MANEJO DE LA DIABETES EN PACIENTES CON OBESIDAD SEVERA

Dr. Ignacio Márquez
Residente 3er año.
Servicio de Medicina Interna
H.R.U Carlos Haya. Málaga

Caso clínico

Varón de 57 años:

- No alergias medicamentosas conocidas.
- Fumador de 60 paquetes/año hasta el año 2005.
- En ese mismo año, infarto agudo de miocardio con fracción de eyección del 50 % siendo diagnosticado durante el ingreso de Hipertensión Arterial, Diabetes Mellitus y Síndrome de Apnea del sueño.
- Anemia de meses de evolución para la que rechazó estudio.
- No refiere intervenciones quirúrgicas previas.

Caso clínico

- Tratamiento habitual con dosis diarias de omeprazol 20 mg, ácido acetilsalicílico 150 mg, atorvastatina 40 mg, ezetimiba 10 mg, candersartan/hidroclorotiazida 32/12,5 mg, torasemida 20 mg.

  Metformina 2.550 mg. Insulina glargina 42-0-108 UI, e insulina aspart 24-44-24 UI.

- Ingresa procedente de Consulta Externa de Medicina Interna por edemas progresivos de miembros inferiores con lesiones eccematosas pruriginosas sobreañadidas resistentes al tratamiento prescrito por Dermatología. Asociaba además un mal control glucémico pese a incremento progresivo en las dosis de insulina.

Caso clínico

- Exploración física: TA 100/70 mmHg. **Peso 125,1 kg. Talla 1,61 m. IMC 46,28 kg/m².** Cuello corto. Tonos cardiacos rítmicos, débiles, sin soplos. Murmullo vesicular conservado sin ruidos añadidos. Abdomen blando, depresible, indoloro y sin megalias. **Extremidades con edemas crónicos indurados con eccema sobreañadido**.

- Analítica: Hglob 11,5 g/dl, Hto 37,4%, VCM 79,4. Glucemia 138 mg/dl, urea 68 mg/dl, Cr 0,8 mg/dl, colesterol total 134 mg/dl, TG 156 mg/dl, HDL 34 mg/dl, LDL 69 mg/dl; iones y perfil hepático con valores dentro de los límites de la normalidad**. HBA1C 11,9%.** Microalbuminuria 6,6 mg/24 horas. Peptido C normal.

Caso clínico

- Radiografía de tórax: Signos de broncopatía crónica.
- ECG: ritmo sinusal a 95 lpm con pequeña onda Q en cara inferior.
- Ecocardiograma sin hallazgos significativos.
- Ecodoppler venoso de miembros inferiores sin signos de trombosis venosa profunda.
- **Cultivo de exudado de las lesiones cutáneas: Serratia liquefaciens y E. Coli sensibles a cefotaxima.**

Caso clínico

- Dermatología: linfedema verrucoso por dermatitis de estasis sobreinfectado, prescribiendo tratamiento con antihistamínicos y crema de gentamicina.

- Se procede a alta con antibioterapia oral, terapia insulínica con glargina 74-0- 106 UI e insulina aspart 32 UI, 50 UI y 28 UI en desayuno, almuerzo y cena respectivamente, además de su tratamiento previo habitual.

1. **Relación entre obesidad y desarrollo de diabetes.**

2. Situación actual del problema

Diabetes Care 30:1562–1566, 2007

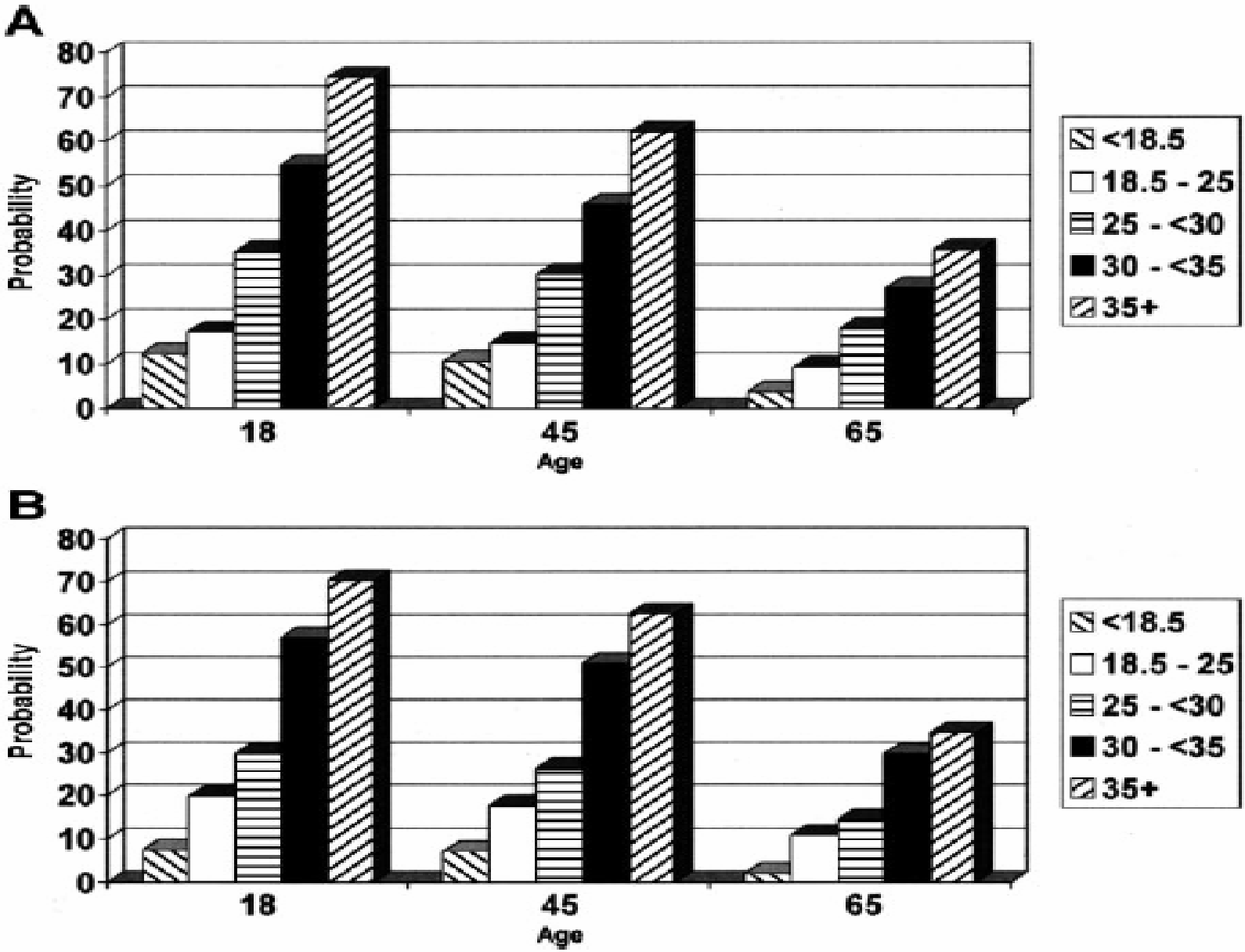
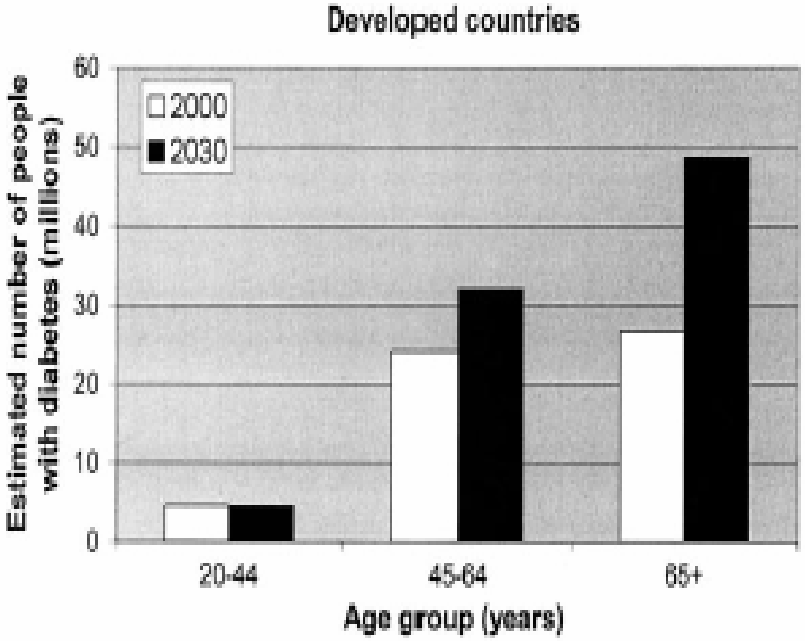
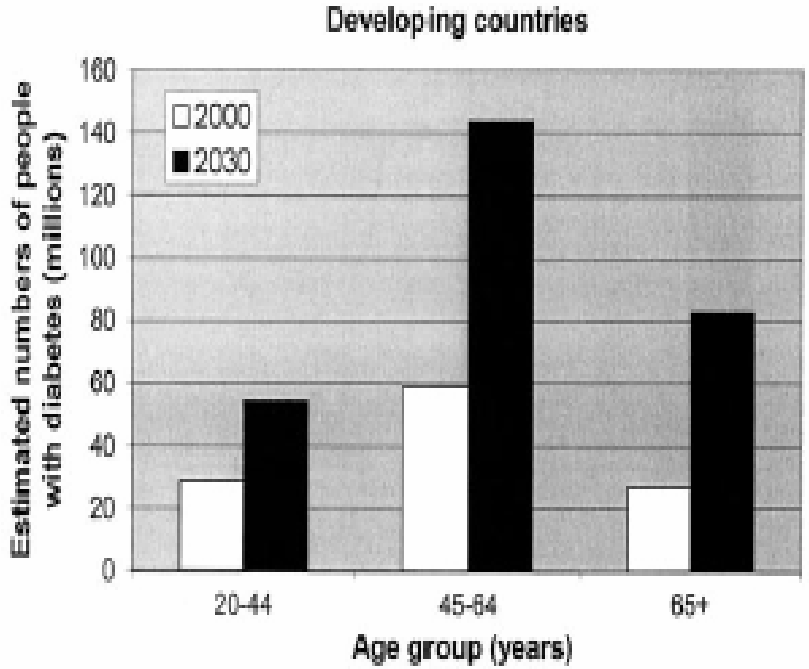


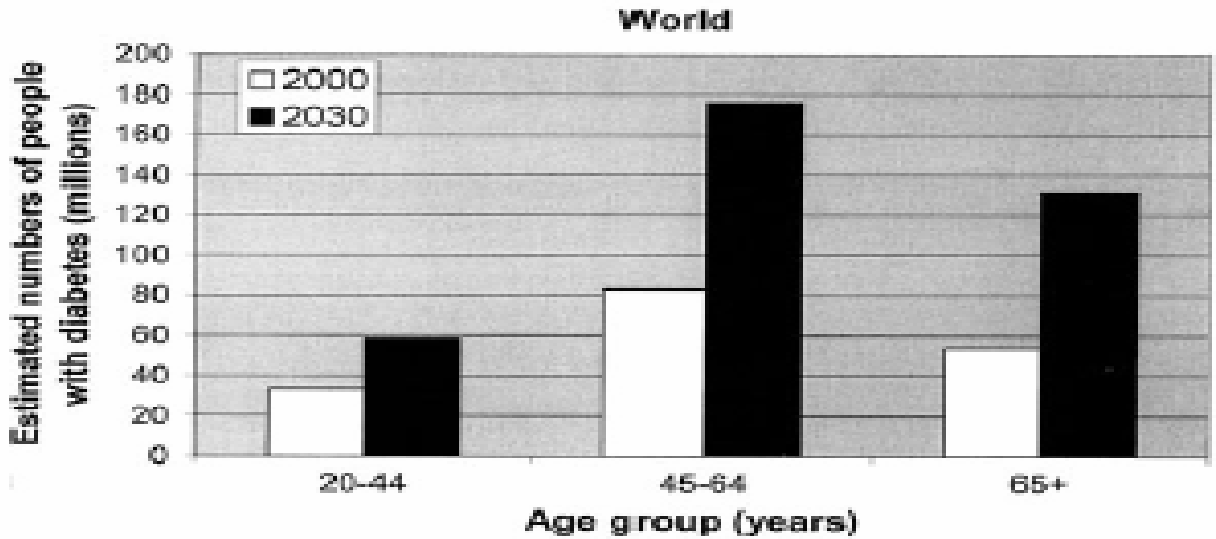
Figure 1— *Remaining average lifetime risk of diabetes by age and BMI among women (A) and men (B).*

1. Fuerte relación entre obesidad y desarrollo de diabetes.

2. **Situación actual del problema**


Developed countries
Estimated number of people with diabetes (millions)
0
10
20
30
40
50
60
2000
2030
20-44
45-64
65+
Age group (years)

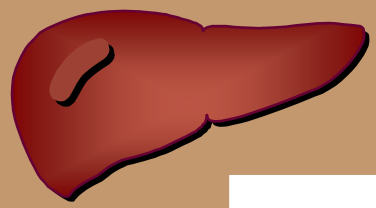

Developing countries
Estimated numbers of people with diabetes (millions)
0
20
40
60
80
100
120
140
160
2000
2030
20-44
45-64
65+
Age group (years)


