associació catalana de diabetis
12è CONGRÉS
GIRONA | 14 i 15 de març de 2013
Auditori Palau de Congressos

PULMÓ i DIABETIS MELLITUS TIPUS 2

(pulmó diabètic / sweet sleep)

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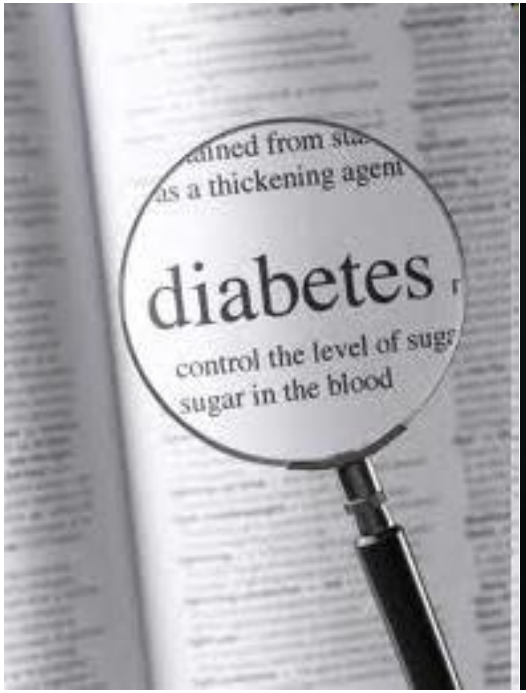
hospital universitari arnau de vilanova

Vall d'Hebron Institut de Recerca VHIR

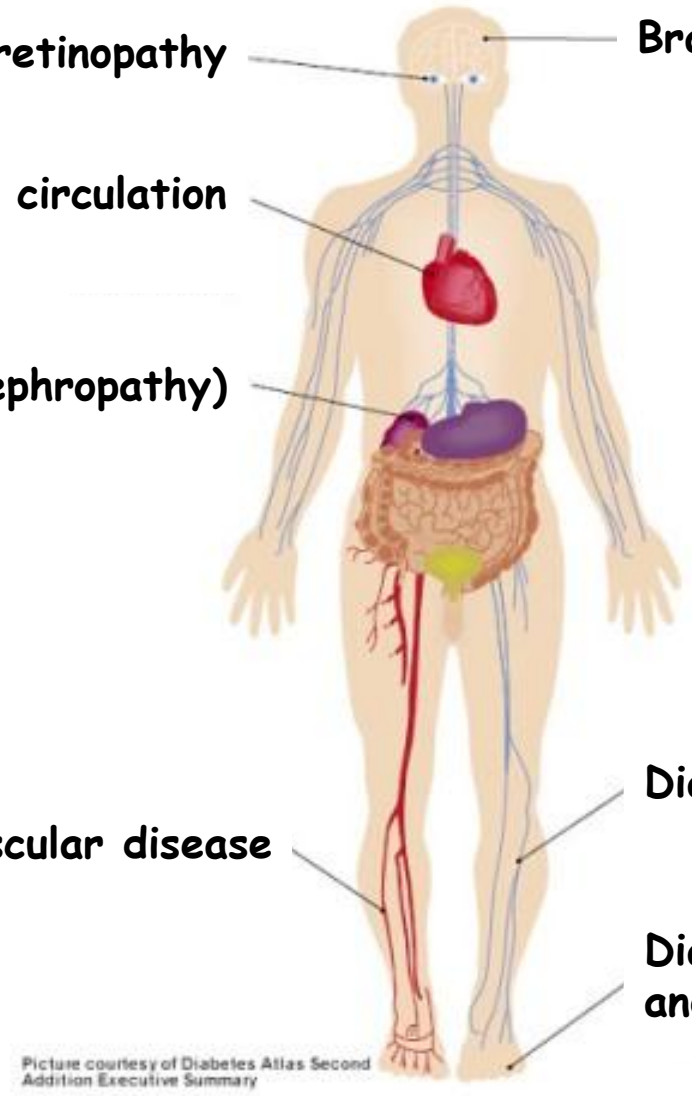
ciberdem

EASO European Association for the Study of Obesity

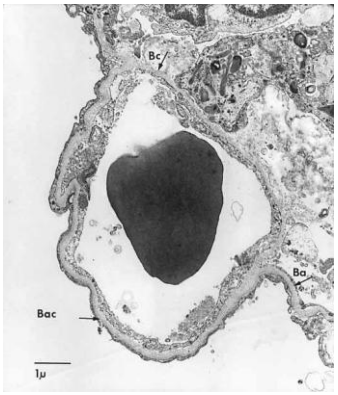


Diabetis i pulmó tenen molt més en comú del que molts de nosaltres creiem.

Complicacions tardanes de la diabetis



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.

Els pulmons no són una excepció

OBJECTIUS

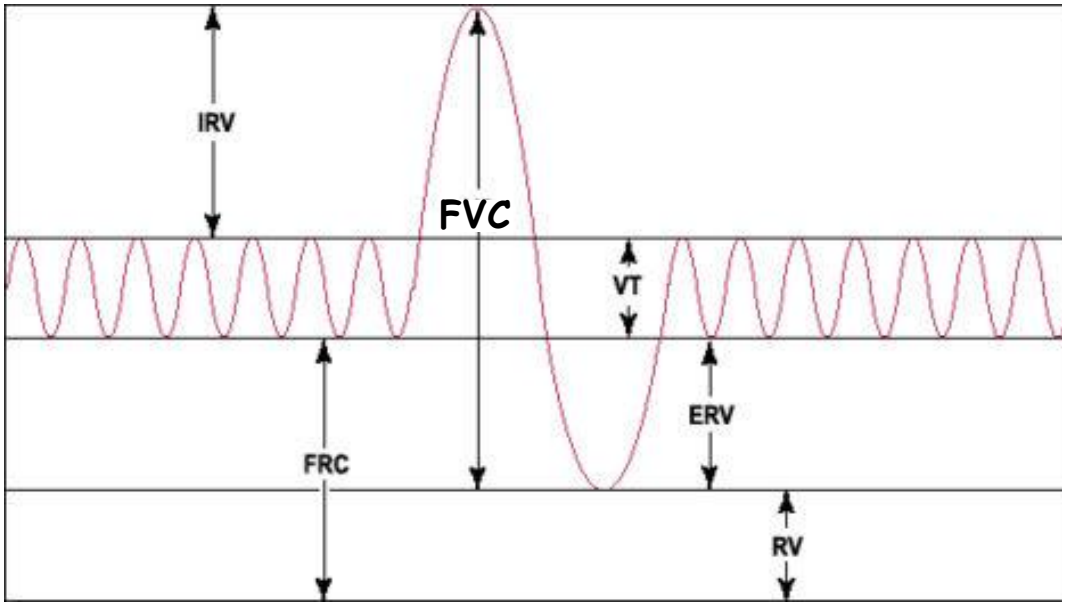
.- Efecte deleteri de la diabetis tipus 2 sobre el pulmó:

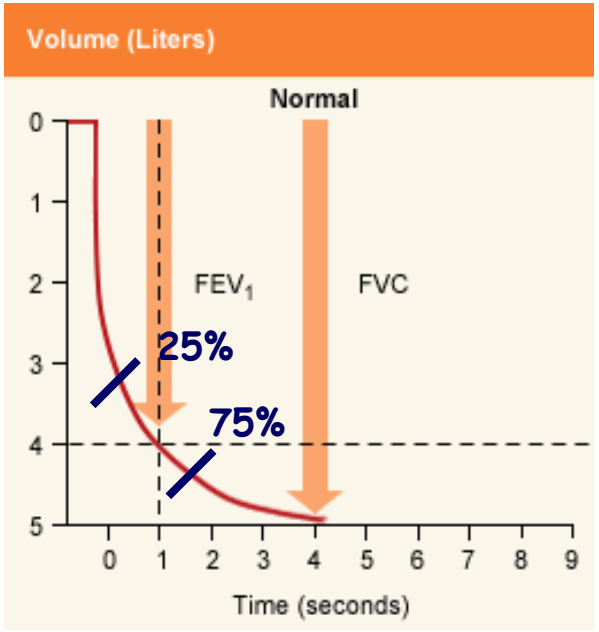
- funció respiratòria
- respiració durant el son

.- Efectes de la millora del control metabòlic.

breath in,
breath out,
repeat if necessary.

