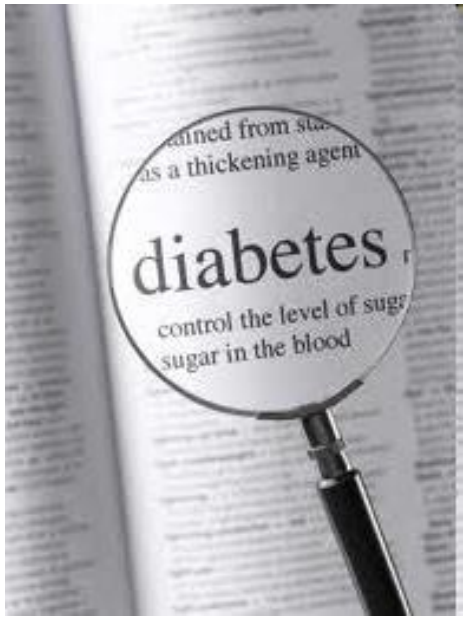
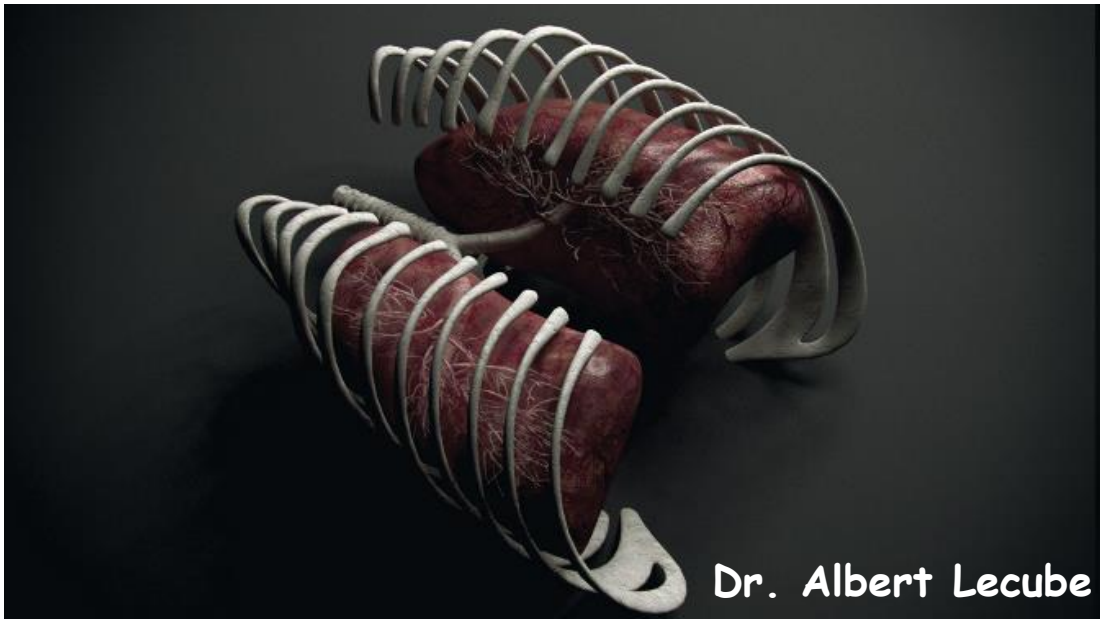
8a JORNADA DE RECERCA DE L'INSTITUT CATALÀ DE LA SALUT





Pot la diabetis influir sobre la funció pulmonar?

Institut Català de la Salut
Hospital Universitari Arnau de Vilanova

Generalitat de Catalunya
Departament de Salut

IRB Lleida
Institut de Recerca Biomèdica

Universitat de Lleida

EASO
European Association for the Study of Obesity

DISCLOSURE INFORMATION

Albert Lecube

I have the following financial relationships to disclose:

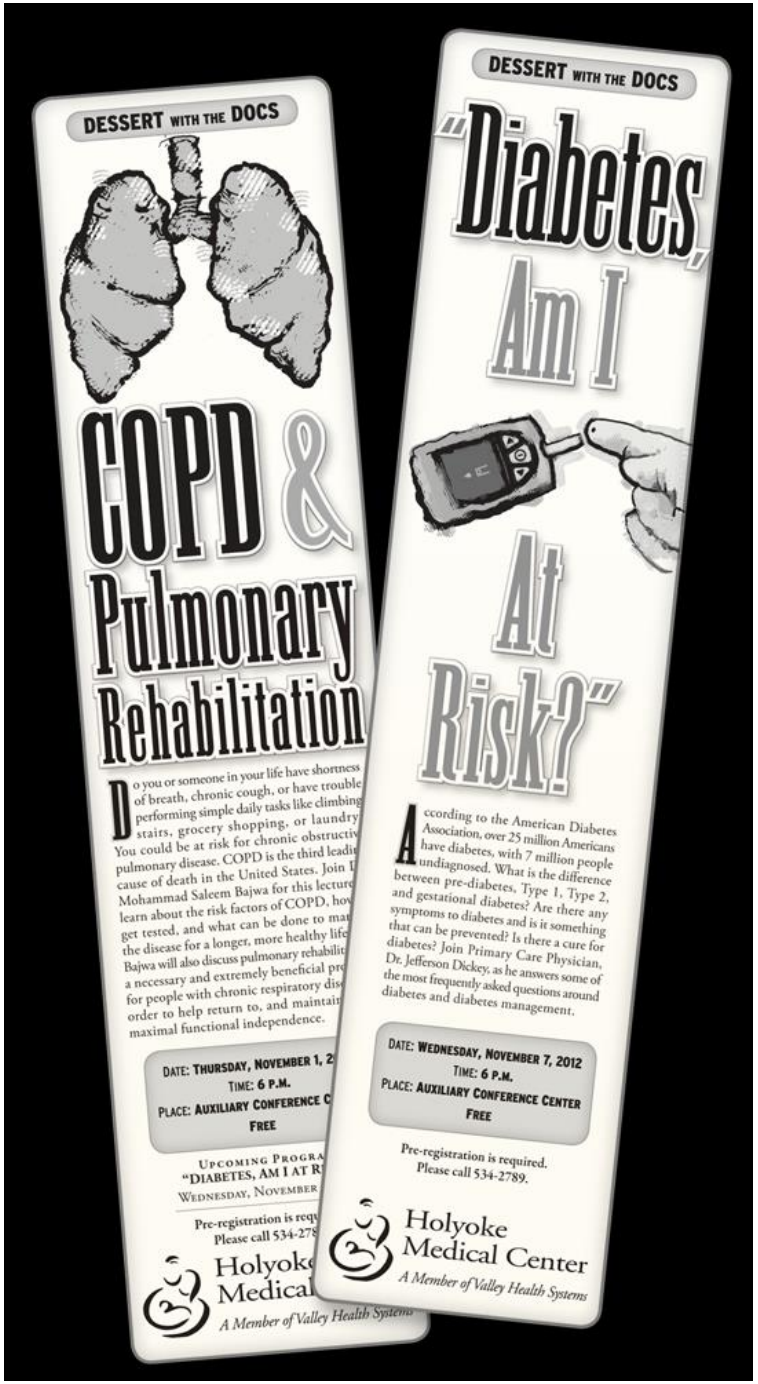
Advisory Board: Novo Nordisk, AstraZeneca, Janssen

Conferences: Novo Nordisk, AstraZeneca, Sanofi Aventis, Eli Lilly

Research Suport: Novo Nordisk, AstraZeneca, Janssen, Menarini, Gendiag

Clinical Trials: Novo Nordisk, Sanofi Aventis, AstraZeneca, Innocoll, Eli Lilly

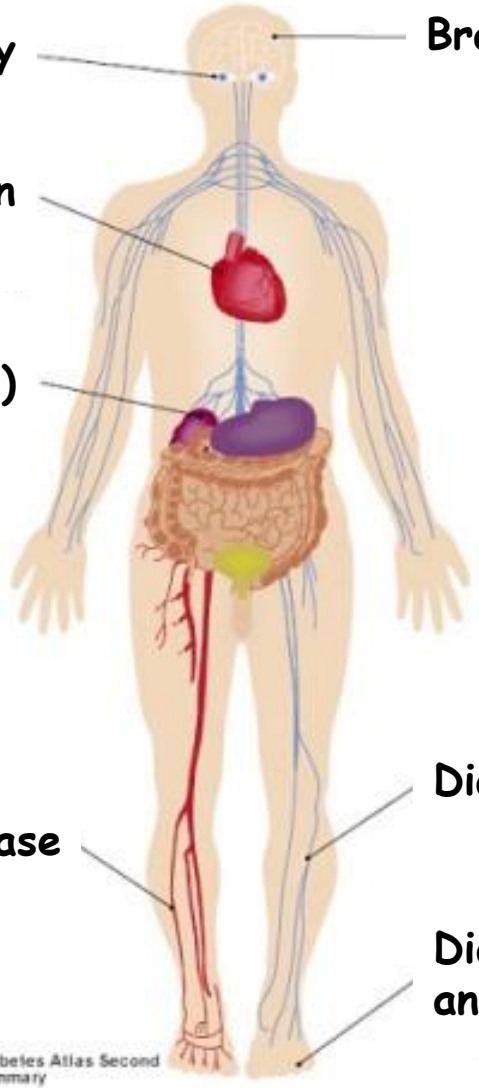

Cardiovascular Disease
Diabetes
Stroke
UNTREATED OSA
Abnormal Heart Rhythms
High Blood Pressure


DESSERT WITH THE DOCS
COPD & Pulmonary Rehabilitation
Do you or someone in your life have shortness of breath, chronic cough, or have trouble performing simple daily tasks like climbing stairs, grocery shopping, or laundry? You could be at risk for chronic obstructive pulmonary disease. COPD is the third leading cause of death in the United States. Join Dr. Mohammad Saleem Bajwa for this lecture to learn about the risk factors of COPD, how to get tested, and what can be done to manage the disease for a longer, more healthy life. Bajwa will also discuss pulmonary rehabilitation, a necessary and extremely beneficial program for people with chronic respiratory disease in order to help return to, and maintain, maximal functional independence.
DATE: THURSDAY, NOVEMBER 1, 2
TIME: 6 P.M.
PLACE: AUXILIARY CONFERENCE C
FREE
UPCOMING PROGRA
"DIABETES, AM I AT R
WEDNESDAY, NOVEMBER
Pre-registration is requ
Please call 534-278
Holyoke Medical
A Member of Valley Health Systems
DESSERT WITH THE DOCS
"Diabetes, Am I At Risk?"
According to the American Diabetes Association, over 25 million Americans have diabetes, with 7 million people undiagnosed. What is the difference between pre-diabetes, Type 1, Type 2, and gestational diabetes? Are there any symptoms to diabetes and is it something that can be prevented? Is there a cure for diabetes? Join Primary Care Physician, Dr. Jefferson Dickey, as he answers some of the most frequently asked questions around diabetes and diabetes management.
DATE: WEDNESDAY, NOVEMBER 7, 2012
TIME: 6 P.M.
PLACE: AUXILIARY CONFERENCE CENTER
FREE
Pre-registration is required.
Please call 534-2789.
Holyoke Medical Center
A Member of Valley Health Systems

Funció pulmonar → DM tipus 2

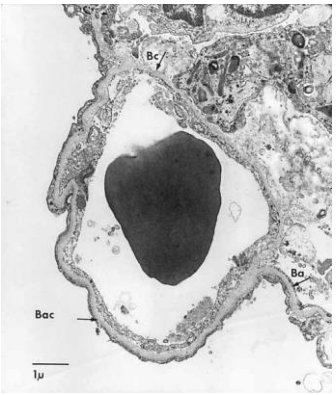
Funció pulmonar ← DM tipus 2

Say me, where are the lungs?



Say me, where are the lungs?

Histological findings from diabetic subjects



thickening of the alveolar epithelia and the pulmonary capillary basal lamina

Correlation between renal and alveoli thickness.

.- fibrosis
.- centrolobular emphysema
.- pulmonary microangiopathy

IN LIVING PATIENTS the basal lamina separating the capillary from the alveolar space is 30% thicker compared with non-diabetic.