World
Estimated numbers of people with diabetes (millions)
0
20
40
60
80
100
120
140
160
180
200
2000
2030
20-44
45-64
65+
Age group (years)

RESISTENCIA A LA INSULINA

DISFUNCIÓN CÉLULA BETA

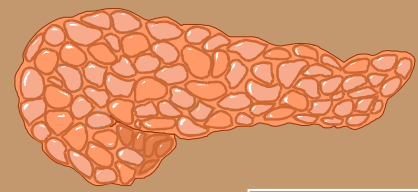
↓ Captación de Glucosa



↑ Producción de Glucosa
↑ Gluconeogénesis
↑ Glucógenolisis

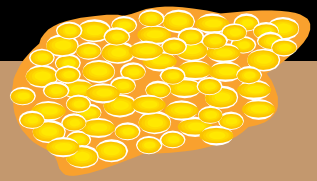
↑ VLDL
↑ TG
↑ LDL densa
↓ HDL

HIPERGLUCEMIA



↓ Secreción de insulina

ADIPOSIDAD ECTÓPICA



RESISTENCIA A LA INSULINA

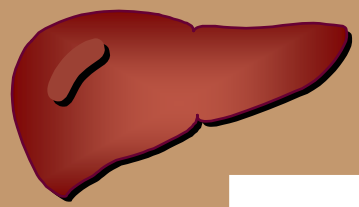
DISFUNCIÓN CÉLULA BETA

↑ IL1, IL6, TNF-α

↑ Leptina, resistina
↓ ADIPONECTINA

↑ AGL

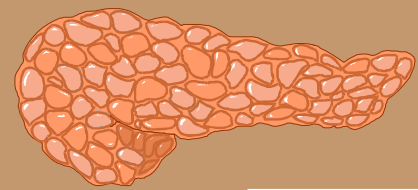
↓ Captación de Glucosa



↑ Producción de Glucosa
↑ Gluconeogénesis
↑ Glucógenolisis

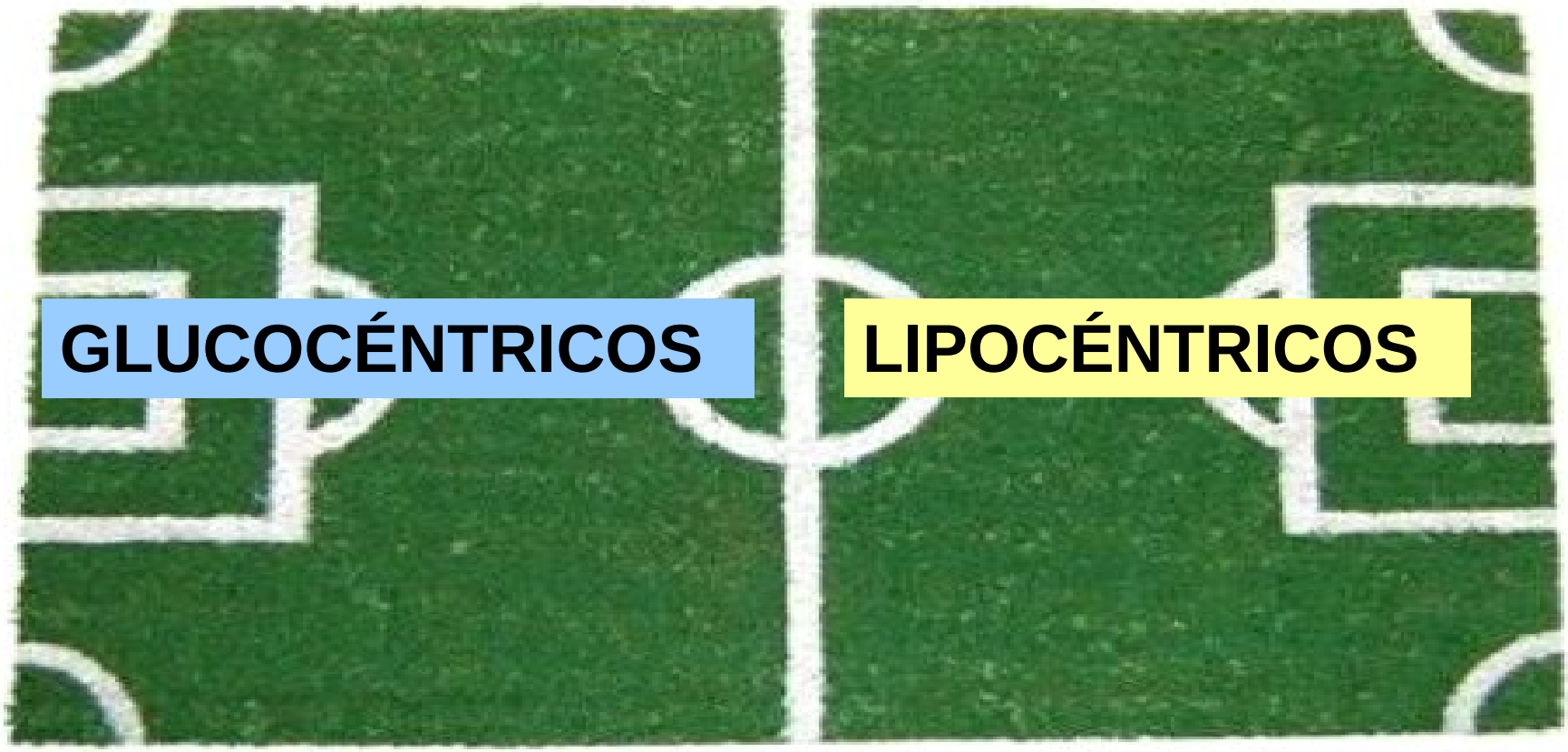
↑ VLDL
↑ TG
↑ LDL densa
↓ HDL

HIPERGLUCEMIA

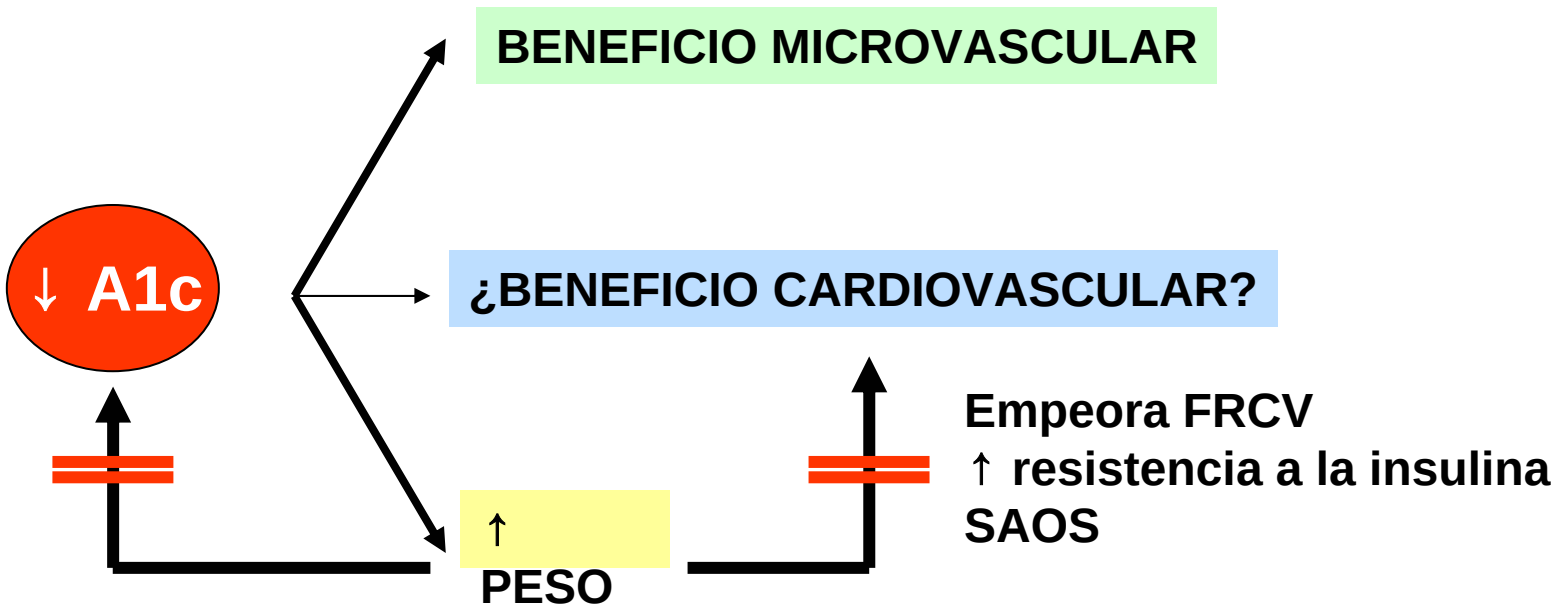


↓ Secreción de insulina

Diabetes tipo 2



TRATAMIENTO DE LA DIABETES



↑ resistencia a la insulina
Disfunción célula beta

neoplasias

calidad de vida
efectos psicológicos / resistencia a intensificación

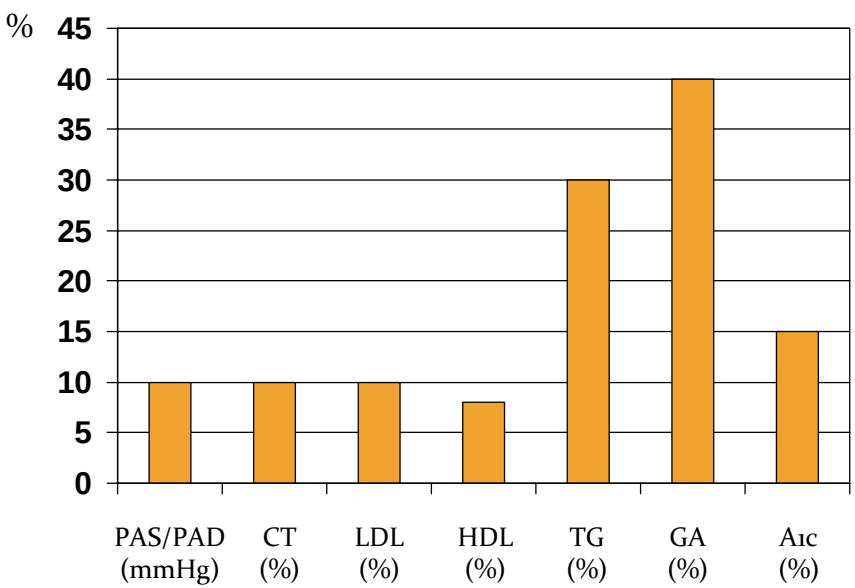
EL CÍRCULO PERVERSO DE LA DIABESIDAD

ENFOQUE LIPOCÉNTRICO. IMPLICACIONES CLÍNICAS

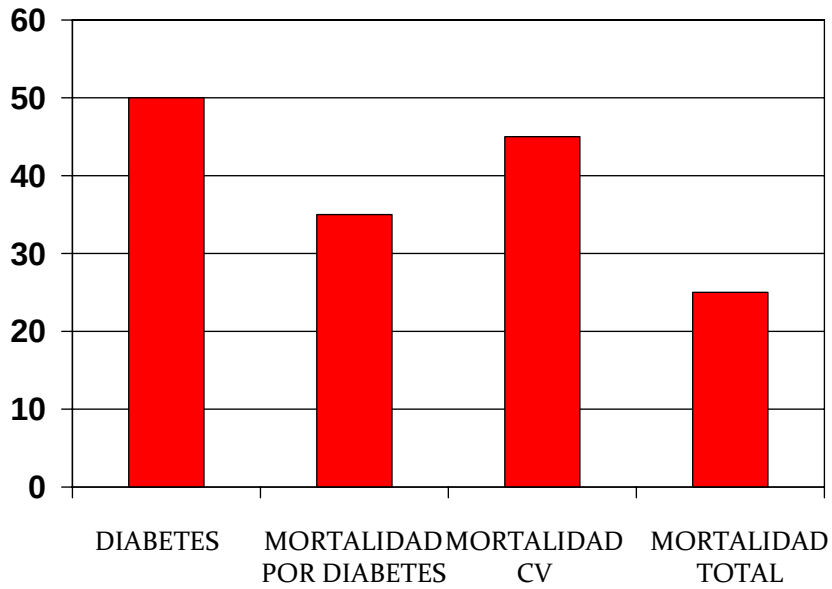
- Dieta y ejercicio.
- Fármacos antidiabéticos que disminuyan apetito/lipogénesis
- Cirugía bariátrica