Avaluació de la funció pulmonar per espirometria i pletismografia





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

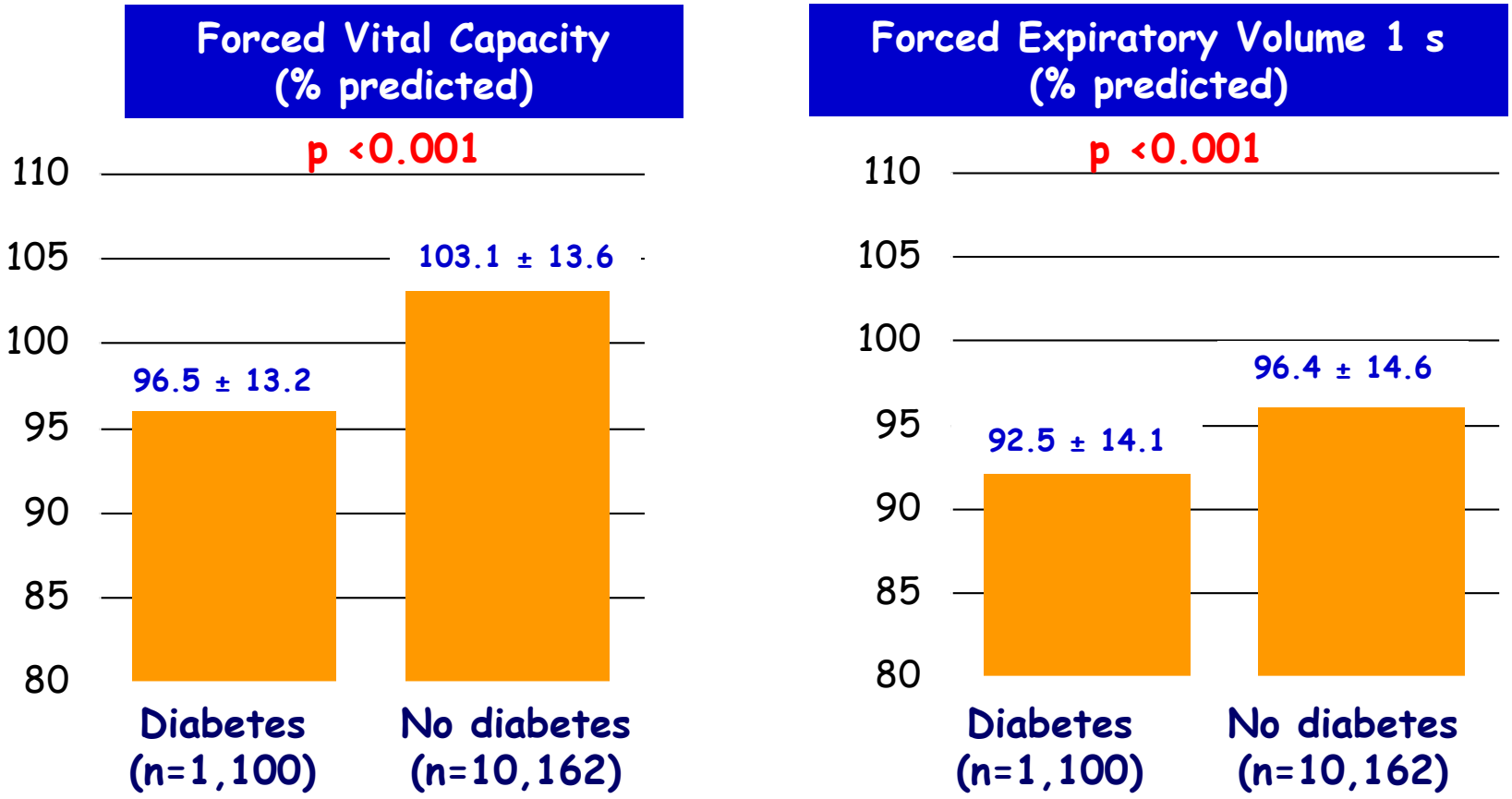
Cross-sectional studies have consistently shown that adults with diabetes have lower spirometric values, ranging from 8 to 10% of the predicted, than their nondiabetic counterparts.

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.

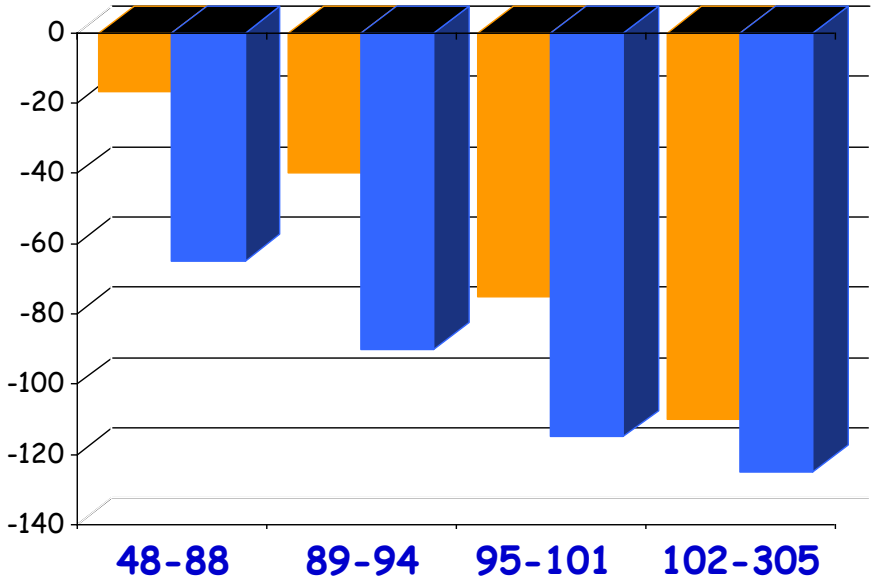
The Atherosclerosis Risk in Communities (ARIC) Study



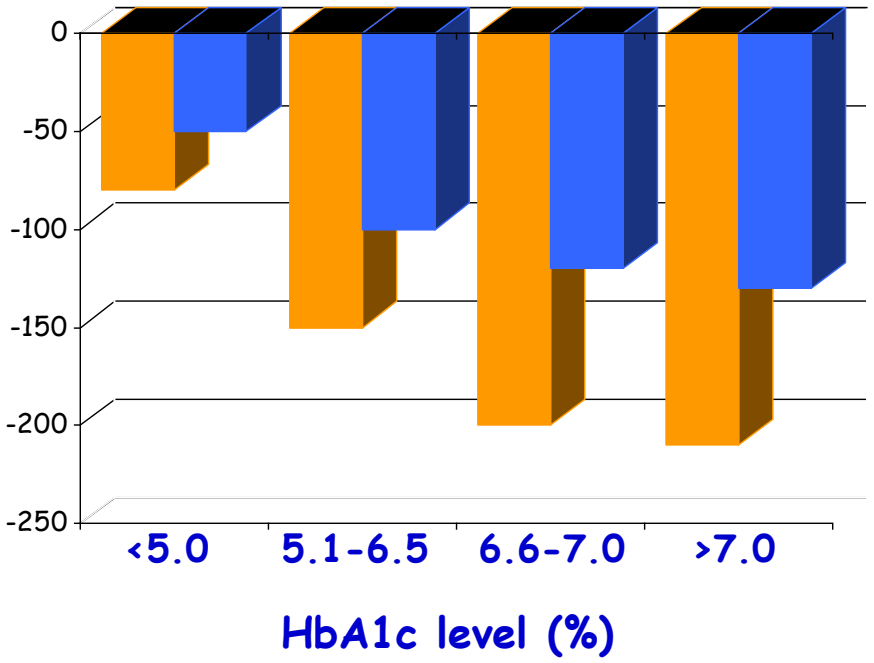
Yeh HC et al. Diabetes Care 2008

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

The Framingham Heart Study



The Atherosclerosis Risk in Communities (ARIC) Study



FVC (ml)

FEV_1 (ml)

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

Longitudinal studies use to show a more rapid decline of spirometric values in type 2 diabetic patients.

