COPD & NUTRITIONAL ABNORMALITIES

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Statement on Potential Conflicts of Interest

No conflict related to the current presentation

Non-Restricted Research Grants

Menarini

Advisory Committees

AstraZeneca
Boehringer Ingelheim
GSK
Teva

COPD & NUTRITION

What is COPD ?

- A common, preventable and treatable disease, characterized by airflow limitation (*FEV_1/FVC < 70 %*)

- **Significant Extrapulmonary Manifestations**

- in Skeletal Muscles (Peripheral & Respiratory muscles)
- in Nutritional Status (Body Weight & Composition)
- in the Pulmonary Circulation and Blood
- in Bones and Phosphocalcic Metabolism
- in Kidneys and Water-Electrolyte Balance
- etc...

COPD & NUTRITION

What is COPD ?

- A common, preventable and treatable disease, characterized by airflow limitation … exacerbations and **comorbidities** contribute to the overall severity in individual patients"

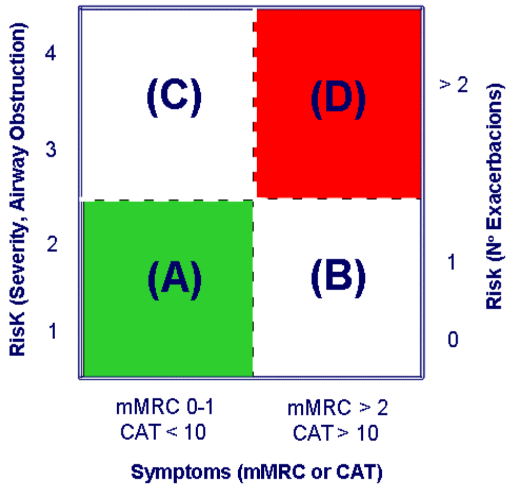
- **Frequent Comorbidities & Aging**

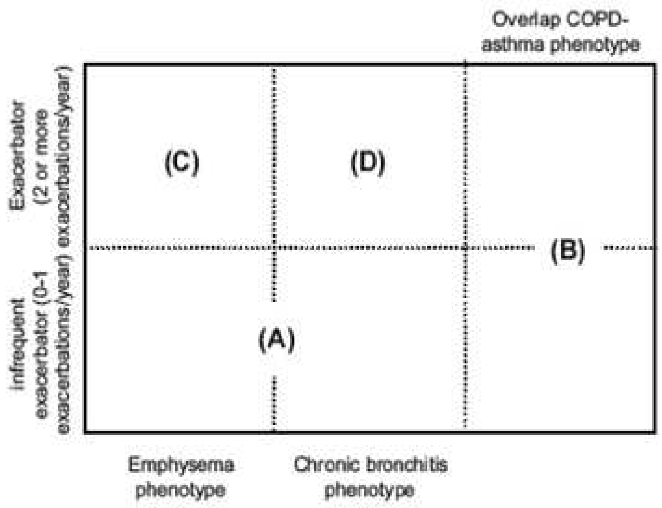
- Coronary Heart disease, Arteriosclerosis, Stroke
- Cancer (Lung, Larynx, Oropharynx, Esophagus, Bladder, Kidney...)
- Diabetes, other endocrine disorders
- Rheumatoid Arthritis

- Physiological and Pathological Aging

Nutritional abnormalities & Sarcopenia

COPD & NUTRITION





BODE Index

- B: ***B**ody-mass Index*
- O: *Airflow **O**bstruction*
- D: ***D**yspnea*
- E: ***E**xercise Capacity*

B. Celli et al. N Engl J Med 2004

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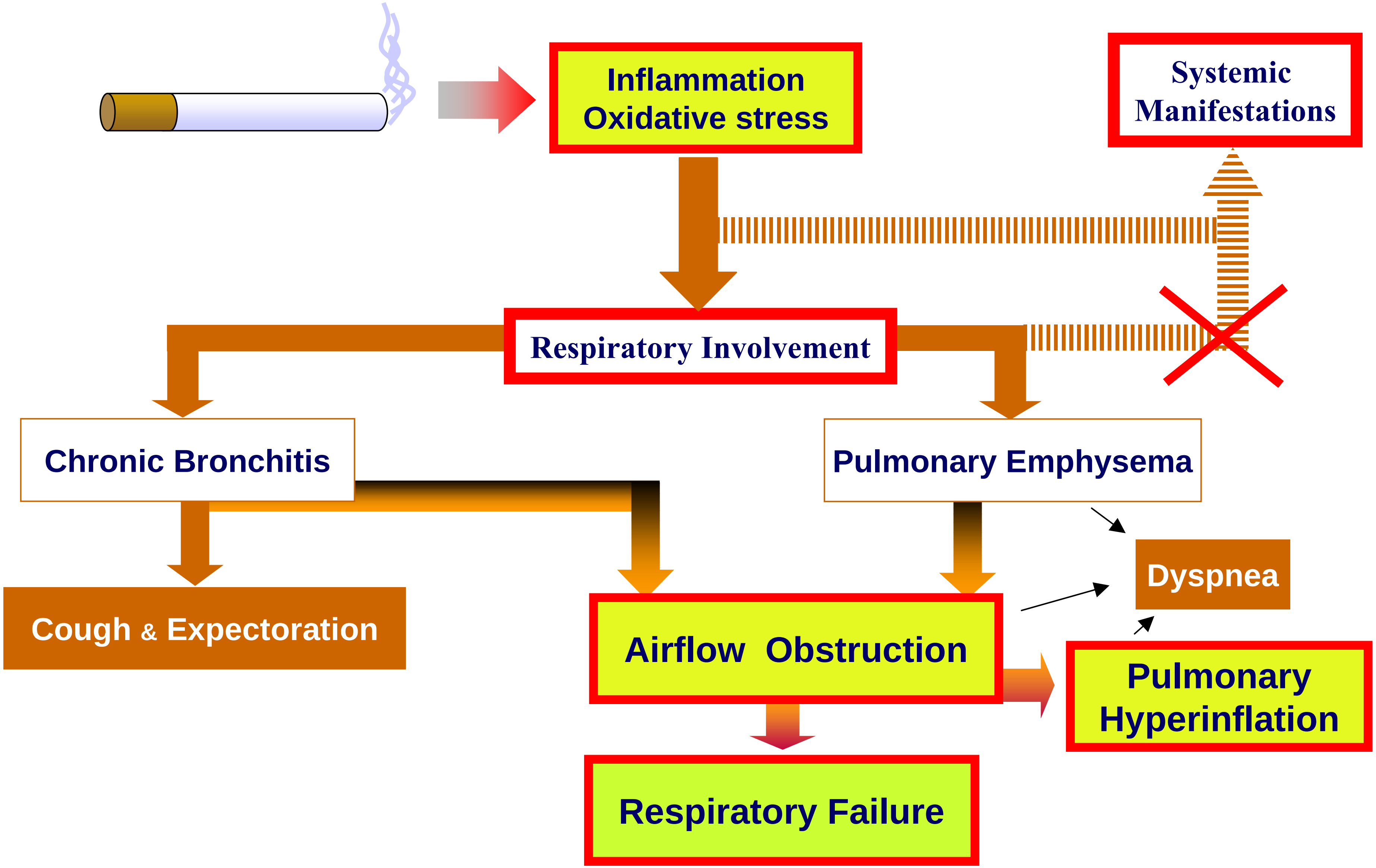

EPIDEMIOLOGY

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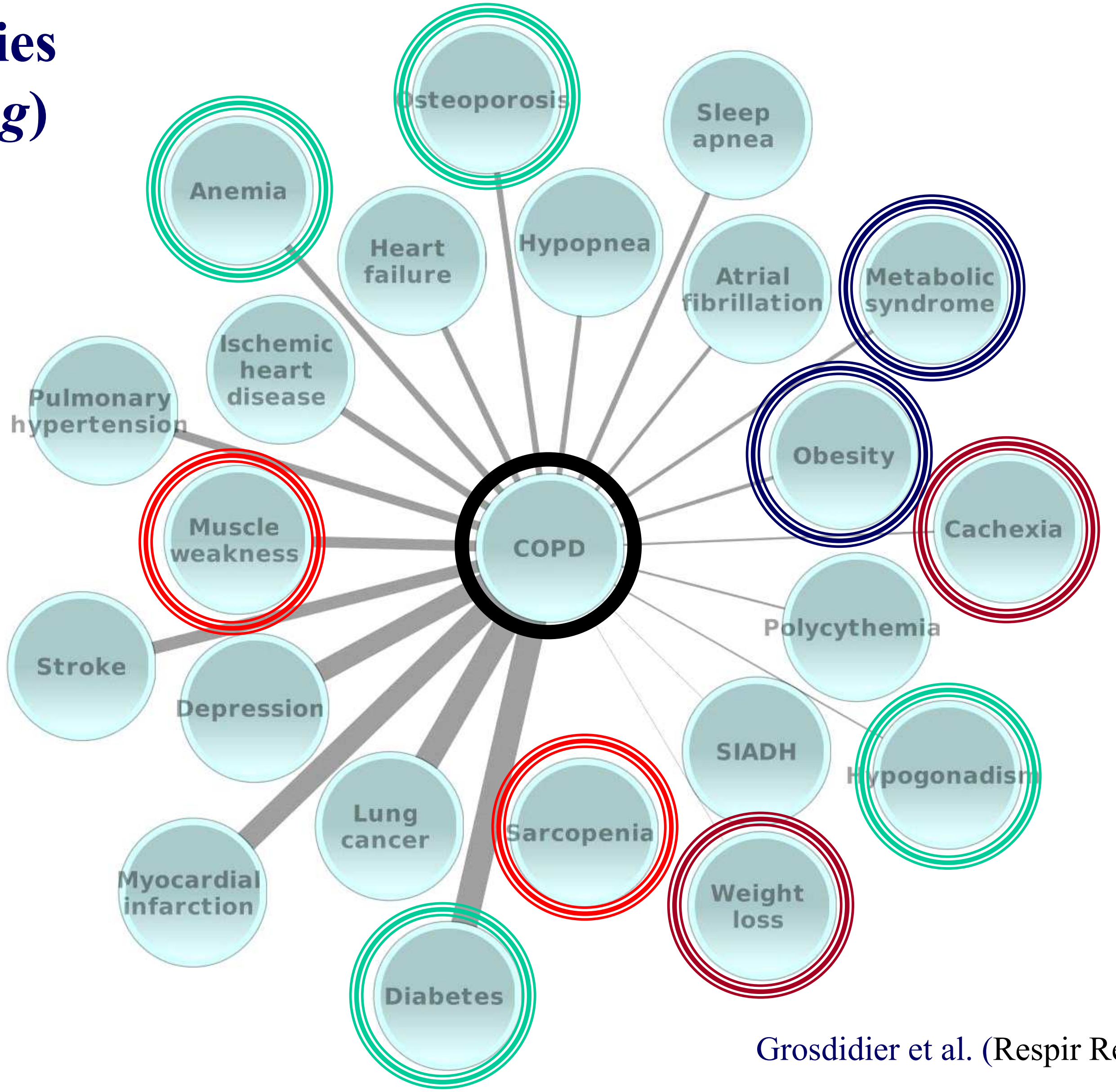
Comorbidities
(*Text Mining*)



Grosdidier et al. (Respir Res 2014;15:111)

