Comorbilidades en EPOC: diabetes mellitus y osteoporosis

Dr. Chih Hao Chen Ku, FACE
Servicio de Endocrinología, Hospital San Juan de Dios
Departamento de Farmacología y Toxicología Clínica, Universidad de Costa Rica

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Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Genzyme
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche

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Agenda

- Comorbilidades en EPOC
  - DM y síndrome metabólico
    - Prevalencia
    - Impacto de DM en EPOC
    - Impacto de tratamiento
  - Osteoporosis
    - Cuándo tamizar
    - Cómo interpretar estudios
    - Medidas no farmacológicas

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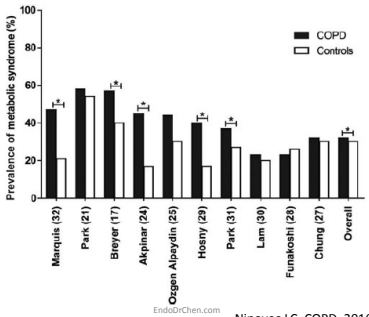
DIABETES MELLITUS

Asociación con EPOC

- Tabaquismo
- Inactividad física
- Obesidad central
  - Bajo FEV1 comparado con peso normal
  - Menos actividad física lleva a mayor sobrepeso
- Sarcopenia
- Glucocorticoides
- hipogonadismo

Prevalencia de síndrome metabólico



Nipovec LC. COPD. 2016. Early online.

Síndrome metabólico y EPOC

	MetS	Non-MetS	p−value
Age, y	69 ± 4 (n = 537, 6 studies)	68 ± 5 (n = 604, 6 studies)	0.135
Sex, %female	31 (n = 561, 7 studies)	25 (n = 694, 7 studies)	**0.011**
BMI, kg/m^2	29.9 ± 1.7 (n = 561, 7 studies)	24.6 ± 1.7 (n = 694, 7 studies)	**<0.001**
FEV_1, %predicted	54 ± 8 (n = 414, 5 studies)	51 ± 9 (n = 504, 5 studies)	**<0.001**

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Nipovec LC. COPD. 2016. Early online.

EPOC y DM

	General population (n=62,086)	Negative screen for COPD (n=59,707)	Positive screen for COPD (n=2,187)	COPD subjects completing detailed COPD questionnaire (n=1,392)	Adjusted OR (95% CI)	P-value
Any comorbidity	29,272 (47.1%)	27,774 (46.5%)	1,447 (66.2%)	930 (66.8%)	2.63 (2.40–2.89)	<0.0001
Cardiovascular diseases	14,561 (23.5%)	13,827 (23.2%)	701 (32.1%)	443 (31.8%)	1.81 (1.64–1.99)	<0.0001
Diabetes	9,576 (15.4%)	9,100 (15.2%)	451 (20.6%)	293 (21.0%)	1.44 (1.30–1.61)	<0.0001
Asthma	2,169 (3.5%)	1,809 (3.0%)	359 (16.4%)	212 (15.2%)	7.96 (7.00–9.04)	<0.0001
Digestive diseases	3,668 (5.9%)	3,425 (5.7%)	243 (11.1%)	142 (10.2%)	2.56 (2.22–2.95)	<0.0001
Eye diseases	6,748 (10.9%)	6,373 (10.7%)	374 (17.1%)	212 (15.2%)	1.96 (1.74–2.20)	<0.0001

Note: ORs and P-values were calculated by comparing the population positively screened for COPD to the population negatively screened for COPD (reference group), adjusted for age and sex.
Abbreviations: OR, odds ratio; CI, confidence interval.