Vrako R et al. Am Rev Respir Dis 1979; Kodolova IM et al. Arkh Patol 1982; Sandler M. Arch Intern Med 1990; Farina J et al. Virchows Arch 1995; Weynard B et al. Respiration 1999.

OBJECTIVES

.- **Harmful effects of T2D on:**

- lung function
- sleep breathing disorders
- sleep fragmentation

.- **Effects of improving glycemic control on:**

- nocturnal desaturations
- pulmonary function

breath in,
breath out,
repeat if necessary.

OBJECTIVES

.- **Harmful effects of T2D on:**

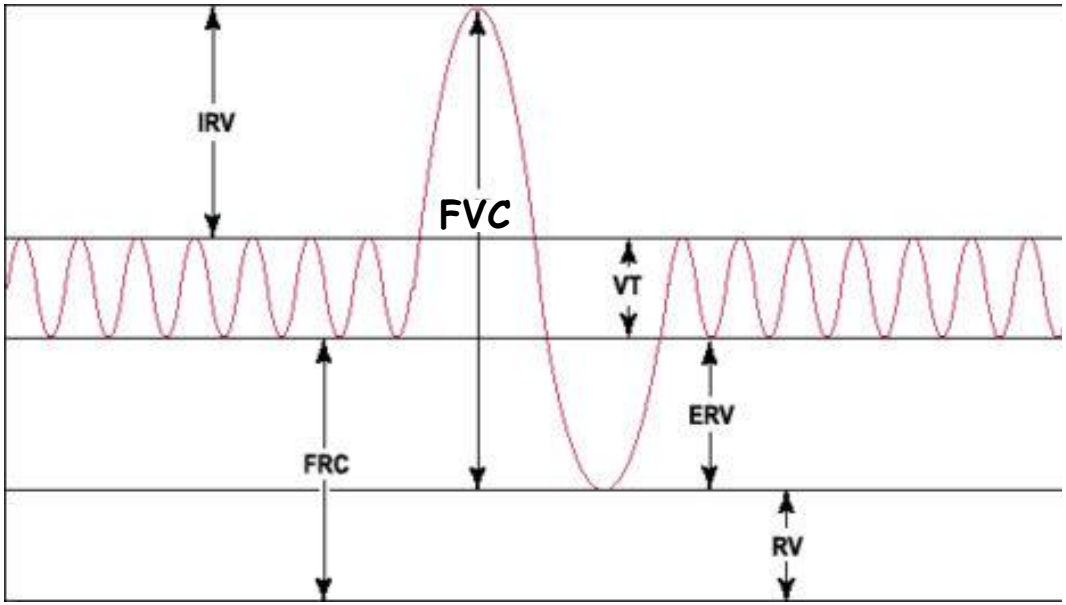
- lung function
- sleep breathing disorders
- sleep fragmentation

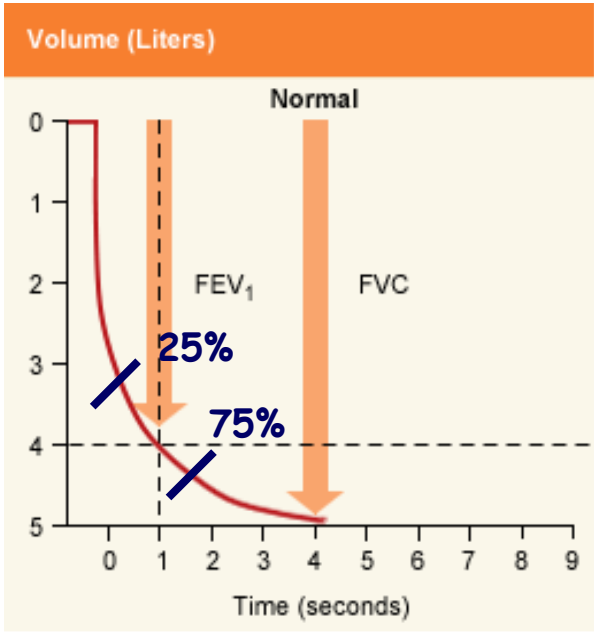
.- **Effects of improving glycemic control on:**

- nocturnal desaturations
- pulmonary function

breath in,
breath out,
repeat if necessary.

Evaluació de la funció pulmonar per espirometria i pletismografia





FVC: Forced Vital Capacity (Capacitat Vital Forçada)
RV: Residual Volume
FEV_1 o VEMS: Volume Espirat Màxim en el 1er segon de l'espiració forçada
FEF_{25-75}: Fluxe Espiratorio Forçat entre el 25 i 75% de la FVC

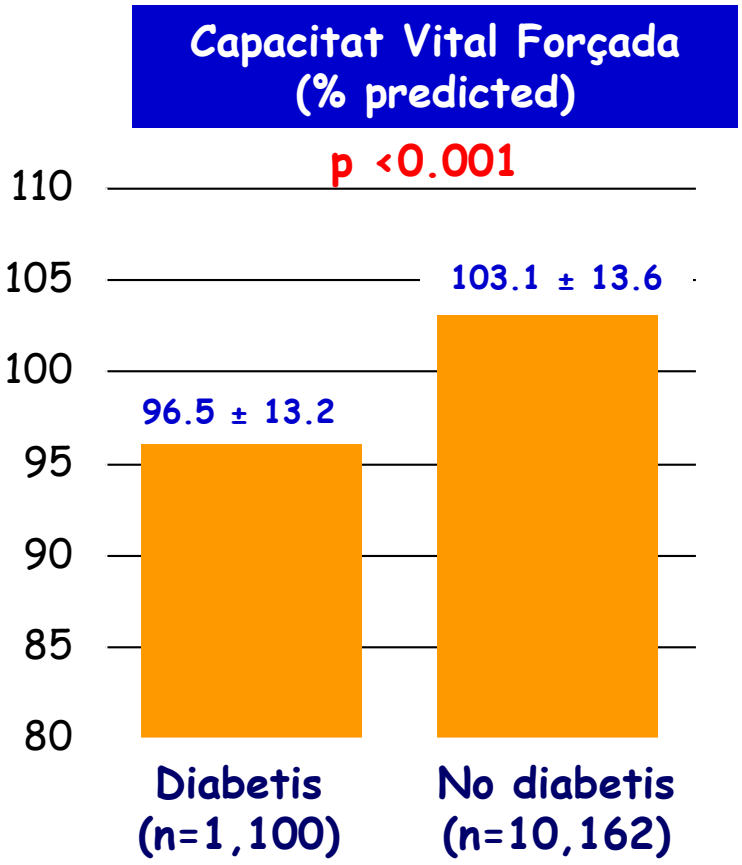
Cross-sectional studies have consistently shown that adults with diabetes have lower spirometric values, ranging from 8 to 10% of the predicted, than their nondiabetic counterparts.

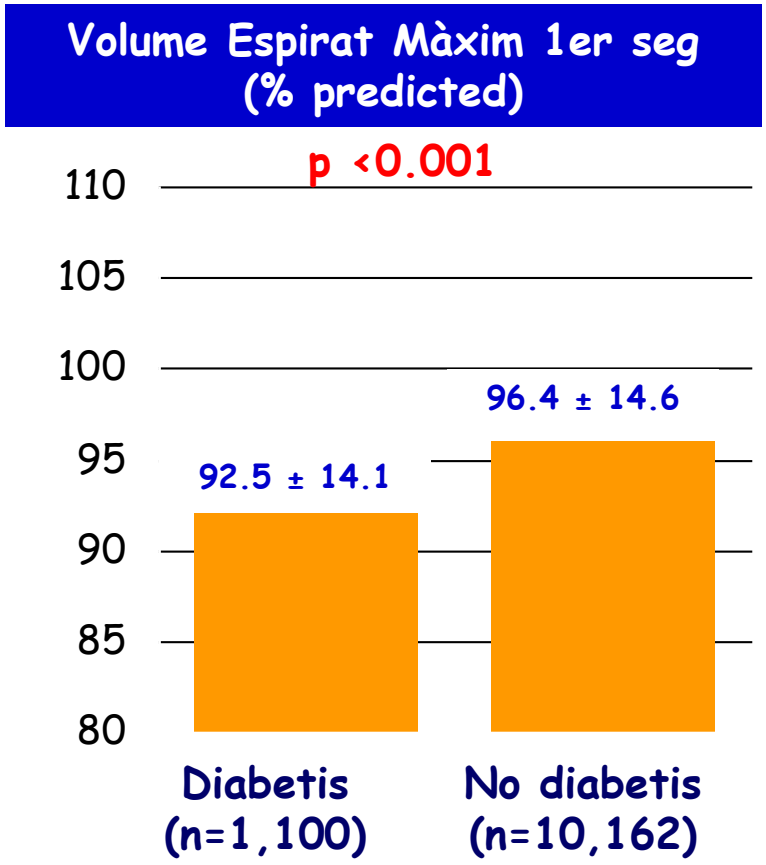
The Atherosclerosis Risk in Communities (ARIC) Study
The Copenhagen City Heart Study
The Fremantle Diabetes Study
The Framingham Heart Study
The Rancho-Bernardo Study

Barrett-Connor E et al. Diabetes care 1996; Lange P et al. Eur Respir J 2002; Walter E et al. Am J Respir Crit Care Med 2003; Davis WA et al. Diabetes Care 2004; Yeh HC et al. Diabetes Care 2008

Cross-sectional studies have consistently shown that adults with diabetes have lower spirometric values, ranging from 8 to 10% of the predicted, than their nondiabetic counterparts.

The Atherosclerosis Risk in Communities (ARIC) Study

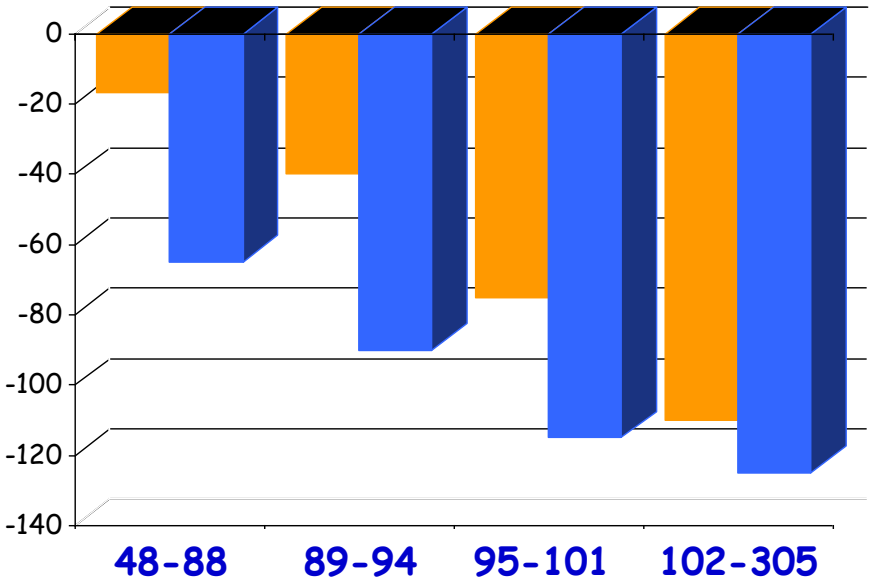




Yeh HC et al. Diabetes Care 2008

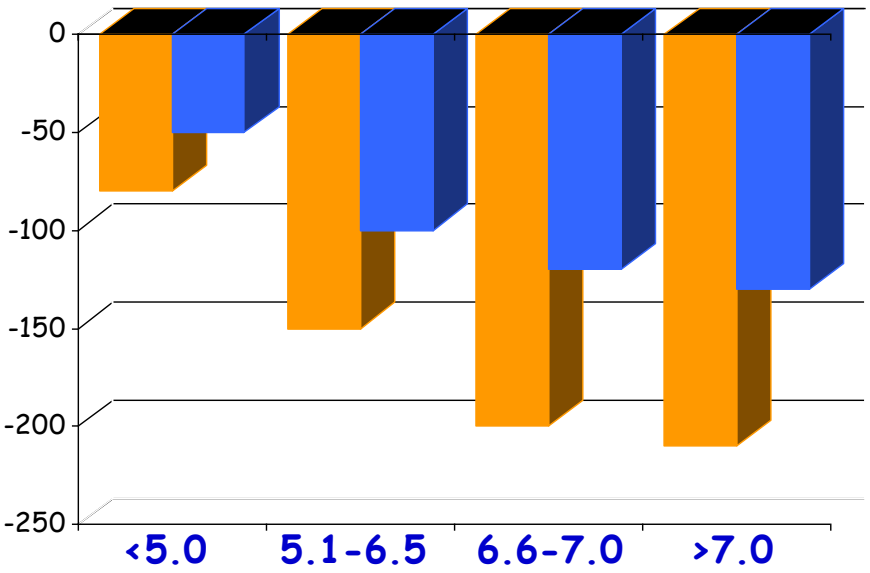
Graded, inverse associations between fasting glucose, HbA1c, and spirometric values