3 years of follow-up The Atherosclerosis Risk in Communities (ARIC) Study

ΔFVC (ml/year):	No diabetes (n=10,162)	↓ 58 (56-59)	
	Diabetes (n=1,100)	↓ 64 (59-69)	p = 0.01

7 years of follow-up The Fremantle Diabetes Study (n=125, without control group)

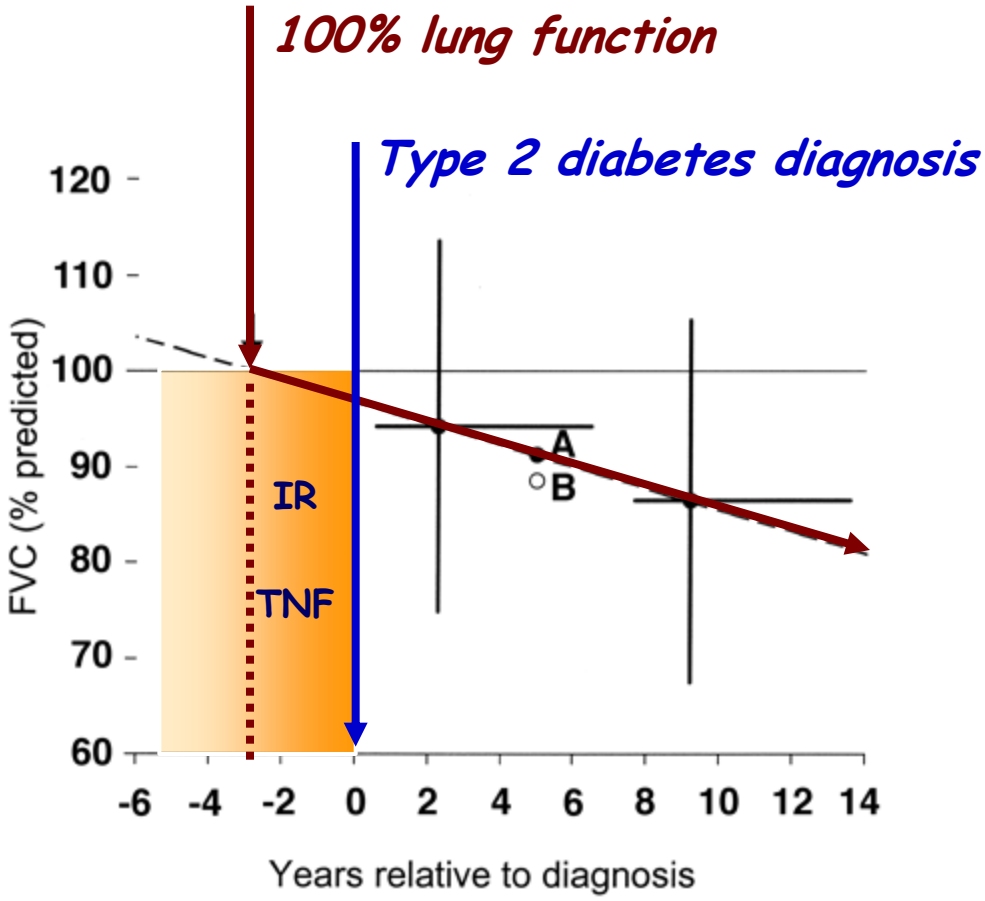
ΔFVC: ↓ 68 ml/year
ΔFEV_1: ↓ 71 ml/year

Approaching double of reported in general population (≤ 40 ml/year)

However, based on a 15 years follow-up, the decline in lung function in diabetes (n=226) was similar to that observed in nondiabetic subjects (n=11,345) in the Copenhagen City Heart Study.

Lange P et al. Eur Respir J 2002.
Davis WA et al. Diabetes Care 2004.
Yeh HC et al. Diabetes Care 2008

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

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

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	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
VR (%)	99.8 ± 22.3	80.3 ± 15.2	< 0.001

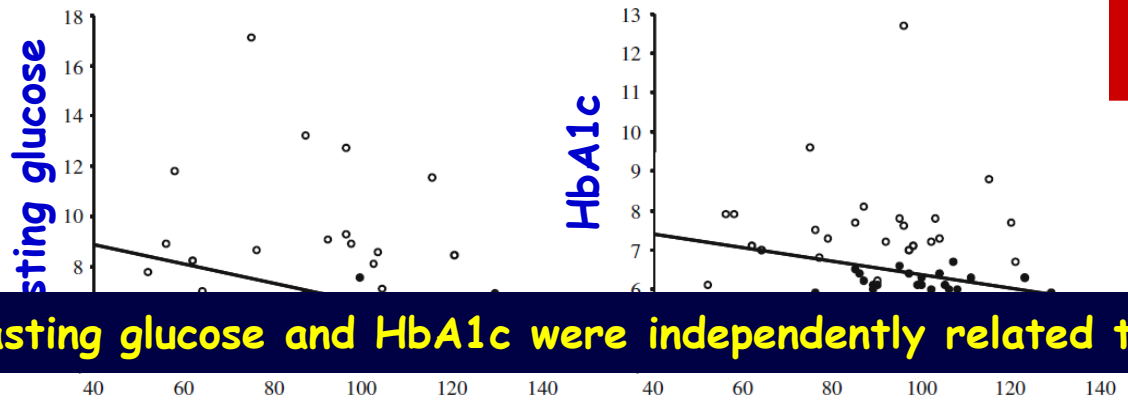
Patró ventilatori obstructiu: 12 % *vs.* 0%, p = 0.012

[FEV_1 <80% y FEV1/FVC <70%]

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

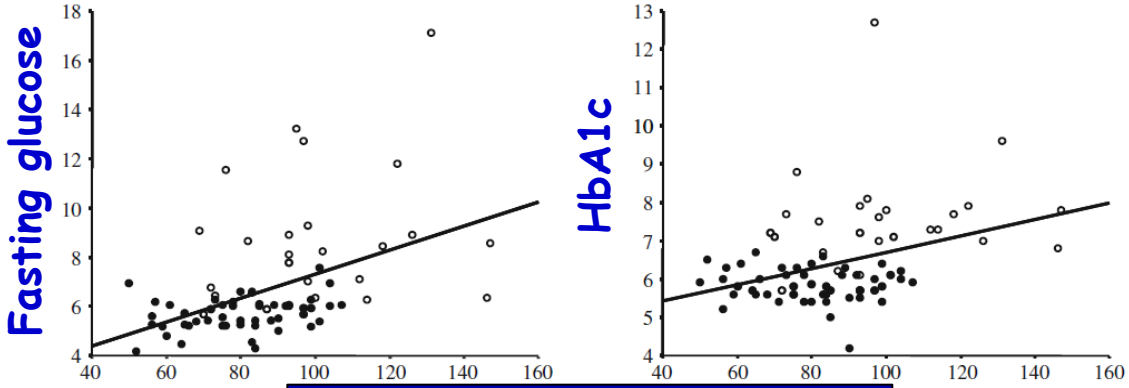


r = -0.236
p = 0.043

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

Volum Espirat Màxim 1s (%pred)

r = 0.454
p <0.001



r = 0.364
p = 0.001

Volum residual (%pred)


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

ARE SPIROMETRIC CHANGES CLINICALLY RELEVANT?

	Type 2 diabetes	No diabetes	p
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?

Diabetologia 2010; 53: 1210-6

ARE SPIROMETRIC CHANGES CLINICALLY RELEVANT?

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.