corporal

Mejoría de los factores de riesgo



Reducción de morbimortalidad

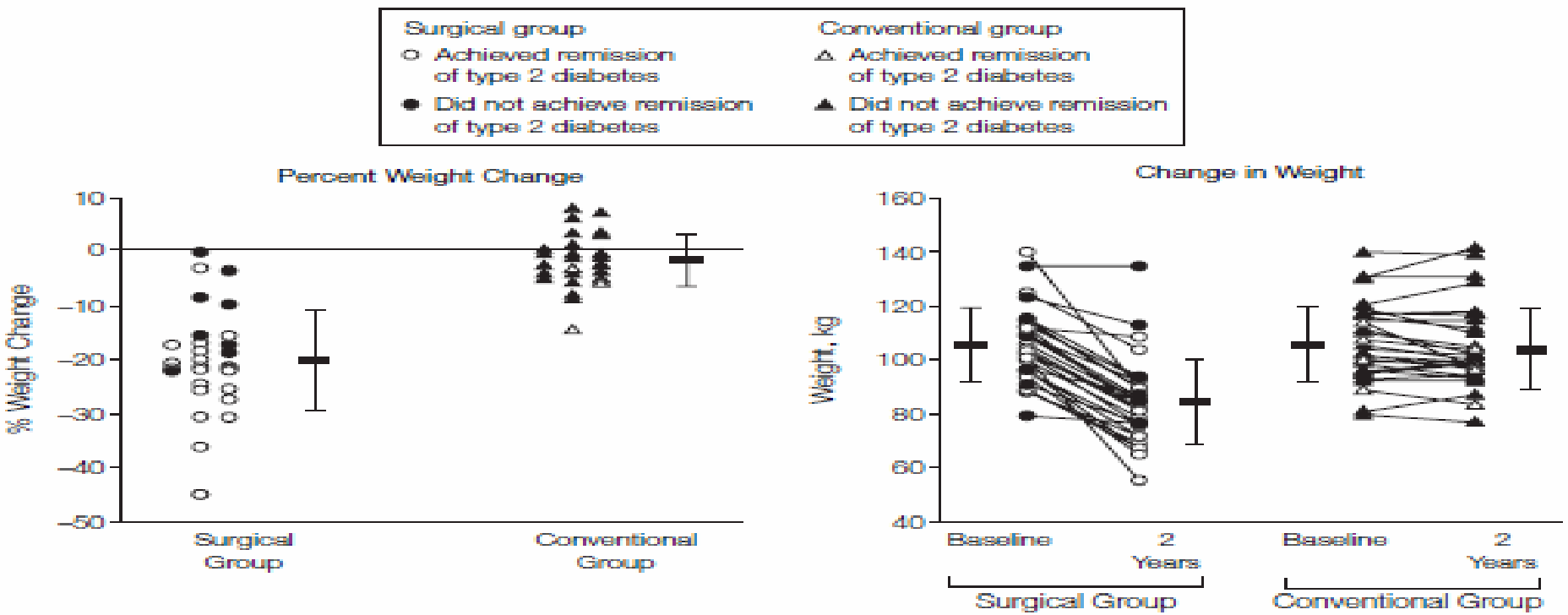


Jung RT. Br Med Bul. 1997;53:307-21.

Adjustable Gastric Banding and Conventional Therapy for Type 2 Diabetes

A Randomized Controlled Trial

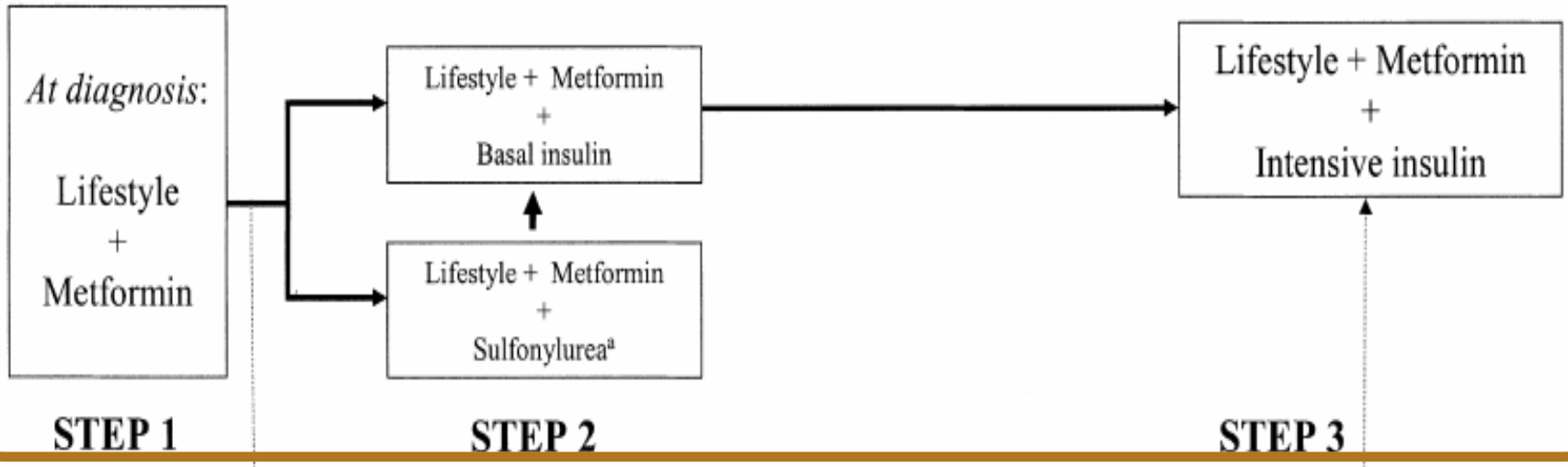
Figure 2. Percentage of Weight Loss Achieved Over the 2-Year Study Period (n=60) and Individual Weight Measures at Baseline and at 2 Years



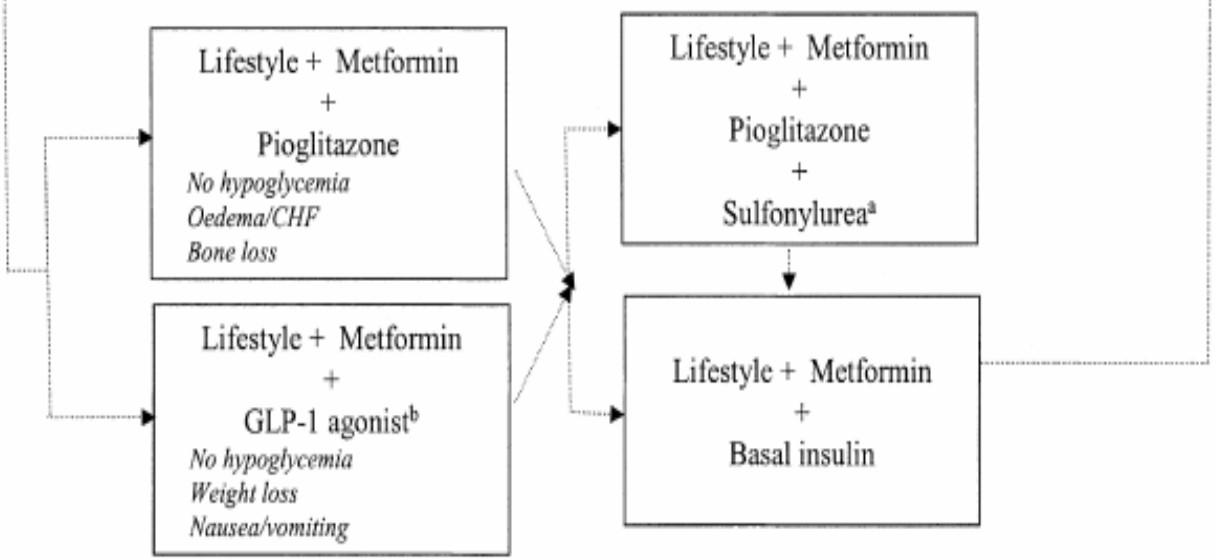
Remission indicates those achieving remission of type 2 diabetes (see "Methods") at 2 years. Data markers with error bars indicate mean (SD).

JAMA. 2008;299(3):316-323

Tier 1: Well-validated core therapies



Tier 2: Less well validated therapies



A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes
Nathan DM et al. Diabetes Care 2009; 32:193–203.

Diabesidad

1. Antidiabéticos orales y ganancia de peso.
2. Insulinización y ganancia de peso.
3. Terapias con disminución de peso.

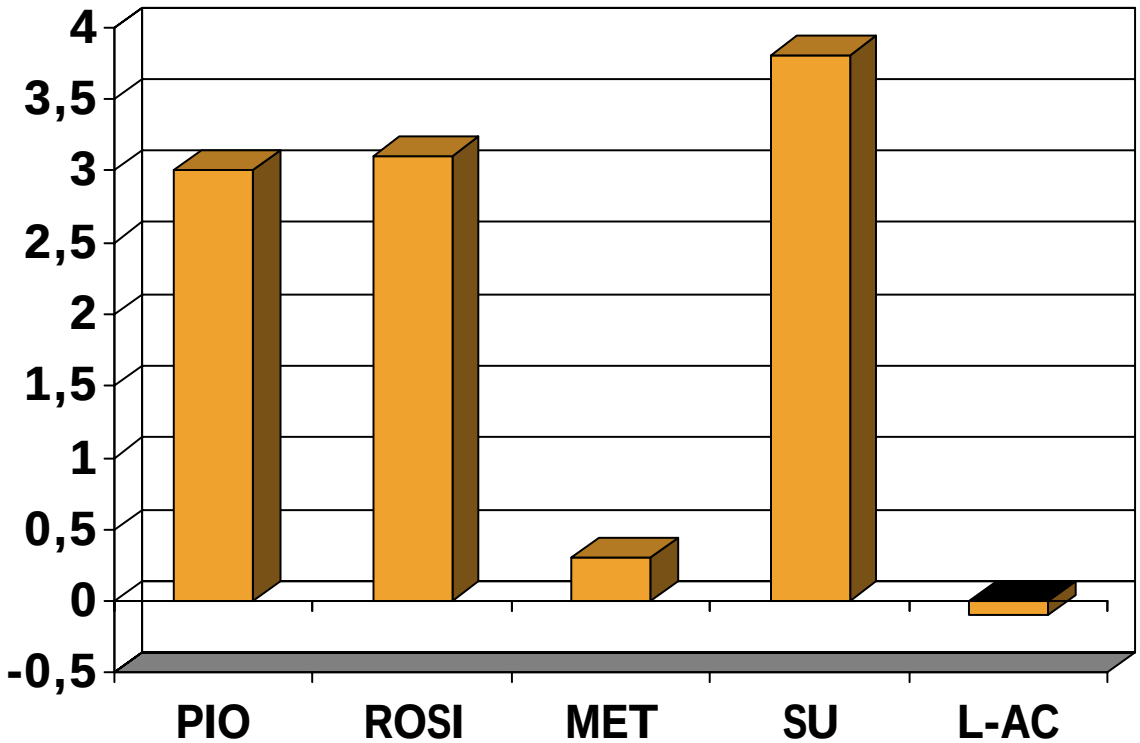
Diabesidad

1. **Antidiabéticos orales y ganancia de peso.**
2. Insulinización y ganancia de peso.
3. Terapias con disminución de peso.

Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus

Shari Bolen, MD, MPH; Leonard Feldman, MD; Jason Vassy, MD, MPH; Lisa Wilson, BS, ScM; Hsin-Chieh Yeh, PhD; Spyridon Marinopoulos, MD, MBA; Crystal Wiley, MD, MPH; Elizabeth Selvin, PhD; Renee Wilson, MS; Eric B. Bass, MD, MPH; and Frederick L. Brancati, MD, MHS

Cambios en el peso corporal (kg) frente a placebo



Ann Intern Med. 2007;147:386-399.

Diabesidad

1. Antidiabéticos orales y ganancia de peso.
2. **Insulinización y ganancia de peso.**
3. Terapias farmacológicas para disminución de peso.

Insulinas y peso

- Disminución del gasto energético.
  - Disminución del metabolismo basal.
  - Disminución de la glucosuria.
- Incremento de la ingesta calórica.
  - Defensive Snacking
  - Resistencia central al efecto anorexígeno insulínico
- Efecto anabólico