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Nutirtional Abnormalities

Low Weight →→→ **CAQUEXIA**

- ✓ **Anorexy**
- ✓ **Weight loss**

- ★ Muscle Weakness
- ★ Exercise Limitation
- ★ ↓ **QoL**

20-25% of COPD patients from Eastern Europe (low BMI; no data on FFMI)
10-30% of COPD patients from Northern Europe & North America (20-50% low FFMI)

Wan E. Et al. AJRCMB 2011; 45:304-310; Lainscak M. et al. J Cachexia Sarco Musc 2011; 2:81-86
Sundh J. et al. COPD 2011; 8:173-181; García-Aymerich J. et al. Chest 2009: 136:62-70
Balcells E. et al. Resp Med 2009: 103:1293-1302; Vermeeren M. et al. Resp Med 2006; 100:1349-1355
Vestbo J et al. AJRCCM 2006; 173:79-83; Coronell C. et al. Clin Nutr 2002; 21:437-438

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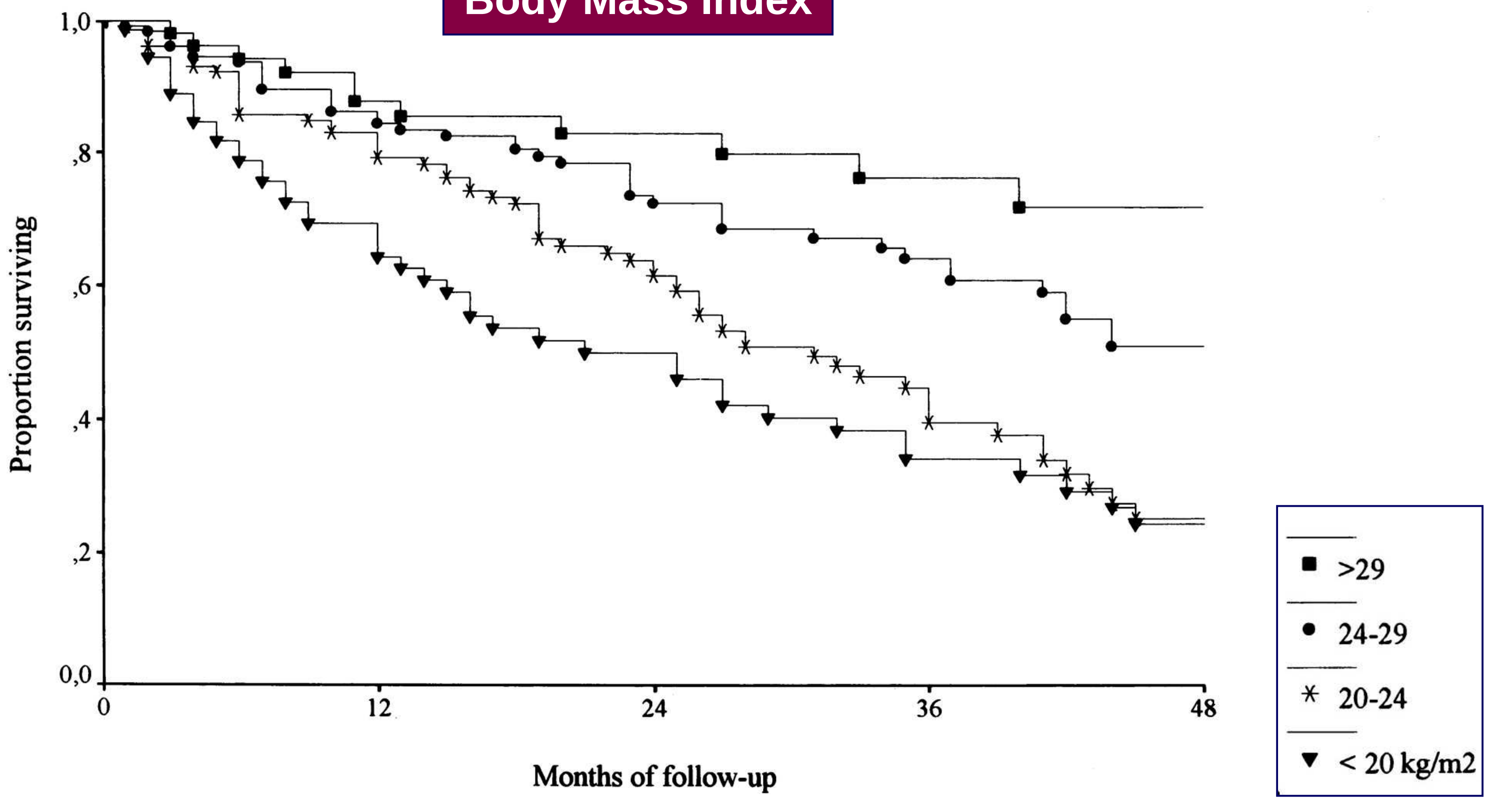
Nutrition - Body Composition

Body Mass Index



Low BMI (< 25 kg/m²): Increased risk of Death
Weight gain (> 2 kg / 8 weeks): Reduces risk of Death

Schols et al., AJRCCM 1998; 157:1791-1797

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ASSESSMENT

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ANTHROPOMETRY

BMI: Thresholds for Low BMI, ≤ 18, ≤ 20, ≤ 21 Kg/m^2

BMI *can overestimate the actual nutritional status*

Plicometer (triceps skin fold), with *Caliper*

Thigh Circumference

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BODY COMPOSITION

Humans

Water	60%	(
Lipids	20%	(
Proteins	15%	
Minerals	5%	

Image

- Radiology
- CT Scan
- DEXA (Dual-energy X-ray absorptiometry)
- MRI (Magnetic resonance imaging)
- Ultrasound

Physico-Chemical

- Electrical Bioimpedance
- Neutron analysis
- Spectrophotometry
- Solute dilution

Isotopic

- Markers in biological fluids

Densitometry

- Hydrostatic weighing

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ELECTRICAL BIOIMPEDANCE

Resistance that a body opposes to electrical current

Equations to calculate:

- Fat-free mass (FFM, Kg or %)
- Fat-free mass index (FFMI)
- Fat mass (Kg or %)
- Total body water (liters or %)
- Body Density (g/ml)

FFMI thresholds for 'Malnutrition':
≤ 16 Kg/m^2 in men, & ≤ 15 Kg/m^2 in women

FFMI: Best relationship than BMI with severity & complications

Ischaki et al. Chest 2007

FFMI: Especially useful in women (discrepancies between BIM and FFMI)

Vermeeren et al. Respir Med 2006

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DEXA (Dual-energy X-ray absorptiometry)

X-ray absortiometry of each body tissues **(bone, fat & skeletal muscle)**

- **Bone Mineral Content (BMC, gr)**
- **Bone Mineral Density (BMD, gr)**
- **Fat mass (gr, %)**
- **Fat-Free mass (FFM, gr, %)**

- **FFM + BMC (gr)**

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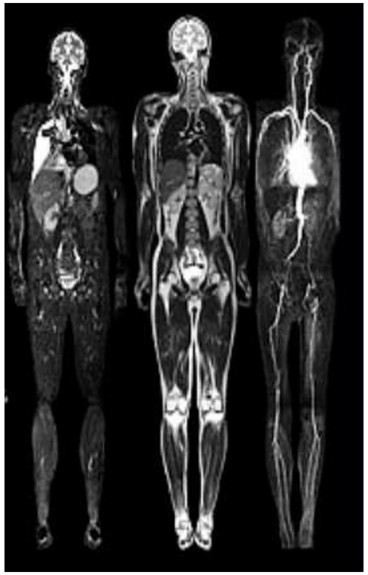
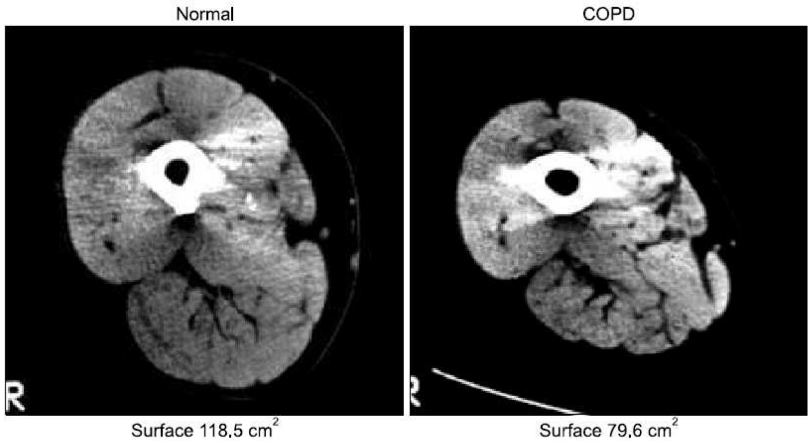
CT Scan (Computed Tomography)

Great topographic definition

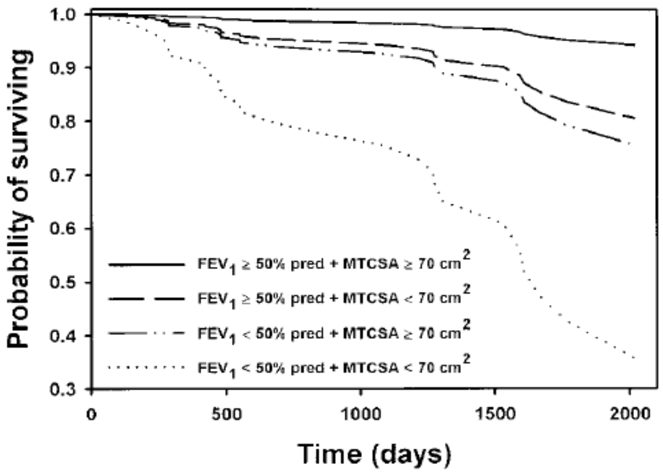
(e.g. subcutaneous fat vs.. abdominal fat, different muscles or muscle groups)

Equations





Ferrari et al. Int J Chron Obstruct Pulmon Dis 2015
Natanek et al. Muscle nerve 2013
Mathur et al. Phys Ther 2008



Marquis et al. AJRCCM 2002

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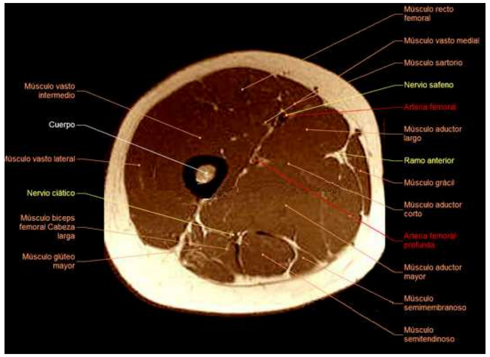
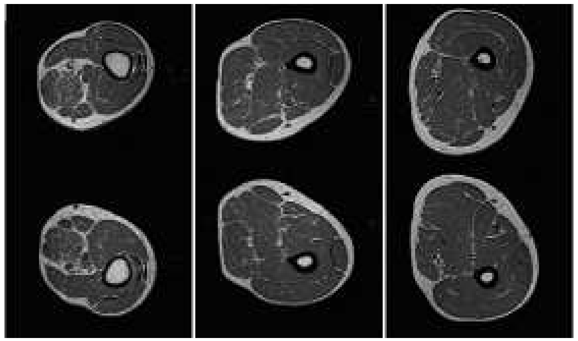
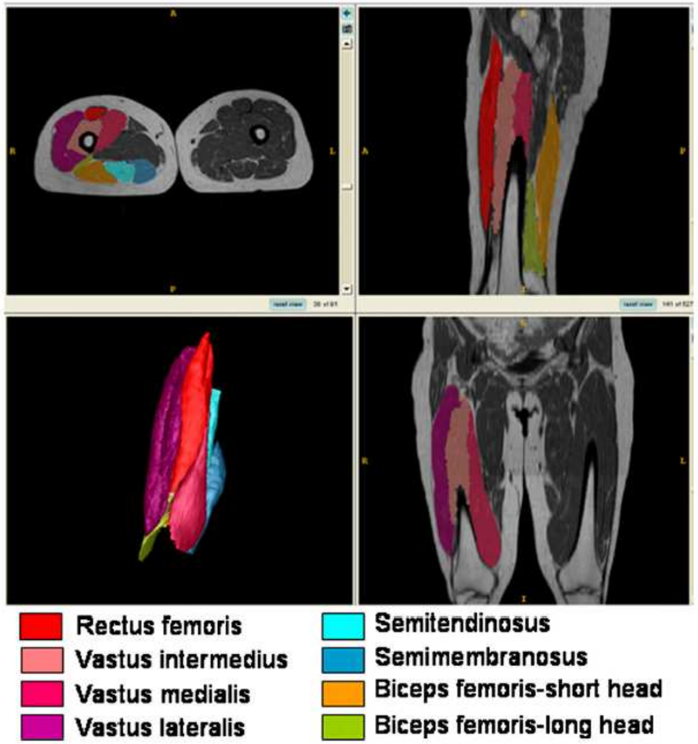
MRI (Magnetic Resonance Imaging)