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

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≈10%

Diabetologia 2010; 53: 1210-6

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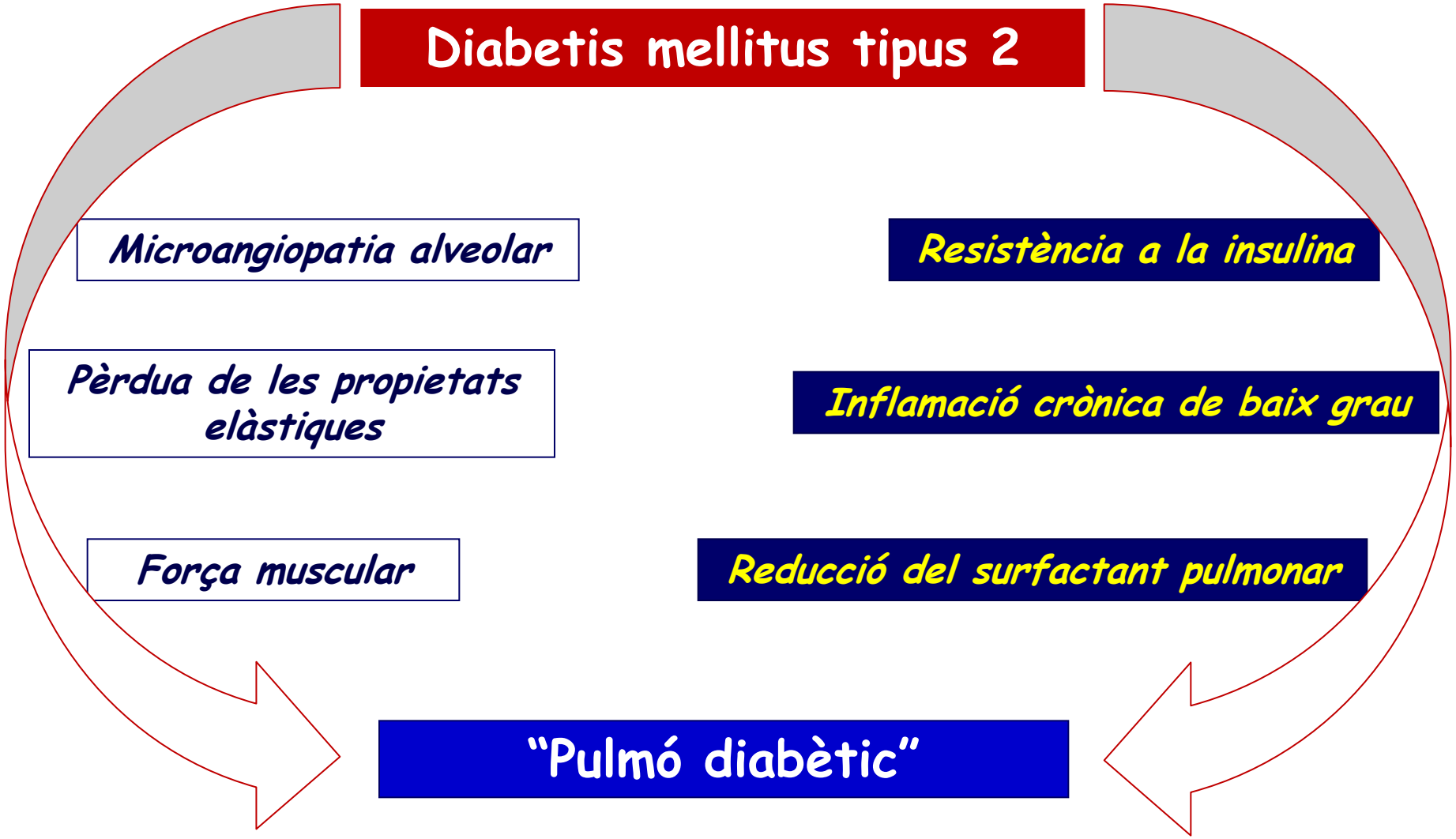
In diabetic patients, a 10% decrease in FEV_1 (% pred) is associated with a 12% increase in all-cause mortality.

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;

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

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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

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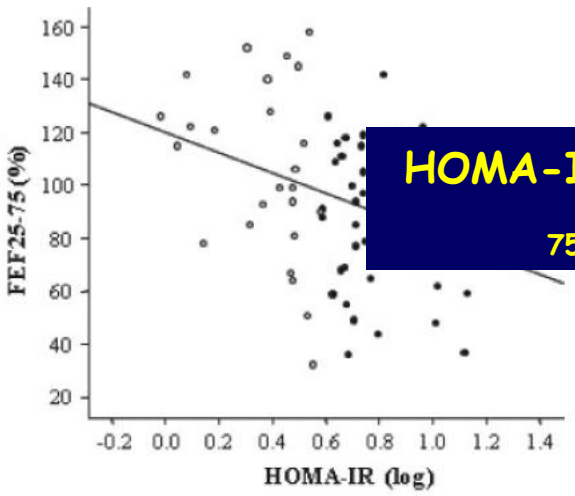
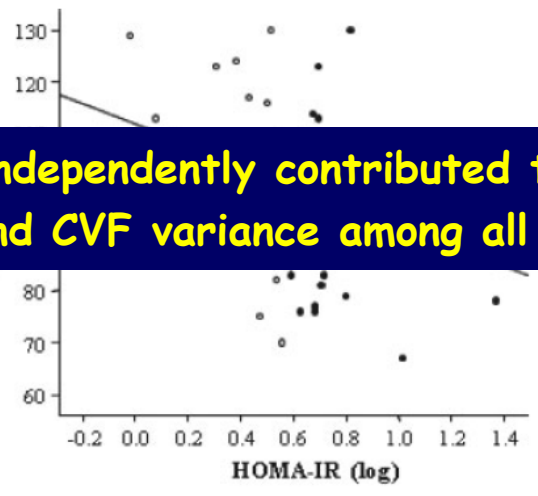
FEF_{25-75} (%)



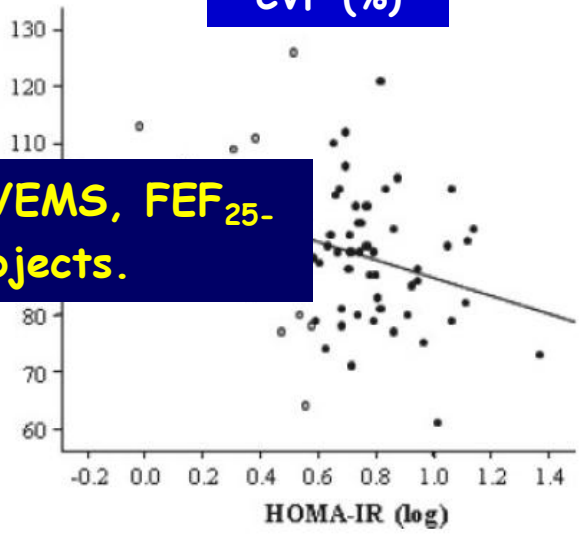
r = -0.339; p = 0.004

VEMS (%)



r = -0.370; p = 0.001

CVF (%)



r = -0.327; p = 0.003

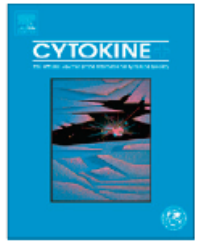
HOMA-IR independently contributed to VEMS, FEF_{25-75}, and CVF variance among all subjects.

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

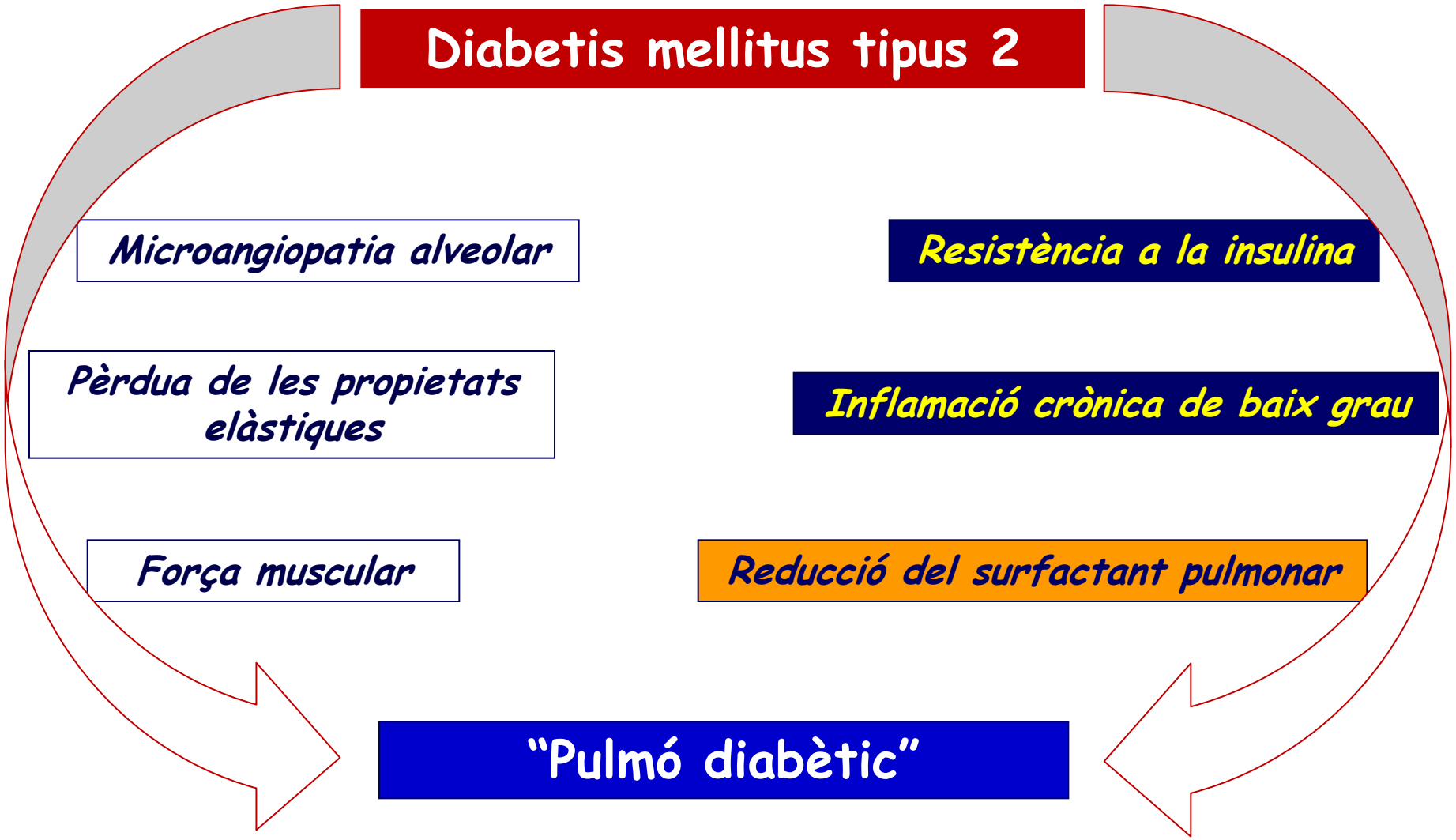
A. Lecube [a,*], G. Sampol [b], X. Muñoz [b], R. Ferrer [c], C. Hernández [a], R. Simó [a]