The Framingham Heart Study



Quartiles of blood glucose (mg/dl)

The Atherosclerosis Risk in Communities (ARIC) Study



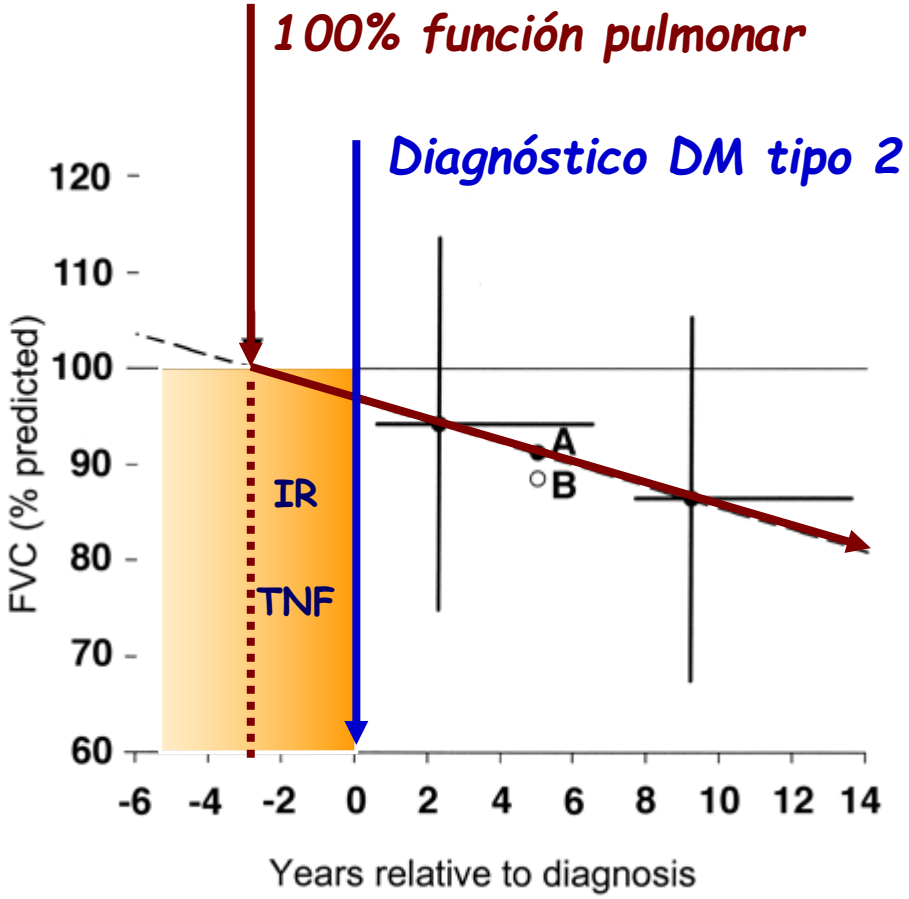
HbA1c level (%)

CVF (ml)

VEMS (ml)

Yeh HC et al. Diabetes Care 2008
Walter E et al. Am J Respir Crit Care Med 2003

Lung function measures start to decrease aproximatelly three years before the diagnosis of diabetes



Linear extrapolation intercept at 100% lung function 2.8 years before diagnosis.

Davis WA et al. Diabetes Care 2004

ARTICLE

Type 2 diabetes impairs pulmonary function in morbidly obese women: a case–control study

A. Lecube · G. Sampol · X. Muñoz · C. Hernández · J. Mesa · R. Simó

	Type 2 diabetes	No diabetes	p
n (women)	25	50	
Age (years)	44.0 ± 8.7	44.0 ± 7.8	0.984
BMI (Kg/m^2)	49.2 ± 6.6	49.0 ± 5.1	0.912
Glucose (mmol/l)	8.6 ± 2.7	5.6 ± 0.6	< 0.001
HbA1c (%)	7.5 ± 1.4	5.8 ± 0.4	< 0.001

Diabetologia 2010; 53: 1210-6

ARTICLE

Type 2 diabetes impairs pulmonary function in morbidly obese women: a case–control study

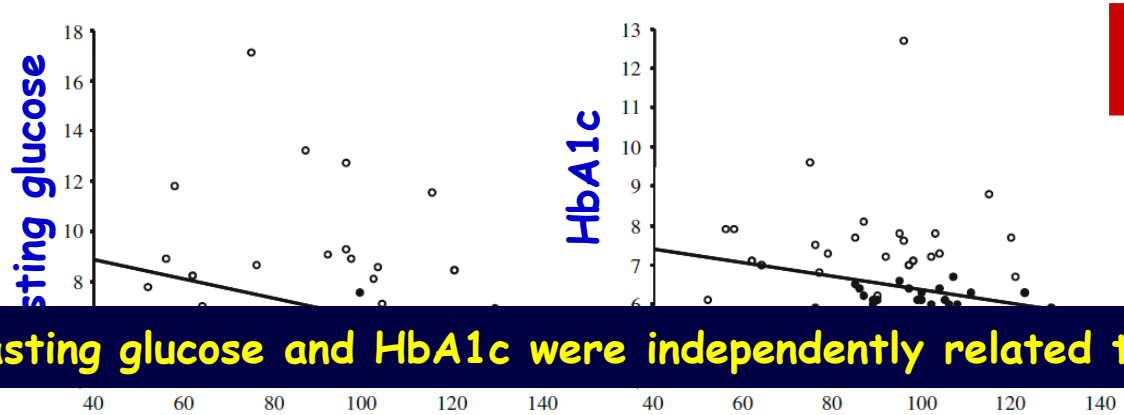
A. Lecube · G. Sampol · X. Muñoz · C. Hernández · J. Mesa · R. Simó

	Type 2 diabetes	No diabetes	p
VEMS (%)	88.4 ± 19.7	100.1 ± 12.4	0.011
FEF_{25-75}	72.5 ± 40.7	97.8 ± 24.4	0.014
CVF (%)	85.1 ± 17.2	93.3 ± 20.1	0.081
VEMS/CVF ratio	81.4 ± 10.1	85.8 ± 5.2	0.049
TLC (%)	96.9 ± 13.2	94.4 ± 9.4	0.354
VResidual (%)	99.8 ± 22.3	80.3 ± 15.2	< 0.001

Diabetologia 2010; 53: 1210-6

Type 2 diabetes impairs pulmonary function in morbidly obese women: a case–control study

r = -0.283
p = 0.014

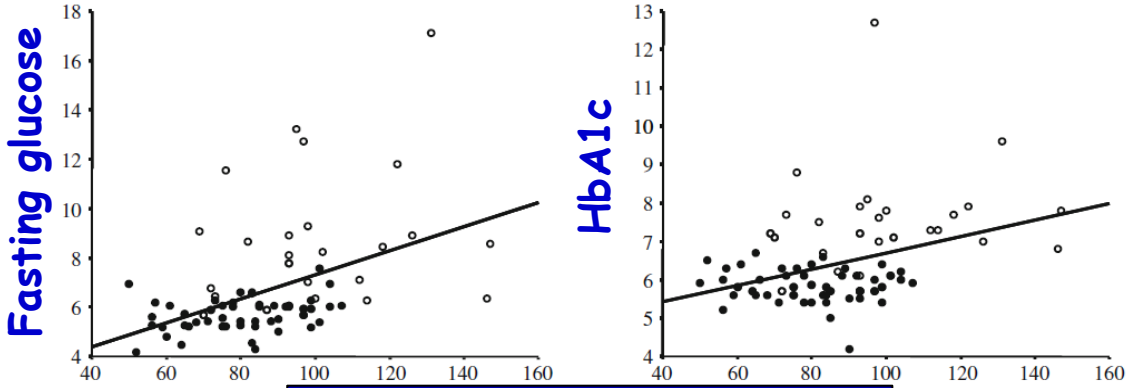


r = -0.236
p = 0.043

Both, fasting glucose and HbA1c were independently related to FEV_1 and RV

Volumen Espirado Máximo 1s (%pred)

r = 0.454
p <0.001



r = 0.364
p = 0.001

Volumen residual (%pred)


Diabetis tipus 2 i el control glucèmic estan directament relacionats amb el deteriorament de la funció respiratòria.

SON AQUESTS CANVIS CLÍNICAMENT RELLEVANT?

29-year follow-up of the Buffalo Health Study

The FEV_1 (% pred) is a long-term predictor for overall survival rates in the general population.

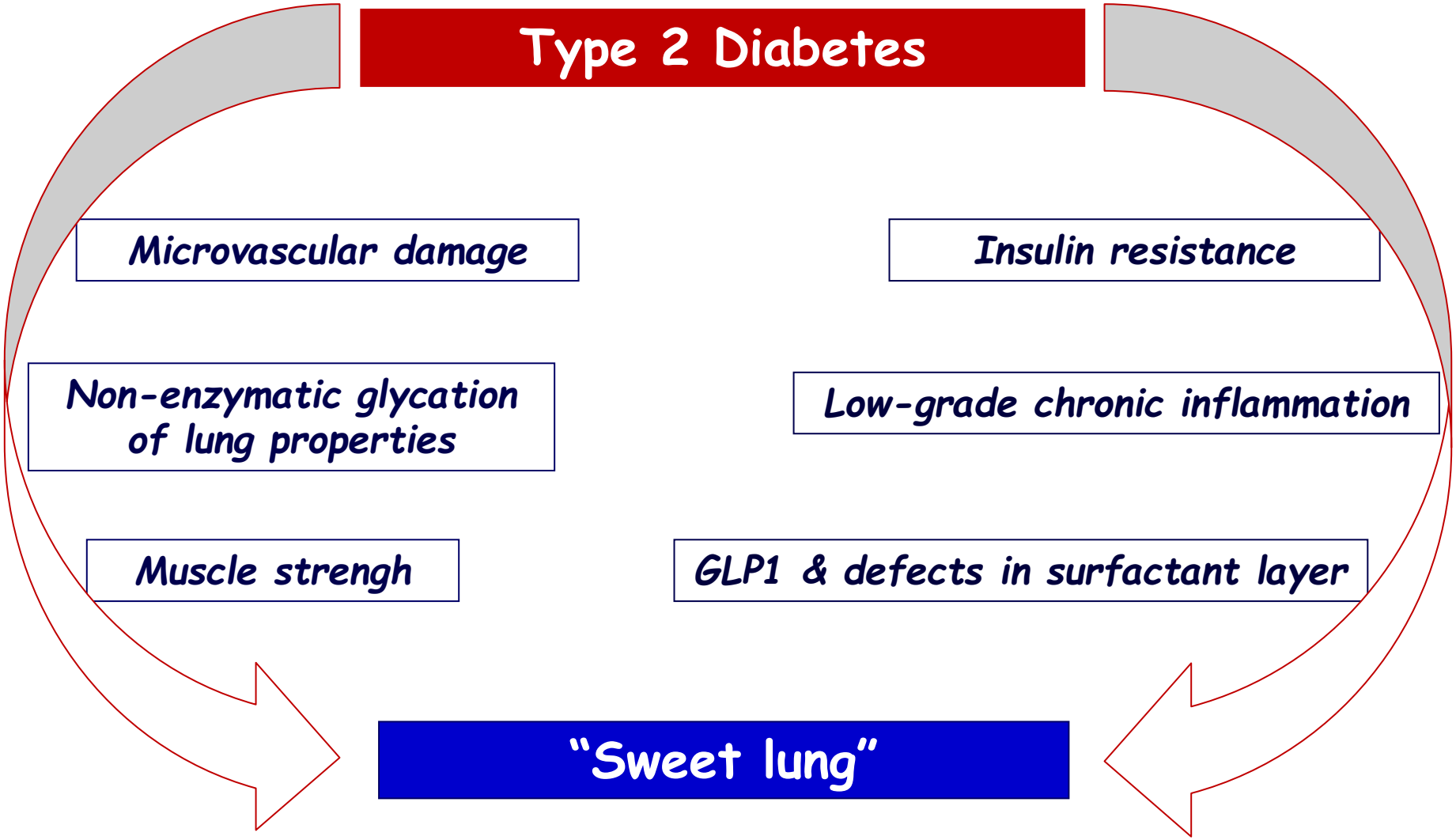
7-year follow-up of the Fremantle Diabetes Study

In diabetic patients, a 10% decrease in FEV_1 (% pred) is associated with a 12% increase in all-cause mortality.