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Mahboud B. Int J COPD. 2016;11:273

DM y exacerbaciones

Table 4 Presence of comorbidities in COPD subjects with or without exacerbation

	No exacerbation (n=731)	Exacerbation (n=661)	P-value
Comorbidities, n (%)			
None (n=704)	390 (55.4%)	314 (44.6%)	0.03
Any (n=688)	341 (49.6%)	347 (50.4%)	
Type of comorbidity, n (%)			
Cardiovascular diseases (n=344)	175 (50.8%)	169 (49.1%)	0.65
Diabetes (n=250)	133 (53.2%)	117 (46.8%)	0.15
Asthma (n=99)	39 (39.4%)	60 (60.6%)	0.003
Digestive diseases (n=56)	34 (60.7%)	22 (39.3%)	0.02
Eye diseases (n=74)	41 (55.4%)	33 (44.6%)	0.19

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Mahboud B. Int J COPD. 2016;11:273

EPOC y riesgo de desarrollar DM

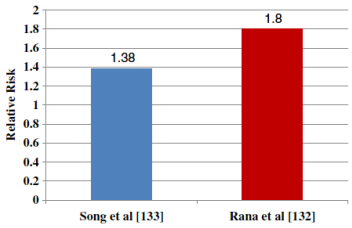

Figure 2 COPD and the risk of type 2 DM (adapted from references) [133,134].

Riesgo mortalidad en pacientes con EPOC y DM

Table 3 Adjusted HRs of various glucose metabolism abnormalities for late death after obstructive lung disease exacerbation

	All patients, N=153, aHR (95% CI)	Patients without doctor's diagnosis of diabetes, N=130, aHR (95% CI)
Doctor's diagnosis of diabetes	3.03 (1.28 to 7.18)*	ND
Screening diabetes	0.70 (0.31 to 1.59)*	0.72 (0.30 to 1.67)
All diabetes	1.29 (0.68 to 2.44)*	ND
Fasting hyperglycaemia >6.9 mmol/l	1.09 (0.52 to 2.29)	0.92 (0.42 to 2.02)
Highest fasting glucose value	1.10 (1.01 to 1.20)†	1.10 (0.96 to 1.25)†
Postprandial hyperglycaemia >11.1 mmol/L	1.18 (0.60 to 2.30)	1.04 (0.50 to 2.12)
Highest postprandial glucose value	1.07 (1.00 to 1.16)†	1.05 (0.94 to 1.19)†

In each case, the following confounders were included in the Cox multivariate regression analysis: age, body mass index, Karnofsky score, presence of chronic obstructive pulmonary disease, oxygen saturation and urea.
*Compared with patients without any form of diabetes.
†Adjusted HR is calculated per 1 mmol/L of plasma glucose.

Koskela HO. BMJ Open. 2015;5:e006794

Causas de muerte

Table 4 The underlying causes of death

Group	Cancer	Cardiovascular	Obstructive lung diseases	Miscellaneous
No diabetes (N=110, 38 deaths (34%))	7 (8%)	9 (24%)	19 (50%)	3 (8%)
Doctor's diagnosis of diabetes (N=23, 11 deaths (48%))	2 (18%)	5 (46%)	4 (36%)	0 (0%)
Screening diagnosis of diabetes (N=20, 8 deaths (40%))	2 (25%)	1 (12%)	5 (62%)	0 (0%)
All patients (N=153, 57 deaths (37%))	11 (19%)	15 (26%)	28 (49%)	3 (5%)

Koskela HO. BMJ Open. 2015;5:e006794

Manejo en exacerbaciones

- Durante la excerbación la hiperglicemia puede ser por:
  - Beta 2 agonistas
  - Gluccorticoides sistémicos
  - Hiperglicemia de stress
  - Historia de DM

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GC inhalados

- De los pacientes con EPOC de recién diagnóstico:
  - 6.3% tienen DM
  - Esteroides inhalados RR 1.23 (95% IC 1.07-1.47)
  - Estatinas RR 1.48 (95% IC 1.27-1.72)

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Ajmera MR. Value Health.2015;18:A335

