Análogos de GLP-1 en el Tratamiento de la Diabetes mellitus

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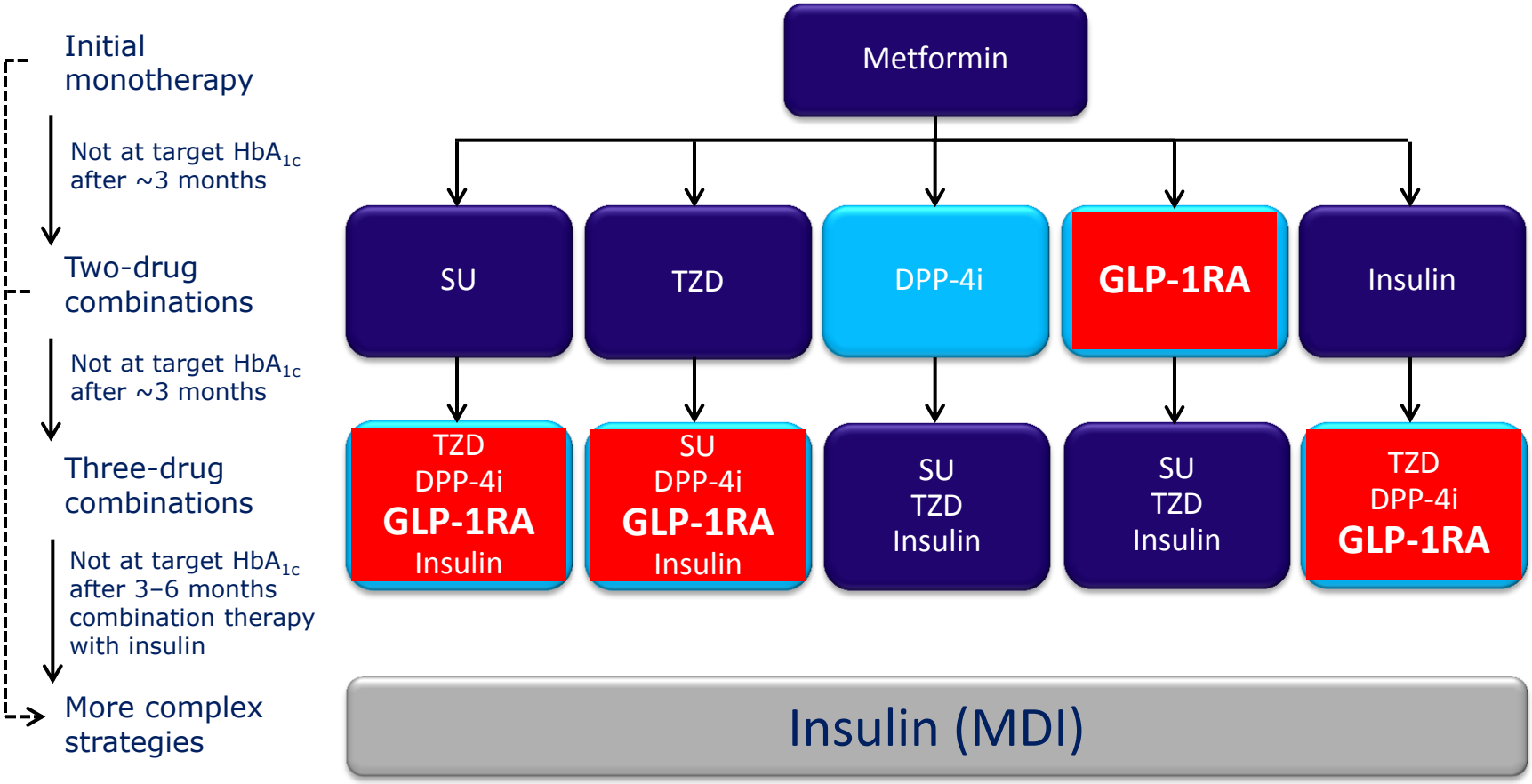
Clínica Anglo Americana

Sociedad Peruana de Endocrinología

ADA/EASD position statement 2012

Healthy eating, weight control, increased physical activity



ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; GLP-1RA, glucagon-like peptide-1 receptor agonists; MDI, multiple daily injections; SU, sulphonylurea; TZD, thiazolidinedione.

Inzucchi *et al. Diabetologia* 2012;55:1577–96.

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*

- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2 **
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

GLP-1 RA

MET or other first-line agent +

- DPP4-i
- TZD
- ** SGLT-2
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

GLP-1 RA

2ND LINE AGENT +

- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

MET or other first-line agent

If not at goal in 3 months proceed to or intensify insulin therapy

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits

⚠ = Use with caution

PROGRESSION OF DISEASE

… un poco de Historia (1)

Bayliss, WM, Starling EH. The Mecanism of Pancreatic Secretion.
J Physiol. 28: 325-53 (1902)

Edie ES. Further Observations on the Treatment of Diabetes mellitus By Acid Extract of Duodenal Mucous Membrane.
Biochem J 1: 446-54 (1906)

Le Barre J. introduce el término Incretina (IncretIn): factor Intestinal que estimula la disminución de glucosa (1932).
Creutzfeldt W. The (Pre) History of the Incretin Concept. Regul Pept 2005; 128: 87-91

En los 60´s se puede dosar la Insulina con mayor facilidad:

Elrick H, Stimmler L, Hlad CJ, Arai Y. Plasma Insulin Response to Oral and Intravenous Glucose Administration.
J Clin Endocrinol Metab 24: 1076-82 (1964)

Diabéticos (——) vs. Normales (– – –)