Great topographic definition

(e.g. different muscles or muscle groups, muscle tissue from intramuscle fat)







HajGhanbari et al. Acad Radiol 2011

Robles et al.Med Sci Sports Exerc. 2015

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Ultrasounds

Useful for Specific Areas
(e.g. Muscle or Fat mass)

Diaphragm Image

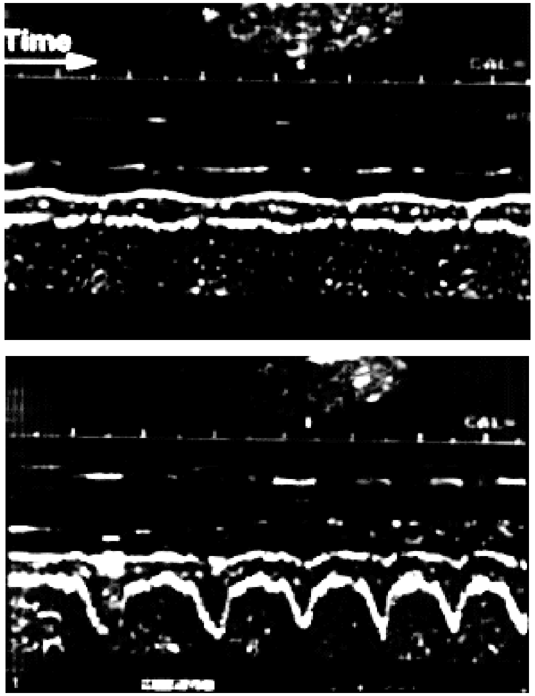
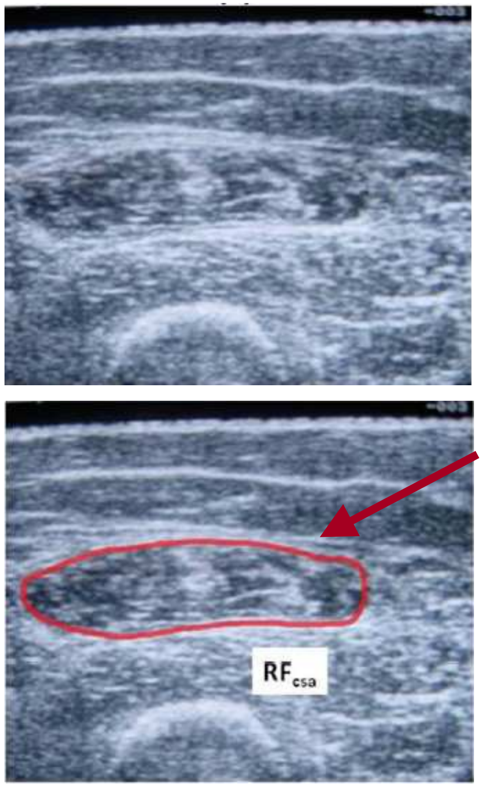


Image of a resting (top) and contracting (bottom) Diaphragm

Orozco-Levi et al. (Arch Bronconeumol 2010)

Thigh Image



Area corresponding to the *Rectus Femoris* portion of the Quadriceps muscle

Menos et al. Respir Res 2012

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Hydrostatic weighing Densitometry	Air displacement Plethysmography (ADP)

Archimedes principle
Global Body Density

General principles of plethysmography
Lean mass & Fat mass

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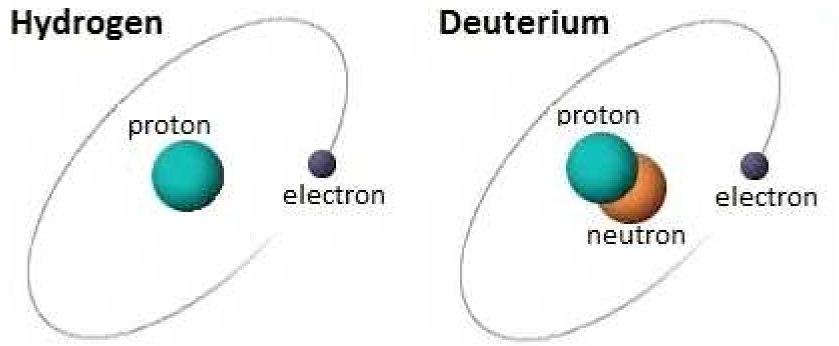
Deuterium (Deu) dilution

Mass Spectrometer: $^{2}H_2O$ (Deuterium oxide) concentration

Dilution is calculated from Deuterium administered and eliminated by urine

- Total Body Water (TBW)
- Fat Free Mass
- Fat Mass



THE SITUATION TODAY

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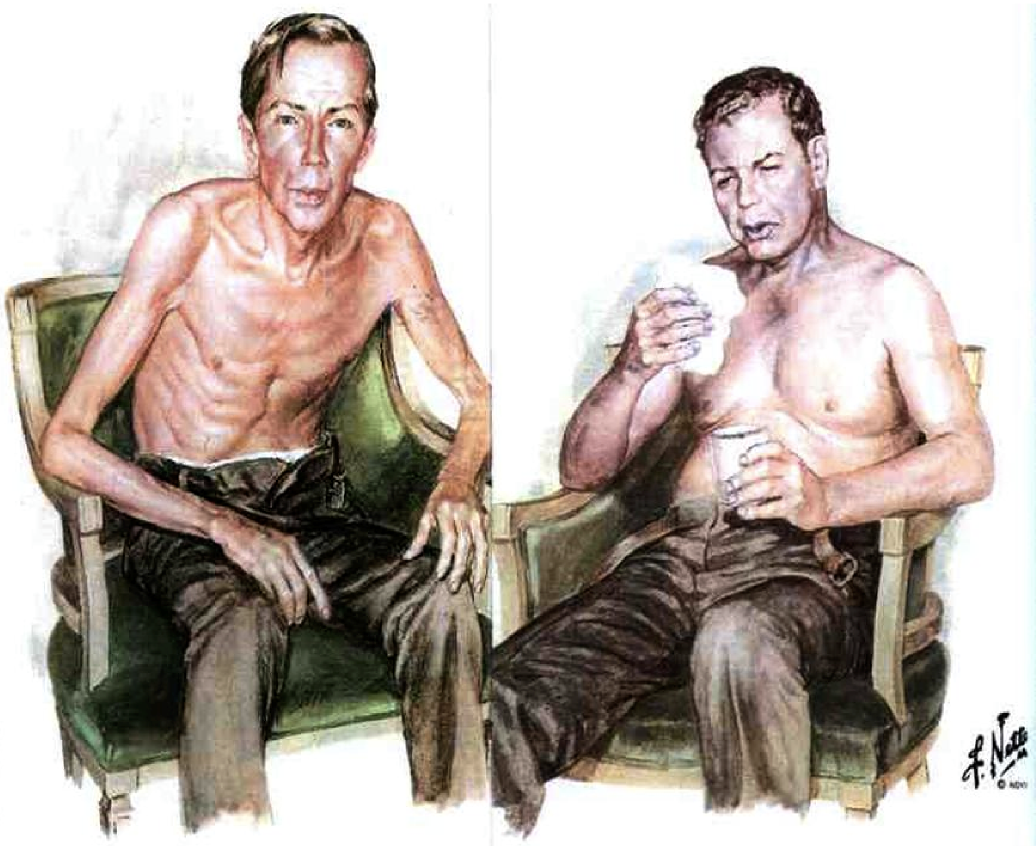
COPD PHENOTYPES



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"A phenotype is any trait or characteristic of an organism, that results from the interaction between the genotype and the environment"

"A phenotype is a characteristic of the disease that **classifies patients**, being **related to relevant clinical outcomes** (symptoms, exacerbations, response to treatments, death)"

Therefore, it involves ***specific management*** *(and ...****specific treatments****)*

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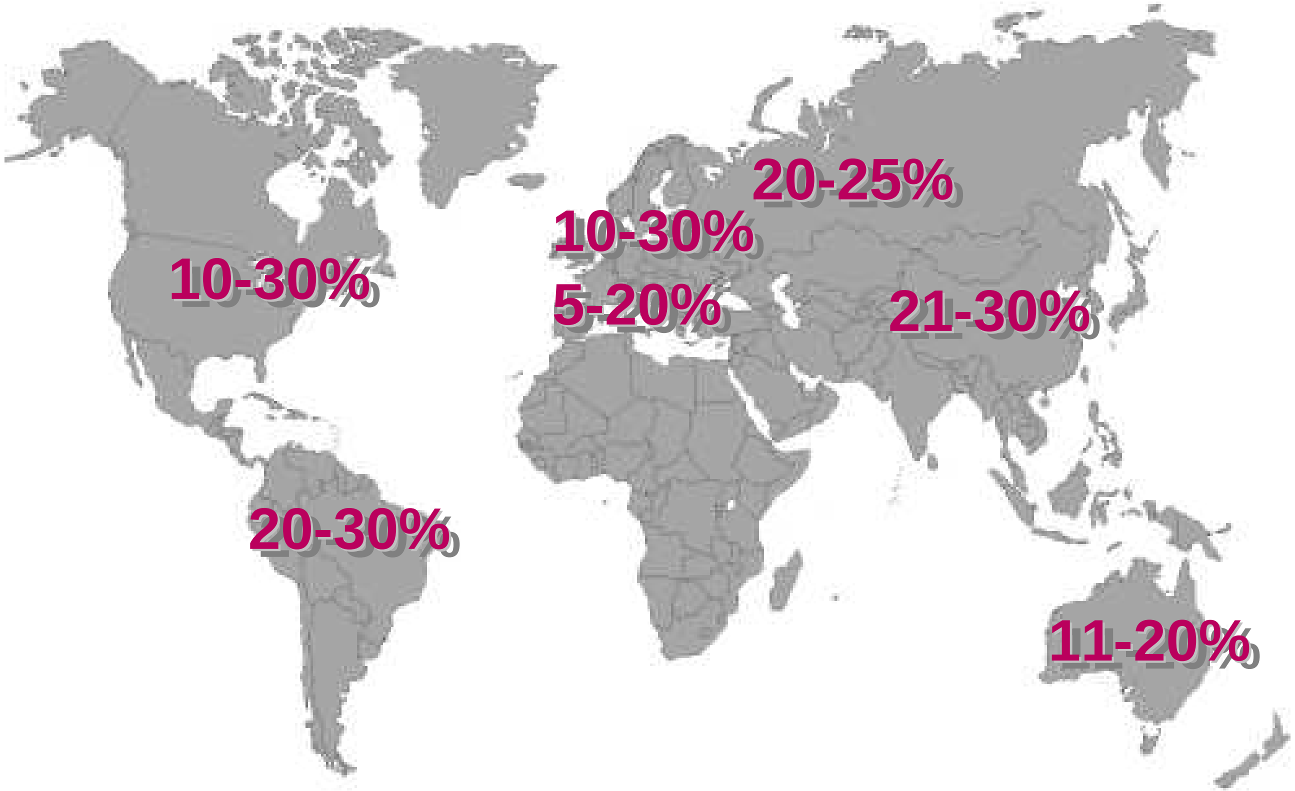
LOW BMI



