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
What is COPD?

- A common, preventable and treatable disease, characterized by airflow limitation ($\text{FEV}_1/\text{FVC} < 70\%$)

**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...
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

**Nutritional abnormalities & Sarcopenia**
BODE Index

- B: Body-mass Index
- O: Airflow Obstruction
- D: Dyspnea
- E: Exercise Capacity

COPD & NUTRITION

Inflammation
Oxidative stress

Systemic Manifestations

Respiratory Involvement

Chronic Bronchitis
Cough & Expectoration

Pulmonary Emphysema
Dyspnea

Airflow Obstruction
Pulmonary Hyperinflation

Respiratory Failure
COPD & NUTRITION

EPIDEMIOLOGY
Comorbidities (Text Mining)

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

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
COPD & NUTRITION

ASSESSMENT
ANTHROPOMETRY

**BMI:** Thresholds for Low BMI, ≤ 18, ≤ 20, ≤ 21 Kg/m²

*BMI can overestimate the actual nutritional status*

Plicometer (triceps skin fold), with *Caliper*

Thigh Circumference
BODY COMPOSITION

Humans

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>60%</td>
</tr>
<tr>
<td>Lipids</td>
<td>20%</td>
</tr>
<tr>
<td>Proteins</td>
<td>15%</td>
</tr>
<tr>
<td>Minerals</td>
<td>5%</td>
</tr>
</tbody>
</table>

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
COPD & NUTRITION

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/m² in men, & ≤ 15 Kg/m² 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*
DEXA (Dual-energy X-ray absorptiometry)

X-ray absorptiometry 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)
CT Scan (Computed Tomography)

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

Equations

Natanek et al. Muscle nerve 2013
Mathur et al. Phys Ther 2008

Marquis et al. AJRCCM 2002
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
Ultrasounds

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

Diaphragm Image

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

Thigh Image

Area corresponding to the Rectus Femoris portion of the Quadriceps muscle

Orozco-Levi et al. (Arch Bronconeumol 2010)

Menos et al. Respir Res 2012
Hydrostatic weighing
Densitometry

Archimedes principle
Global Body Density

Air displacement
Plethysmography (ADP)

General principles of plethysmography
Lean mass & Fat mass
Deuterium (Deu) dilution

Mass Spectrometer: $^2\text{H}_2\text{O}$ (Deuterium oxide) concentration

Dilution is calculated from Deuterium administered and eliminated by urine
- Total Body Water (TBW)
- Fat Free Mass
- Fat Mass

![Deuterium and hydrogen comparison](image1.png)
THE SITUATION TODAY
COPD PHENOTYPES
“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)
COPD & NUTRITION

LOW BMI

Phenotype with severe lung function impairment
Phenotype with moderate lung function impairment but hospital admissions
Systemic Phenotype (obese, dyslipidemic & cardiovascular problems)
OBESITY

COPD & NUTRITION

A CLINICAL PROBLEM
COPD & NUTRITION

Skeletal Muscles

Muscle Fascicles

Fibers

Myofibrils

SARCOMERA

Respiratory Muscles

Limb Muscles

COPD & NUTRITION

COPD & NUTRITION
COPD & NUTRITION

MUSCLE DYSFUNCTION

Gosselink et al. AJRCCM 1996
Respiratory Muscles: Ventilatory Limitation

Strength and Endurance of Respiratory Muscles are both reduced in COPD

*Rochester ARRD 79, Vilaró RM 2012, Ramírez-Sarmiento Thorax 2002*

Reduced Ventilatory Capacity: Exercise limitation, Exacerbations

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
COPD & NUTRITION

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

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


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

- **CARDIOVASCULAR SYSTEM**
  
  Heart Failure

- **BONES**
  
  Osteoporosis, ↑ Fractures

- **Other**: Anemia, coagulation problems, etc...
COPD & NUTRITION

FACTORS
COPD & NUTRITION

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 ?

