle protein synthesis
- Cytokines may also directly or indirectly stimulate proteolysis of myosin heavy chains

  (Acharyya et al. 2004; Guttridge et al. 2000)
- COPD patients frequently take inhaled or systemic glucocorticoids, which further contribute to a catabolic state.

COPD and lung cancer

- COPD is not only a risk factor for lung cancer, but also for death from lung cancer
- The presence of moderate or severe airflow obstruction is a significant predictor of incident lung cancer

(Mannino DM et al. Arch Intern Med 2003;113:1475-1480)

- Hypoxia-inducible transcription factors (HIF) may promote angiogenesis and involved in both ischemic diseases and cancer

(Constans A et al The Scientist 2004;18:20-21)

COPD and lung cancer

- Evidence suggests that angiogenic dysplasia is a prelude to invasive carcinoma

  (Keith RL et al. Clin Cancer Res 2000;5:1616-1625)

- 49% of lung cancer patients have COPD and as many as 12% of COPD patients between the age of 65–69 yrs die as a consequence of lung cancer

  (Vilkman S et al. Respiration 1997; 64: 281–284)

- Predisposition of COPD to lung cancer may be due to - impaired mucociliary clearance, genetic predisposition , oxidative stress-mediated inflammation and carcinogenesis process

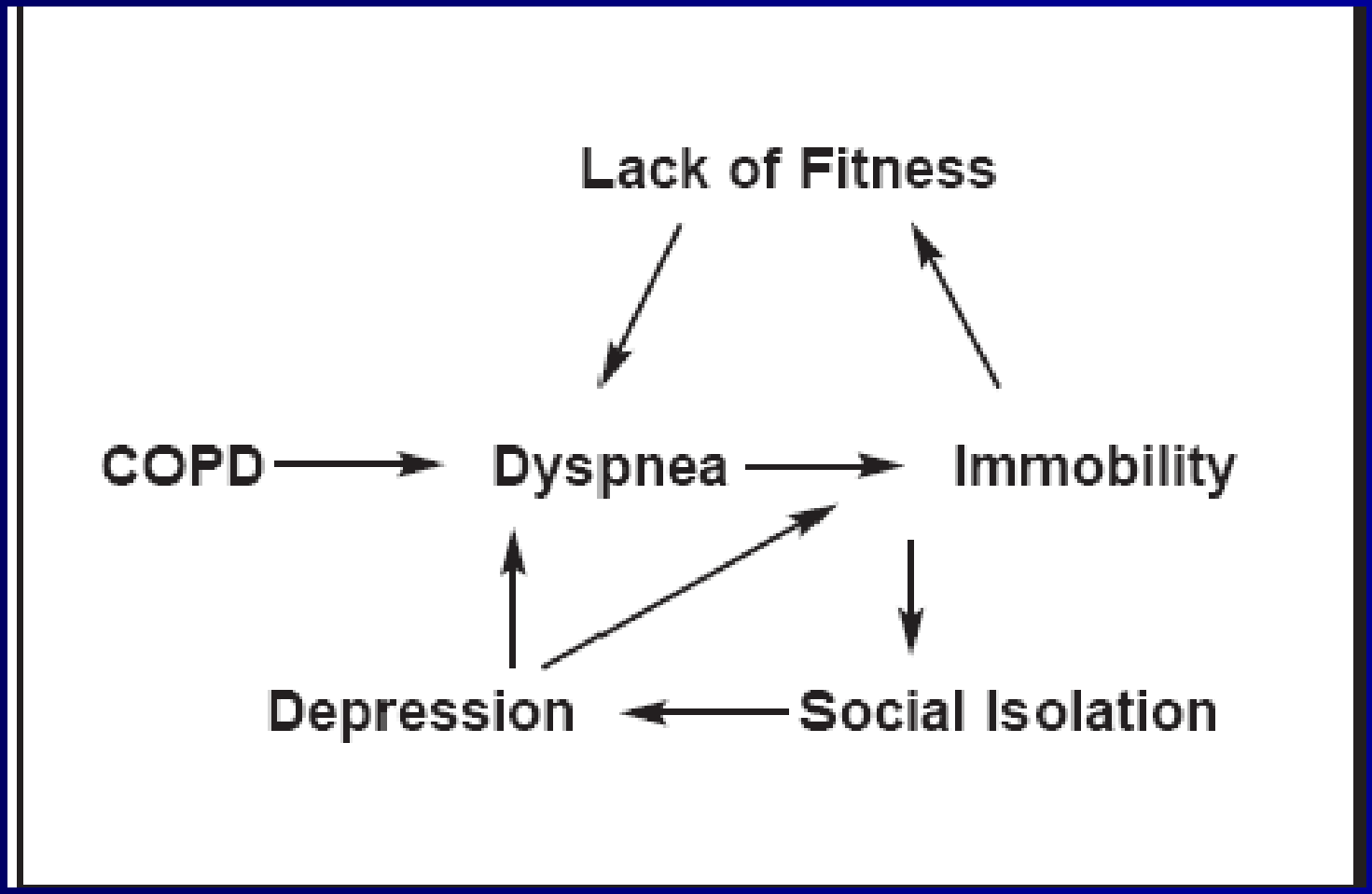
  (Cancer Detect Prev 2002; 26: 308–312)

Psychiatric disorders

- Prevalence of psychiatric disorders in COPD ranged from 30 to 58%
- Depression and anxiety appear to be the most commonly observed psychological problems in COPD
- The prevalence of depression has been estimated as between 10 and 79.1%
- The pattern and extent of cognitive dysfunction reported in COPD vary across patients, and appear to be associated with disease severity

(Hynninen KM et al.J Psychosom Res 2005;59:429–443)

The Cycle of Physical, Social, and Psychosocial Consequences of COPD



Psychiatric disorders

- Mild hypoxemia may be associated with impairment in higher cerebral functioning, including abstract reasoning, auditory and visual attention, verbal and nonverbal learning and recall, and reasoning and motor skills

- Improvement in visual memory, verbal memory, and motor speed among subjects with COPD after 6 months of continuous oxygen therapy.

  (Krop HD et al. Chest 1973;64:317–322)

- Patients with COPD after a 30-day exercise rehabilitation program that included instructional/educational components, psychosocial counseling, and stress reduction Improved complex attention

  (Emery CF et al.Chest 1991;100:613–617)

Psychiatric disorders

- Mortality is 3.11 times higher among severely depressed patients than non depressed patients
- Greater mortality at 4 years in depressed patients, even when there were no difference

(Chest 2002, 121:1441-1448)

- COPD with anxiety or depression face greater levels of cognitive decline, more functional limitations, lower self-efficacy, and more serious life events

(Kunik M et al. Chest 2005; 127(4):1205-11)

Conclusion

- COPD is a chronic inflammatory disease of the lungs
- Progression is often characterized by the development of extra-pulmonary diseases
- These systemic manifestations contribute a great deal to reduced quality of life and increased mortality in COPD patients
- Systemic manifestations of COPD should be treated aggressively, as they add to the overall morbidity and mortality of COPD patients.
- In general, smoking cessation and pulmonary rehabilitation can be recommended to patients to modify some of these processes

Take home massage

- COPD must be considered a systemic disease,
- Extra pulmonary manifestations must be considered in the evaluation of its severity
- Treatment of these manifestations could modify the prognosis of patients