Ausin P et al. Respir Med 2016; Ding Y et al. IJCOPD 2015; Costa TM et al. J Bras Neumol 2015; Monteiro F et al. Lung 2012; Wan E. Et al. AJRCMB 2011; 45:304-310; Lainscak M. et al. J Cachexia Sarco Musc 2011; 2:81-86; Sundh J. et al. COPD 2011; 8:173-181; García-Aymerich J. et al. Chest 2009: 136:62-70; Balcells E. et al. Resp Med 2009: 103:1293-1302; Humphreys K et al. Nutrition & Dietetics 2008; Vermeeren M. et al. Resp Med 2006; 100:1349-1355; Vestbo J et al. AJRCCM 2006; 173:79-83; Coronell C. et al. Clin Nutr 2002; 21:437-438

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PAC-COPD Study

Síntomas respiratorios y estado de salud
- Hipersecreción mucosa crónica
- Disnea
- Calidad de vida relacionada con la salud

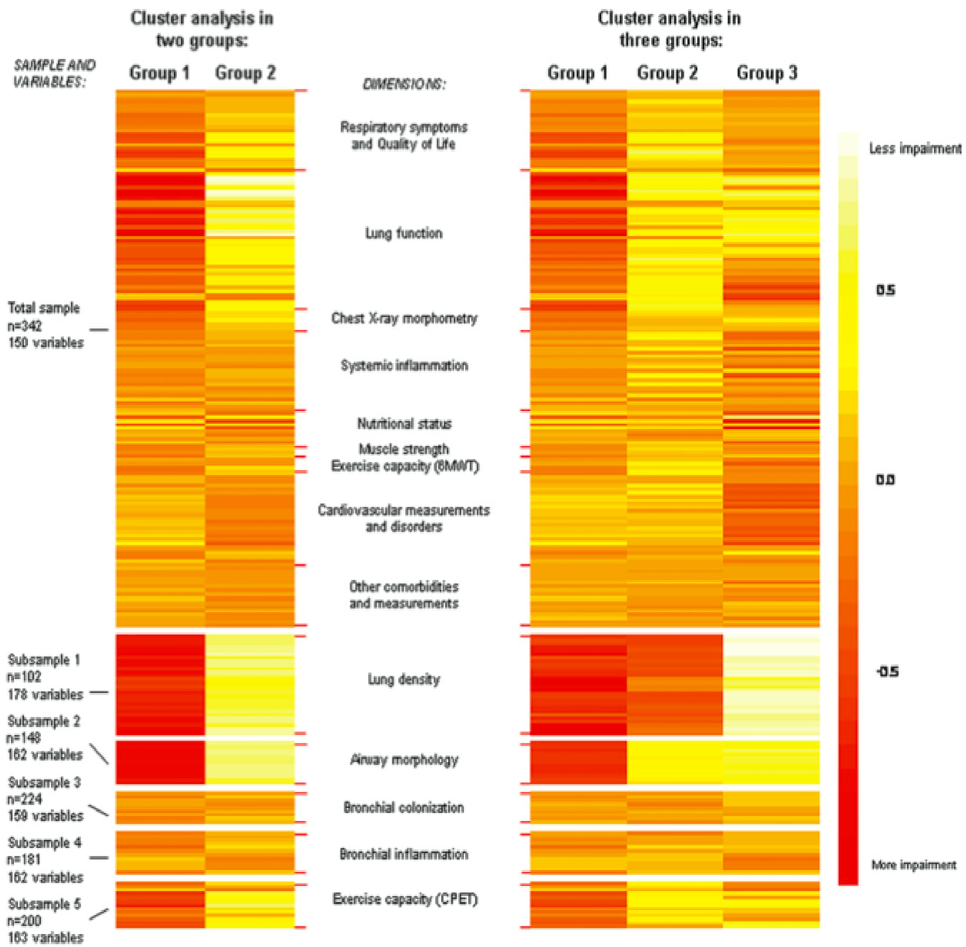
Exacerbaciones
- Exacerbaciones
- Colonización
- Infección

Anomalías de la función respiratoria
- FEV_1, FEV_1/FVC
- Gravedad (FEV_1)
- Hiperreactividad bronquial
- Reversibilidad
- Hiperinsuflación dinámica
- Capacidad inspiratoria
- Intercambio de gases: PaO_2, $PaCO_2$, DCLO

Alteraciones estructurales
- Enfisema
- Bronquitis crónica
- Bronquiolitis
- Bronquiectasia

Inflamación local y sistémica
- Inflamación local: marcadores inflamatorios o células en el esputo o tejido pulmonar
- Inflamación sistémica: marcadores inflamatorios o células en la sangre o suero
- Proteólisis
- Estrés oxidativo
- Remodelación vascular

Efectos sistémicos
- Estado nutricional
- Músculos estriados (respiratorios y periféricos)
- Capacidad de ejercicio
- Trastornos cardiovasculares



Phenotype with severe lung function impairment

Phenotype with moderate lung function impairment but hospital admissions

Systemic Phenotype (obese, dyslipidemic & cardiovascular problems)

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OBESITY

Rodriguez DA et al. Respir Med 2014; Nagorni-Obradovic LM et al. Prim Care Resp Med 2014; Dimov D et al. Chron Respir Dis 2013; García-Olmops L et al. BMC Family Practice 2013; Zhou Y et al. COPD 2013; Vozoris NT et al. Can Respir J 2012; Monteiro F et al. Lung 2012; McDonald VM et al. Age Ageing 2011; Eisner MD et al. Respir Res 2007; Steuten LM et al. Prim Care Respir J 2006

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A CLINICAL PROBLEM

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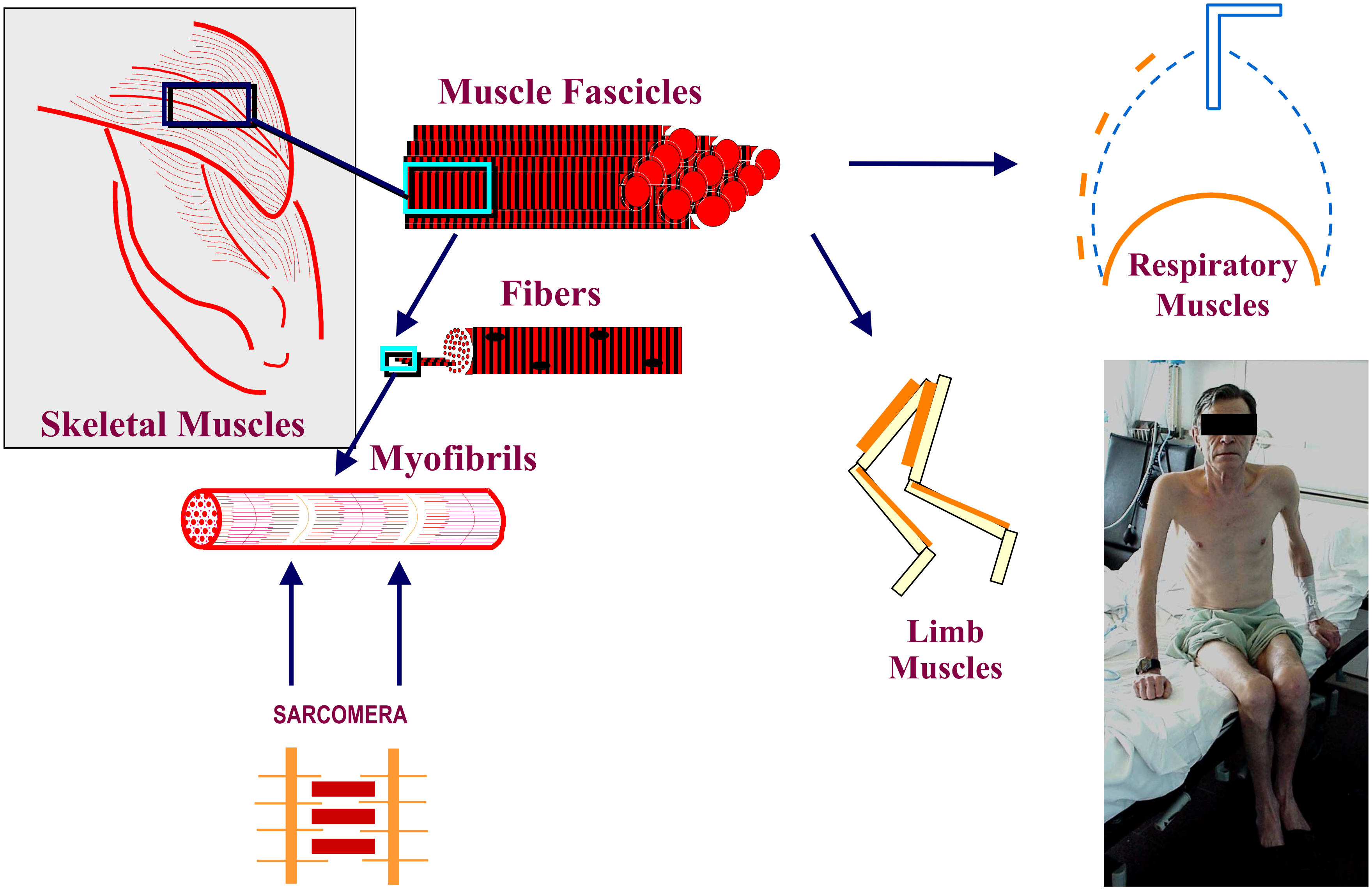