↑↑ ↑↑

↓↓ ↓↓
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

COPD & NUTRITION

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

  - **Hypercapnia Acidosis**
  - **Hypoxia**
  - **Increases in Ventilatory Requirements**
  - **Increases in Airway Resistance**
  - **Pulmonary Hyperinflation**
  - **Shortened Muscle**
  - **Work under Hypoxic + Acidotic Conditions**

Increase in the Work of Breathing

↑ Energy Expenditure

Epstein, Clin Chest Med 94
Scalvini, Monaldi 96
COPD & NUTRITION

- Imbalance between Anabolic and Catabolic Hormones
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

GH is a Peptide Hormone
- Adenohypophysis

- Anabolic Effects
  - Increases IGF-1: Protein Synthesis
  - Inhibits Protein oxidation and Catabolism

- Stimulates Ca++ retention & Bone Mineralization
- Promotes Muscle growth & Regeneration
- Improves Immune response

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

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

COPD & NUTRITION

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
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!!


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

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

**VARENICLINE** (Champix©)
Stimulates neuronal nicotine receptors

**E-CIGARETTE use (?)**
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

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

COPD & NUTRITION

REVERSE INACTIVITY & DECONDITIONING

Optimization of Physical Activity
Rehabilitation - Physiotherapy: Training

• Benefits
  – Improves Lung Function
  – Improves Exercise Tolerance
  – Reduces Breathlessness
  – ↓ Hospitalizations (n°, 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 muscle oxidative stress


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
COPD & NUTRITION

COUNTERBALANCING OXIDATIVE STRESS

DIET ANTIOXIDANTS

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

Fruit Consumption \(\rightarrow\) Reduce Mortality

Vitamin E

Intervention: To increase fruit 100 g/day la fruta \(\rightarrow\) reduces Mortality by 24%

COPD & NUTRITION

COUNTERBALANCING SYSTEMIC INFLAMMATION

- Anti-TNFα (Infliximab, IV):
  - Placebo-controlled clinical trial
  - 22 COPD patients (14 Infliximab vs 8 placebo)
  - Absence of effects

- Randomized, placebo-controlled clinical trial
  - 234 COPD patients (3mg/kg or 5 mg/Kg Infliximab vs placebo)
  - Absence of effects in the overall COPD population
  - Post-hoc: underweight COPD improved exercise capacity

- Van der Vaart et al. AJRCCM 2005
- Rennard et al. AJRCCM 2007

Anti-IL6 (Tocilizumab)

Anti-IL1 (Anakinra, Canakinumab)

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
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 × 8 weeks)
    - ↑ Body Weight, ↑ Fat Free Mass
    - ↑ Respiratory Muscle Strength

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

Schols et al. AJRCCM 1995

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: ∼ VO₂max & WRmax
  - ↑ lactate

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

7 malnourished COPD (FEV₁ 45% pred.)
No controls
Recombinant GH
- ↑↑ Body weight & Muscle mass
- ↑ Respiratory & Muscle strength (MIP)

8 malnourished COPD (FEV₁ 39% pred.) vs. controls Recombinant GH, sbc (x 3 weeks)
- ↑↑ Body weight & Muscle mass
- No effects on MIP, HG & 6’WD

Exercise capacity ?

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)

COPD & NUTRITION

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 (FEV₁, 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 (FEV₁, 33% pred.)
↓ Symptoms & ↑ QoL (MRC & SGRQ)
↑ Respiratory muscle strength, = Limb muscle strength
= Food intake, = Body weight, = Muscle mass
= Exercise Capacity (6′WD)

COPD & NUTRITION

GROWTH HORMONE DYSFUNCTION or DEFFICIENCY

Tesamorelin (ThGRF1-44), (GH Secretagogue)

GRF Analogue. Peptide (44 AA). Administration: Sbc, 2 mg/day (8 h effect)
Very stable, maintained activity in plasma. Minor side effects but elevated price

- Anabolic (↑GH & IGF-1): ▲ Protein synthesis & ▼ Proteolysis,
  ▲ Lipolysis (energy), ▲ Ca++ retention,
  ▲ Immune response

- Administration: Sbc, 2 mg

Tesamorelin, sbc 2 mg/d
  ▲ Body weight & ▲ Muscle mass
  ▲ Limb & ▲ Respiratory Muscle Strength

THANK YOU
COPD & NUTRITION

Vitamina D

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

- 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
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
**Dopamina**

- 8 EPOC en VM. Sin grupo control
- **Dopamina** EV (10 µg/kg/min x 30’)
  - Aumenta fuerza diafragma (30%)
  - Aumenta QT y flujo sanguíneo al diafragma

_Aubier et al. Ann Intern Med 89_

**Sensibilizadores al Calcio**

Se unen a Troponina C y 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_