- Hiperinsulinismo periférico

Eficacia de la terapia intensiva

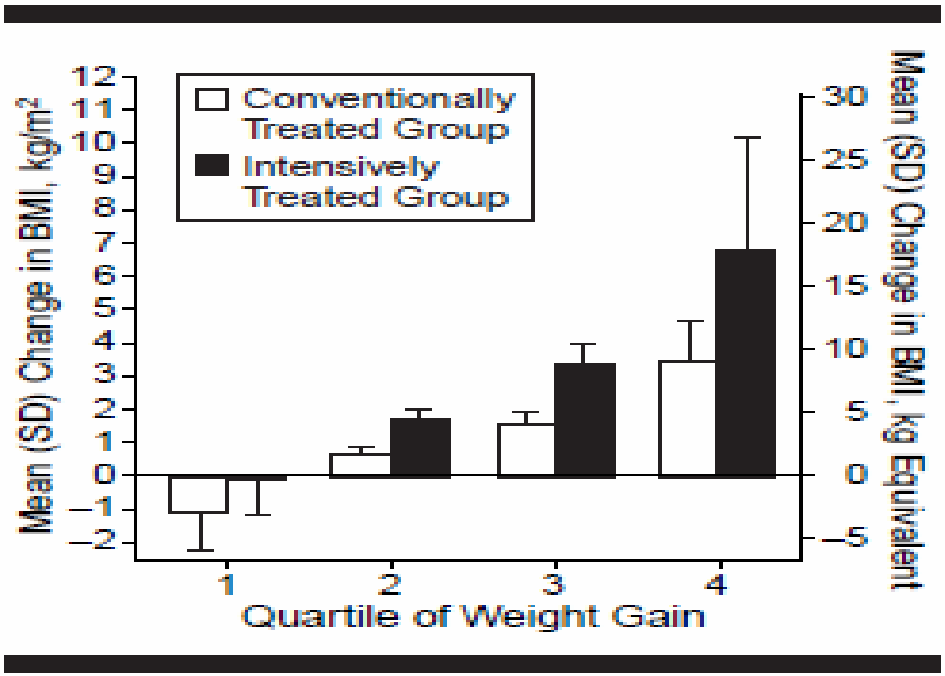
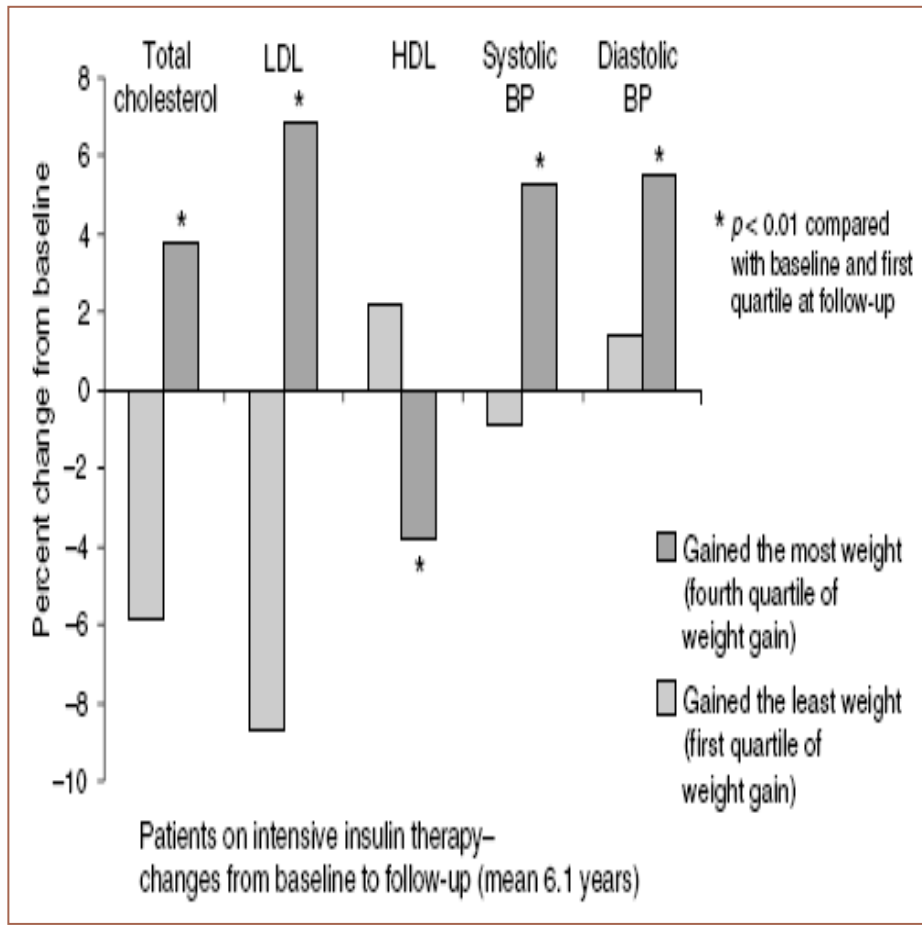
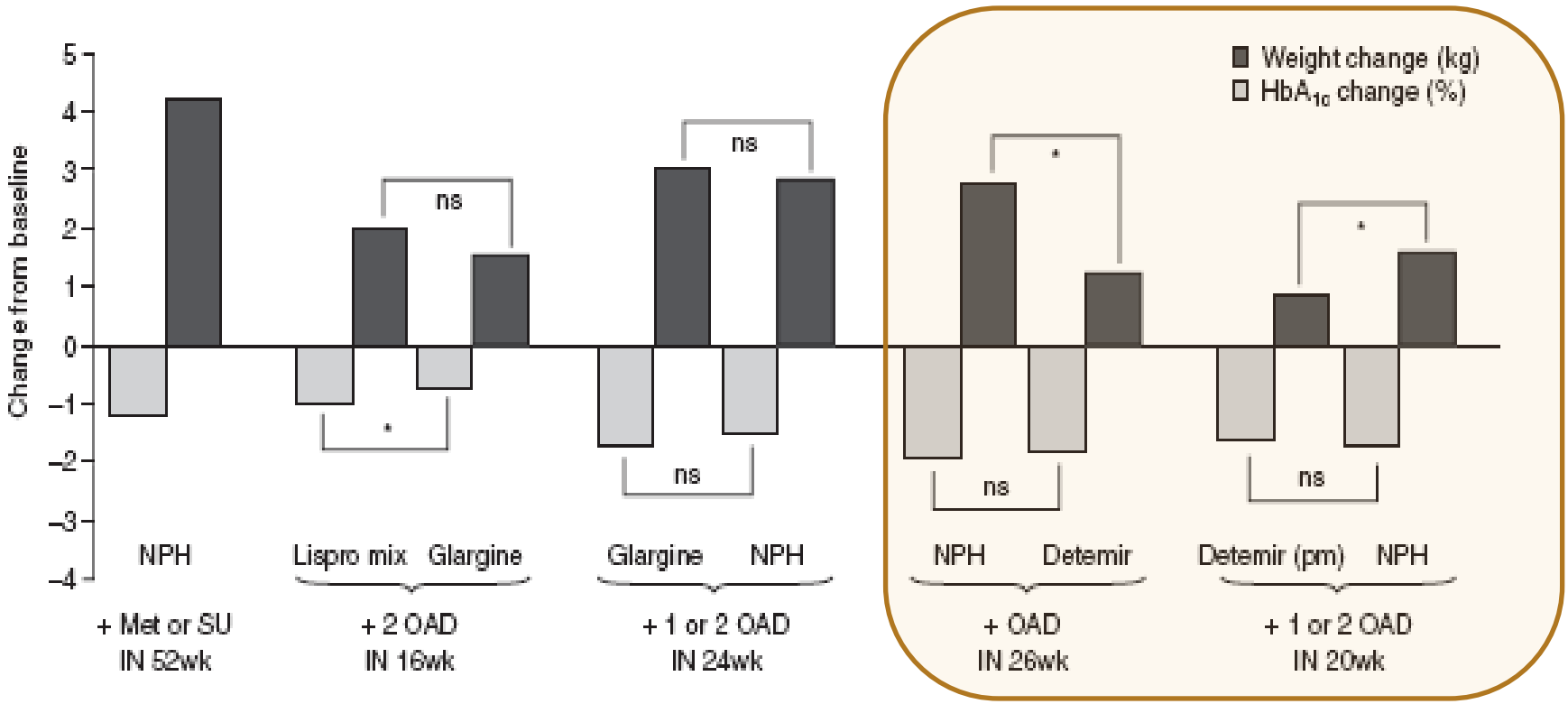


Figure 1.—Increases in body mass index (BMI) (a measure of weight in kilograms divided by the square of height in meters) and the equivalent weight in kilograms from baseline to follow-up in the quartiles of weight gain in the conventionally and intensively treated groups.



Insulinas y peso



Drug Safety 2007; 30 (12)

Detemir y ganancia de peso

Posibles mecanismos:

- Menor riesgo de hipoglucemias (menor variabilidad)
- Reduce la adiposidad visceral.
- Unión a la albúmina:
  - Mayor ratio actividad hepática/ periférica.
  - Efecto anorexígeno central.

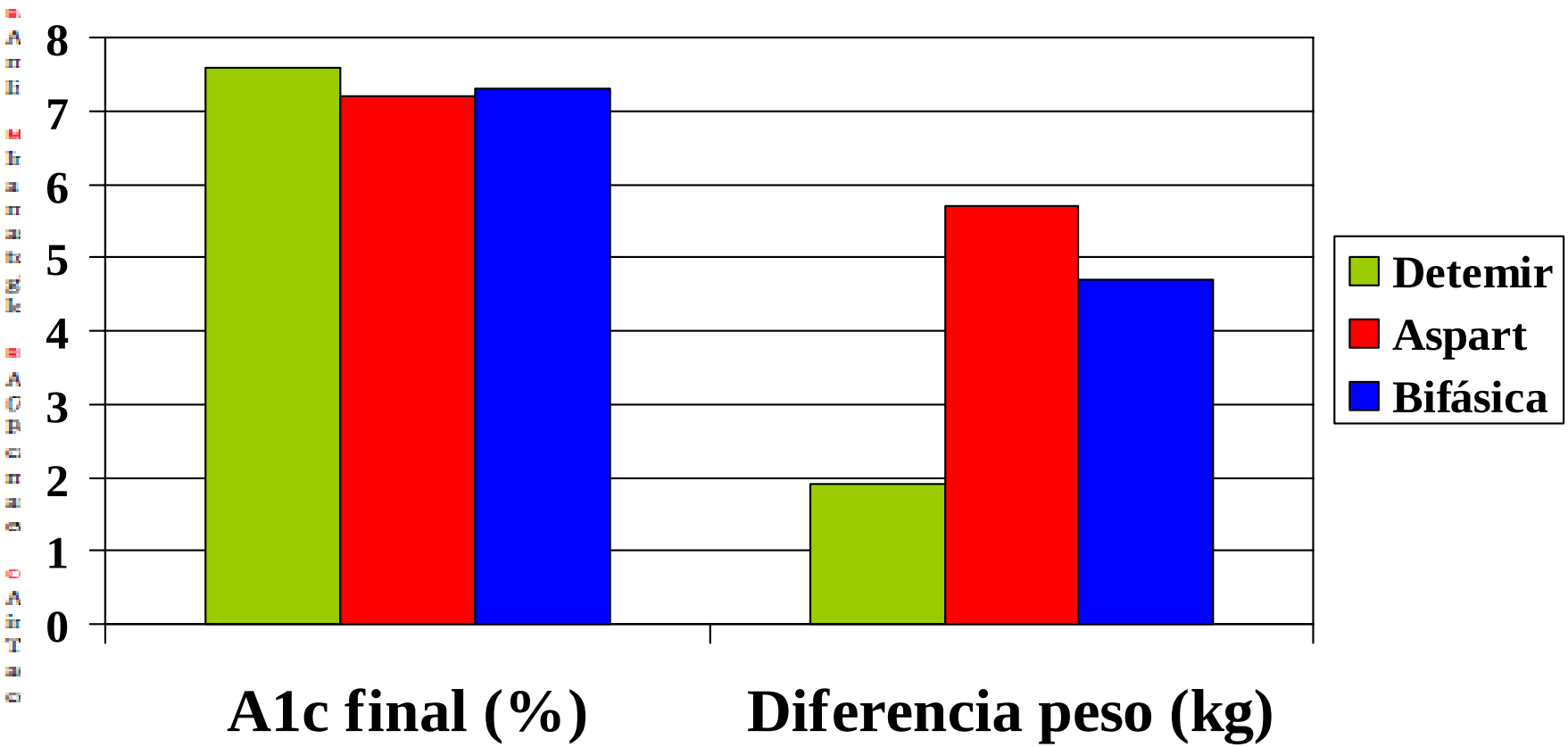
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Joanne F. Keenan, B.A., Sanjoy Paul, Ph.D., and Jonathan C. Levy, M.D., F.R.C.P., for the 4-T Study Group*