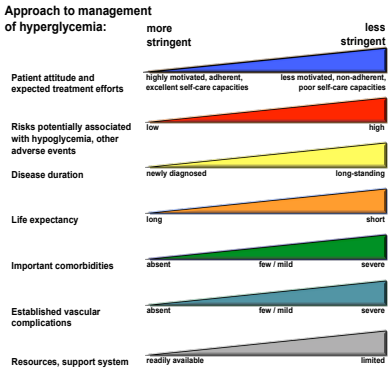
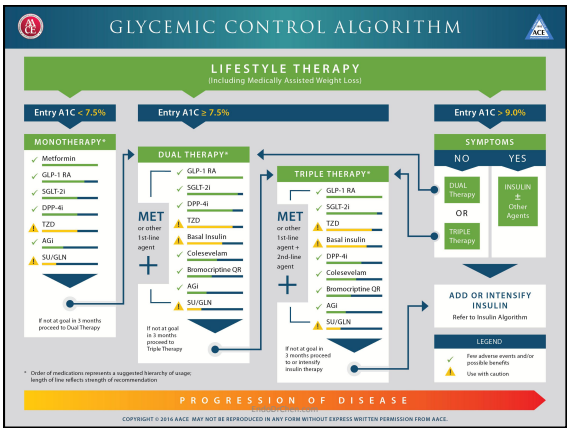


Figure 1

EndoDrChen ;*Diabetes Care*, *Diabetologia*. 19 April 2012 [Epub ahead of print]
(Adapted with permission from: Ismail-Beigi F, et al. *Ann Intern Med* 2011;154:554)



Fármacos en EPOC

- Metformin
  - Precaución en presencia de hipoxemia
    - Exacerbaciones, hipoxemia crónica
    - Si está resuelto no hay contraindicación
  - Primera línea de tratamiento en mayoría de guías de tratamiento
  - En general se recomienda suspenderlo en el agudo
- Ninguno de los otros fármacos están contraindicados

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OSTEOPOROSIS

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Definición

- Desorden esquelético caracterizado por un compromiso en la fortaleza ósea que predispone a mayor riesgo de fractura
- Fortaleza ósea
  - Densidad ósea
    - Pico masa ósea
    - Cantidad de pérdida masa ósea
  - Calidad ósea
    - Arquitectura, remodelamiento, microfracturas, mineralización

Prevalencia

- 35-72% osteopenia
- 36-60% osteoporosis
- 40% con fracturas vertebrales

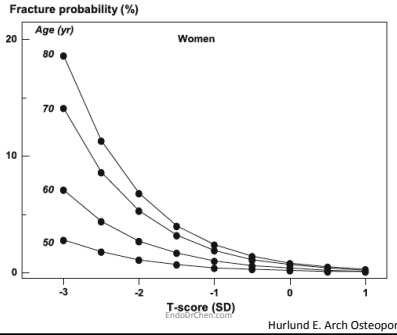
Fisiopatología

- Papel de GC orales o inhalados
- Liberación de citoquinas inflamatorias
- Menor actividad física
- Menor exposición solar
- Tabaquismo es tóxico para el hueso también

EPOC y osteoporosis

- Tabaquismo es tóxico para el hueso
- Sarcopenia
- Inflamación
- Inmovilización
- Menor ejercicio
- Menor exposición solar: déficit de vitamina D

BMD y riesgo de fratura



Hurlund E. Arch Osteoporos. 2013;8:136

Factores de riesgo para fracturas

- Edad
- Sexo
- IMC
- Fractura de fragilidad previa
- Historia de fractura de cadera en padres
- Tratamiento con GC (>5 mg prednisona por >3 meses)
- tabaquismo

Hurlund E. Arch Osteoporos. 2013;8:136

Factores de riesgo para fracturas

- Alcohol >3 u por día
- Artritis reumatoide
- Causas secundarias de osteoporosis:
  - Hipogonadismo no tratado
  - Enfermedad inflamatoria intestinal
  - Inmovilización prolongada
  - Transplante de órganos
  - DM-1
  - Desórdenes tiroideos
  - EPOC

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Hurlund E. Arch Osteoporos. 2013;8:136

DEXA

- Gold standard
- DMO medido por DEXA explica el 70% de la fortaleza ósea
- Criterios diagnósticos para mujeres postmenopaúsicas u hombres mayores de 50 años
- Limitantes: DMO puede estar aumentado en OA y enfermedades degenerativas