Hazard ratios for death among diabetic subjects

From chronic obstructive pulmonary disease and related conditions ..... 1.27 (95% CI, 1.07-1.50)

Schünemann HJ et al. Chest 2000.
Davis WA et al. Diabetes Care 2004.
Emerging Risk Factors Colaboration. N Engl J Med 2011.



Schnapf BM et al. Am Rev Respir Dis 1984; Ramírez LC et al. Am J Med 1991; Lazarus R et al. Metabolism 1997; Chance WW et al. Diabetes Care 2008;

Type 2 Diabetes

Microvascular damage

Insulin resistance

Non-enzymatic glycation of lung properties

Low-grade chronic inflammation

Muscle strengh

GLP1 & defects in surfactant layer

"Sweet lung"

Schnapf BM et al. Am Rev Respir Dis 1984; Ramírez LC et al. Am J Med 1991; Lazarus R et al. Metabolism 1997; Chance WW et al. Diabetes Care 2008;

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2010; **26**: 639–645.
Published online 29 September 2010 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/dmrr.1131

RESEARCH ARTICLE

Insulin resistance is related to impaired lung function in morbidly obese women: a case–control study

A. Lecube, G. Sampol, X. Muñoz, P. Lloberes, C. Hernández, R. Simó.

	HOMA-IR≥3.8	HOMA-IR<3.8	p
n (women)	50	25	
Age (years)	41.9 ± 8.9	40.5 ± 9.5	0.534
BMI (Kg/m^2)	48.9 ± 6.9	48.5 ± 6.0	0.798
Glucose (mmol/l)	5.7 ± 0.5	5.5 ± 0.6	0.116
HbA1c (%)	5.9 ± 0.4	5.6 ± 0.6	0.112
HOMA-IR	5.9 (3.9-23.5)	2.8 (1.0-3.8)	< 0.001

Diabetes Metab Res Rev 2010; 26: 639-45

DIABETES/METABOLISM RESEARCH AND REVIEWS
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	HOMA-IR≥3.8	HOMA-IR<3.8	p
VEMS (%)	96.3 ± 112.3	103.9 ± 15.6	0.025
FEF_{25-75}	88.9 ± 25.4	105.4 ± 33.7	0.026
CVF (%)	89.6 ± 11.4	95.4 ± 13.2	0.054
FEV_1/FVC ratio	84.7 ± 4.6	89.8 ± 1.7	0.066
TLC (%)	95.9 ± 9.0	99.0 ± 12.5	0.245
VR (%)	84.4 ± 20.6	82.6 ± 31.3	0.778

Diabetes Metab Res Rev 2010; 26: 639-45

DIABETES/METABOLISM RESEARCH AND REVIEWS
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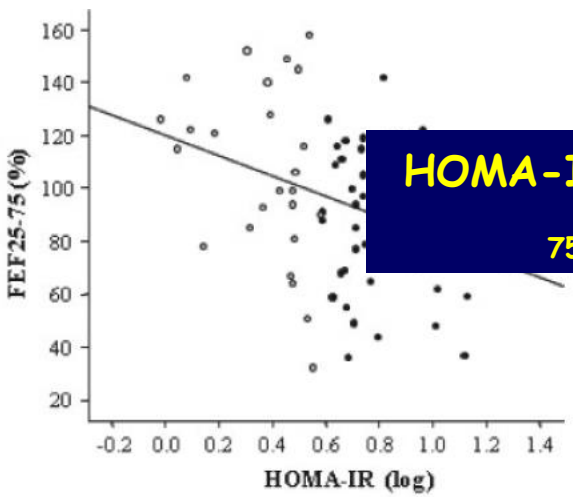
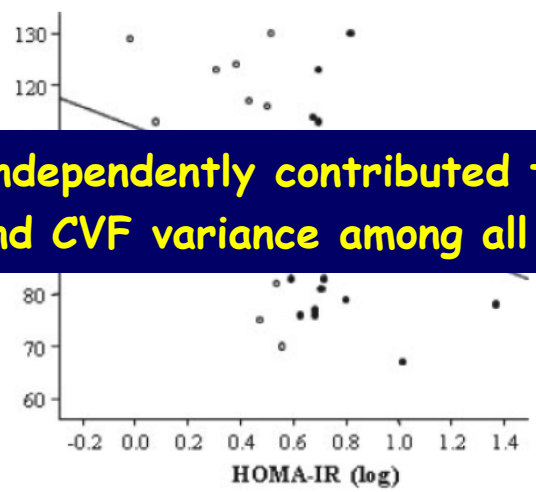
FEF_{25-75} (%)



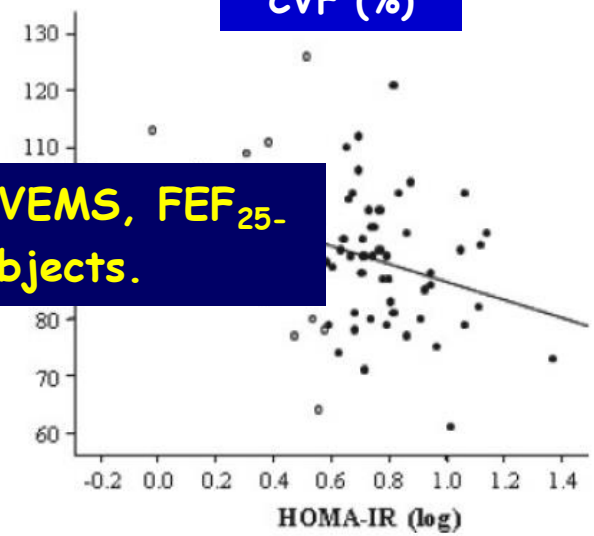
r = -0.339; p = 0.004

VEMS (%)



r = -0.370; p = 0.001

CVF (%)



r = -0.327; p = 0.003

HOMA-IR independently contributed to VEMS, FEF_{25-75}, and CVF variance among all subjects.

Diabetes Metab Res Rev 2010; 26: 639-45

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/issn/10434666

Short Communication

TNF-α system and lung function impairment in obesity

A. Lecube [a,*], G. Sampol [b], X. Muñoz [b], R. Ferrer [c], C. Hernández [a], R. Simó [a]

31 consecutive non-diabetic morbidly obese (48.1 ± 6.1 Kg/m^2) without complications

	sTNFα-R1	
	r	p
VEMS (%)	-0.437	0.012
FEF_{25-75}	-0.370	0.040
CVF (%)	-0.483	0.005
TLC (%)	-0.134	0.487
VR (%)	0.014	0.946

sTNFα-R1, but not sTNFα-R2, was independently associated with FEV_1 and FVC.

Cytokine 2011; 54: 121-4

Diabetes mellitus tipo 2

Microangiopatía alveolar

Pérdida de las propiedades elásticas

Fuerza muscular

Resistencia a la insulina

Inflamación crónica de bajo grado

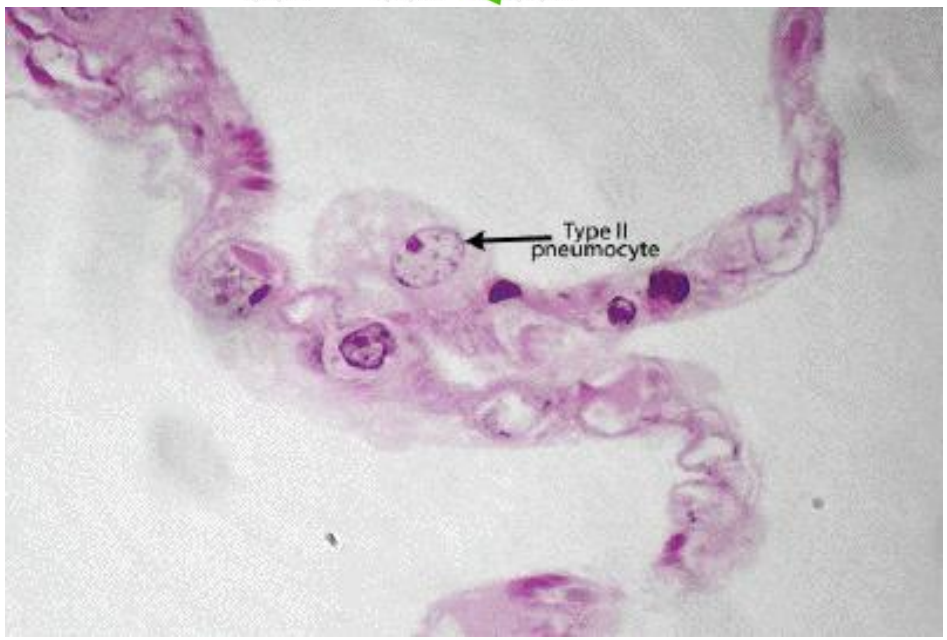
GLP-1 y surfactante pulmonar

"Sweet lung"

Schnapf BM et al. Am Rev Respir Dis 1984; Ramírez LC et al. Am J Med 1991; Lazarus R et al. Metabolism 1997; Chance WW et al. Diabetes Care 2008;

GLP-1 receptor has been found in significant amounts in the human lung

GLP-1



Experimental studies have shown that GLP-1 plays a role in the stimulation of surfactant production by type II pneumocytes

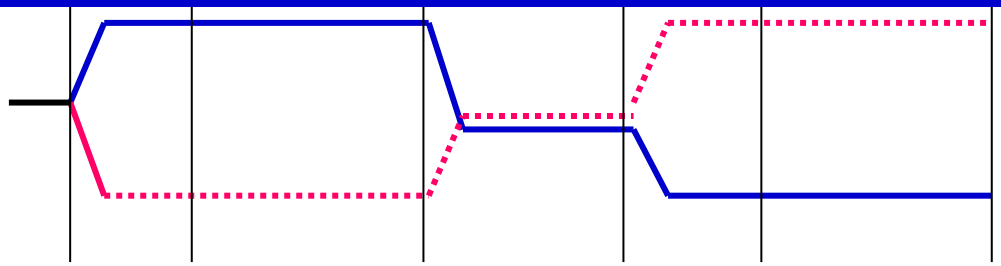
Benito et al. Endocrinology 1998; Vara et al. Am J Respir Crit Care Med 2001; Ahrén et al. Horm Metab Res 2004; Körner M et al. J Nucl Med 2007;

Poden les teràpies basades en incretines millorar la funció pulmonar en la diabetis mellitus tipus 2?