ABSTRACT



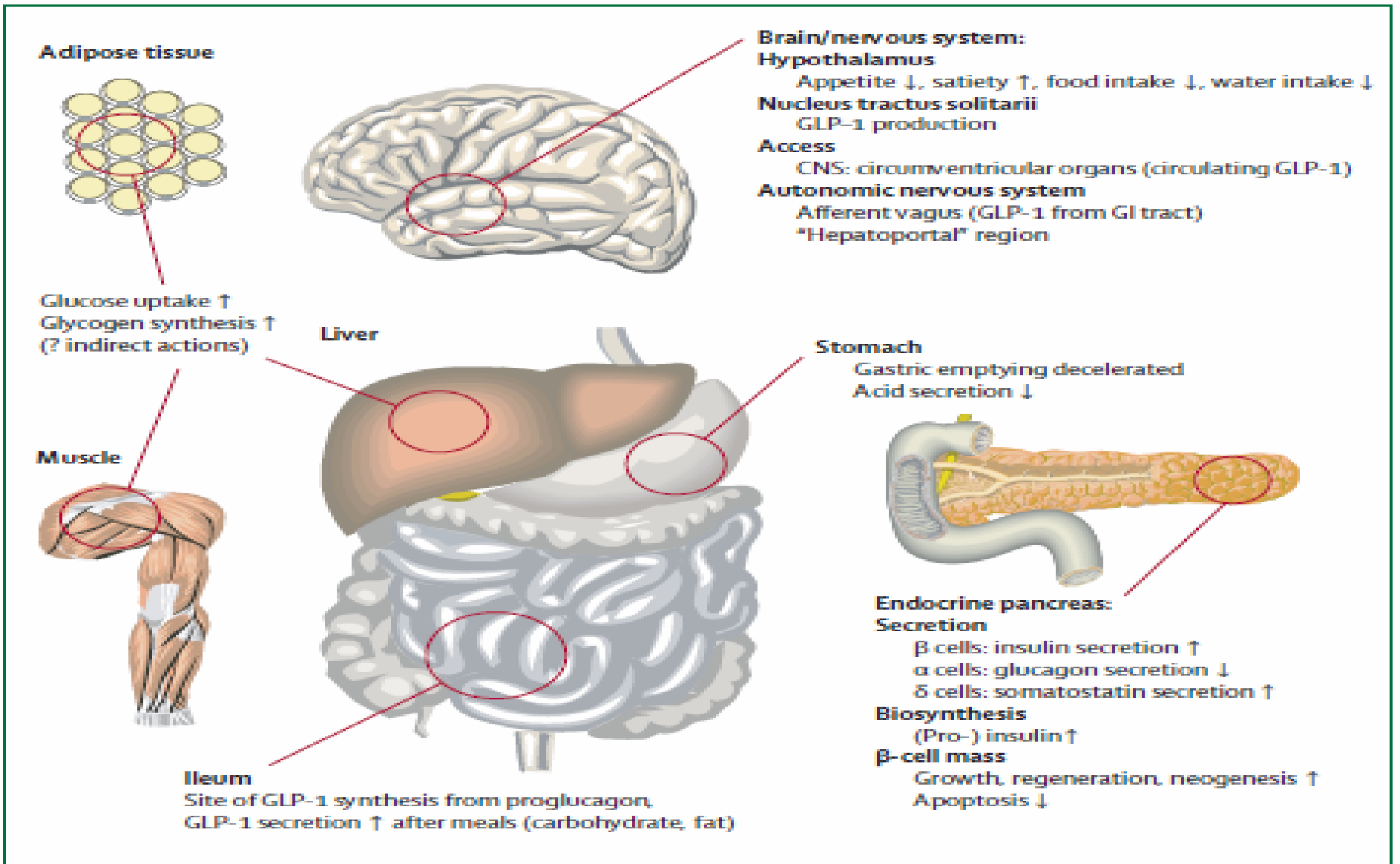
Diabesidad

1. Antidiabéticos orales y ganancia de peso.

2. Insulinización y ganancia de peso.

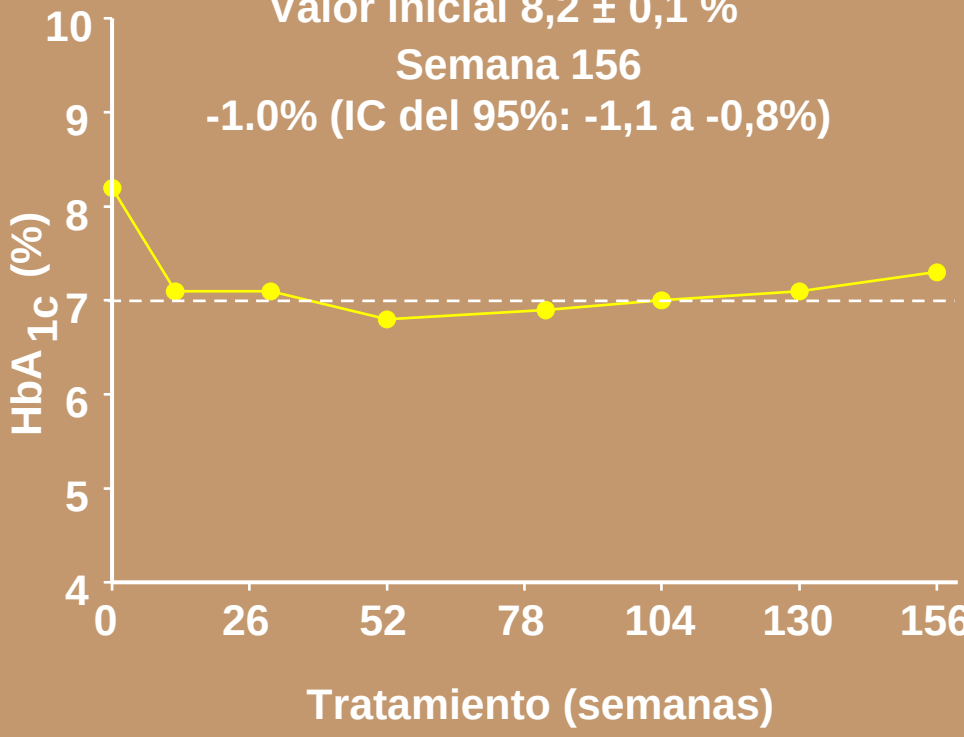
3. **Terapias farmacológicas para disminución de peso.**

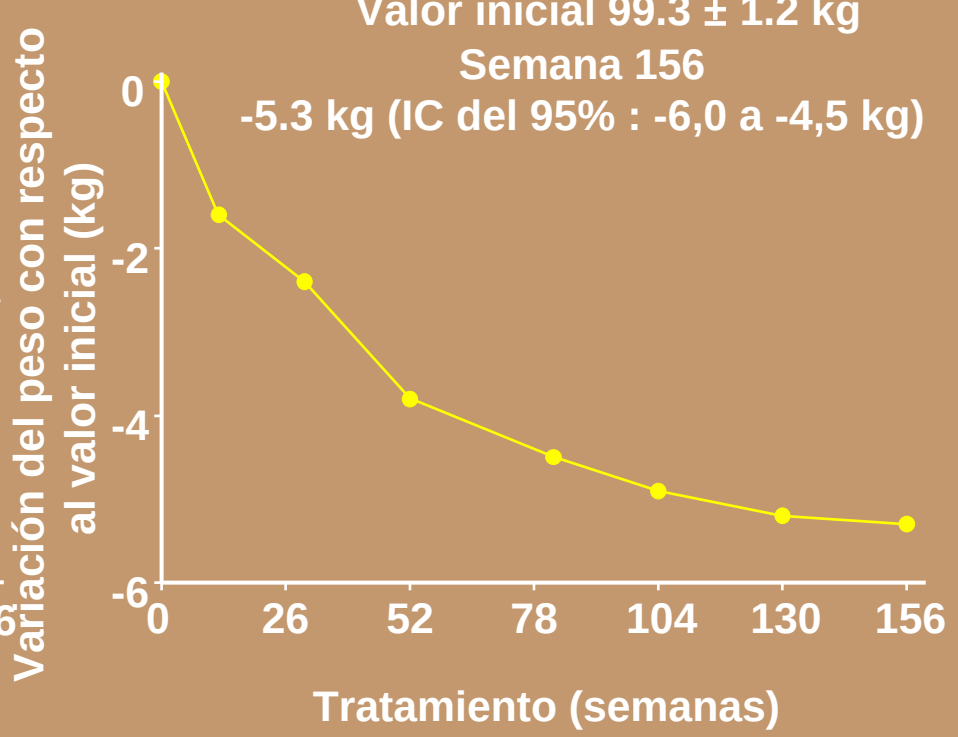
Incretinas


Adipose tissue
Glucose uptake ↑
Glycogen synthesis ↑
(? indirect actions)
Muscle
Brain/nervous system:
Hypothalamus
Appetite ↓, satiety ↑, food intake ↓, water intake ↓
Nucleus tractus solitarii
GLP-1 production
Access
CNS: circumventricular organs (circulating GLP-1)
Autonomic nervous system
Afferent vagus (GLP-1 from GI tract)
"Hepatoportal" region
Liver
Stomach
Gastric emptying decelerated
Acid secretion ↓
Endocrine pancreas:
Secretion
β cells: insulin secretion ↑
α cells: glucagon secretion ↓
δ cells: somatostatin secretion ↑
Biosynthesis
(Pro-) insulin ↑
β-cell mass
Growth, regeneration, neogenesis ↑
Apoptosis ↓
Ileum
Site of GLP-1 synthesis from proglucagon,
GLP-1 secretion ↑ after meals (carbohydrate, fat)

Agent	Blood pressure		Fasting lipids			Non-traditional CV markers	Effect on β-cell function	Δ Body weight (kg)	Expected decrease in HbA1c (%)
	SBP (mm Hg)	DBP (mm Hg)	Triglycerides (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)				
Metformin	+7 to −5 [65,89]	0 to −5 [65,89]	−8% [89]	+2.6% [89]	−8% [89]	Decreases TNF-α and PAI-1; improves endothelial function [96,99]	No clear effect [113,120]	Weight neutral or −1 to −2 [76,94]	~1.5 [61,89]
Sulfonylureas	−5 to +7 [65,70]	0 to −5 [65,70]	Effects not known	Effects not known	Effects not known	Effects not known	No positive effects [121]; may increase β-cell apoptosis [114]	+1 to +5 [65,76]	~1.5 [61,78]
Non-sulfonylurea secretagogues (meglitinides)	−4 [91]	Effects not known	Effects not known	Effects not known	Effects not known	Improves endothelial function [97]	Improves HOMA-B [122]	+0.7 to +2.4 [81,98]	0.5–1.5 [61]
Alpha-glucosidase inhibitors	−1 mm Hg [87]	−3 mm Hg [87]	−10% [95]	Effects not known	Effects not known	Effects not known	No positive effects [123,124]	Weight neutral [61]	0.5–0.8 [61,79]
TZDs	−5 [65,103]	−4 [103]	−14% [82]	+11% [82]	+1.2 [82]	Improves endothelial dysfunction; decreases PAI-1 [77,90]	Improves HOMA-B and PR:I levels [115]	+1 to +5 [65]	−0.5 to −1.4 [61]
Insulin	Varies by formulation; no effect to +2 [79]	No clinically relevant effects [70]	No clinically relevant effects [93]	No clinically relevant effects [93]	No clinically relevant effects [93]	Effects not known	Improves HOMA-B [125]	+1 t… [7…103,104]	1.5–3.5 [61]
Exenatide	−1 [84]	−3 [84]	−16% [84]	+12% [84]	−1.4% [84]	Effects not known	Improves HOMA-B and PR:I levels [101,111,112,126]	−4.4 [84]	−0.8 to −1.1 [84,101]
Liraglutide	−8 [108]	−3 [108]	−22% [108]	No consistent changes among Rx groups [108]	No consistent changes among Rx groups [108]	Decreases PAI-1 and BNP levels [88]; inhibits TNF-α *in vitro* [80]	Improves HOMA-B and PR:I levels [110,117,118]	−4.4 [107]	−0.8 to −1.4 [108,109]

Variación en la HbA_{1c} y en el Peso a lo Largo de 3 años de Tratamiento con Exenatida

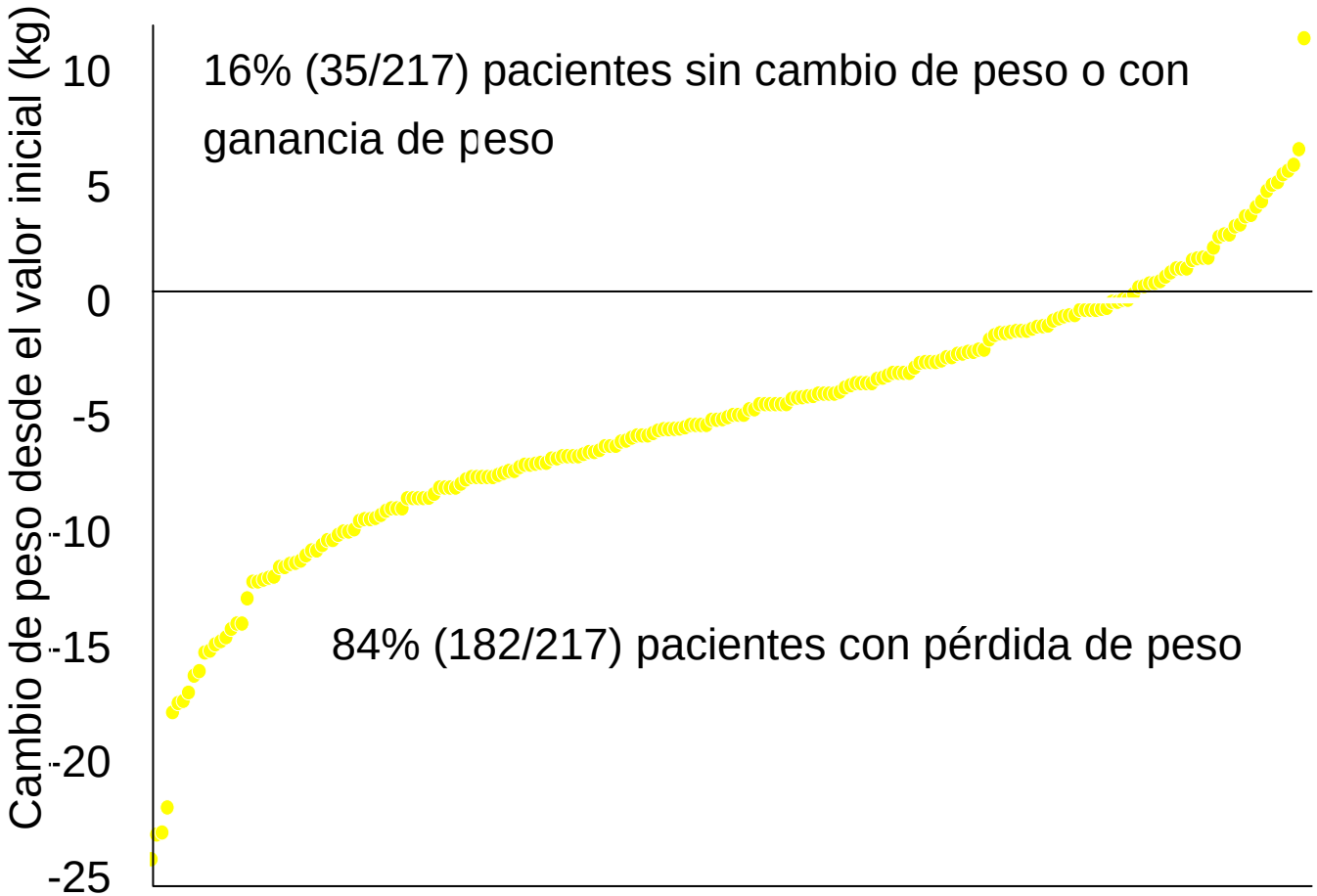




N=217; Media ± EE.