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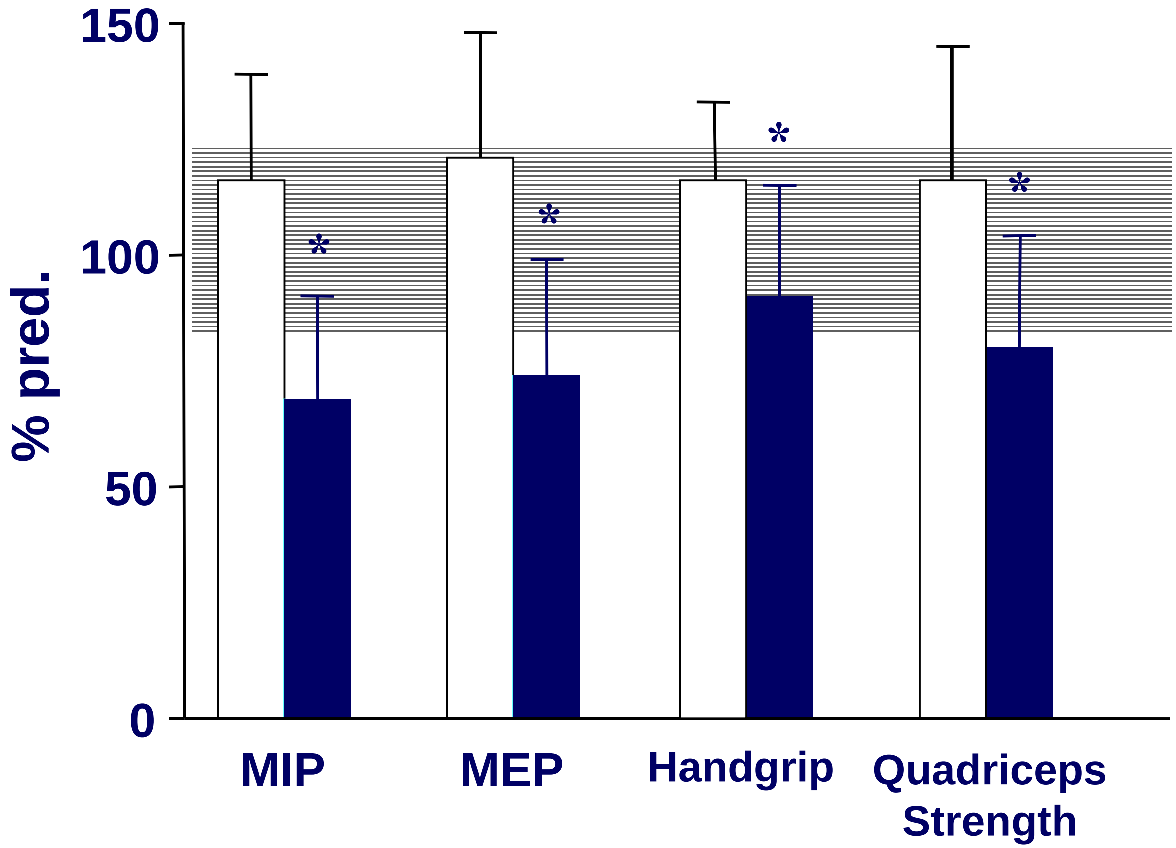
MUSCLE DYSFUNCTION



Gosselink et al. AJRCCM 1996

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Respiratory Muscles: Ventilatory Limitation

Strength and Endurance of Respiratory Muscles are both reduced in COPD

Rochester ARRD 79, Vilaró RM 2012, Ramirez-Sarmiento Thorax 2002

Reduced Ventilatory Capacity: Exercise limitation, Exacerbations

Palange JAP 2008, Gosker JAP 2008, Purro Int Care Med 2009, Ramírez-Sarmiento ERJ 2010, Vilaró RM 2012

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Limb Muscles: Exercise Limitation

Strength and Endurance of Respiratory Muscles are both reduced in COPD

Decramer ARRD 94, Hamilton AJRCCM 95
Gosselink AJRCCM 96, etc

A significant % of patients stop the exercise by lower limb symptoms

Killian ARRD 92; Hamilton, AJRCCM 95

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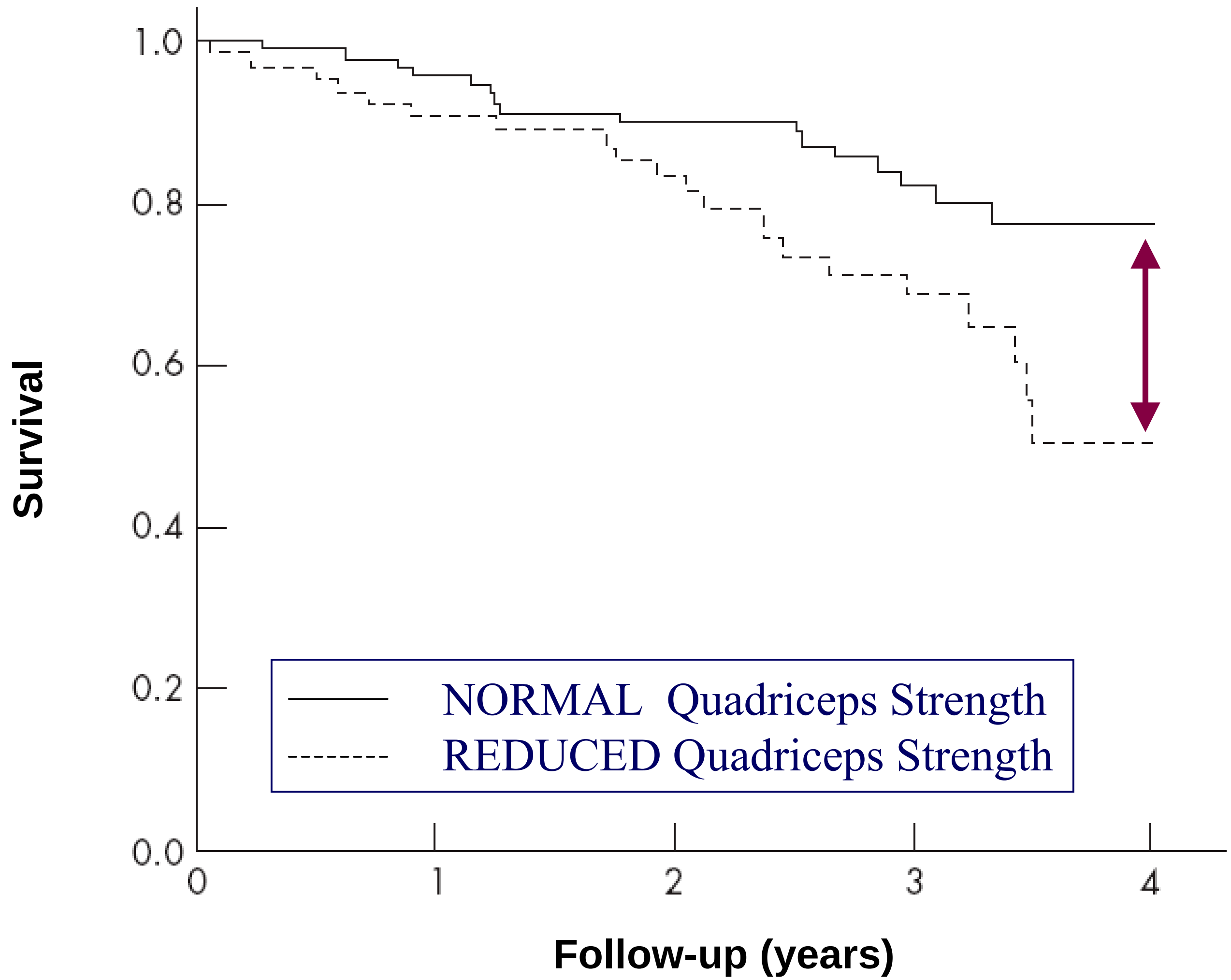

Swallow et al. Thorax 2007; 62:115-120

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MALNUTRITION in COPD

- **RESPIRATORY SYSTEM**
  Animal Models: destruction of septa, airspace elongation, tendency to collapse (↓ surfactant)

  Sahebjami et al. J Appl Physiol 1992; Sridhar Proc Nutr Soc 1999; Foley et al. J Cardiopulm Rehabil 2001; De Benedetto et al. Monaldi 2003

- **IMMUNE SYSTEM**
  Dysfunction (facilitates infections)

- **CARDIOVASCULAR SYSTEM**
  Heart Failure

- **BONES**
  Osteoporosis, ↑ Fractures

- **Other:** Anemia, coagulation problems, etc...

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FACTORS

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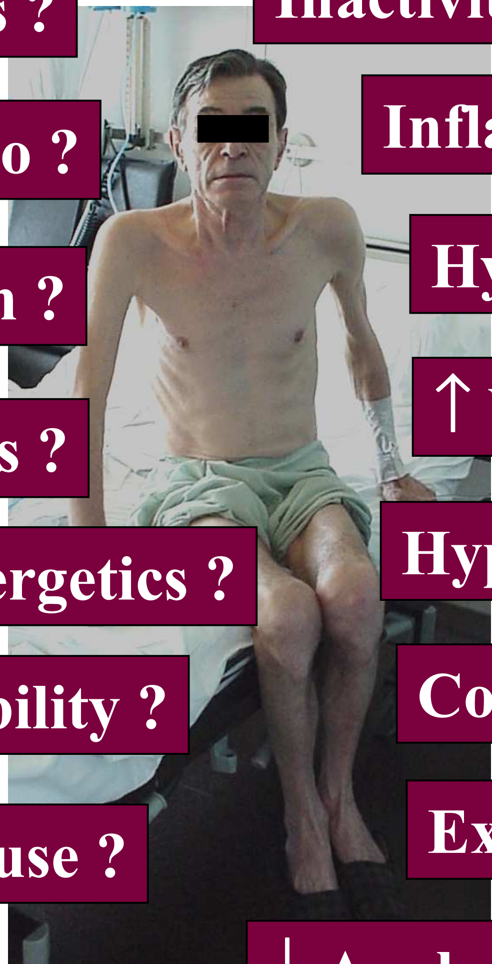

Drugs ?

Tobacco ?

Depression ?

Oxidative Stress ?

Impaired Bionergetics ?

Genetic Susceptibility ?

Alcohol abuse ?

Inactivity - Sedentarism ?

Inflammation ?

Hypoxia ?

↑ Work of Breathing ?

Hypercapnia- Acidosis ?

Comorbidities - Aging ?

Exacerbations ?

↓ Anabolic Hormones ?