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

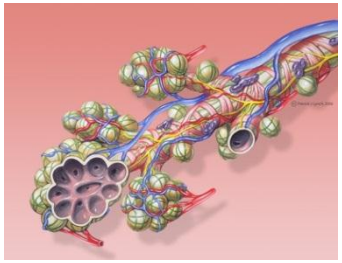
sTNFα-R1, but not sTNFα-R2, was independently associated with FEV_1 and FVC.

Cytokine 2011; 54: 121-4



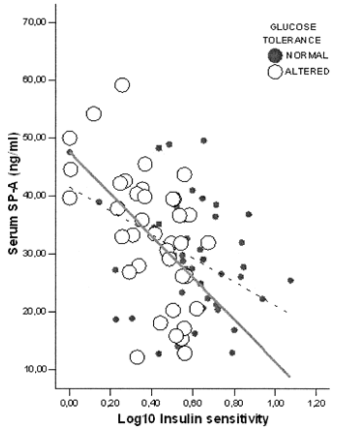
Schnapf BM et al. Am Rev Respir Dis 1984; Ramírez LC et al. Am J Med 1991; Lazarus R et al. Metabolism 1997; Chance WW et al. Diabetes Care 2008;

GLP-1, surfactant and glucose abnormalities



Surfactant is involved in maintaining airway stability and diameter

Increased circulating levels of surfactant protein A (surrogate of damage in the alveolocapillary barrier) are associated with altered glucose tolerance and diabetes



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

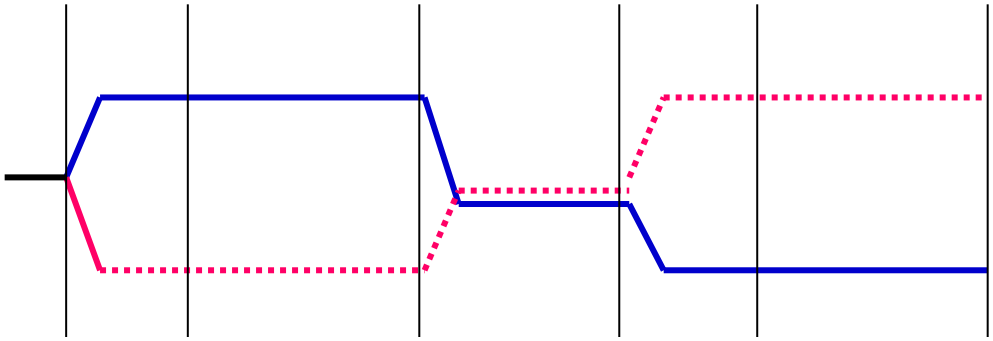
Experimental studies have shown that GLP-1 plays a role in the stimulation of surfactant production by pneumocytes

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; Fernández-Real JM et al. Diabetes Care 2008

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

EXELUNG Clinical Trial
(EudraCT: 2010-023518-29)
Sponsor: Spanish Clinical Trial Network (CAIBER)

Double-blind randomized, crossover, placebo-controlled study,
with two parallel groups (exenatide sc/12 h *vs.* placebo sc/12 h) of 14-weeks



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
- serum levels of surfactant A protein, and
- inflammation markers in the exhaled air

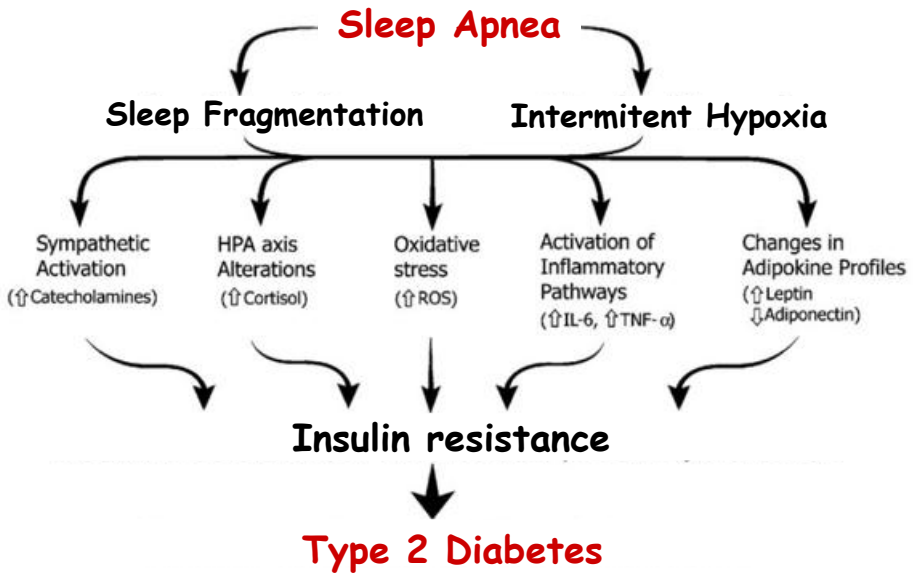
OBJECTIUS

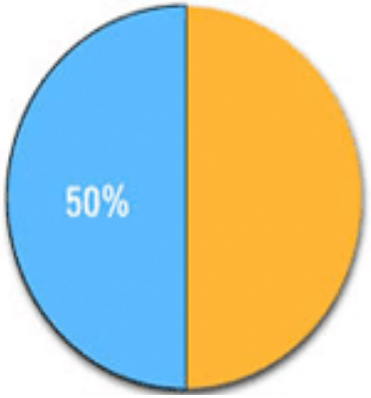
.- Efecte deleteri de la diabetis tipus 2 sobre el pulmó:

- funció respiratòria
- respiració durant el son

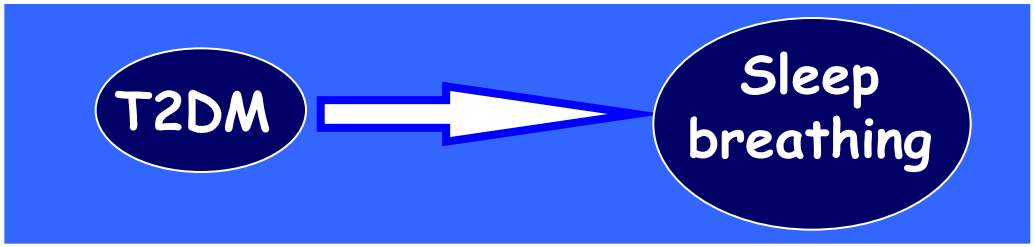
.- Efectes de la millora del control metabòlic.

breath in,
breath out,
repeat if necessary.





Més del 50% dels pacients amb diabetis tipus 2 tenen algun grau d'apnea de la son.