Klonoff DC, et al. *Curr Med Res Opin* 2008;24:275-286.

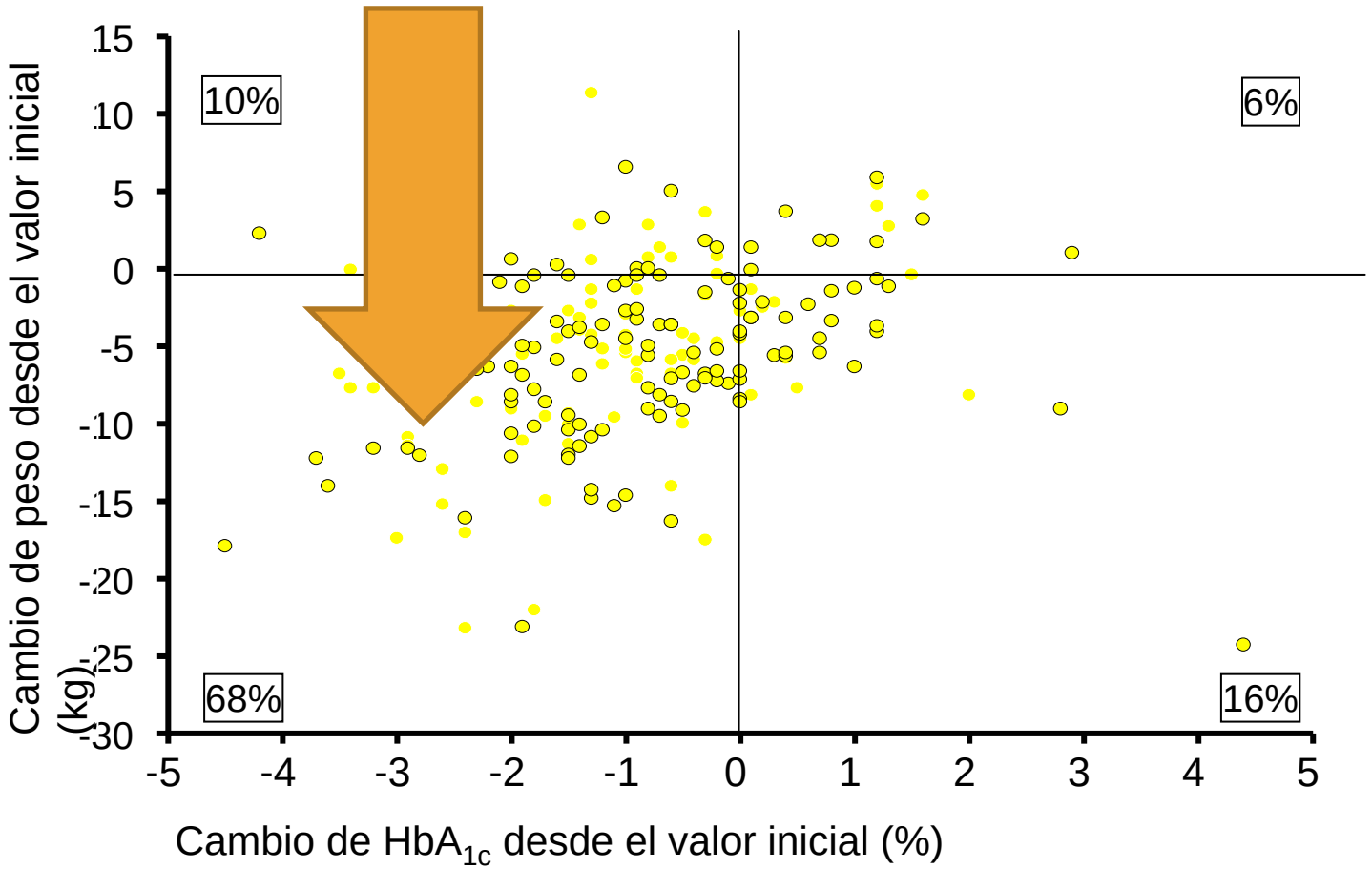
El 84% de los Pacientes que Completaron 3 años de Tratamiento Mostraron Pérdida de Peso



N=217.

Klonoff DC, et al. *Curr Med Res Opin* 2008;24:275-286.

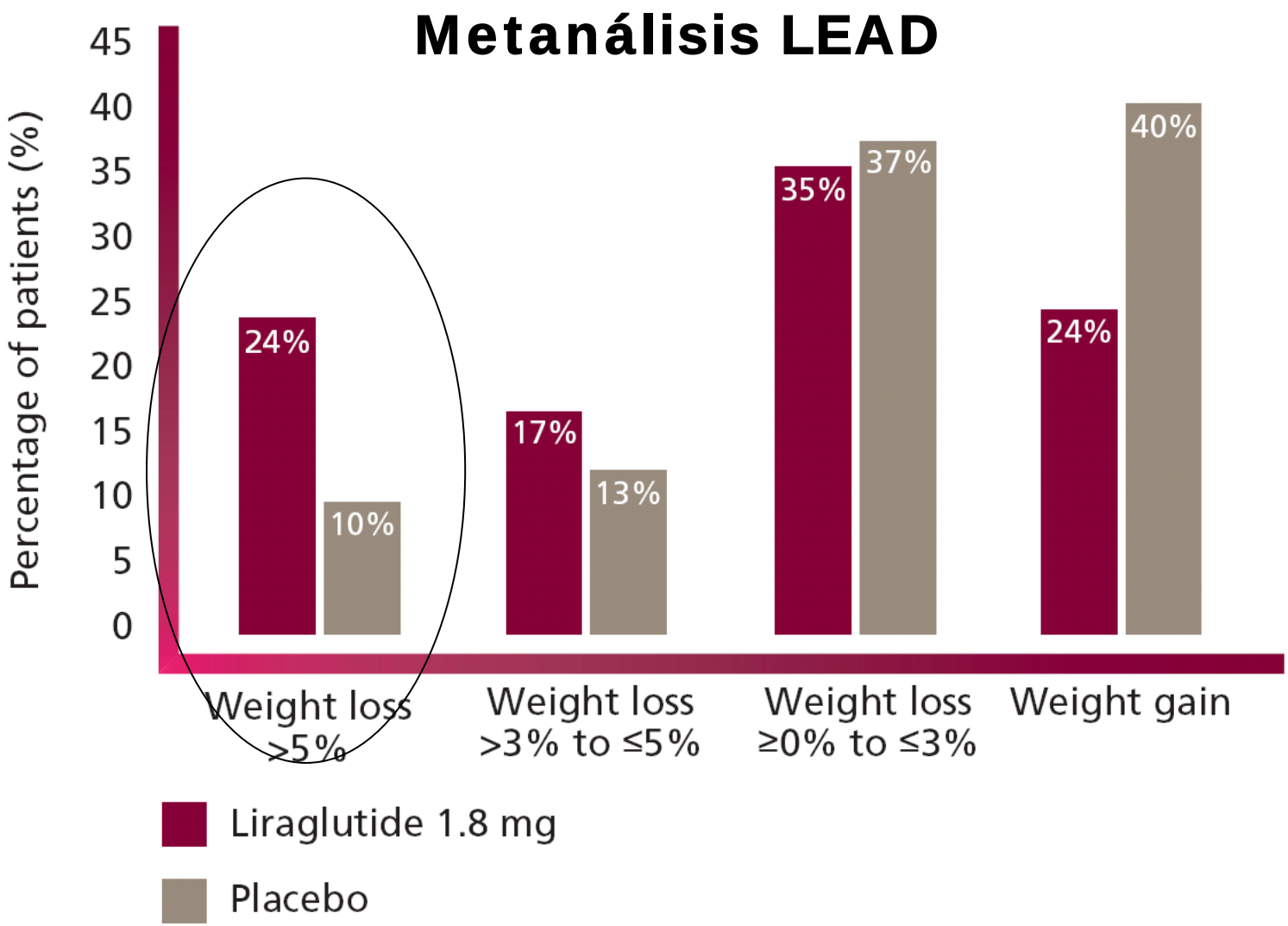
El 68% de los Pacientes que Completaron 3 Años de Tratamiento Presentaban Pérdida de Peso y Reducción de HbA_{1c}



N=217.

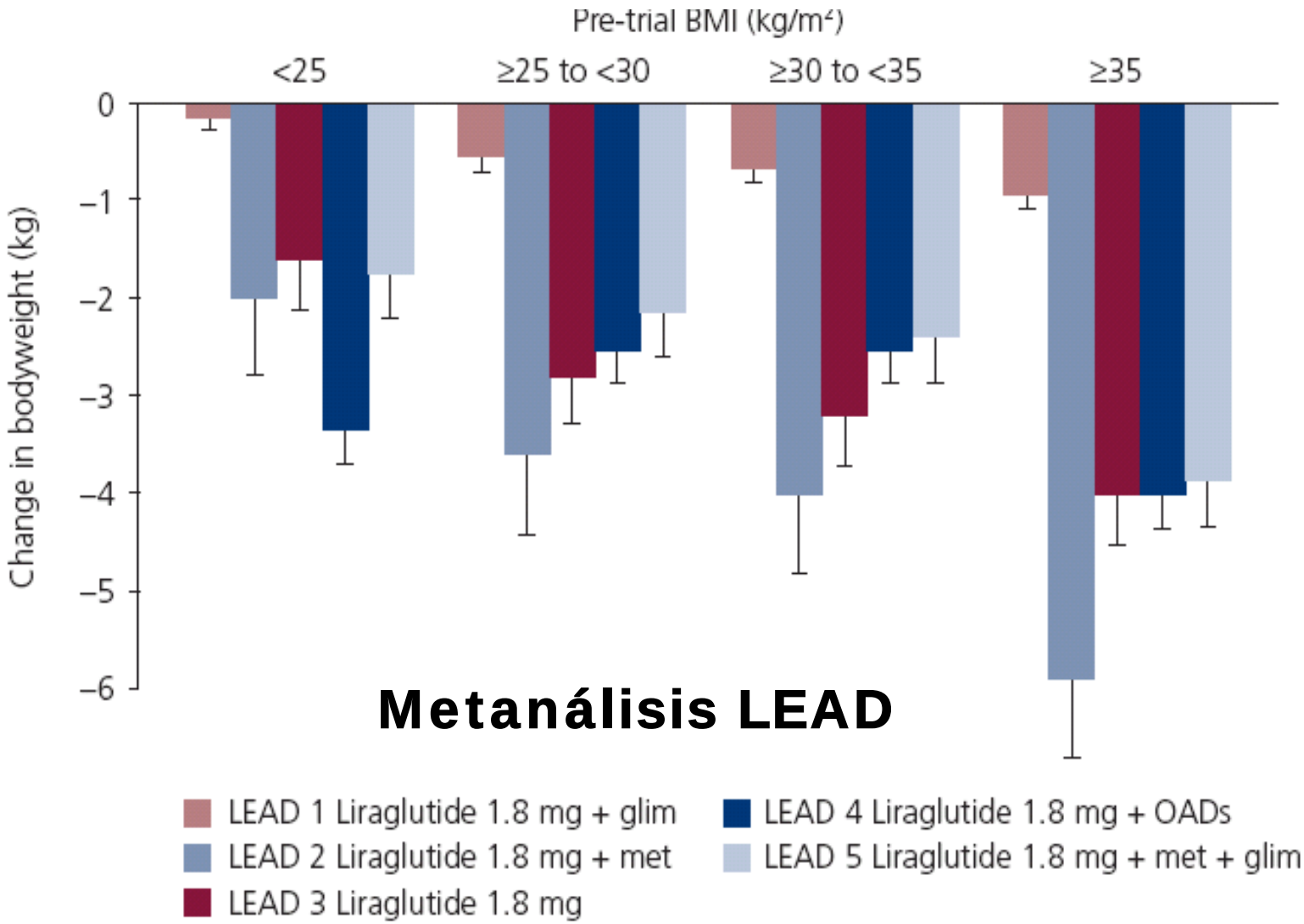
Klonoff DC, et al. *Curr Med Res Opin* 2008;24:275-286.