Respuesta Distinta de Insulina y Glucagon tras Comida

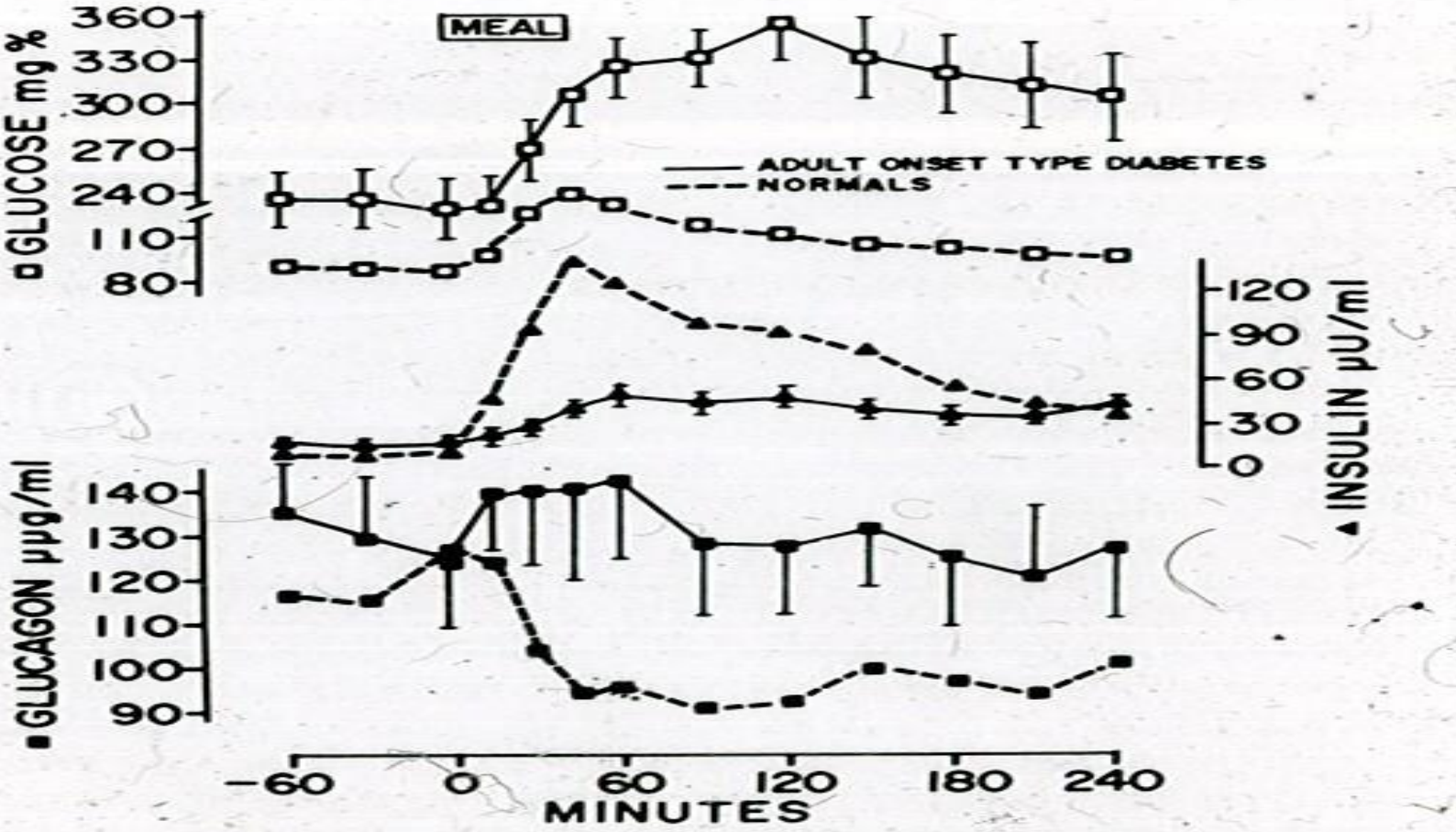
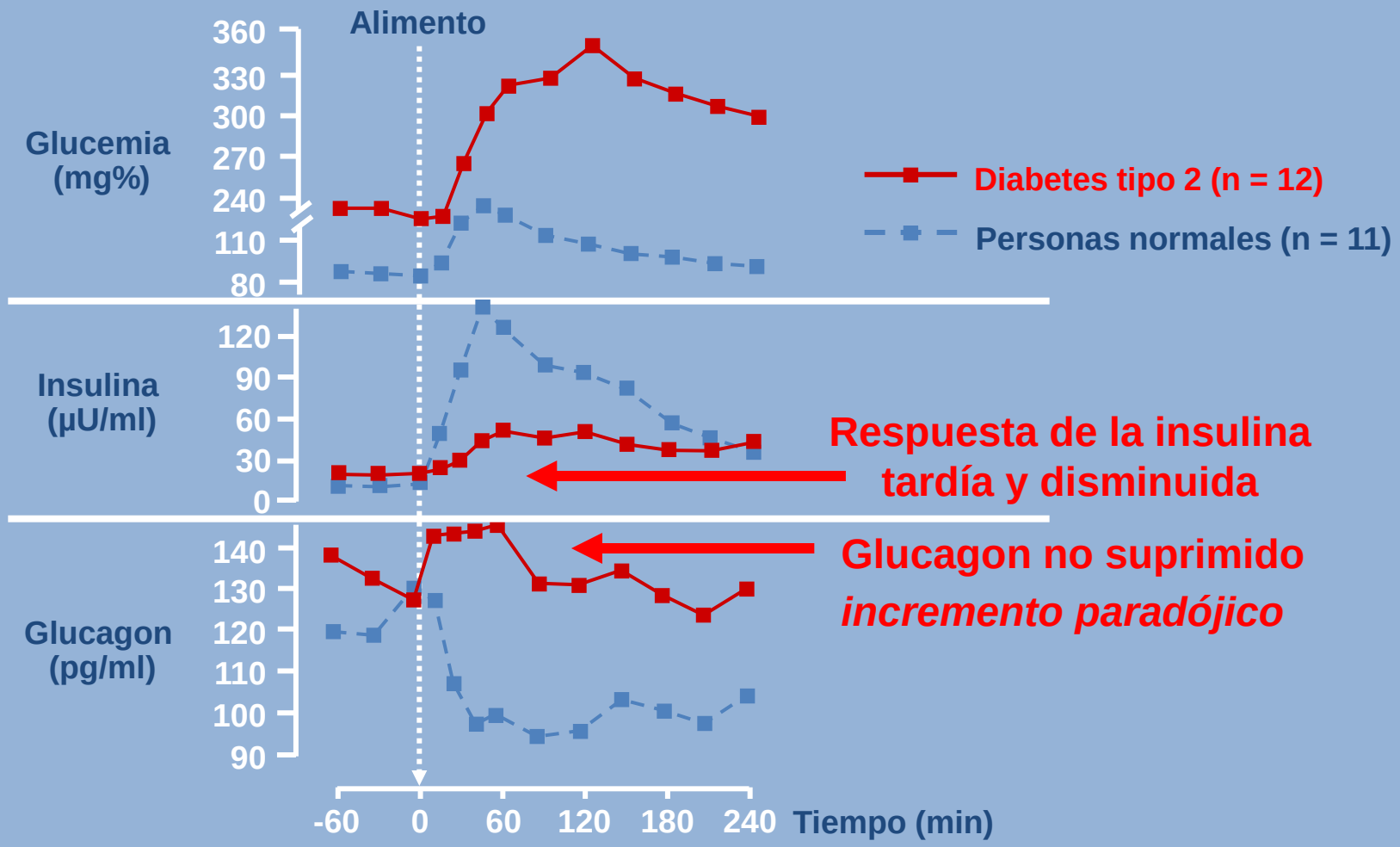


Figure 9–22. The effect of a carbohydrate meal on plasma glucose, insulin, and glucagon. Note the poor insulin response and the lack of glucagon suppression in the diabetic subjects. (From Müller, D., et al.: *New Eng. J. Med. 283*:109, 1970.)