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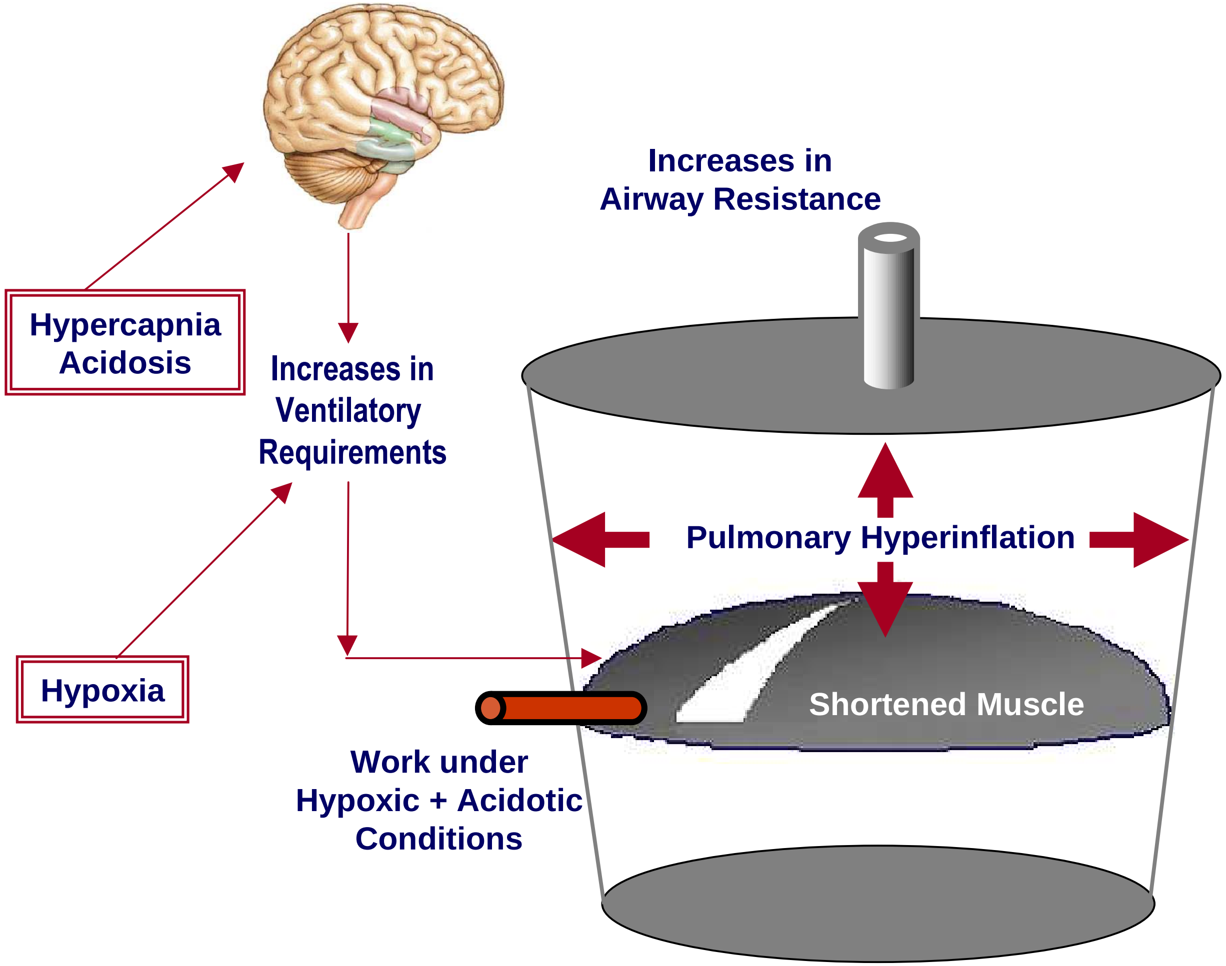
- **TOBACCO Smoking has an Anorectic Effect**
  Stop smoking: Weight gain
  Continue to smoke: Weight maintenance or loss

- **TOBACCO Smoking *per se* promotes Proteolysis and Lipolysis**
  induces Insulin resistance
  induces Skeletal Muscle Dysfunction

Degens et al. AJRCCM 2015; Rom et al Ann NY Acad Sci 2012; Lycett et al. Addiction 2011; Gastaldelli A et al. Curr Pharm Des 201o; Barreiro et al. AJRCCM 2010

COPD & NUTRITION

- **INSUFFICIENT CALORIC INTAKE** (anorexia + increased energy expenditure)



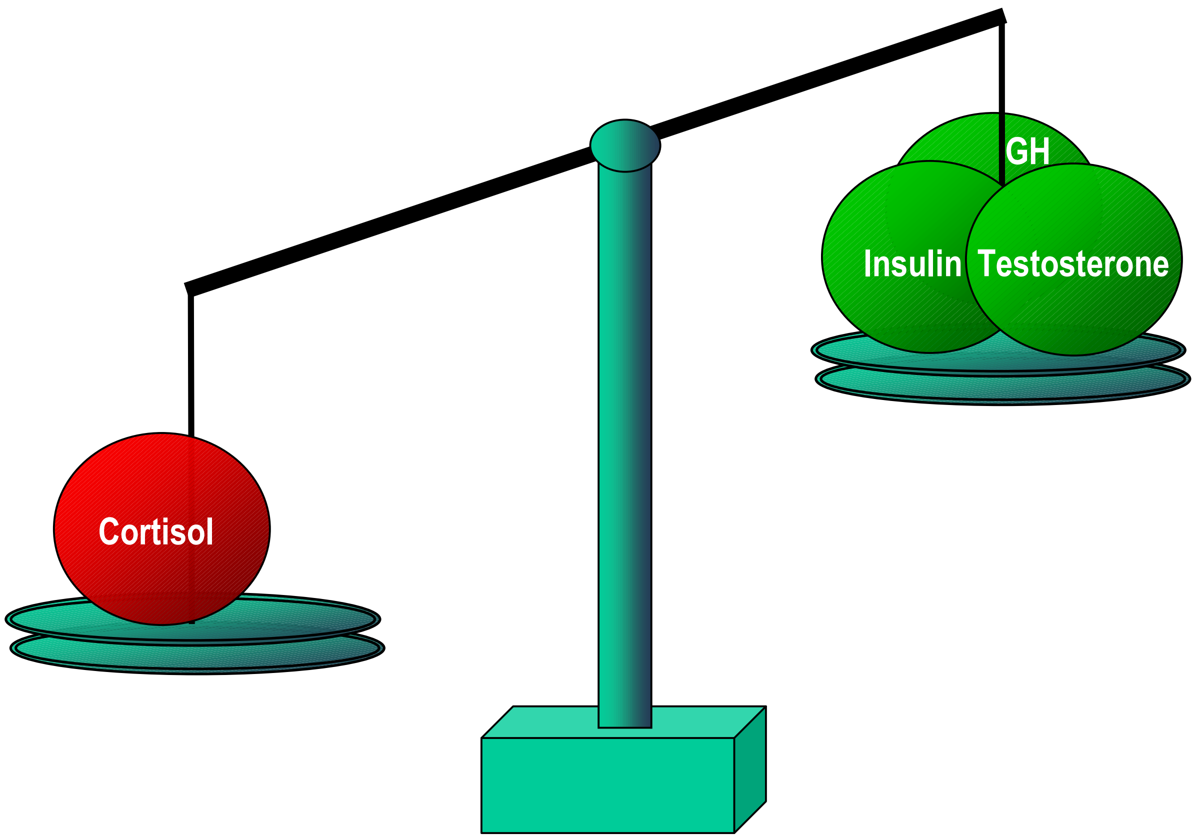
Increase in the Work of Breathing

↑ **Energy Expenditure**

Epstein, Clin Chest Med 94
Scalvini, Monaldi 96

COPD & NUTRITION

- Imbalance between Anabolic and Catabolic Hormones



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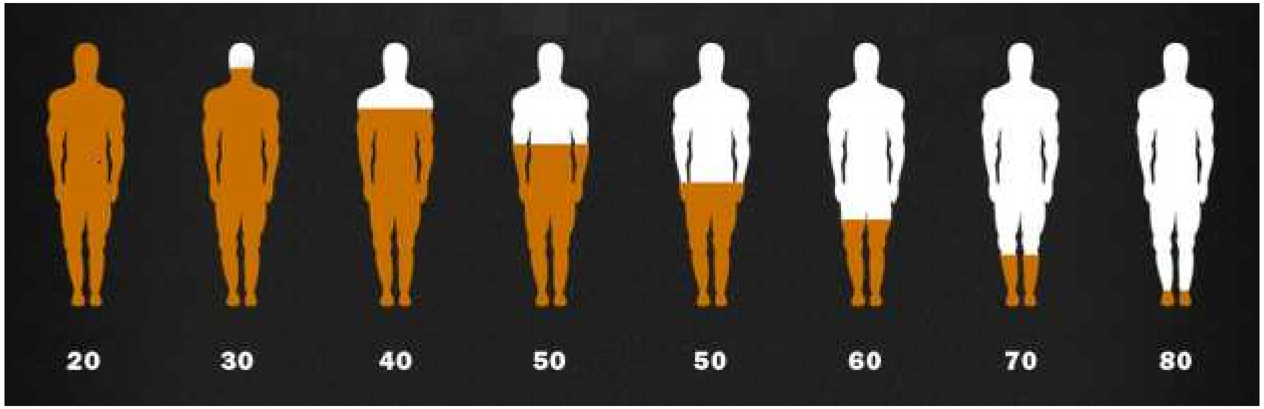
▪ HYPOGONADISM in COPD

Male Hormones regulate muscle mass
Hypogonadism is more prevalent in older people with chronic diseases



COPD

Increased prevalence of Hypogonadism (20-70 % **?**)

Little impact on muscle strength and exercise capacity

Balasubramanian et al. Curr Op Pulm Med 2012; Laghi et al. AJRCCM 2005; Van Vliet et al AJRCCM 2005; Kamischke et al. ERJ 1998; *Bhasin et al. J C Endocr Metab 2010; Debigare et al. Chest 2003*

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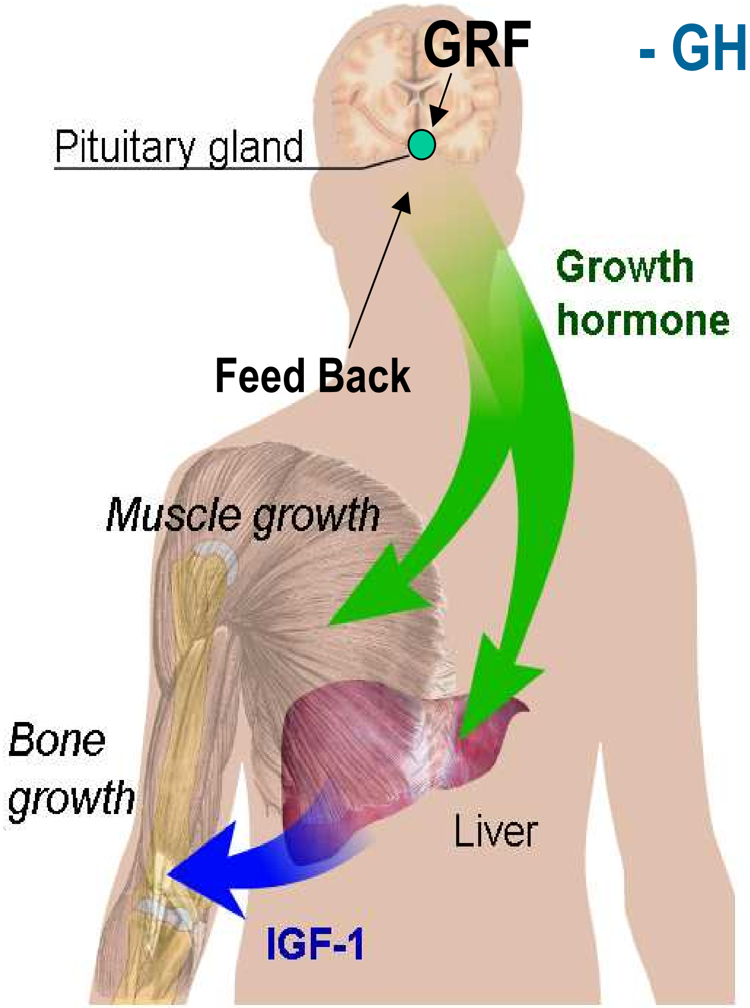
GROWTH HORMONE axis DYSFUNCTION



- GH levels in COPD can be: ↓, =, or even ↑ but

GRF *Feed back* → GH → IGF-1

GH is a Peptide Hormone

- Adenohypophysis

✓ Anabolic Effects

- Increases IGF-1: Protein Synthesis
  Lipolysis (↑ energy)
- Inhibits Protein oxidation and Catabolism

✓ Stimulates Ca^{++} retention & Bone Mineralization

✓ Promotes Muscle growth & Regeneration

✓ Improves Immune response

Anand et al Circulation 1992; Mador et al Respir Res 2001; Creutzberg et al. ERJ 2003; Wehrenberg et al Endocrinology 2003

COPD & NUTRITION

▪ HYPOXIA and NUTRITIONAL STATUS

- Hypoxia induces changes in peptides involved in food consumption
  (Leptin, Ghrelin, AMP activated proteïnkinase)
- Hypoxia is involved in Mitochondrial Biogenesis & Autophagy
  (through HF-1)
- Hypoxia induces systemic Inflammation and Oxidative Stress

▪ HYPERCAPNIA - ACIDOSIS and NUTRITION

- Hypercapnia induces Intracellular Acidosis → Inhibition of Protein Synthesis
- Hypercapnia results in a decrease in PCr & ATP/ADP ratio

Raguso et al. Nutrition 2011; Hayot et al. Mol Cell Endocrinol 2011; Gonzalez et al. Adv Exp Med Biol 2010; Howald et al. Int J Sports Med 1990; Gosker et al. ERJ 2002; Takabatake et al. AJRCCM 2000;

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EXACERBATIONS

- HYPOXIA
- HYPERCAPNIA
- DRUGS (Systemic steroids)
- DECONDITIONING
- SYSTEMIC INFLAMMATION
- NEGATIVE NUTRITIONAL BALANCE

} MALNUTRITION & Muscle Weakness

Negative protein balance
Reduced MyoD & IGF-1

Spruit et al Thorax 2003; Crul et al EJCI 2007; Troosters et al. AJRCCM 2010

COPD & NUTRITION

MANAGEMENT & THERAPY

COPD & NUTRITION

SMOKING CESSATION

Quitting smoking is the most efficient (cost-effective) measure to reduce the risk of developing COPD or stop its progression

As far as 20-40% of COPD patients continue to smoke !!