75% de los pacientes pierden peso con liraglutide



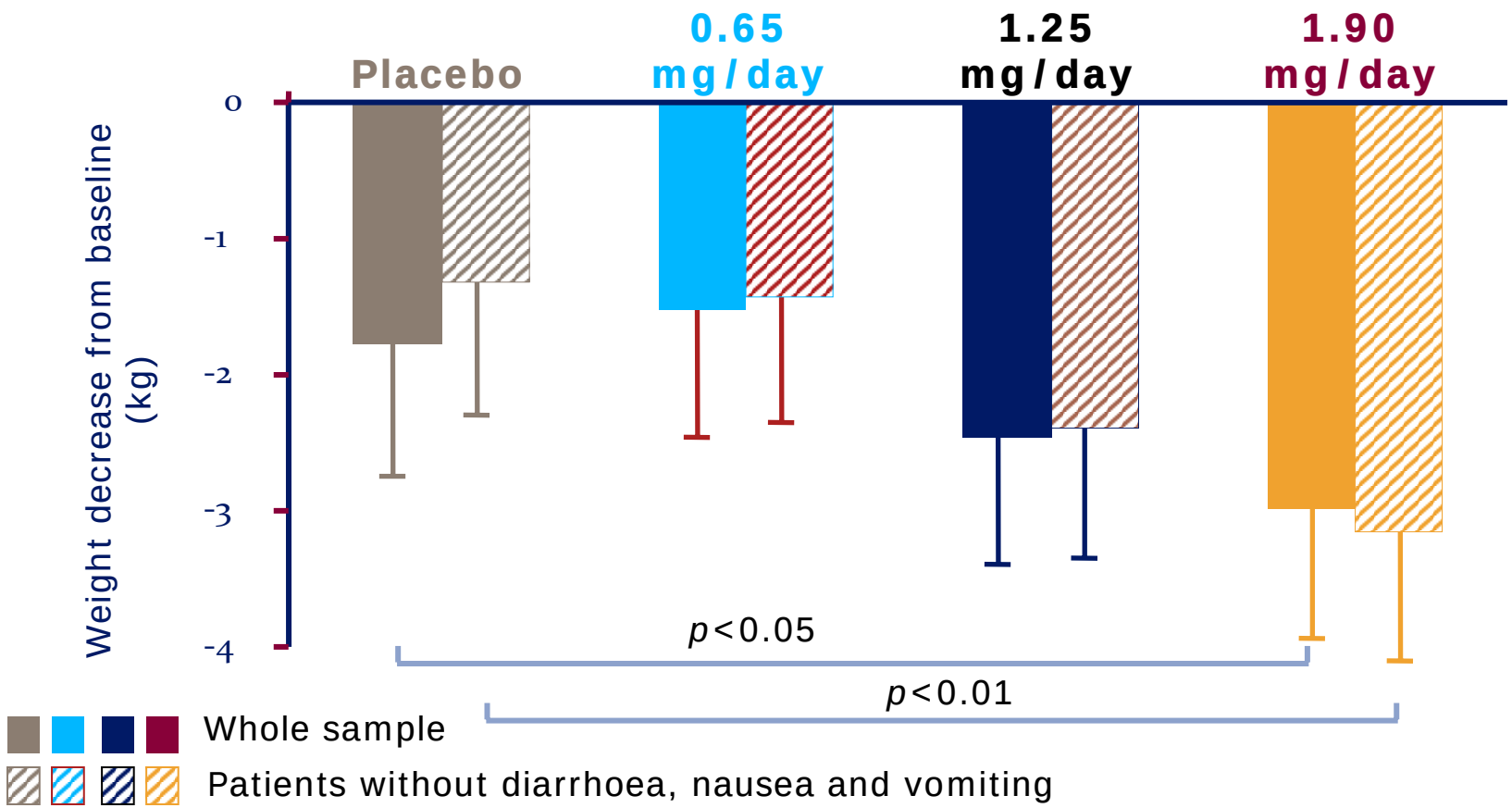
Schmidt et.al. Diabetologia 2009; 52 (Suppl. 1): S289 (Abstract 737)

Pérdida de peso se relaciona con BMI basal



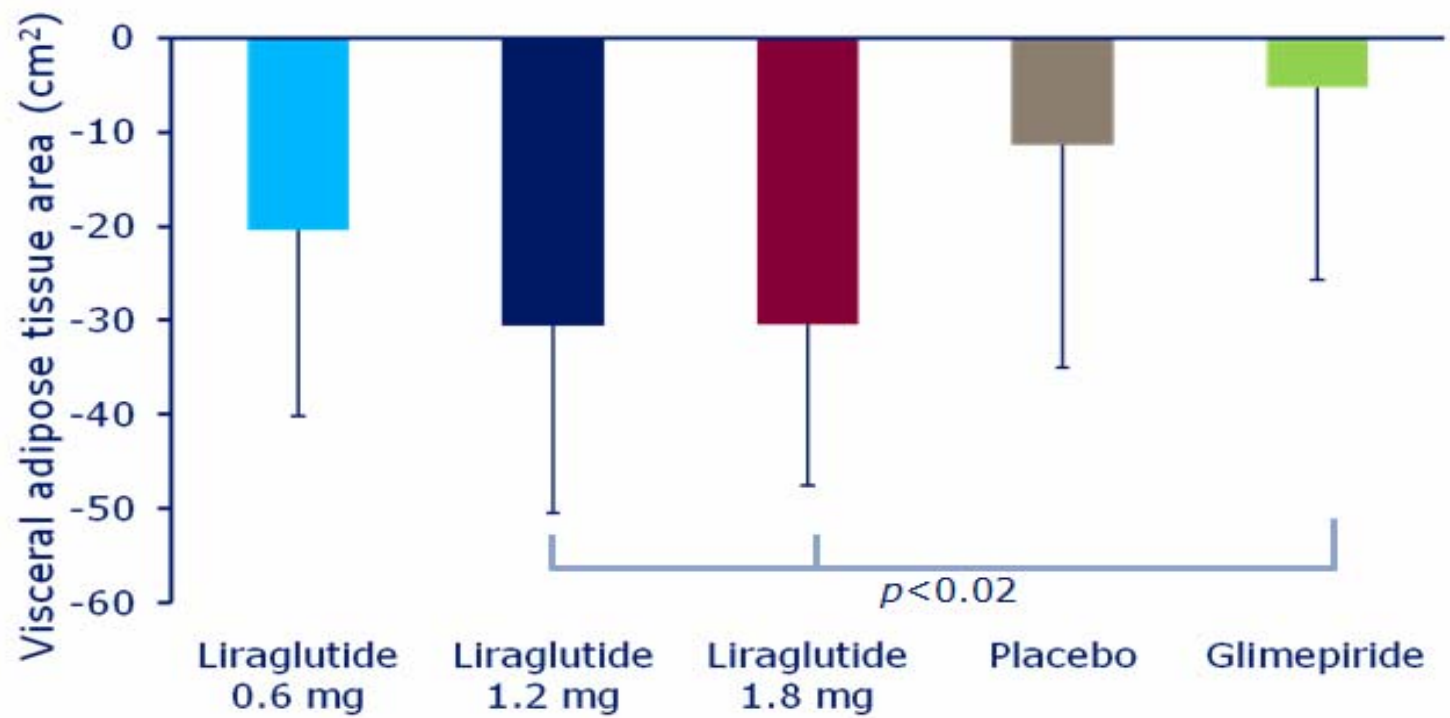
Schmitz et.al. Diabetologia 2008;51(Suppl.1):S354

Pérdida de peso independiente de efectos GI



Vilsbøll *et al. Diabetes* 2006;55(Suppl. 1):A27

Visceral adipose tissue area (LEAD-2)



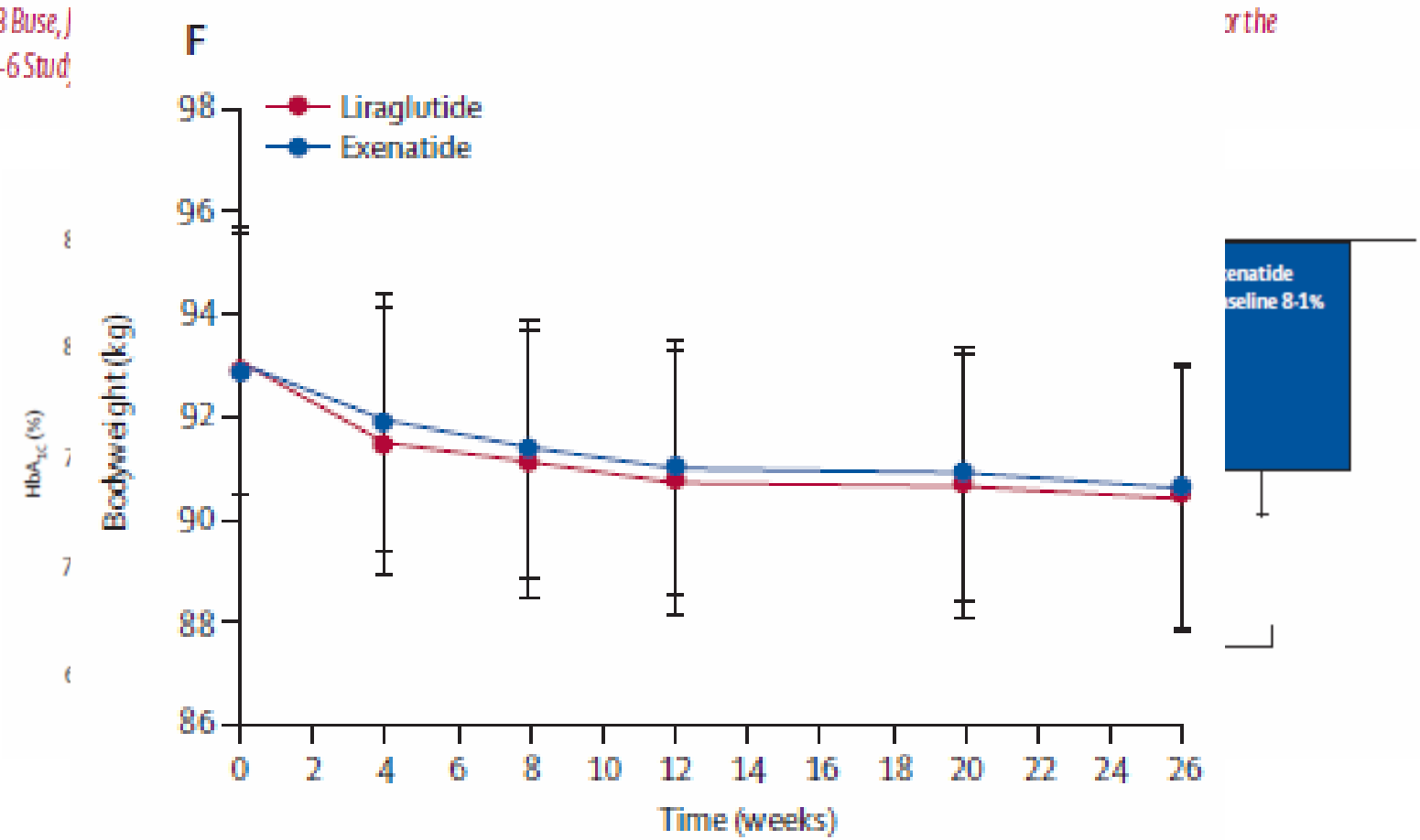
*$p<0.02$ for treatment difference in changes versus glimepiride

Mean±2SE

Jendle J. et.al. Diabetes Obes Metab. 2009 Dec;11(12):1163-72.

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

John B Buse, J
LEAD-6 Study



Lancet 2009; 374: 39–47

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

*John B Buse, Julio Rosenstock, Giorgio Sesti, Wolfgang E Schmidt, Eduard Montanya, Jason H Brett, Marcin Zychma, Lawrence Blonde, for the LEAD-6 Study Group**

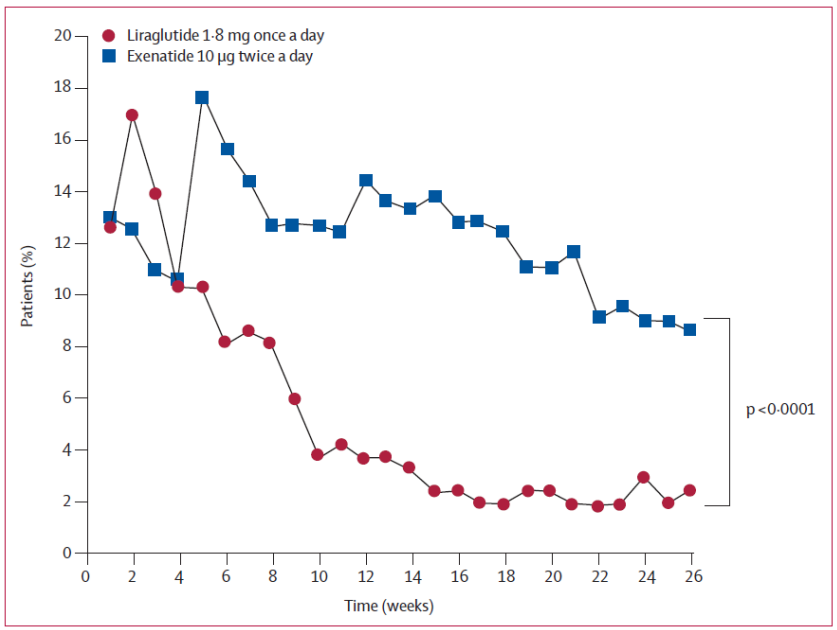


Figure 3: **Proportion of patients with an episode of nausea between baseline and week 26**