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PLoS one

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

Albert Lecube[1☯*], Gabriel Sampol[2☯], 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

PLoS One 2009; 4: e4692

OPEN ACCESS Freely available online

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	Type 2 diabetes	No diabetes	p
SAS (%)	80.0	78.3	0.855
Epworth Sleepiness	7.3 ± 4,6	6.5 ± 4.1	0.453
CT90 (%)	20.2 ± 30.2	6.8 ± 13.5	0.027

SAS: Sleep apnea syndrome

AHI: Apnea-hypopnea index

CT90: the cumulative percentage of time spent with O_2 saturations <90%

PLoS One 2009; 4: e4692

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Albert Lecube[1,3]*, Gabriel Sampol[2,3], 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 diabetes tipus 2 afavoreix de forma independent la hipoxèmia nocturna greu

Com s'explica aquesta hipoxèmia nocturna en la diabetis mellitus tipus 2?

	DM tipus 2	Controls	p
n	119	238	-
Edat (anys)	50,5 ± 10,8	50,9 ± 11,4	0,715
IMC (Kg/m^2)	42,9 ± 7,9	42,2 ± 8,1	0,354
P. cintura (cms)	125,2 ± 15,8	122,2 ± 15,2	0,097
P. coll (cms)	40,9 ± 3,7	41,0 ± 3,6	0,903
Glucosa (mg/dl)	170,7 ± 58,5	98,3 ± 11,6	< 0.001
HbA1c (%)	7,9 ± 1,6	5,6 ± 0,3	< 0.001

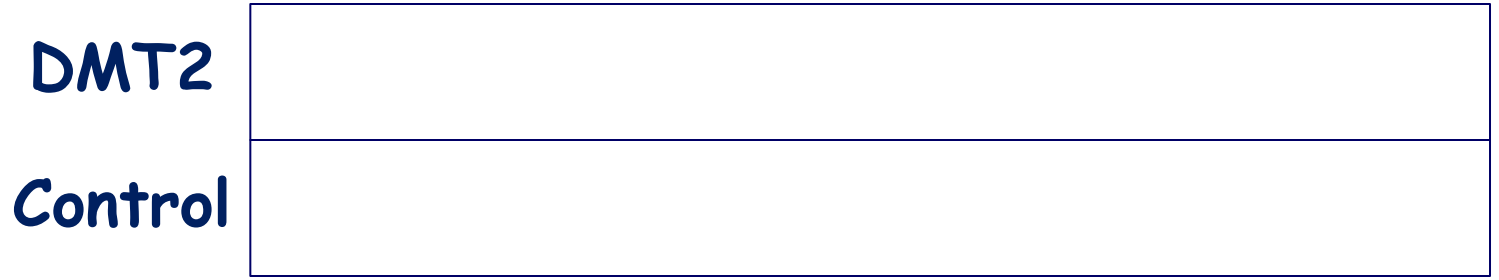
Com s'explica aquesta hipoxèmia nocturna en la diabetis mellitus tipus 2?

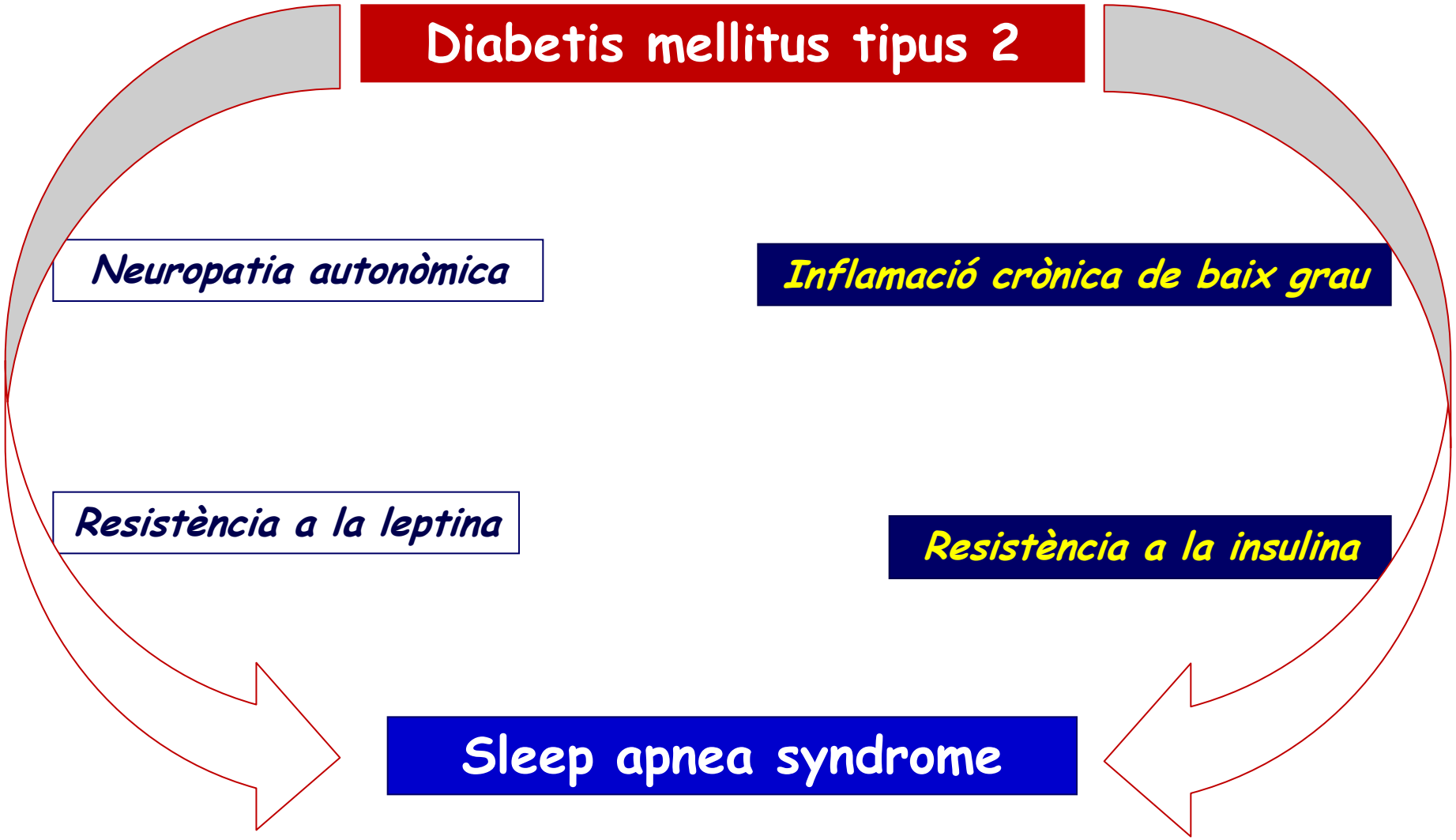
	DM tipus 2	Controls	p
n	119	238	-
IAH (events/h)	34,3 ± 9,2	26,7 ± 1,8	0,017
Hipoapnees (e/h)	18,5 ± 1,2	16,4 ± 0,7	0,951
Apnees (e/h)	15,9 ± 7,1	10,3 ± 1,2	0,048

Com s'explica aquesta hipoxèmia nocturna en la diabetis mellitus tipus 2?

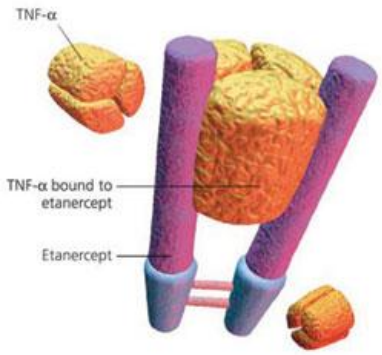
	DM tipus 2	Controls	p
CT90 (%)	18,3 ± 4,2	10,7 ± 3,9	0,042
Hipersomnia	7,5 ± 2,6	6,1 ± 0,2	0,012
Desaturacions 2% (e/h)	37,6 (3-284)	26,6 (0-129,1)	0,016

I si equiparem també els pacients pel seu IAH?





Ficker JH et al. Eur Respir J 1998; Bottini P et al. Eur Respir J 2003; Resnick HE et al. Diabetes Care 2003; Campo A et al. Eur Respir J 2007.