LIRALUNG Clinical Trial
(EudraCT: 2014-005125-12)

Multicentre, randomized, double blind, crossover, placebo-controlled clinical trial to evaluate the effect of liraglutide on lung function in patients with T2DM

First patient, first visit: June/July 2016

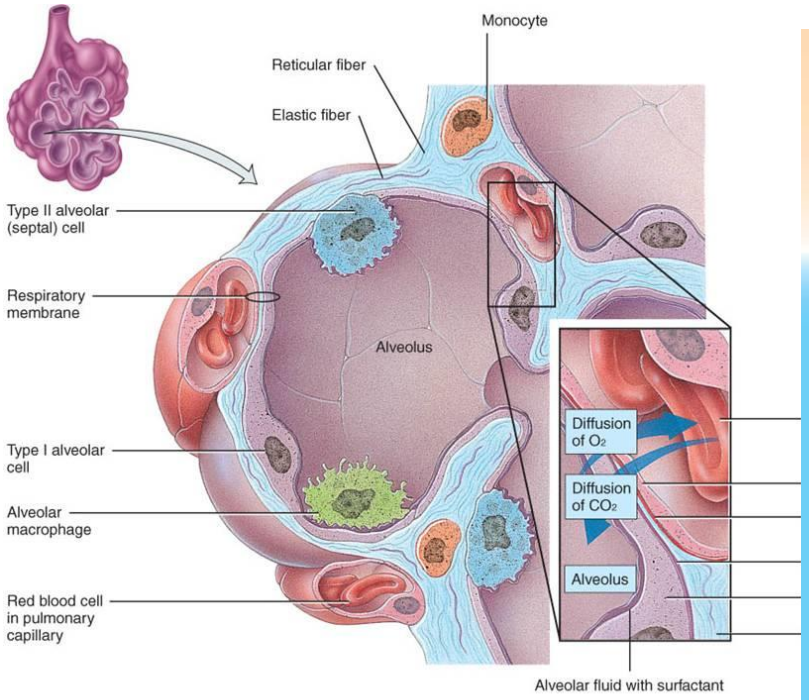


Type 2 diabetic patients with HbA1c between 7.0 and 10.0%, BMI ≥30 Kg/m^2, <u>and no known lung disease</u>

Primary objective:
- Forced Expiratory Volume in 1 second

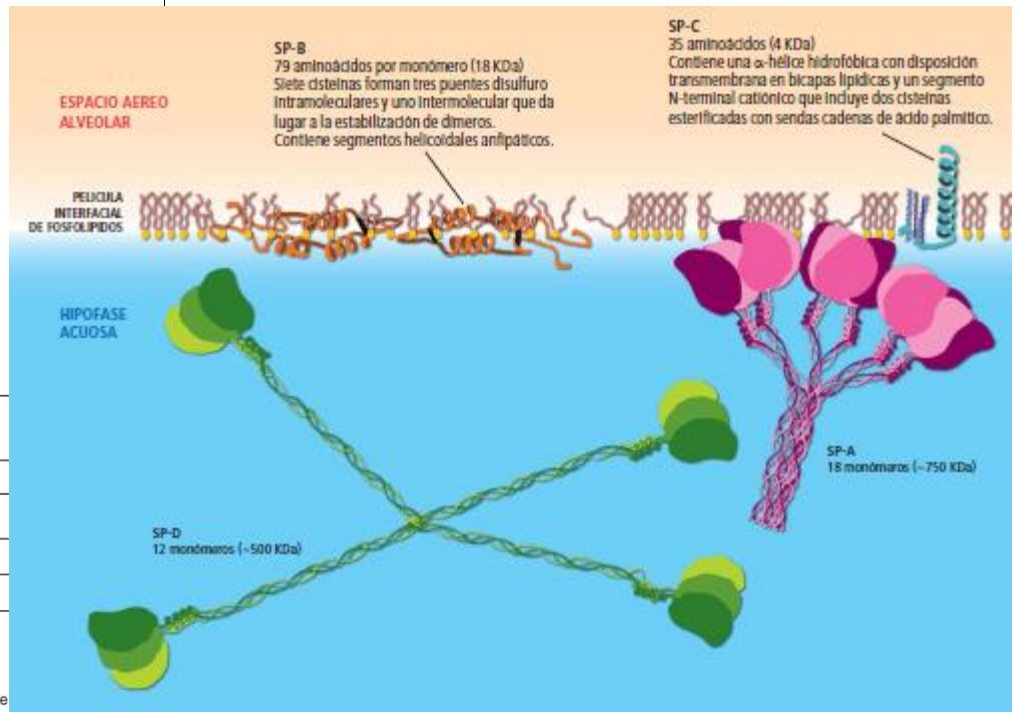
Secondary objectives:
- rest of spirometric parameters
- respiratory parameters during sleep, and
- serum levels of surfactant proteins.

Surfactant is involved in maintaining airway stability and diameter



(a) Section through an alveolus showing its cellular components

(b) Details of respiratory membrane

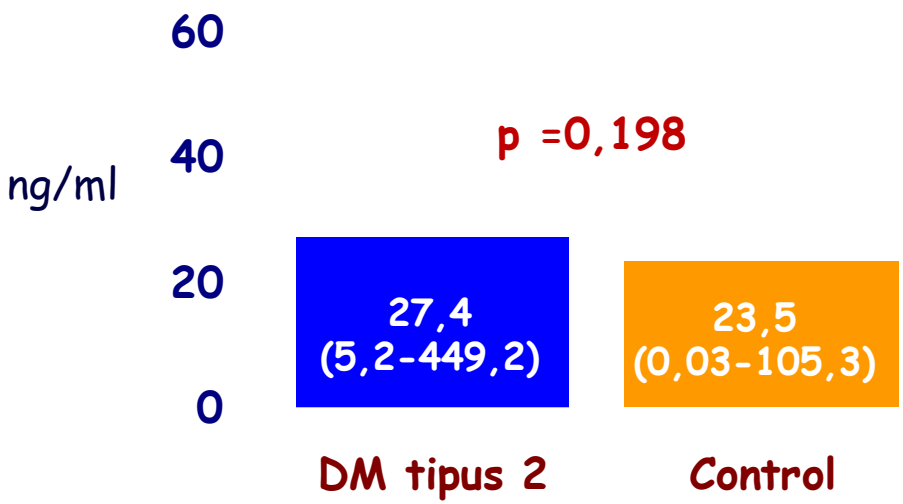


Benito et al. Endocrinology 1998; Vara et al. Am J Respir Crit Care Med 2001; Ahrén et al. Horm Metab Res 2004; Körner M et al. J Nucl Med 2007;

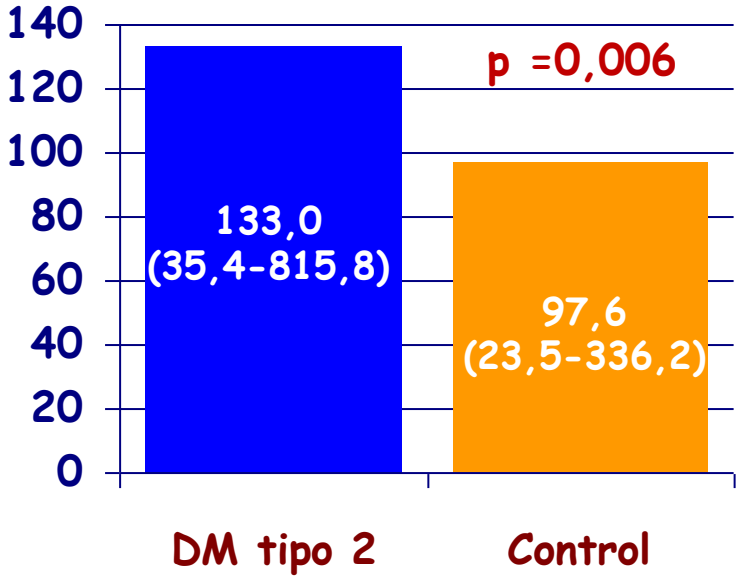
Surfactant and type 2 diabetes

	Type 2 diabetes	Non diabetes	p
n	49	98	-

Close matched for age, gender, BMI, and waist and neck circumferences.



Proteïna A del surfactant pulmonar



Proteïna D del surfactant pulmonar

OBJECTIVES

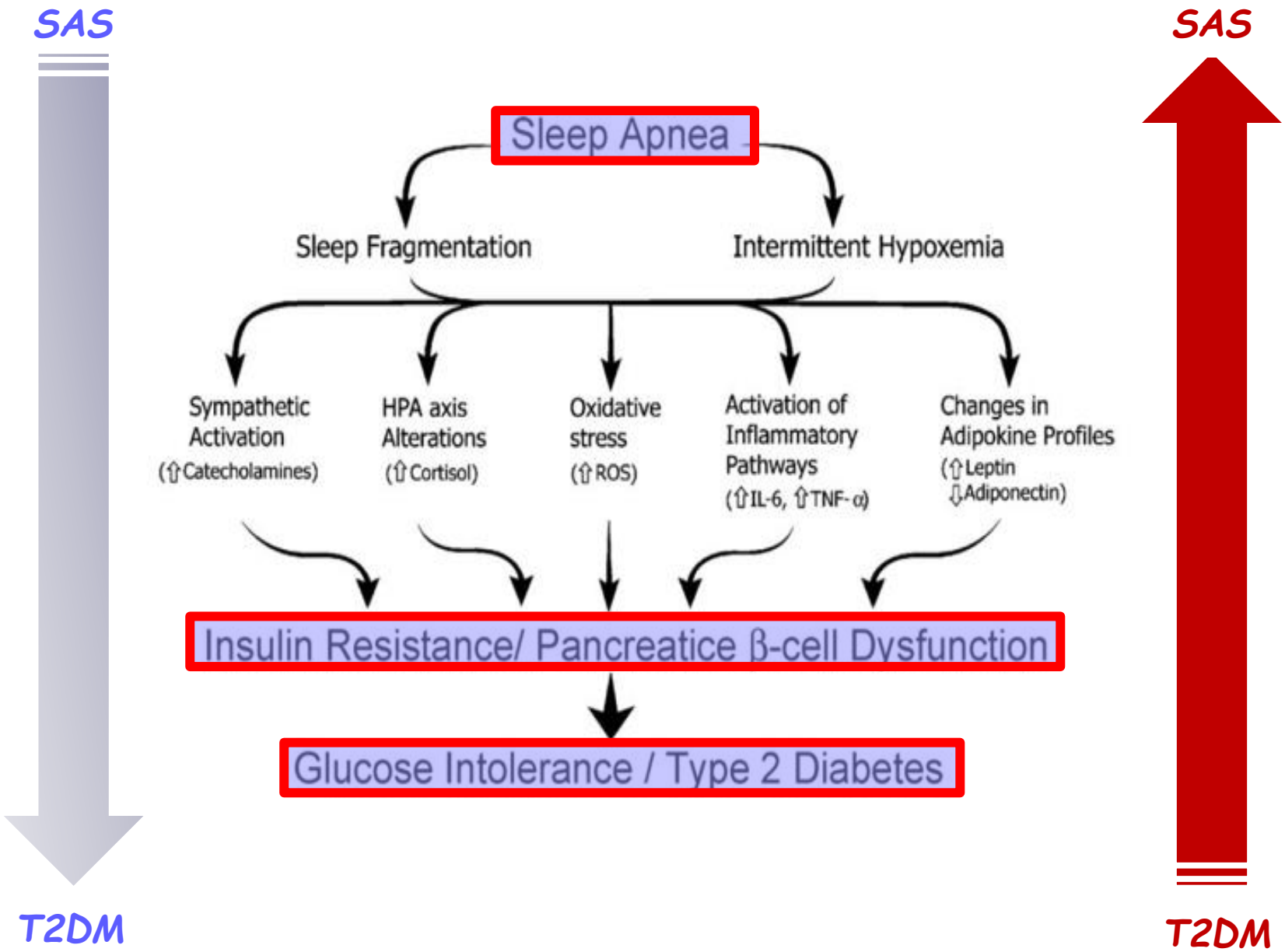
.- **Harmful effects of T2D on:**

- lung function
- sleep breathing disorders
- sleep fragmentation

.- **Effects of improving glycemic control on:**

- nocturnal desaturations
- pulmonary function

breath in,
breath out,
repeat if necessary.