Cortesía Dr. F Garmendia

Secreción Insulina y Glucagon Post-Ingesta en Personas Sin y Con Diabetes tipo 2



Adaptado de Müller WA y cols. N Engl J Med 283:109,1970

¿Motivos
para
estas diferencias?

J. Physiol. (1970), **209**, *pp.* 57–64
With 4 text-figures
Printed in Great Britain

FURTHER PURIFICATION OF A POLYPEPTIDE DEMONSTRATING ENTEROGASTRONE ACTIVITY

BY J. C. BROWN, V. MUTT AND R. A. PEDERSON

From the Department of Physiology and Surgery, University of British Columbia, Vancouver, British Columbia, Canada, and the Kemiskaer Institution II, Karolinska Institutet, Stockholm, Sweden

(*Received 17 December 1969*)

SUMMARY

1. The further purification of a polypeptide having potent enterogastrone activity, without CCK–PZ effects, is described.
2. The material was inhibitory when doses of 1·0 μg/kg.hr were administered intravenously. Amino acid analyses demonstrated the absence of proline, a high content of glutamine and a preponderance of lysine over arginine. Tryptic degradation destroys the inhibitory effect of the polypeptide. Further studies must be performed before the physiological status of the polypeptide can be ascertained.

INTRODUCTION

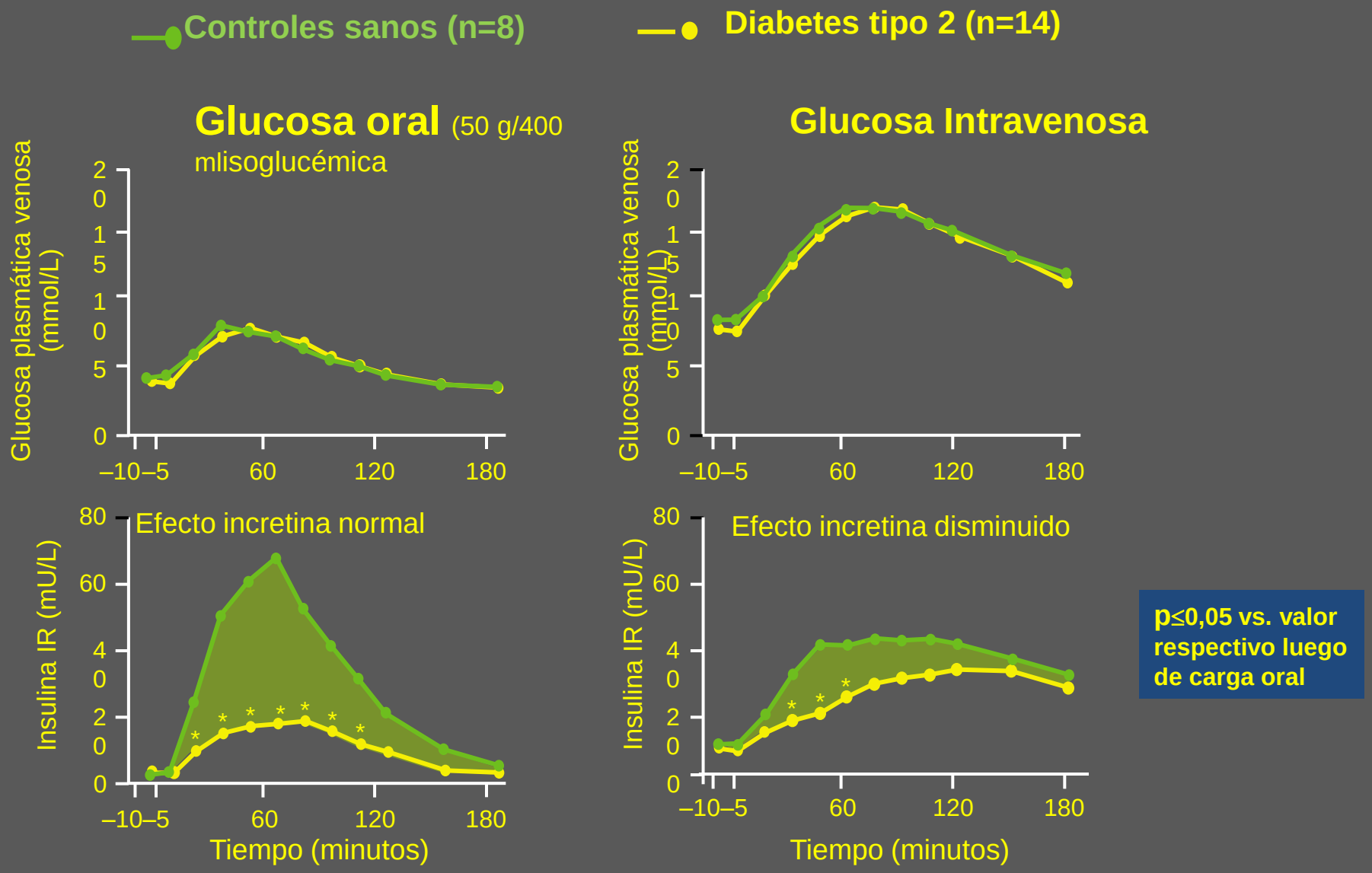
Brown, Pederson, Jorpes & Mutt (1969) previously described the isolation of a material with enterogastrone (EG) activity from a partially purified preparation of the gastrointestinal hormone cholecystokinin–pancreozymin (CCK–PZ, GIH research laboratory, Karolinska Institutet, Stockholm, Sweden). The isolated material was highly inhibitory for H^+ secretion, antral and fundic motor activity and pepsin secretion, and did not possess any significant cholecystokinin or secretin activity.

This report deals with the further purification of this material.