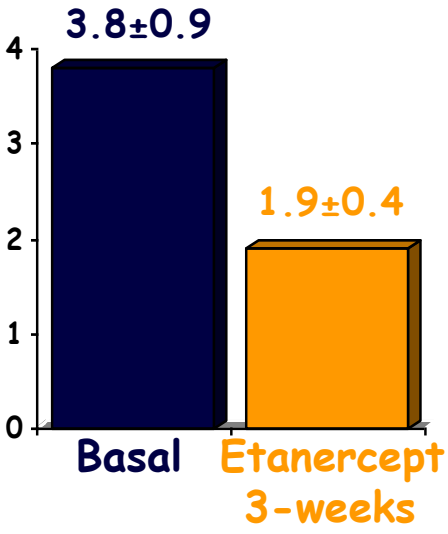


Marked decrease in sleepiness in patients with sleep apnea by etanercept

- placebo-controlled double-blind
- 8 obese men (38.6 ± 2.6 Kg/m$^{2)}$
- AHI: 55.9 ± 11.6 events/h
- 43.7 ± 3.8 years

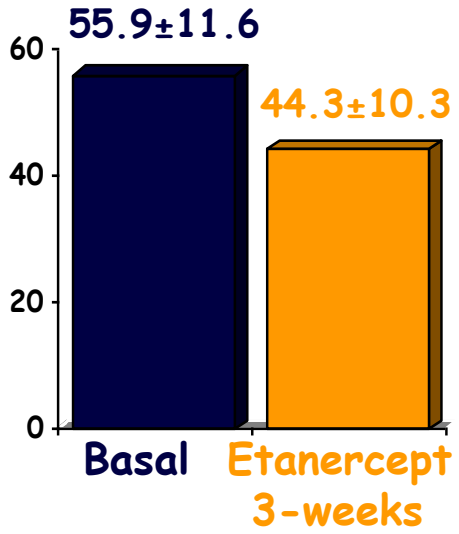
IL-6

P < 0.01



AHI

P < 0.05



Vgontzas AN et al. J Clin Endocrinol Metab 2004.

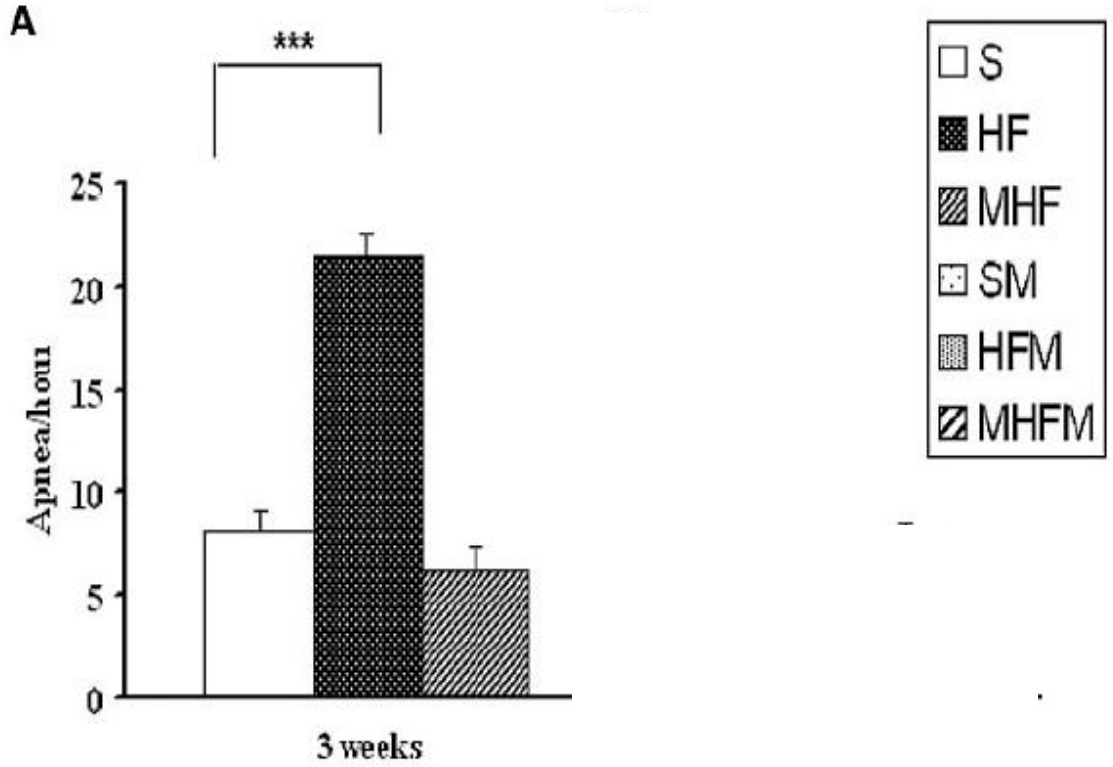
Sprague-Dawley

Sleep apnea is induced by a high-fat diet and reversed and prevented by metformin in non-obese rats.

3 weeks feeding

- 10 rats with a **standard diet (S)**
- 8 rats with a **high-fat diet (HF)** → **insulin-resistant rats**
- 10 rats with a **high fat diet + metformin (MHF)**

4th week, all rats treated with metformin: SM, HFM, MHFM



Ramadan W et al. Obesity (Silver Spring) 2007

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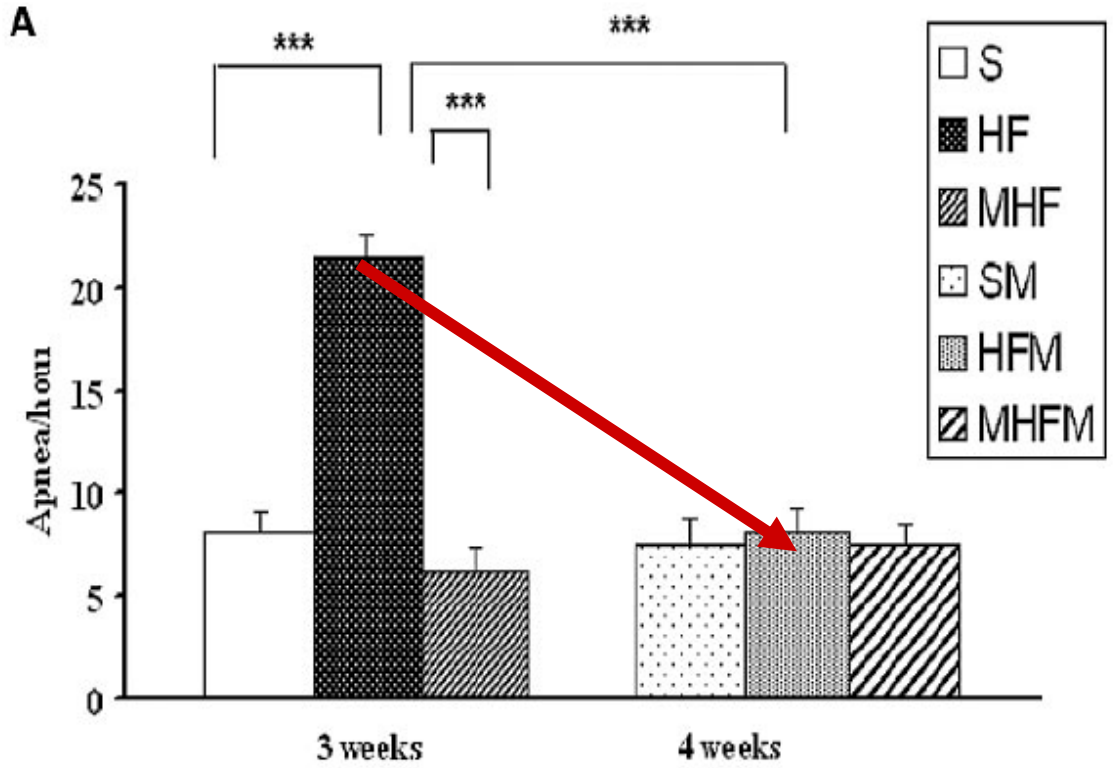


Ramadan W et al. Obesity (Silver Spring) 2007

OBJECTIUS

.- **Efecte deleteri de la diabetis tipus 2 sobre el pulmó:**

- funció respiratòria
- respiració durant el son

.- **Efectes de la millora del control metabòlic**

breath in,
breath out,
repeat if necessary.

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.