SAS
SAS
Sleep Apnea
Sleep Fragmentation
Intermittent Hypoxemia
Sympathetic Activation
(⇧Catecholamines)
HPA axis Alterations
(⇧Cortisol)
Oxidative stress
(⇧ROS)
Activation of Inflammatory Pathways
(⇧IL-6, ⇧TNF-α)
Changes in Adipokine Profiles
(⇧Leptin
⇩Adiponectin)
Insulin Resistance/ Pancreatice β-cell Dysfunction
Glucose Intolerance / Type 2 Diabetes
T2DM
T2DM

OPEN ACCESS Freely available online PLoS one

Diabetes Is an Independent Risk Factor for Severe Nocturnal Hypoxemia in Obese Patients. A Case-Control Study

Albert Lecube[1,3]*, Gabriel Sampol[2,3], Patricia Lloberes[2], Odile Romero[3], Jordi Mesa[1], Cristina Hernández[1], Rafael Simó[1]

	Type 2 diabetes	No diabetes	p
n (women)	30	60	-
Age (years)	43.2 ± 8.0	42.1 ± 8.0	0.529
BMI (Kg/m^2)	49.1 ± 6.3	49.1 ± 6.4	0.989
Glucose (mmol/l)	9.0 ± 3.4	5.6 ± 0.6	< 0.001
HbA1c (%)	7.7 ± 1.1	5.9 ± 0.3	< 0.001
CT90 (%)	20.2 ± 30.2	6.8 ± 13.5	0.027

CT90: porcentaje del tiempo de sueño con saturaciones de O_2 <90%

PLoS One 2009; 4: e4692

OPEN ACCESS Freely available online PLoS one

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Albert Lecube[1]*, Gabriel Sampol[2], Patricia Lloberes[2], Odile Romero[3], Jordi Mesa[1], Cristina Hernández[1], Rafael Simó[1]

Multiple linear regression analysis of variables associated with CT90

	Beta	p
AHI (log)	0.387	<0.001
$PaCO_2$ (mmHg)	0.227	0.013
T2DM (yes/no)	0.220	0.007
PaO_2 (mmHg)	-0.222	0.013
BMI (kg/m^2)	-0.094	0.279
Age (yrs)	-0.001	0.859

R^2 = 0.582


La diabetis tipus 2 afavoreix de forma independent la hipoxèmia nocturna greu.

Registres polisomnogràfics: són tots iguals?

PLOS | ONE

RESEARCH ARTICLE

Characterization of Sleep Breathing Pattern in Patients with Type 2 Diabetes: Sweet Sleep Study

Albert Lecube[1,2]*, Gabriel Sampol[3], Cristina Hernández[1], Odile Romero[3], Andreea Ciudin[1], Rafael Simó[1]

PLoS One 2015; e0119073

La importància de ser diabètic

	DM tipus 2 (n=125)	Controls (n=125)	p
Edat (anys)	53,3 ± 11,2	52,3 ± 10,6	0,279
Dones (%)	62,6	62,6	-
IMC (Kg/m^2)	41,2 ± 8,8	42,0 ± 8,5	0,450
IAH (events/h)	31,3 (10,2-106,3)	31,1 (10,3-106,3)	0,934

També equiparats per perímetres de cintura (p=0,258) i de coll (p=0,445)

Hipopnees (e/h)	16,1 (0,0-75,3)	20,2 (0,0-71,4)	0,005
Apnees (e/h)	7,4 (0,1-85,7)	5,0 (0,0-105,6)	0,036

PLoS One 2015; e0119073

alguna repercussió del "sweet sleep" en la simptomatologia diürna?

QUESTIONARI D' EPWORTH

.- 8 preguntes que avalúen la facilitat per quedar-se dormit en situacions habituals
.- puntuació: entre 0 i 24
.- major de 8 es considera patològic, i greu si igual o major de 11

Plos One 2016 [epub ahead of print]

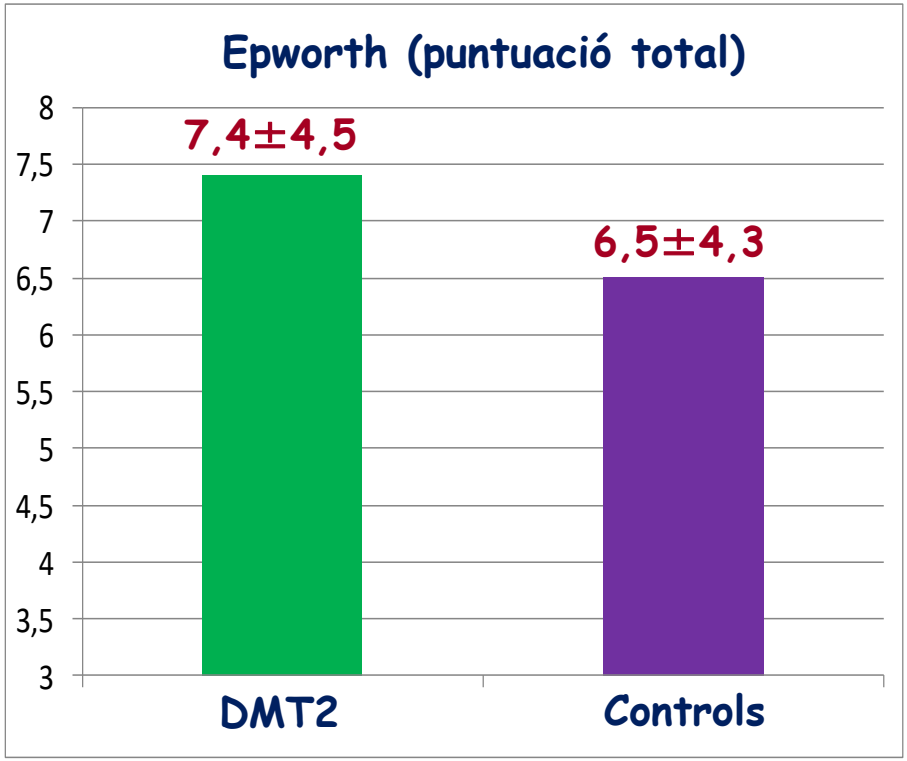
QUESTIONARI D'EPWORTH

població d'estudi

	DM tipus 2	Controls	p
n	413	413	-
Dones, n (%)	215 (52,0)	215 (52,0)	-
Edat (anys)	55,9 ± 10,4	55,0 ± 10,0	0,712
IMC (Kg/m^2)	36,8 ± 8,1	36,4 ± 9,0	0,458
C. de cintura (cm)	115,5 ± 16,0	114,8 ± 17,2	0,583
P. de collo (cm)	40,1 ± 5,9	40,8 ± 4,2	0,185
Glucèmia (mg/dl)	164,5 ± 56,5	97,4 ± 11,6	< 0,001
HbA1c (%)	7,9 ± 1,6	5,7 ± 0,4	< 0,001

Plos One 2016 [epub ahead of print]

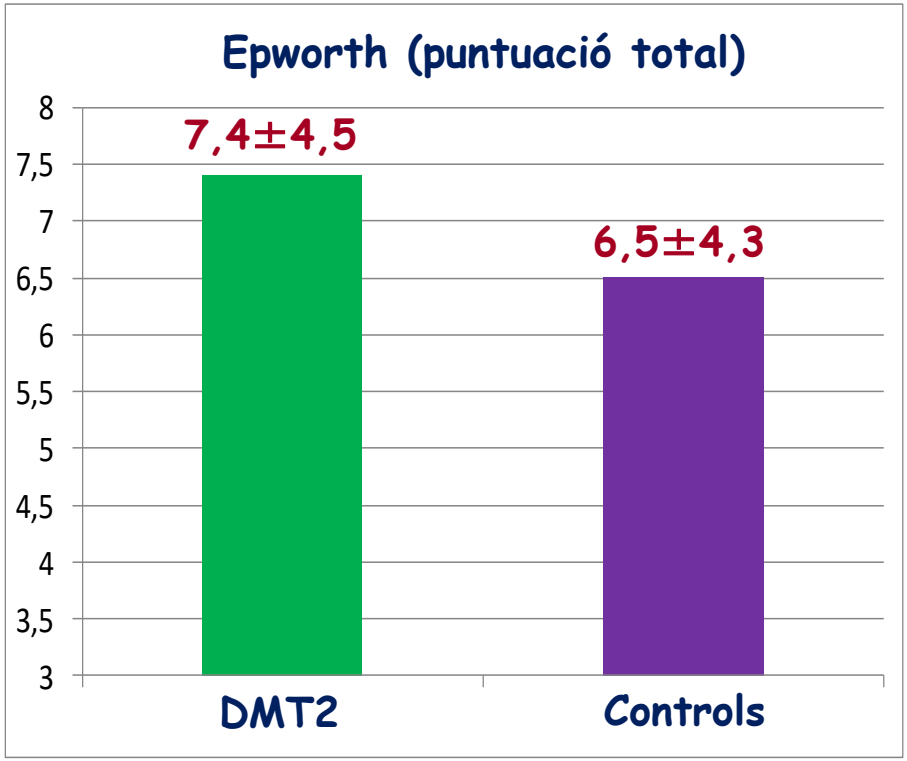
QUESTIONARI D'EPWORTH



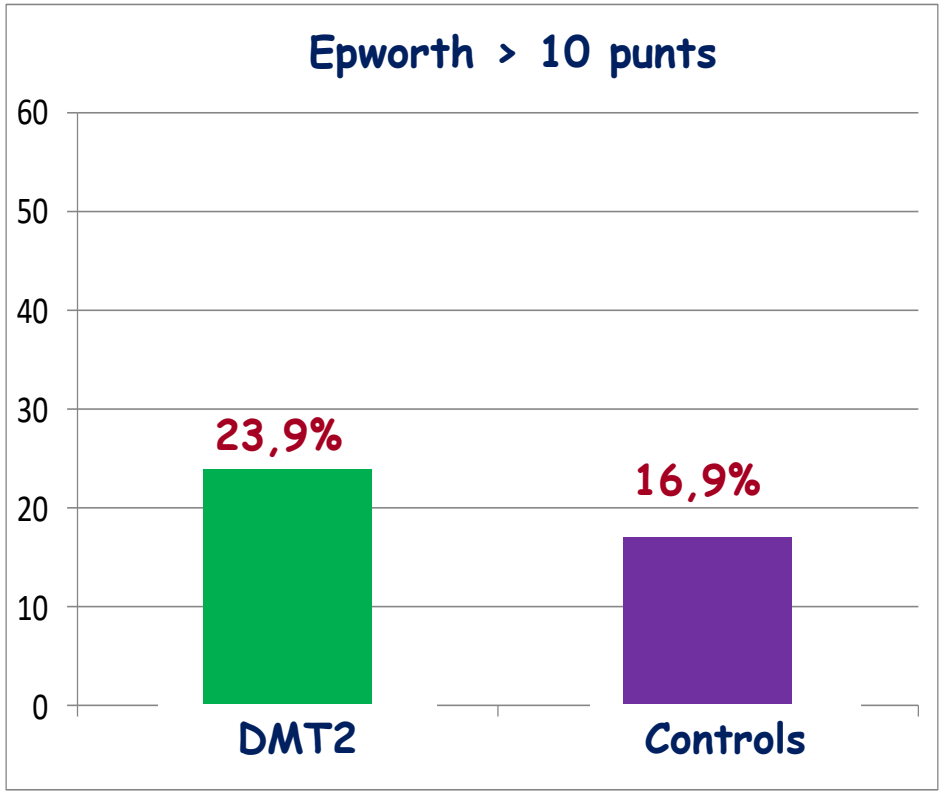
p = 0,003

Plos One 2016 [epub ahead of print]