METHODS

Fractions were tested for enterogastrone activity (EG) in three conscious dogs, prepared several months previously with a pouch of the fundus of the stomach, which was vagally and sympathetically denervated. A plateau of H^+ secretion was obtained using gastrin pentapeptide (1·5–4·0 μg/kg.hr) infused intravenously. These doses gave approximately 70 % of maximal acid secretion which varied in these preparations from 500 to 900 μ-equiv/15 min approximately. The infusion of EG samples was commenced only after three consecutive periods of H^+ secretion were within

Respuesta a la Ingestión PO *vs.* Infusión IV de Glucosa



*IR = immunoreactive

… un poco de Historia (2)

Bell, G. I., Sanchez-Pescador, R., Laybourn, P. J. & Najarian, R. C. Exon duplication and divergence in the human preproglucagon gene.

Nature 304, 368–371 (1983).

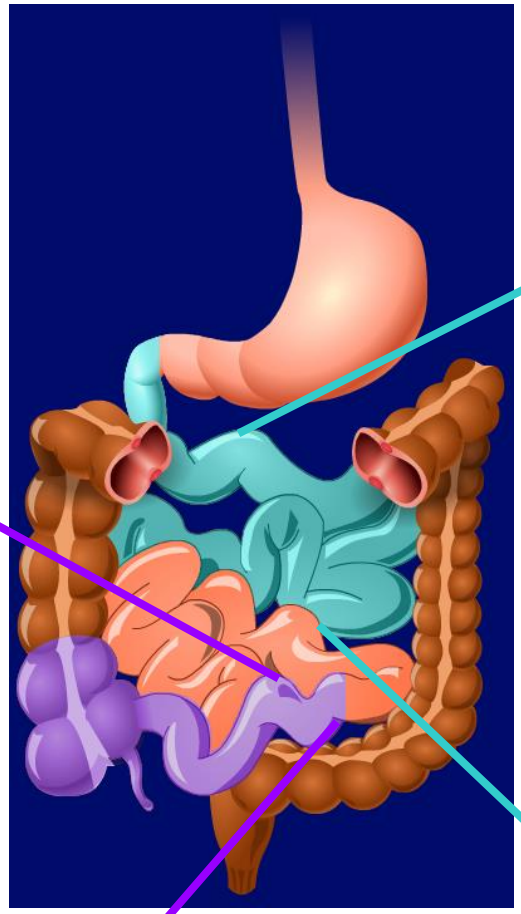
Gutniak, M., Ørskov, C., Holst, J. J., Åhren, B. & Efendic, S. Antidiabetogenic effect of glucagon-like peptide-1 amide in normal subjects and patients with diabetes mellitus.

N. Engl. J. Med. 326, 1316–1322 (1992).

Nauck, M. A., Bartels, E., Ørskov, C., Ebert, R. & Creutzfeldt, W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-amide infused at near-physiological insulinotropic hormone and glucose concentrations.

J. Clin. Endocrinol. Metab. 76, 912–917 (1993).

SÍNTESIS Y SECRECIÓN DE GLP-1 y GIP



Células L
(ileon y colon)

Proglucagon

GLP-1 [7-37]

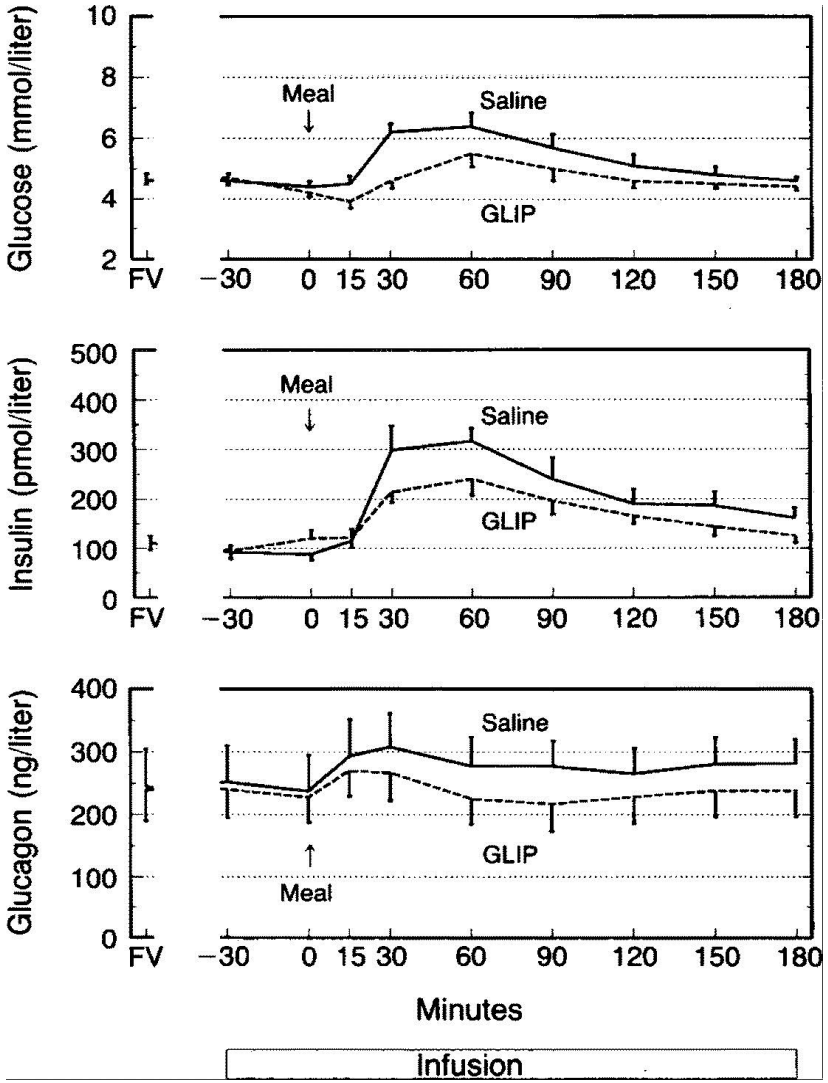
GLP-1 [7-36NH_2]

Células K
(yeyuno)

ProGIP

GIP [1-42]

Efectos de la Infusión de GLIP o Salino en el Promedio de las Concentraciones Post Prandiales de Glucosa, Insulina y Glucagon en 8 Sujetos Normales