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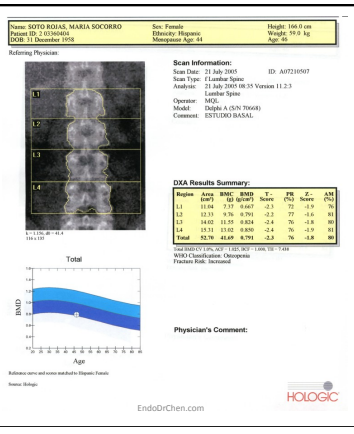

Name: SOTO ROJAS, MARIA SOCORRO
Patient ID: 2 03360404
DOB: 31 December 1958

Sex: Female
Ethnicity: Hispanic
Menopause Age: 44

Height: 166.0 cm
Weight: 59.0 kg
Age: 46

Referring Physician:

Scan Information:
Scan Date: 21 July 2005 ID: A07210507
Scan Type: F Lumbar Spine
Analysis: 21 July 2005 08:35 Version 11.2.3
Lumbar Spine
Operator: MQL
Model: Delphi A (S/N 70668)
Comment: ESTUDIO BASAL

DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	PR (%)	Z - Score	AM (%)
L1	11.04	7.37	0.667	-2.3	72	-1.9	76
L2	12.33	9.76	0.791	-2.2	77	-1.6	81
L3	14.02	11.55	0.824	-2.4	76	-1.8	80
L4	15.31	12.02	0.850	-2.4	76	-1.9	81
Total	**52.70**	**41.69**	**0.791**	**-2.3**	**76**	**-1.8**	**80**

Total BMD CV 1.0%, AGE = 1.025, BCF = 1.000, TE = 7.419
WHO Classification: Osteopenia
Fracture Risk: Increased

Physician's Comment:

Total

BMD

Age

Reference curve and scores matched to Hispanic Female

Source: Hologic

HOLOGIC

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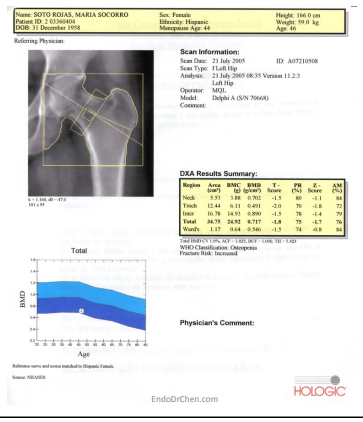
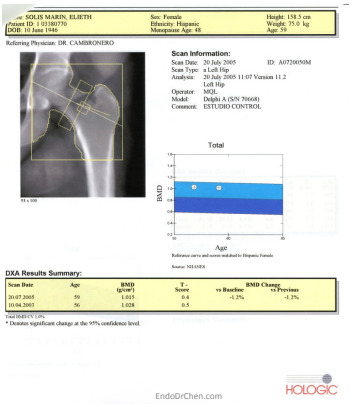
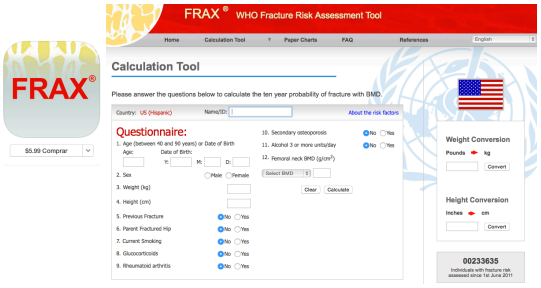




Criterio de OMS para osteoporosis

	T-Score
Normal	> -1
Osteopenia	-1 to -2.5
Osteoporosis	< -2.5
Osteoporosis severa	una o más fracturas de fragilidad independientemente de DMO

Kanis JA et al, J Bone Miner Res, 1994;9:1137-1141



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Caso ejemplo

- Femenina de 65 años, peso 72 kg, talla 170 cm, con T -2.5 en cuello femoral. AHF negativo. No otros factores de riesgo