Karch A et al. Respir Med 2016; Jebrak G et al. Rev Mal Respir 2015; Donaire D et al. Arch Bronconeumol 2011; Viejo et al. Resp Med 2006

NICOTINE REPLACEMENT THERAPY (NRT) , Gum & Patches
Replacement of habituation

BUPROPION
Dishabituation. Antidepressant. Selective inhibitor of the neuronal Catecholamines & Serotonin reuptake

VARENICLINE (Champix©)
Stimulates neuronal nicotine receptors

E-CIGARETTE use (?)

COPD & NUTRITION

GETTING a BETTER ENERGY BALANCE

- **DIET ADVICE: To avoid Alcohol and choose Healthy food**
  - This is enough to maintain adequate Body Weight & FFMI

- **For Low BMI - Underweight Patients:**

NUTRITIONAL SUPPLEMENTS (High Caloric Intake, ≥ 3 m)

- Increases Body Weight & Muscle Mass
- Improves Respiratory & Limb Muscle Strength
- However, the effects are rapidly lost if suspended

NUTRITIONAL INTERVENTION + TRAINING (> 8 weeks)

- Increases Body Weight, FFMI & Muscle Mass
- Improves Muscle Strength and Exercise capacity

Berthon BS et al. Nutrients 2015; Hanson C. Et al. IJCOPD 2014; Itoh M et al. Nutrients 2013; Weekes et al. Thorax 2009; Creutzberg et al. Nutrition 2003; Efthimiou et al. ARRD 1988

COPD & NUTRITION

▶ **For Low BMI - Underweight Patients:**

APPETITE STIMULANTS

Megestrol: Synthetic derivative of Progesterone. Oral
Stimulates appetite. Antiinflammatory effects
↑ Body Weight, but by ↑ body fat
Can induce hypogonadism, PE (at high doses), CNS disorders

Taylor et al BMJ Support Palliat Care 2016; Femia et al. BioDrugs 2005; Weisberg et al. Chest 2002

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REVERSE INACTIVITY & DECONDITIONING

Optimization of Physical Activity

Rehabilitation - Physiotherapy: Training

- **Benefits**
  - Improves Lung Function
  - Improves Exercise Tolerance
  - Reduces Breathlessness
  - ↓ Hospitalizations (nº, days)
  - Reduces Anxiety & Depression
  - Improves Survival
  - Improves QoL

- **Limitations**
  - Benefits fall when programs stop

    Minitraining
  - Requires motivation

    Positive Reinforcement
  - Very limited patients ?

    Electric & Magnetic Stimulation

    Drugs

COPD & NUTRITION

AVOID HYPOXIA & HYPERCAPNIA

LTOT

Good Control of the disease (DRUGS)

NIMV

COPD & NUTRITION

COUNTERBALANCING OXIDATIVE STRESS

ANTIOXIDANTS

N-Acetyl Cysteine (NAC):

Oral (3 mmol/kg x 14 d) vs. placebo, 12 dogs

High respiratory loads induce muscle oxidative stress (DPHG)

- NAC reduces musle oxidative stress

Barreiro et al. J Appl Physiol 2006

Ascorbate:

IV (2 g) vs. placebo. Crossover trial. 10 COPD patients

- Ascorbate reduces systemic oxidative stress
- Ascorbate reduces limb muscle fatigue during exercise

Rossman et al. Am J Regul Integr Comp Physiol 2013

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COUNTERBALANCING OXIDATIVE STRESS

DIET ANTIOXIDANTS

- **3000 COPD patients (Italy, Finland & The Nederlands)**
- ***Outcome*: Mortality at 20 years**
- **Adjusted by age and tobacco**

Fruit Consumption
Vitamin E
} **Reduce Mortality**

Intervention: To increase fruit 100 g/day la fruta → reduces Mortality by 24%

Walda et al. Eur J Clin Nutr 2002

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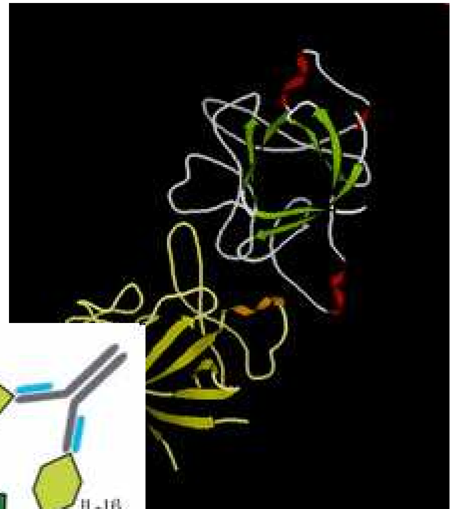
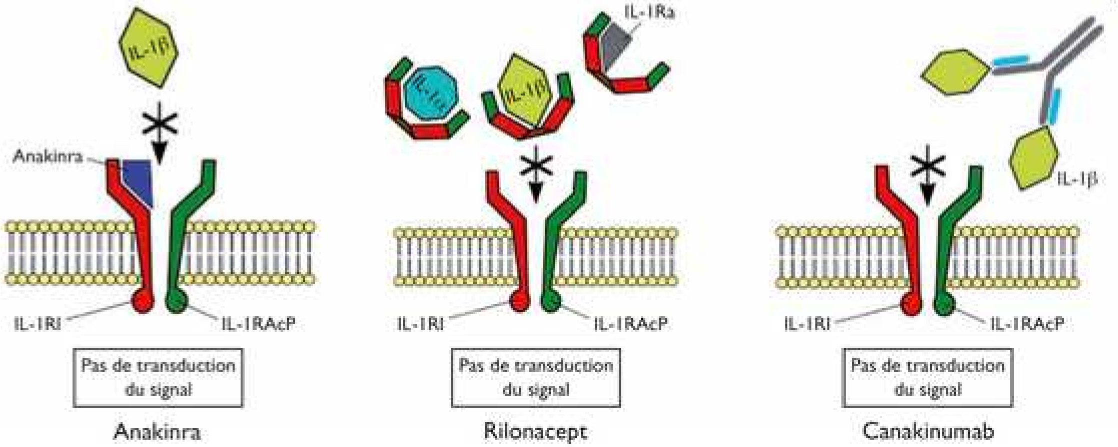
COUNTERBALANCING SYSTEMIC INFLAMMATION

►

Anti-IL6 (Tocilizumab)

Anti-IL1 (Anakinra, Canakinumab)





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Rennard et al. AJRCCM 2007

HYPOGONADISM

TESTOSTERONE

- **Powerful Anabolic Drug. IM or Transcutaneous**
  ↑ Protein Synthesis & ↓ Proteolysis. ↑ Lipolysis
  ↑ Muscle Mass & ↓ Fat Mass
  Side effects: Prostate cancer growth, virilization
  These side effects can be avoided with SARMs (selective modulators of androgen receptors)

ATS-ERS Statement 2014; Dalton et al. J Cachex Sarco Mus 2011

- 47 ♂ COPD patients with hypopgonadism (mild underweight)
  - Testosterone (IM, 1/day x 10 weeks) *vs.* placebo, +/- Training
    - Testosterone levels increase
    - ↑ Muscle Mass, ↑ Limb Muscle Strength
    - Greater effects + Training

Casaburi et al. AJRCCM 2004

COPD & NUTRITION

HYPOGONADISM

OXANDROLONE

Analogous to Testosterone, similar effects. Oral

ATS-ERS Statement 2013

- Open clinical trial, 55 underweight COPD patients (both sexes)
  Oxandrolone, Oral 1/12 h x 4 months
  - ↑ Body weight by ↑ Fat Free Mass. No improvement in exercise tolerance

Yeh et al. CHEST 2002

- Multicenter, randomized, placebo-controlled clinical trial
  142 underweight COPD patients (both sexes)
  Oxandrolone, Oral
  - ↑ Body weight by ↑ Fat Free Mass. No improvement in exercise tolerance

Casaburi et al. CHEST 2002 (abstract)

HYPOGONADISM

NANDROLONE

- 215 COPD (♂ & ♀) (110 low weight) under Rehab
  - Nutritional Intervention (hypercaloric diet) *vs.*
  - Nutritional Intervention (hypercaloric diet) + Nandrolone (IM, low dose, 1/15 days x 8 weeks)
    - ↑ Body Weight, ↑ Fat Free Mass
    - ↑ Respiratory Muscle Strength

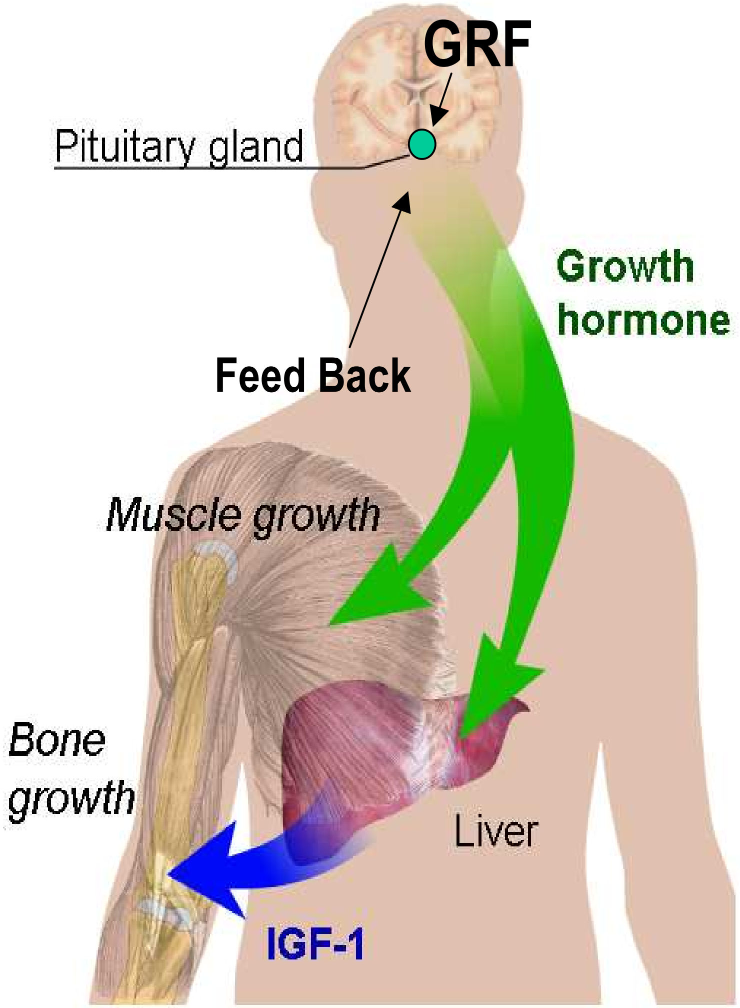
Schols et al. AJRCCM 1995

- Double-blind, randomized, placebo-controlled.
  63 underweight COPD (♂)
  - Nandrolone (IM, low dose, 1/15 days x 8 weeks
    - ↑ Body Weight, ↑ Fat Free Mass
    - = Muscle function, = Exercise capacity