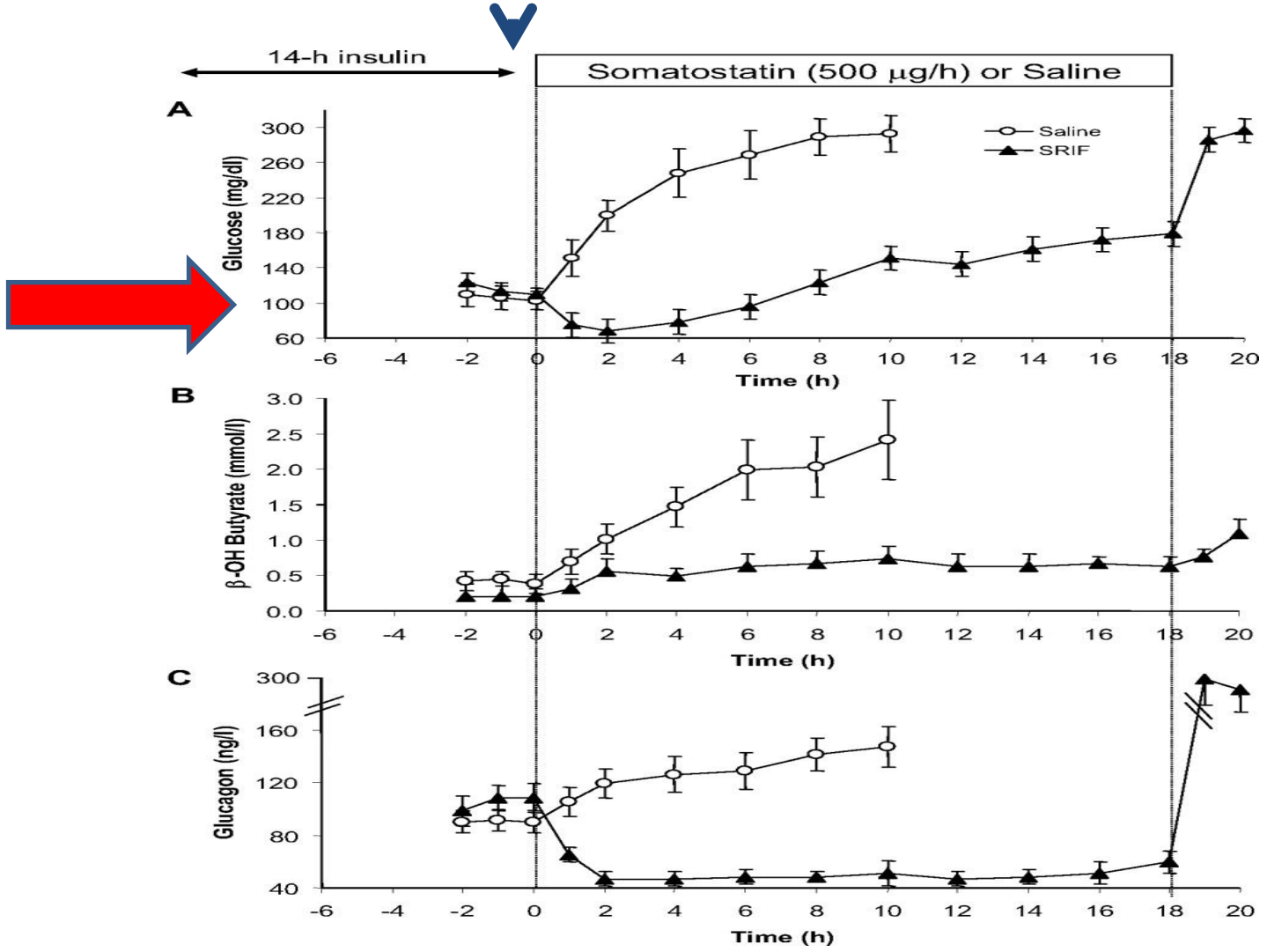


Gutniak M et al. N Engl J Med 1992;326:1316-1322.

The NEW ENGLAND JOURNAL of MEDICINE

Efecto de la Supresión de Glucagon sobre la Glicemia, el β-Hidroxibutirato y el Glucagon en pacientes con Dm1

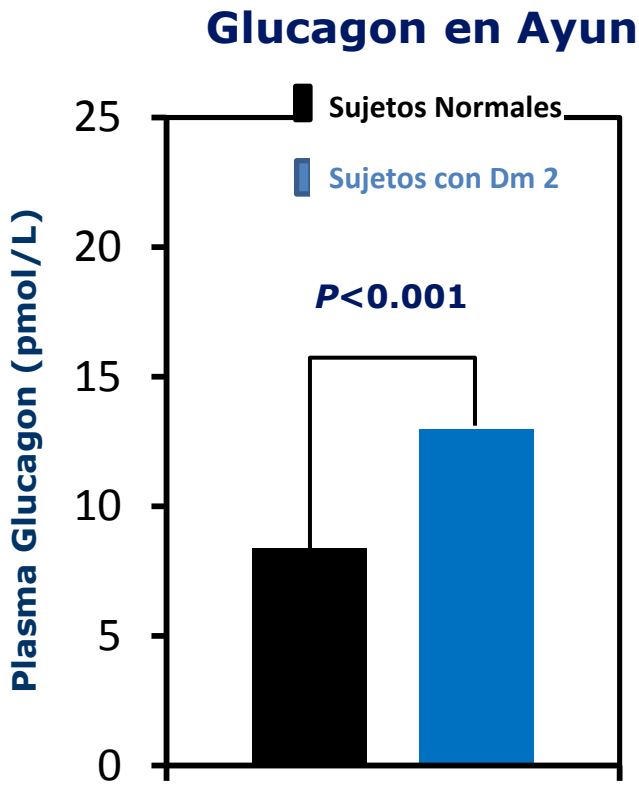
***Abstinencia de Insulina e Infusión de Somastostatina vs. Salino**