QUESTIONARI D'EPWORTH



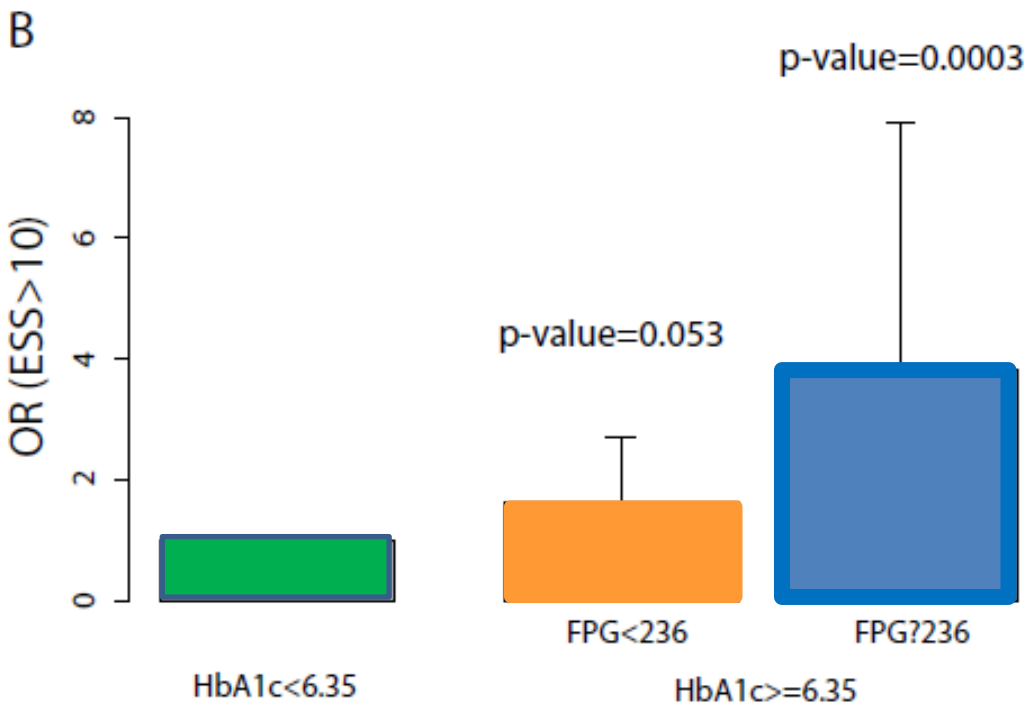
p = 0,003



p = 0,016

Plos One 2016 [epub ahead of print]

QUESTIONARI D'EPWORTH



	Beta (SE)	OR (95% CI)	p value
Intercept (HbA1c < 6.3%)	-1.76 (0.20)	-	-
HbA1c ≥6,3% and FPG <236 mg/dl	0.49 (0.25)	1.63 (1.002 , 2.72)	0.053
HbA1c ≥6,3% and FPG ≥236 mg/dl	1.34 (0.37)	3.81 (1.82 , 7.91)	0.0003

Plos One 2016 [epub ahead of print]


La DM tipus 2 com
a factor de risc
independent per
una major
somnolència diürna

OBJECTIVES

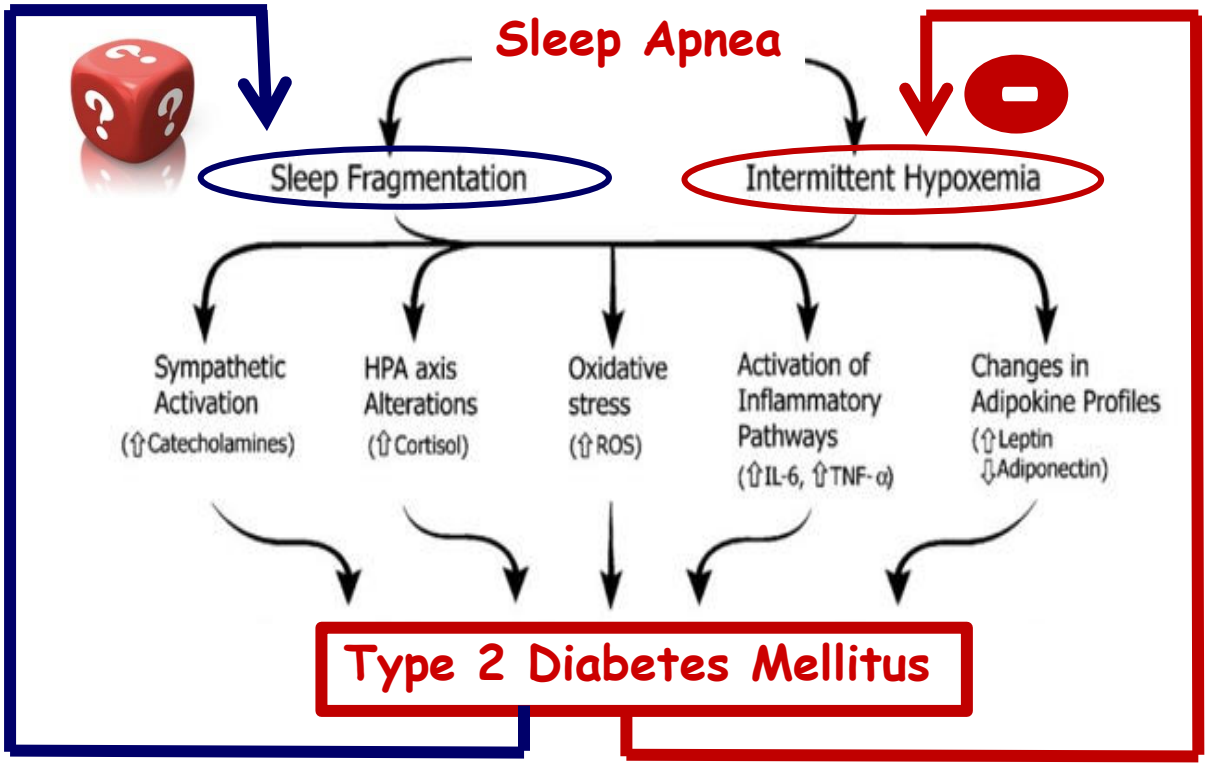
.- **Harmful effects of T2D on:**

- lung function
- sleep breathing disorders
- sleep fragmentation

.- **Effects of improving glycemic control on:**

- nocturnal desaturations
- pulmonary function

breath in,
breath out,
repeat if necessary.



Diabet Med 2016
[Epub ahead of print]

No REM sleep

REM sleep

Sleep cycle

(90-120 min)

Stage 1

Interin between conciousness and sleep. Drowsiness and sleep begin.

Stage 2

More stable sleep occurs. Heart rate slows, and brain does less complicated tasks.

SWS stage

Deep sleep. Body makes repairs. hGH is released. Body temperature and BP decreases.

REM

Brain activity is high and you dream. Eye movement, BP, breathing, heart rate and temp. increase. Memory revitalizes.

Move into REM sleep approx 90 mins after first feeling sleep

SWS: slow wave stage

Diabet Med 2016
[Epub ahead of print]

	DM tipus 2	Controls	p
n	76	76	-
Edat (anys)	54.1 ± 11.1	51.1 ± 14.6	0.342
IMC (Kg/m^2)	39.1 ± 40.5	40.5 ± 7.0	0.453
Circum. cintura (cms)	125.2 ± 15.2	125.3 ± 16.0	0.984
Circum. coll (cms)	40.7 ± 3.8	41.4 ± 4.2	0.543
IAH (events/h)	34.1 (1.0-128.8)	25.9 (1.2-109.1)	0.016
Glucosa (mg/dl)	166.7 ± 56.3	95.8 ± 11.1	< 0.001
HbA1c (%)	8.2 ± 1.5	5.6 ± 0.3	< 0.001

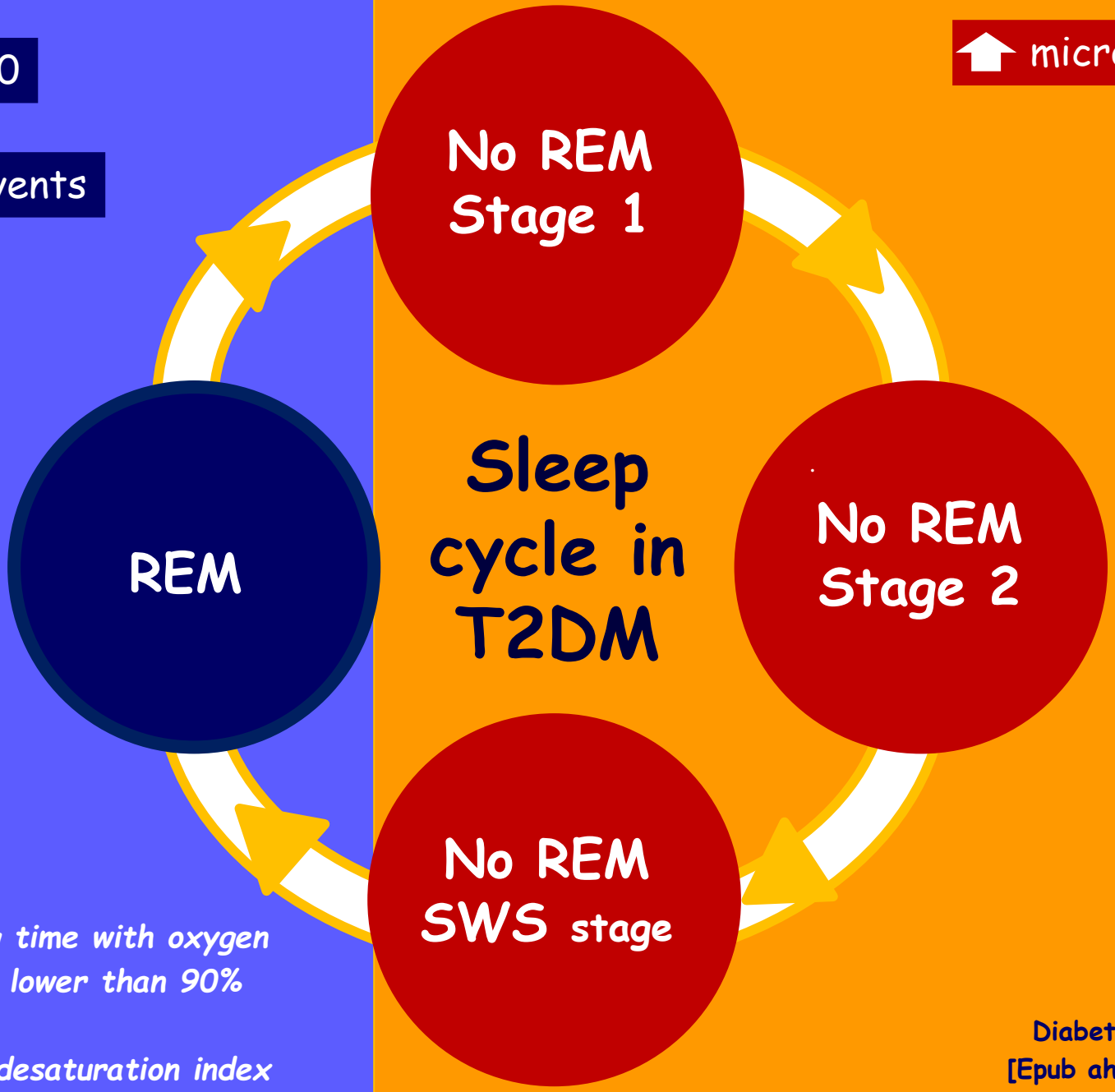
Idéntics resultats en un subgrup de 32 DMT2 i 64 controls equiparats també per IAH

Diabet Med 2016
[Epub ahead of print]

↑ CT90

↑ ODI events

↑ microarousals



CT90: sleeping time with oxygen saturation lower than 90%

ODI: oxigen desaturation index

Diabet Med 2016
[Epub ahead of print]

OBJECTIVES

.- **Harmful effects of T2D on:**

- lung function
- sleep breathing disorders
- sleep fragmentation

.- **Effects of improving glycemic control on:**

- nocturnal desaturations
- pulmonary function

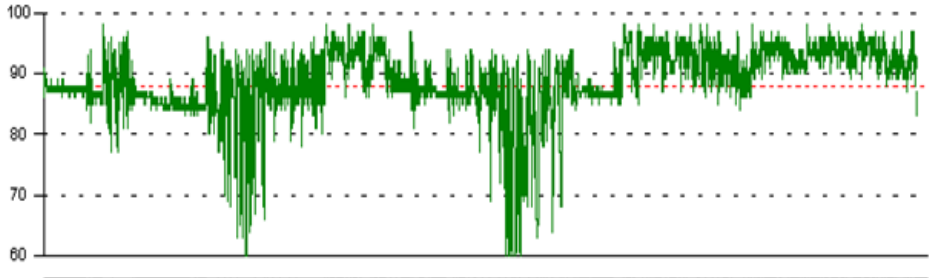
breath in,
breath out,
repeat if necessary.