Creutzberg et al. Chest 2003

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY



✓ **Administration:** Recombinant GH (rhGH)
Sbc, 0.05-0.06 mg/kg/day, ≥ 3 weeks
Side effects +++

✓ **in Healthy subjects:**

↑ Body weight & ↑ Muscle mass

↑ Respiratory muscle strength
~ Limb muscle strength

Exercise capacity: ~ VO_2max & W*R*max
↑ lactate

Graham et al GH IGF Res 2007; Liu et al Ann Intern Med 2008; Meinhardt et al. Ann Intern Med 2010

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

7 malnourished C… …D (FEV$_1$ 39% pred.)
No controls
Recombinant GH … …c (x 3 weeks)
- ↑↑ **Body weigh… …& Muscle mass**
- ↑ **Respiratory …P, HG & 6'WD**

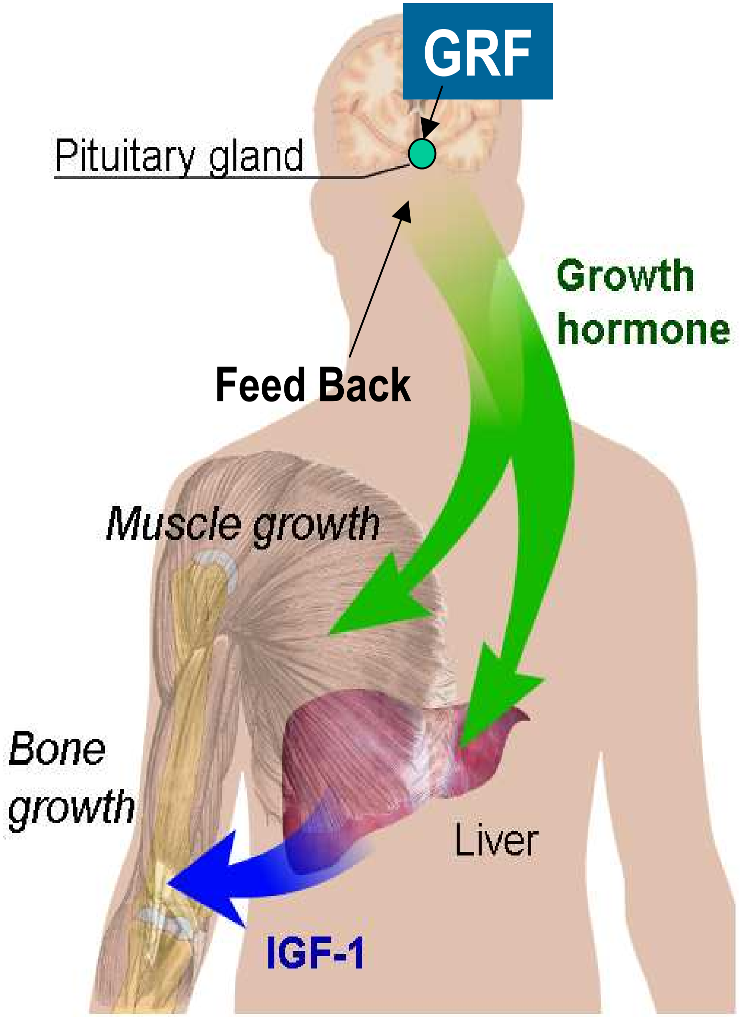
L. Burdet, 1997

Exercise capacity ?

Gullett N. et al. Am J Clin Nutr 2010; 91:1143-1147; Burdet L.et al. AJRCCM 1997; 156:1800.1806; Pape G. et al. Chest 1991; 99:1495-1500

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY



GRF (GH Releasing Factor) (GHRH)

Peptide (40- 44- AA)
GH secretion pulses recovered

Limited usefulness for therapy:

- Intersubject variability in GH response
- Fast degradation in plasma (only 2 h effect)

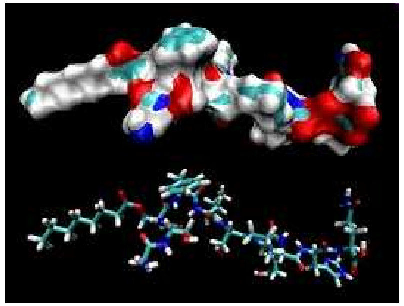
Maltais et al. AJRCCM 2014; Zhu ZS et al. ZNKZZ 2012; Wang et al Expert Opin Invest Drugs 2009; Chappel et al. Clin Endocrinol 1999;

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

GHRELIN (GH Secretagogue)

❖ **Endogenous ghrelin may be ↑ in Underweight COPD patients … (compensatory?)**

Small Peptide hormone (28 AA)
Many different tissues (stomach, pancreas, brain, kidney, lung …)



✓ **Anabolic agent**
- Induce release of GH:
↑ Protein synthesis, ↑ Lipolysis (energy), ↓ Protein oxidation & degradation,
↑ Ca^{++} retention, ↑ Immune response

✓ **Oregixen** (↑ appetite) & ↑ Gut motility

✓ **Antiinflammatory:** ↓ Cytokine levels

✓ **Cardiovascular**: Protects myocardium from ischemia/reperfusion injury
vasodilator (NO), probably angiogenic...

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

GHRELIN in Underweight COPD patients

7 malnourished COPD patients (FEV$_1$ 52% pred.)

Ghrelin IV x 3 weeks

↑ Food intake, ↑ Body weight & ↑ Muscle mass

↑ Limb (HG) & ↑ Respiratory muscle strength (MIP)

↑ Exercise capacity (6'WD)

Antiinflammatory effects on the lung

N. Nagaya, 2005; 128:1187-93

Multicenter, randomized, double-blind, controlled with placebo

Ghrelin (IV x 3 weeks) +/- Training

33 Underweight COPD patients (FEV$_1$ 33% pred.)

↓ Symptoms & ↑ QoL (MRC & SGRQ)

↑ Respiratory muscle strength, = Limb muscle strength

= Food intake, = Body weight, = Muscle mass

= Exercise Capacity (6'WD)

Miki K et al PLoS One. 2012;7(5):e35708; BMC Pulm Med 2013; Lung 2015; J Physiol Sci 2015; Clin Respir. J 2015

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

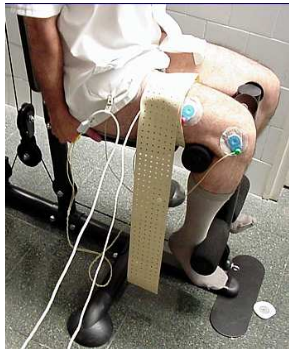
Tesamorelin (ThGRF1-44), (GH Secretagogue)

GRF Analogue. Peptide (44 A **Capromorelin** n: Sbc, 2 mg/day (8 h effect)
Very stable, main **MK-677** vity in plasma. Minor side effects but elevated price

✓ **Anabolic** (↑ GH & IGF-1): ↑ Protein synthesis **Examorelin** is,
↑ Lipo **Sermorelin** ↑ **Ipamorelin** ↑ Immune response

✓ **Administration:** Sbc, 2 m **Tabimorelin**

Multicenter, randomize GHRP-2 lind, *LAB GHRH* controlled study
16 (8 vs 8) COPD patients (FEV **GHRP-6**
Tesamorelin , **sbc 2 mg/d**
↑ **Body weight & ↑ M SM-130, 686**
↑ **Limb & ↑ Respirato**ry Muscle Stre**ngth**



Abstracts: Maltais et al ERJ 2004; Schols et al ERJ 2004; Maltais et al Proc Am Thorac Soc 2005. Citat a Gross J COPD 2011. NO paper published...

THANK YOU

COPD & NUTRITION

Vitamina D

Déficit en Vit D muy prevalente en EPOC (sobre todo EPOC grave)

Janssens et al. Thorax 2010; Romme et al. Ann Med 2013; Jackson et al. Eur Respir J 2013

- Ensayo clínico, aleatorizado, controlado con placebo
  36 EPOC, Vit D (2000 UI/día x 6 semanas, oral) *vs* placebo,
  Vitamina D *en régimen corto*: No cambia capacidad física (escala SPPB)

Bjerk et al. Int J Chron Obstruct Pulmon Dis 2013

- Ensayo clínico, aleatorizado, controlado con placebo
  182 EPOC, Vit D (100 000 UI/mes) *vs* placebo,
  Post-hoc de los 50 que además hacían Rehabilitación
  - Rehab + Vitamina D, ↑ Fuerza de m. Inspiratorios
  Tendencia en m. Espiratorios y m. Cuádriceps

Hornikx et al. Respir Res 2012

COPD & NUTRITION

Aminofilina

- Ensayo aleatorizado, controlado con placebo
  15 EPOC
  - **Teofilina** EV (dosis terapéuticas)
    Aumenta fuerza diafragma (20%)
    Evita la fatiga ante cargas respiratorias

Murciano et al. NEJM 84

Beta-agonistas

- Ensayo aleatorizado, doble ciego, controlado con placebo
  11 EPOC, **Albuterol** vs placebo
    Aumenta fuerza diafragma pero por ↓ hiperinsuflación

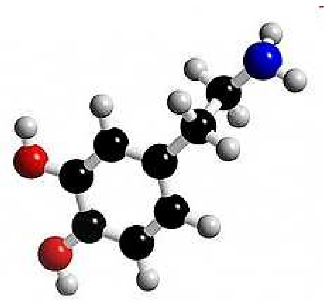
Hatipoglu et al. AJRCCM 99

- Ensayo aleatorizado, doble ciego, controlado con placebo
  16 EPOC, **Broxaterol** vs placebo
    Sin efectos en fuerza, mejora la resistencia de m. Respiratorios

Nava et al. Chest 92

COPD & NUTRITION

Dopamina



- 8 EPOC en VM. Sin grupo control
  - **Dopamina** EV (10 µg/kg/min x 30')

    Aumenta fuerza diafragma (30%)

    Aumenta $\dot{Q}_T$ y flujo sanguíneo al diafragma

Aubier et al. Ann Intern Med 89

Sensibilizadores al Calcio

Se unen a Troponina C i facilita su interacción con el Ca^{++}

Así mejora la contractilidad. También vasodilatadores (aporte de O_2)

Levosimendan IV o Oral. Efecto 70 h. Escasos efectos secundarios

Más efectos en fibras tipo I

Mejora contractilidad de fibras de diafragma de EPOC (*in vitro*)

Mejora resistencia del diafragma de sano (*in vivo*)

VanHees et al. AJRCCM 2009; Doorduin et al. AJRCCM 2012