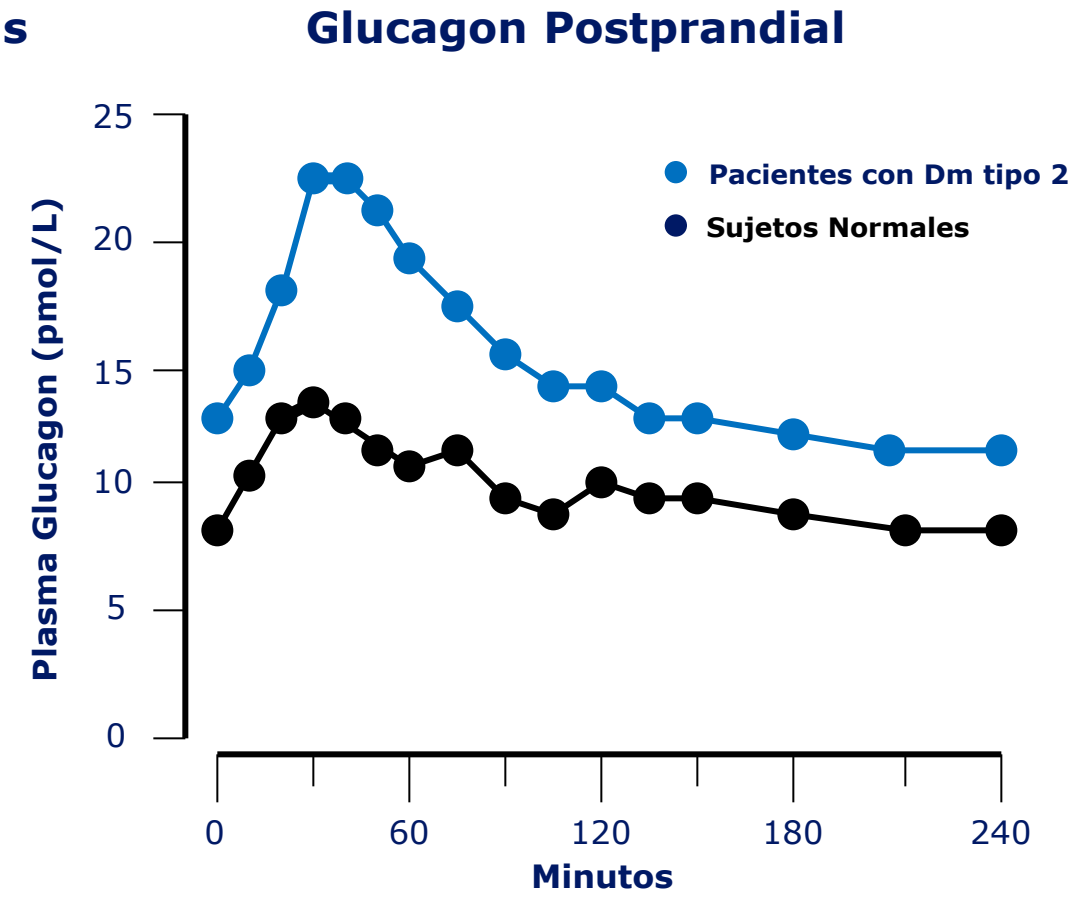


Dunning, B. E. et al. Endocr Rev 2007;28:253-283

ENDOCRINE REVIEWS

Los niveles de Glucagon están Aumentados en Pacientes con Diabetes tipo 2





n: T2DM patients=54; Normal subjects=33
T2DM, type 2 diabetes mellitus

Toft-Nielson MB et al. *J Clin Endocrinol Metab*. 2001;86:3717–3723

… un poco de Historia (3)

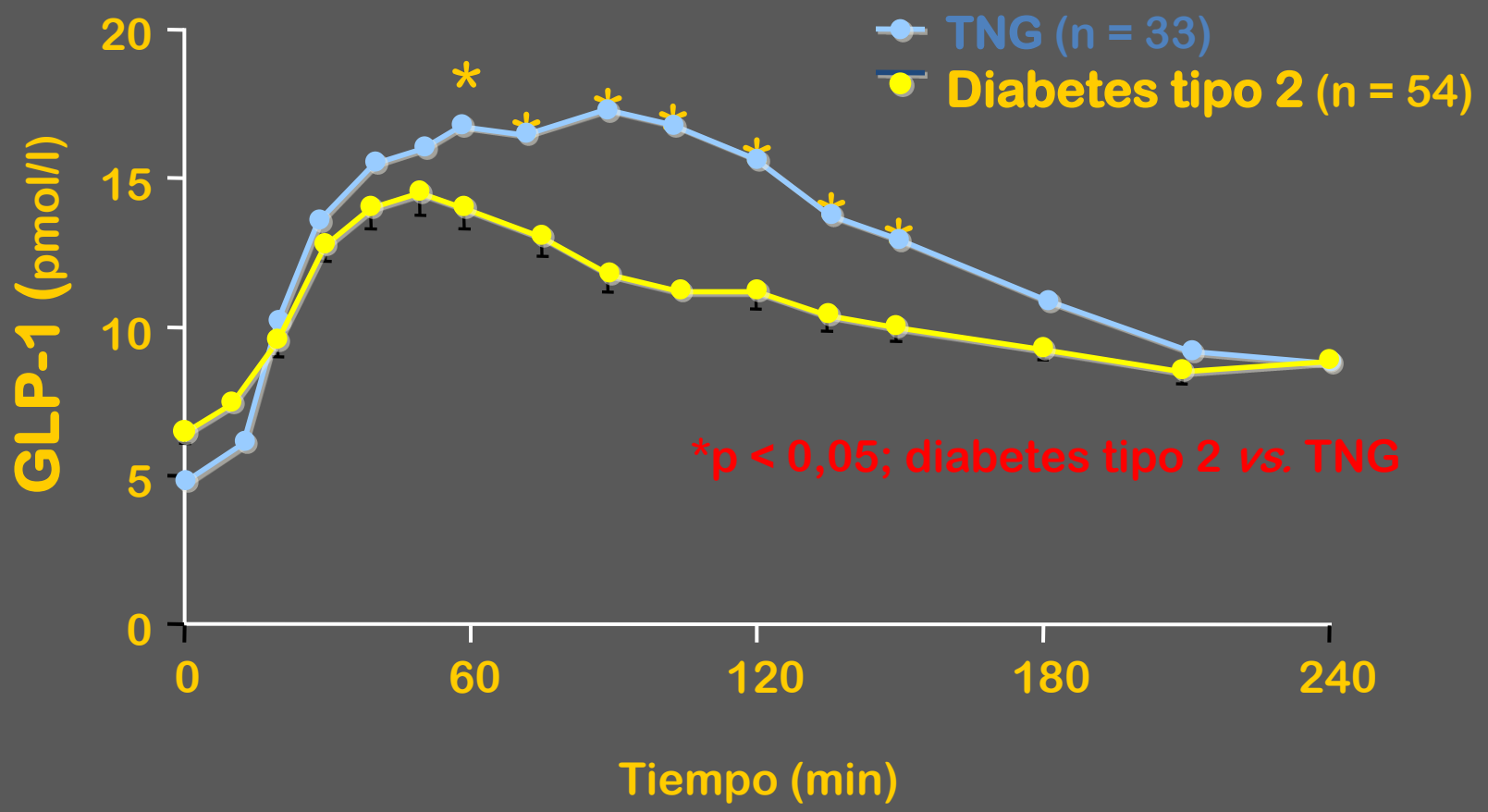
Nauck, M. A. *et al*. **Preserved incretin activity of GLP-1 amide but not of synthetic human GIP in patients with type-2 diabetes mellitus**.