La saturació nocturna d'O_2 s'ha mesurat en 30 pacients amb DM tipus 2 en que es va intensificar el control glucèmic durant 5 dies (i en 10 pacients no diabètics ingressats per d'altres motius)

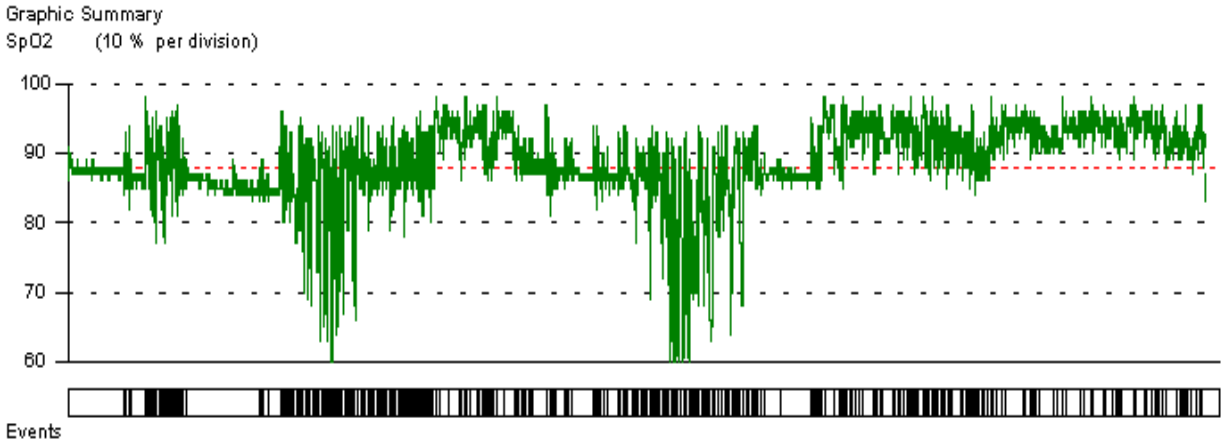


Illustration of a nocturnal oxygen saturation profile

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.

	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

Night glucose profile: 19:00, 21:00, 24:00, 3:00, 7:00

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.

Baseline desaturation events (drops in SpO_2)

	T2DM	Non-diabetic	p
3% (events/h)	29.7 (4.8-107.9)	15.8 (2.3-27.0)	0.006
4% (events/h)	21.7 (1.6-79.3)	5.7 (0.7-24.3)	0.002
6% (events/h)	9.3 (0.3-71.8)	1.3 (0.0-11.4)	0.007
8% (events/h)	4.1 (0.0-64.3)	0.5 (0.0-6.3)	0.078

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.

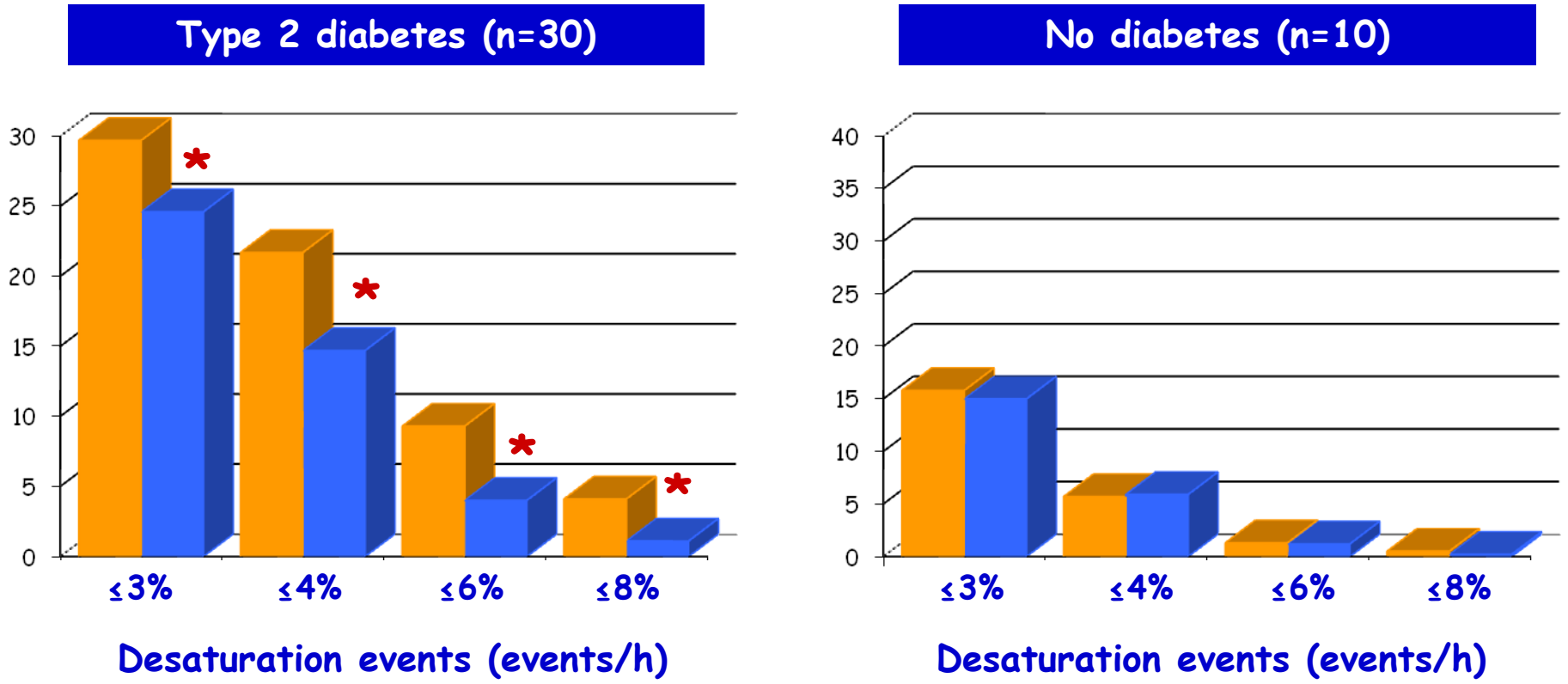
	Day 1	Day 5	p
Age (years)	53.2 ± 8.0	-	-
Women, n (%)	18 (69.2)	-	-
BMI (Kg/m^2)	32.4 ± 6.3	32.1 ± 6.4	0.381
Night glucose profile (mmol/l)	11.2 ± 0.1	7.4 ± 1.5	0.010
Fasting plasma glucose (mmol/l)	8.6 ± 3.2	6.7 ± 2.1	0.035
Fructosamine (mg/dl)	320.1±73.6	304.3±59.6	0.005
HbA1c (%)	10.2±1.9	9.9±1.9	<0.001

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.

Desaturation events in Type 2 DM

	Day 1	Day 5	p
3% (events/h)	29.7 (4.8-107.9)	24.6 (3.1-97.7)	<0.001
4% (events/h)	21.7 (1.6-79.3)	14.7 (0.3-79.4)	0.003
6% (events/h)	9.3 (0.3-71.8)	4.0 (0.0-73.7)	0.023
8% (events/h)	4.1 (0.0-64.3)	1.1 (0.0-69.8)	0.078

La saturació nocturna d'O_2 augmenta després de la millora metabòlica: estudi d'intervenció.



La funció pulmonar hauria de ser considerada per tots aquells que donem assistència als pacients diabètics

La diabetis i el grau de control metabòlic estan relacionats de forma independent amb el deteriorament de la funció respiratòria,

La diabetis mellitus tipus 2 és un factor de risc per la hipoxèmia nocturna greu,

Les rutes metabòliques relacionades amb la resistència a la insulina i la inflamació son crucials en l'inici d'aquestes alteracions.

El pulmó és també un òrgan diana de les complicacions tardanes de la diabetis.


MORE

Complicacions tardanes de la diabetis (properes edicions)

Diabetic retinopathy

Brain and cerebral circulation

Heart and coronary circulation

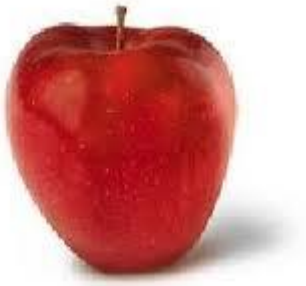
Kidney (nephropathy)

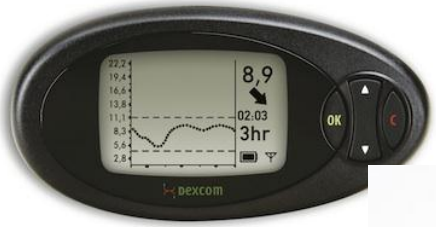
Peripheral vascular disease

Diabetic neuropathy

Diabetic foot (ulceration and amputation)

Picture courtesy of Diabetes Atlas Second Addition Executive Summary





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Gràcies!!