Journal of Diabetes

Effect of glycemic control on nocturnal arterial oxygen saturation: A case-control study in type 2 diabetic patients

Albert LECUBE,[1,2] Andreea CIUDIN,[1] Gabriel SAMPOL,[3] Silvia VALLADARES,[1] Cristina HERNÁNDEZ[1] and Rafael SIMÓ[1]

	T2DM	Non diabetic	p
n	30	10	
Age (years)	62.7 ± 12.4	60.7 ±19.1	0.685
Women, n (%)	21 (70.0)	7 (70.0)	1.000
BMI (Kg/m^2)	32.1 ± 7.4	31.5 ± 6.2	0.830
Neck circumference (cms)	41.1 ±4.1	40.0 ±3.1	0.482
Fasting plasma glucose (mmol/l)	8.7 ± 4.1	5.7 ± 0.9	0.001
HbA1c (%)	10.0 ± 1.9	5.5 ± 0.7	<0.001



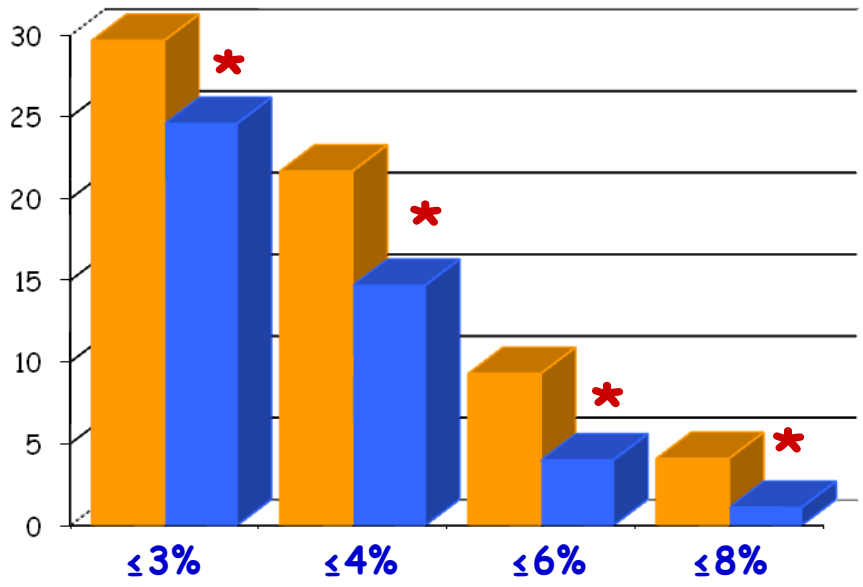
J Diabetes. 2015; 7: 133-8.

Journal of Diabetes

Effect of glycemic control on nocturnal arterial oxygen saturation: A case-control study in type 2 diabetic patients

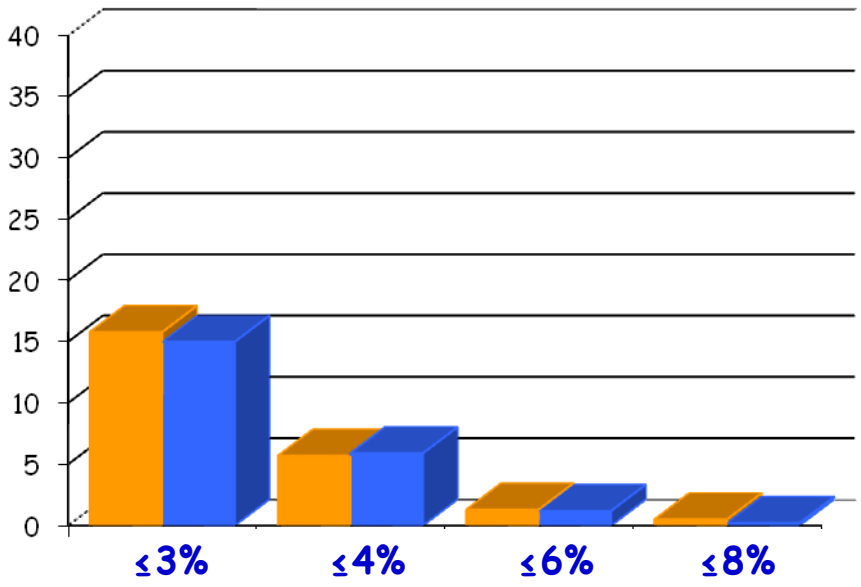
Albert LECUBE,[1,2] Andreea CIUDIN,[1] Gabriel SAMPOL,[3] Silvia VALLADARES,[1] Cristina HERNÁNDEZ[1] and Rafael SIMÓ[1]

Type 2 diabetes (n=30)



Desaturation events (events/h)

No diabetes (n=10)



Desaturation events (events/h)

*: $p<0.01$

Day 1

Day 5

J Diabetes. 2015; 7: 133-8.

Oh yeah, but only 5 days…
and with inpatient subjects iii

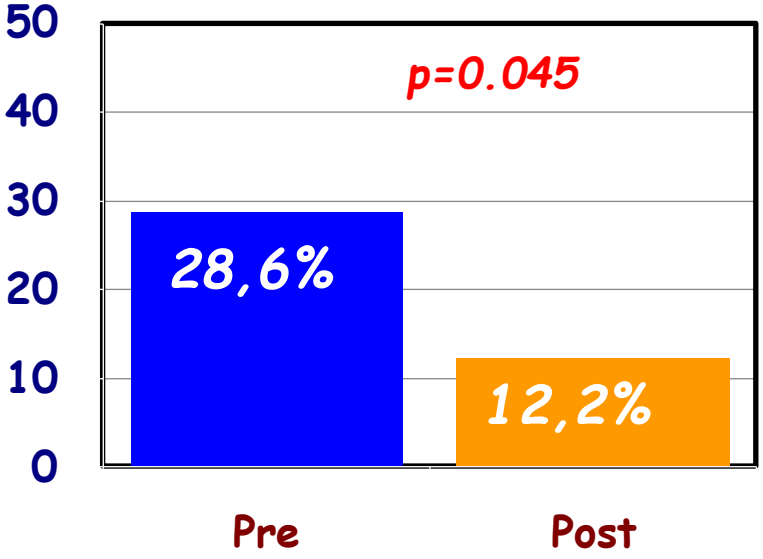
What will happen latter,
in daily clinical practice?

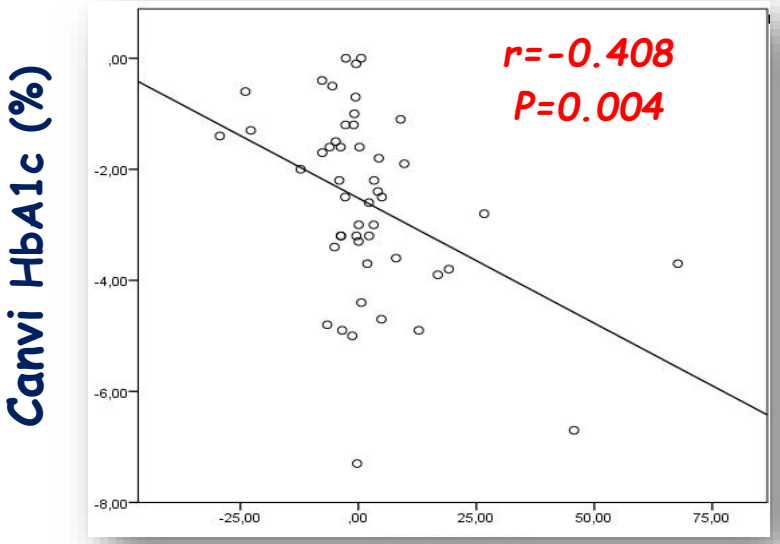
Característiques pre i post intervenció

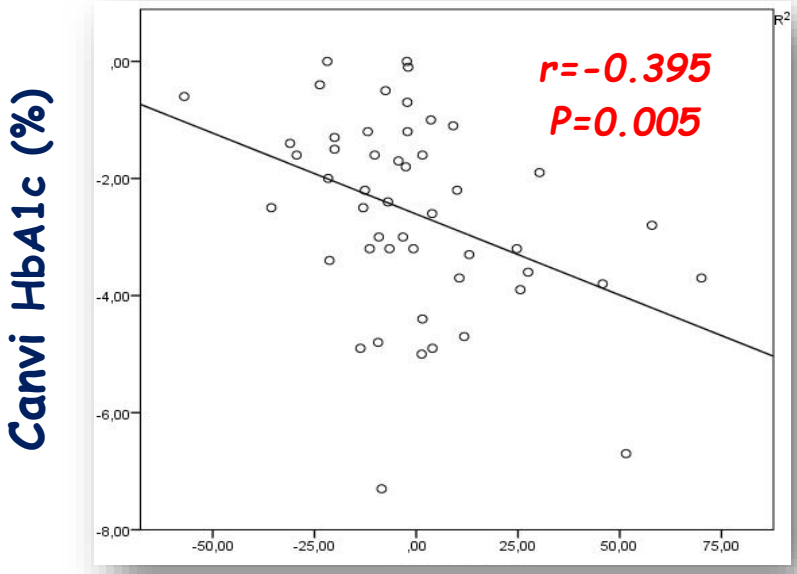
2,6 ± 0,8 mesos
49 pacients

	Pre	Post	p
n	49	49	-
HbA1c (%)	9.7 ± 1.5	7.1 ±1.0	<0.001
IMC (Kg/m^2)	30.8 ± 6.2	30.2 ± 5.9	0.062
Perímetre de coll (cm)	40.5 ±0.6	40.7 ±0.6	0.403

Patró Restrictiu
[CVF<80% & FEV_1/CVF>70%]







Anàlisis multivariant

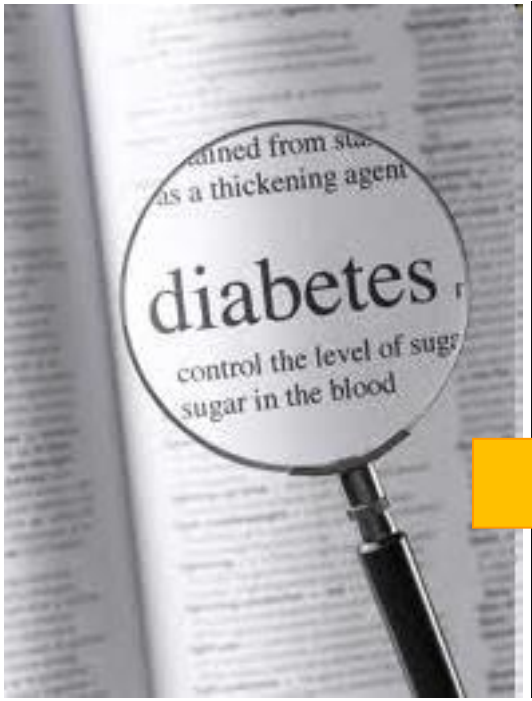
Δ VEF1/CVF com a variable dependent

	Beta	p
Edat	- 0.145	0.299
Sexe	- 0.047	0.738
Anys DMT2	0.023	0.868
ΔIMC	- 0.075	0.596
P. coll	- 0.145	0.286
ΔHbA1c	- 3.732	0.004
R^2 = 16.8		

El mateix passa quan la variable depenent és el FEF25-75% o FEF50%

Pot la diabetis influir sobre la funció pulmonar?

CONCLUSIONS FINALS



SÍ

Girona
3 de Juny de 2016

TAN SOLS RECORDAR...

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Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas

ciberes
Centro de Investigación Biomédica en Red Enfermedades Respiratorias

Agraïments:

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

SEEN
Sociedad Española de Endocrinología y Nutrición

Vall d'Hebron Hospital

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