J. Clin. Invest. 91, 301–307 (**1993**).

Nauck, M. A. *et al*. **Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 amide in type 2 (non-insulin-dependent) diabetic patients**.

Diabetologia 36, 741–744 (**1993**).

En la Diabetes tipo 2 disminuyen los niveles de GLP-1



Test de comida de 240 minutos

Inicio de comida en 0 y fin de comida entre minuto 10 y 15

Adaptado de Toft-Nielsen MB y cols J Clin Endocrinol Metab 2001;86:3717-23.

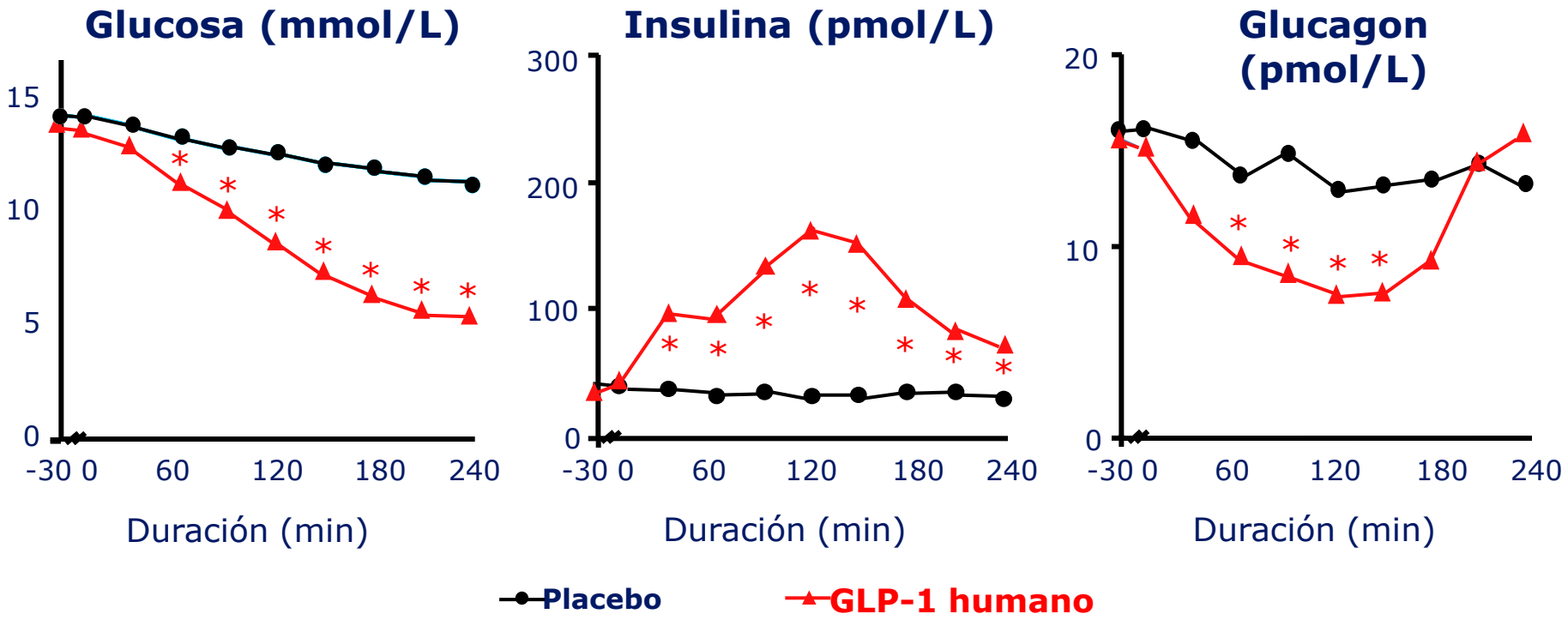
El deterioro de la secreción de GLP-1 en la Dm tipo 2 no es anterior a la Diabetes

- Vaag y cols. 1996: En gemelos discordantes en términos de diabetes tipo 2, GLP-1 disminuyó solamente en el gemelo diabético

- Nyholm y cols. 1999: Los perfiles plasmáticos de 24 horas de GLP-1 eran normales en los hijos sanos de padres con diabetes tipo 2

Efecto de GLP-1 es Dependiente de Niveles de Glucosa

Efecto de infusión de GLP-1 (1.2 pmol/kg/min) durante 4 horas en pacientes con Diabetes tipo 2