Zona	Fracturas osteoporóticas mayores	Fractura cadera
EU hispano	7,6%	1,6%
México	7,8%	2,4%
Colombia	5,4%	1,7%
Ecuador	1,7%	0,6%
Venezuela	3,7%	1,1%

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FRAX

- Subestima el riesgo en pacientes con caídas frecuentes
- Subestima riesgo si BMD bajo en columna y normal en cuello femoral
- Si hay datos de cadera total y cuello femoral, usar éste último
- No utilizarlo si está recibiendo tratamiento, se puede usar luego de 1-2 años de suspensión
- Para causas secundarias, el botón se inactiva cuando se ingresa DMO de cuello femoral

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Cosman F. Osteoporosis Int. 2014; online aug 15

Medidas no farmacológicas

- Ingesta adecuada de proteínas
- Cese de fumado
- Aporte adecuado de calcio
- Suplementación de vitamina D
  - Requerimientos diarios 1200 u por día
  - Dosis mayores en casos de déficit
- Ejercicios de resistencia y equilibrio
- Prevención de caídas
- Evitar exceso de alcohol

Esteroides inhalados

- Evidencia conflictiva con fracturas
- Al parecer la asociación es sobre todo con dosis altas
  - Equivalente a >800 ug por día de budesonide
- Inicialmente manejar con medidas no farmacológicas
- No hay RCT ni recomendaciones oficiales para dar manejo farmacológico con esteroides inhalados

Estudio EOLO

	Fractures vs. no fractures			
	OR	95% CI	*P*	DF
Age (years)	1.03	1.02–1.05	<0.001	1
Gender (M/F)	0.93	0.78–1.13	n.s.	1
BMI (<26.7 kg/m^2)	1.28	1.07–1.54	0.008	1
COPD severity				
Very severe	2.05	1.28–3.28	0.003	
Severe	1.40	1.06–1.82	0.017	
Moderate	1.29	1.01–1.62	0.03	
Mild	1.00			3
Inhaled GCs (μg/day)				
GCs > 1,500	1.40	1.04–1.89	0.03	
750 < GCs ≤ 1,500	1.36	0.93–1.72	n.s.	
GCs ≤ 750	1.26	0.98–1.89	n.s.	
No treatment	1.00			3
Inhaled β_2 agonists (μg/day)				
>400	0.93	0.69–1.25	n.s.	
≤400	1.00			1

This model includes 2,073 patients

Gonnelli S. Calcif Tissue Int. 2010;87:137

Table 1. Clinical factors that may shift an individual to a greater risk category for glucocortcoid-induced osteoporosis.

- Low body mass index
- Parental history of hip fracture
- Current smoking
- ≥3 alcoholic drinks per day
- Higher daily glucocorticoid dose
- Higher cumulative glucocorticoid dose
- Intravenous pulse glucocorticoid usage
- Declining central bone mineral density measurement that exceeds the least significant change

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GrossmanJM. Arthritis Care Res. 2010;62:1515

>50 años

Recommendations	Level of evidence
Low-risk patient	
Alendronate for ≥7.5 mg/day prednisone	A
OR	
Risedronate for ≥7.5 mg/day prednisone	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
Medium-risk patient	
Alendronate for any dose of glucocorticoids	A
OR	
Risedronate for any dose of glucocorticoids	A
OR	
Zoledronic acid for ≥7.5 mg/day prednisone*	B
High-risk patient†	
Alendronate	A
OR	
Risedronate	A
OR	
Zoledronic acid*	B
OR	
Teriparatide‡	B

* Head-to-head comparison data available in the Discussion section of the full paper.
† Any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients.
‡ For ≥5 mg/day prednisone with a duration ≤1 month and for any dose of glucocorticoids with a duration >1 month. Head-to-head comparison data available in the Discussion section of the full paper.

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GrossmanJM. Arthritis Care Res. 2010;62:1515

Preguntas…
chenku2409@gmail.com
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