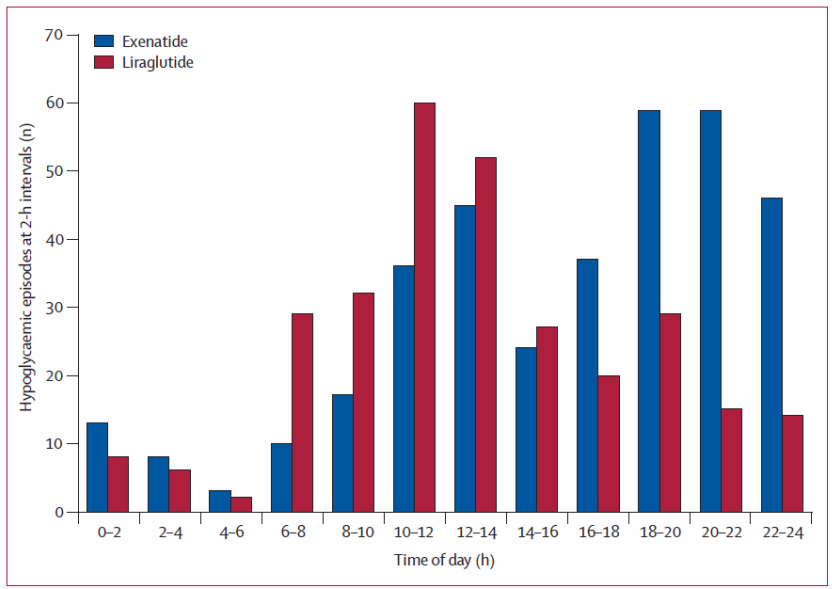


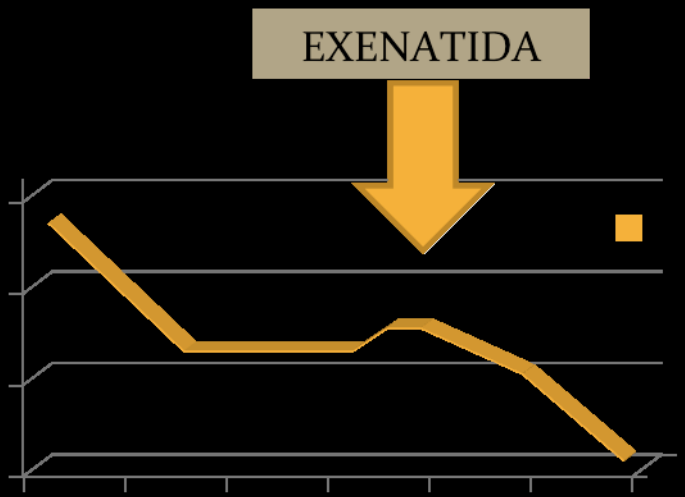
Figure 4: **Number of minor hypoglycaemic episodes at 2-h intervals**
Liraglutide 1·8 mg once a day or exenatide 10 µg twice a day.

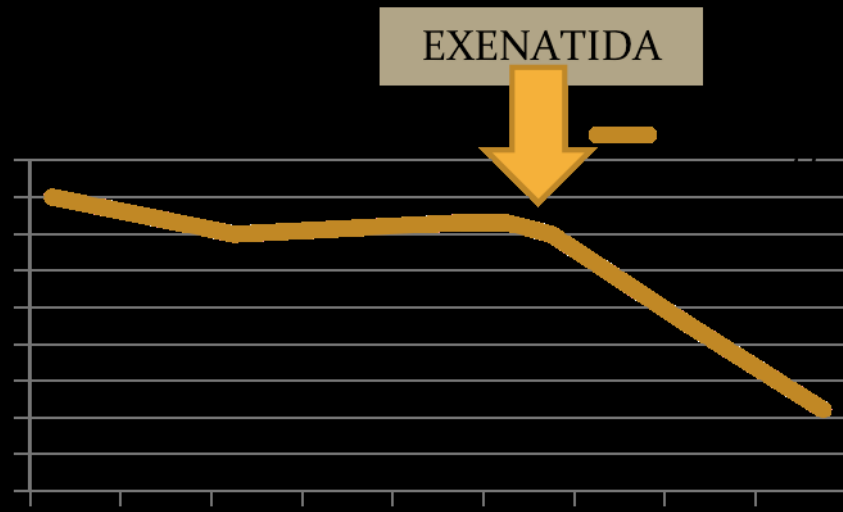
Inhibidores DPP-IV.

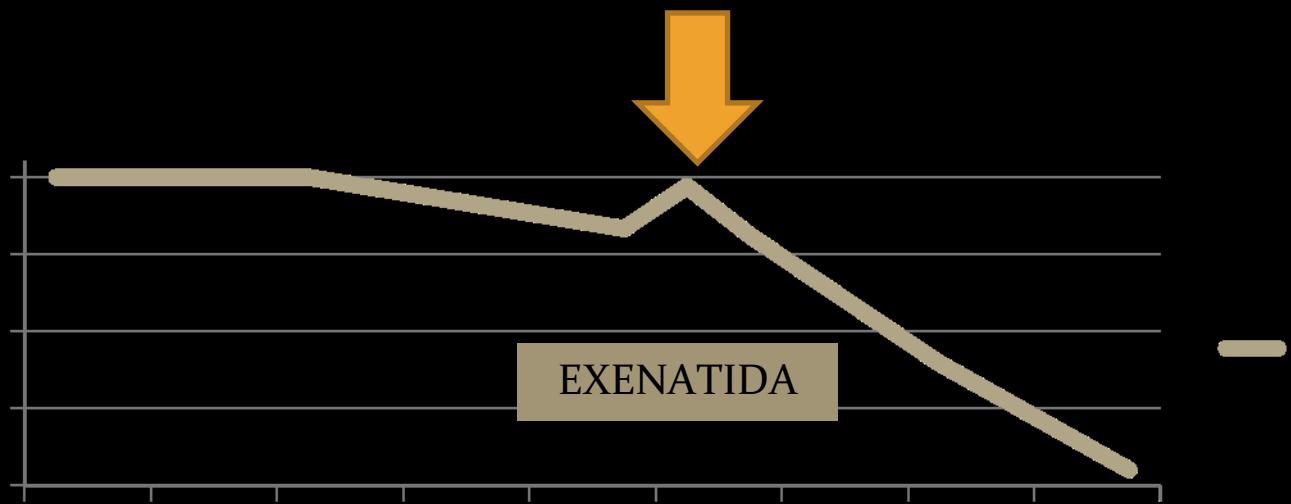
- Incrementan las incretinas endógenas.
- Reducen la actividad del DPP IV en aproximadamente 80%.
- Mejoran el perfil lipídico.
- No retrasan el vaciamiento gástrico.
- No incrementan la sensación de saciedad.
- Efecto neutro en peso.

Volviendo a nuestro paciente…

Evolución







Exenatide

- Indicaciones: Terapia coadyuvante en pacientes diabéticos tipo 2 con mal control glucémico en tratamiento con metformina, sulfonilurea, glitazonas o una combinación de éstos a dosis máximas.

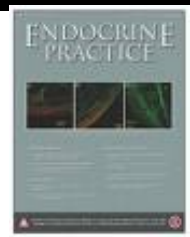
- Principal efecto adverso: gastrointestinales.

Exenatide e Insulina

- Ficha técnica: Exenatida no debe ser utilizado en pacientes con DM tipo 1 ni en DM tipo 2 que requieran tratamiento con insulina debido a un fallo de las células beta pancreáticas.

- Escasos estudios sobre uso concomitante de exenatida + insulina.

Exenatide e Insulina



Exenatide added to insulin therapy: A retrospective review of clinical practice over two years in an academic endocrinology outpatient setting

Yoon NM, Cavaghan MK, Brunelle RL, Roach P.

Clinical Therapeutics 2009;31(7):1511-1523

Conclusion: In this retrospective review of patients with T2DM treated in an outpatient setting, the addition of exenatide to insulin-based therapy was associated with reductions in mean HbA1c, weight, and prandial insulin requirements for treatment periods of up to 27 months, and in total insulin requirements for treatment periods of up to 12 months.

Endocr Pract. 2008 Apr;14(3):285-92.

Safety and efficacy of exenatide in combination with insulin in patients with type 2 diabetes mellitus.

Sheffield CA, Kane MP, Busch RS, Bakst G, Abelseth JM, Hamilton RA

Conclusion: Exenatide in combination with insulin in patients with T2DM was associated with significant reductions in A1C and weight after 1 year of therapy. This was offset, however, by an exenatide discontinuation rate of 36%, primarily due to adverse gastrointestinal effects.

Table 2. **Changes in Glycemic and Cardiovascular Variables***

Variable	Exenatide Group (n = 137)	Placebo Group (n = 122)	Between-Group Difference	P Value
Glycemic indicators†				
HbA_{1c} level ≤7.0%, %				<0.001
HbA_{1c} level ≤6.5%, %				<0.001
HbA_{1c} level, %				
Baseline				
Change from baseline to week			-0.46)	<0.001
Body weight, *kg*				
Baseline				
Change from baseline to week			-1.74)	<0.001
Change in insulin dose‡				
U/d			-0.8)	0.030
U/kg			.00)	0.070
Change in FPG level, *mmol/L*‡§			.32)	0.630
Change in glucose excursion, *mm*				
Morning 2-h value			1.2)	<0.001
Midday 2-h value			3)	0.320
Evening 2-h value			1.1)	<0.001
Cardiovascular‡				
Change in SBP, *mm Hg*			1.0)	0.010
Change in DBP, *mm Hg*			1.6)	<0.001
Change in heart rate, *beats/mi*				<0.010

DBP = diastolic blood pressure; FP
* Data in parentheses are 95% CIs.
† Proportions of participants achievi

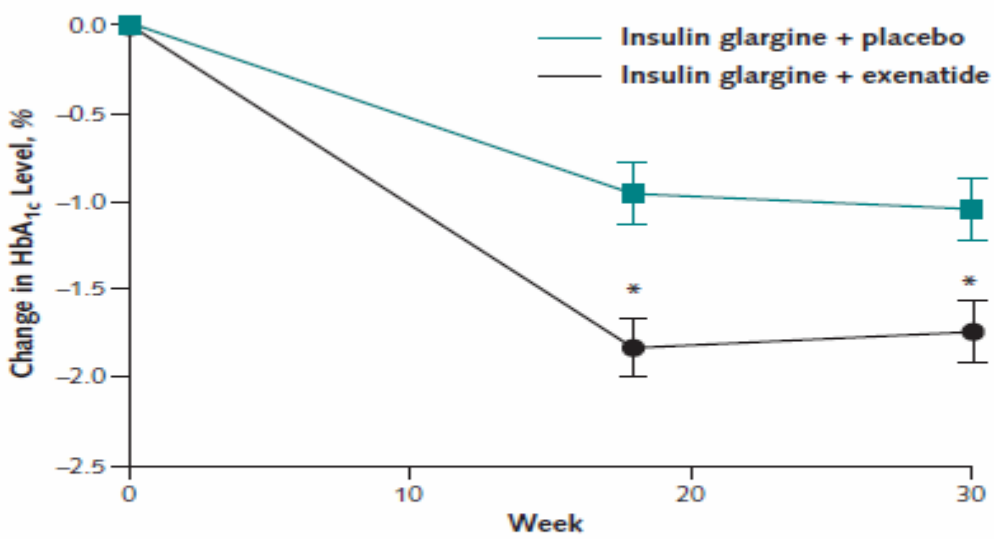
t-random–based multiple imputations.

‡ Estimates for continuous variables are from mixed models with terms for treatment, visit, treatment-by-visit interaction, baseline HbA_{1c} stratum (except for HbA_{1c} analyses), baseline of the variable analyzed, and pooled investigative site, with an unstructured variance–covariance matrix to account for repeated measurements by participant.

§ To convert mmol/L to mg/dL, divide by 0.0555.

‖ Excursions are derived from self-monitored blood glucose profiles.

Figure 2. **Change in HbA_{1c} over 30 weeks.**



Data are least-squares means estimated from a mixed model, in which the postbaseline response variable = treatment + pooled investigator + visit + baseline + (treatment × visit) and the participant is treated as a random effect with an unstructured covariance matrix. Error bars are 95% CIs. HbA_{1c} = hemoglobin A_{1c}.
* $P < 0.001$ for between-group comparisons.

Conclusiones I

- La pérdida de peso mantenida es la intervención más coste-eficaz para el control de la diabetes tipo 2.

- La ganancia de peso asociada al tratamiento AD tiene efectos indeseables:
  - Deterioro de la función de la célula β
  - Incremento de la resistencia a la insulina
  - Deterioro del control glucémico
  - Aumento del riesgo de enfermedad cardiovascular
  - Empeora calidad de vida

Conclusiones II

- Priorizar terapias AD que mejoren la hiperglucemia sin incrementar la sobrecarga lipídica:
  - Dieta + Ejercicio
  - Metformina
  - Incretinas
- Tratamiento de factores de riesgo cardiovascular asociados.
- Necesidad de un enfoque holístico y precoz de la diabesidad

MUCHAS GRACIAS

En pacientes diabéticos tipo 2 obesos no controlados con metformina, ¿Qué fármaco asociaría como primera elección?

- 1.- Sulfonilureas.
- 2.- Pioglitazona.
- 3.- Inhibidor DPPIV.
- 4.- Insulina.
- 5.- Cualquiera de ellos.

¿Qué insulina no condiciona incremento de peso?

- 1.- NPH.
- 2.- NPL.
- 3.- Glargina.
- 4.- Levemir.
- 5.- Ninguna de ellas.

¿Qué sitio de inyección *desaconsejaría* en pacientes con DM2 y obesidad?

- 1.- Muslos.
- 2.- Brazos.
- 3.- Abdomen.
- 4.- Tórax.
- 5.- Es indiferente.

¿Usa manguito de obesos de forma sistemática para la toma de Presión Arterial en sus diabéticos tipo 2?

- 1.- Sí.
- 2.- No.
- 3.- No sabe/No contesta.
- 4.- Es indiferente.

Reexamining the Physical Examination for Obese patientes. JAMA, December 29, 2.010.