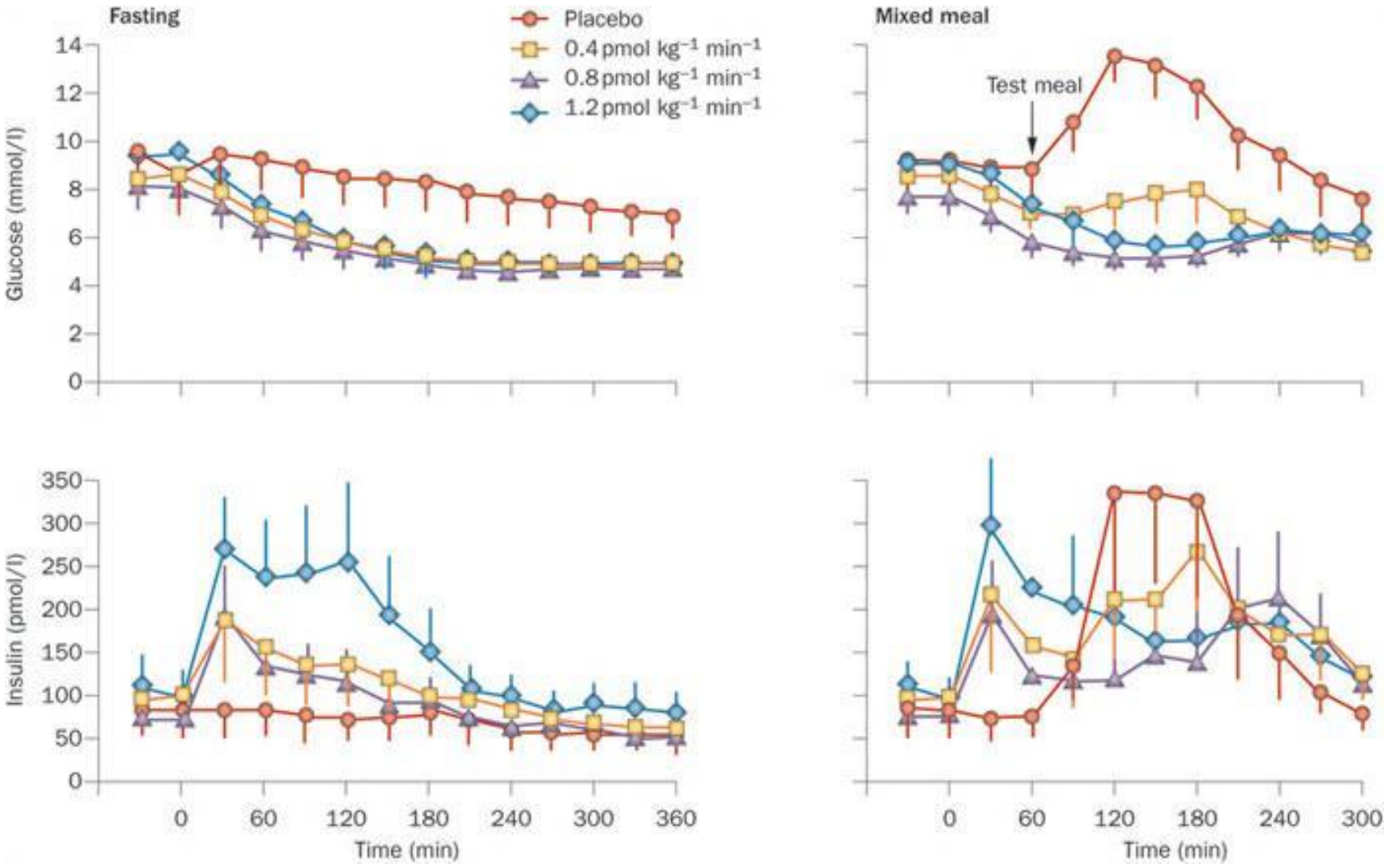


Mean (SE); n=10
*$p<0.05$

GLP-1, glucagon-like peptide-1; SE, standard error

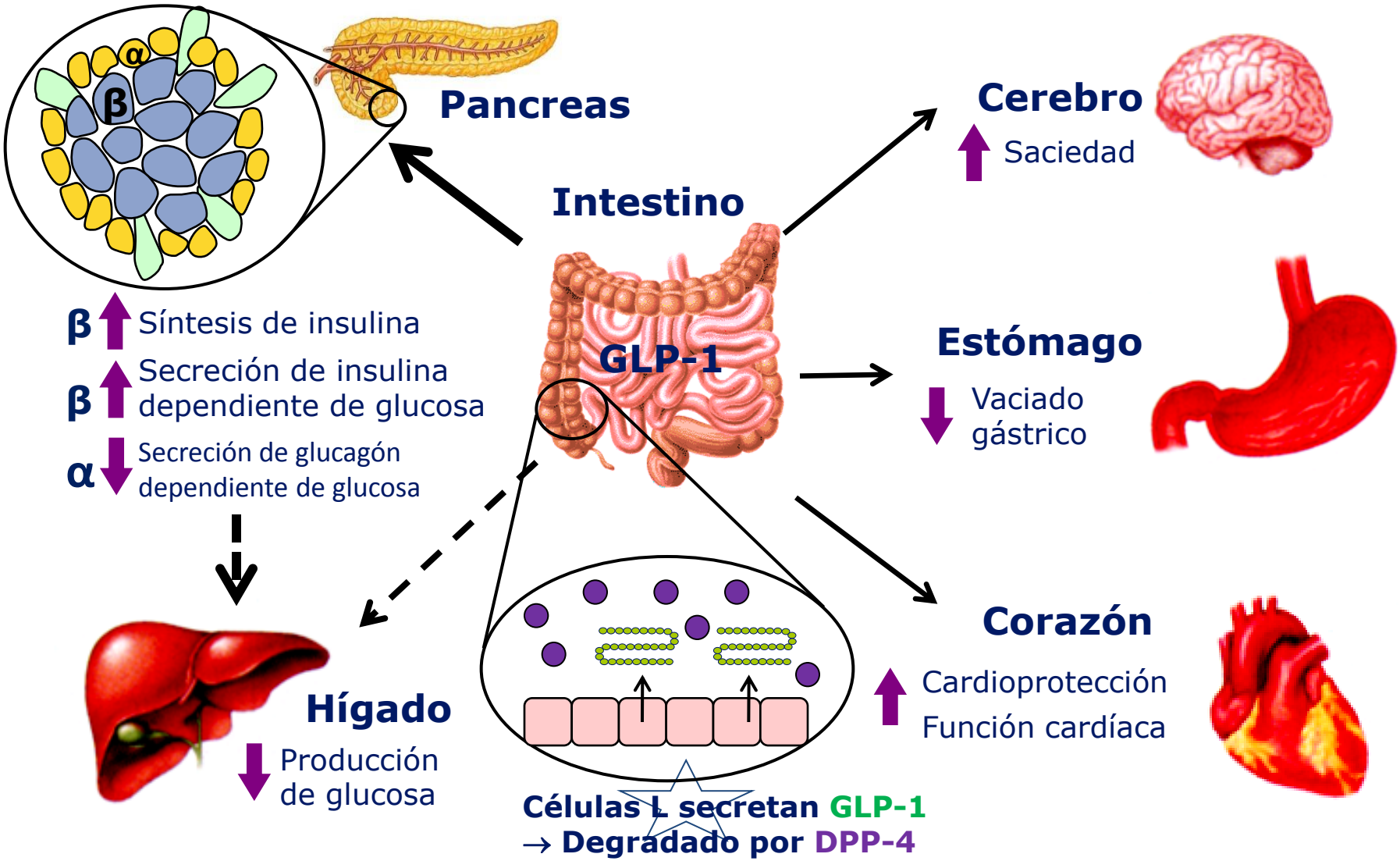
Nauck M *et al. Diabetologi*a 1993;36:741–744

GLP-1 tiene Efecto Dosis-Dependiente sobre Glucosa e Insulina en Ayunas y Post- Comida



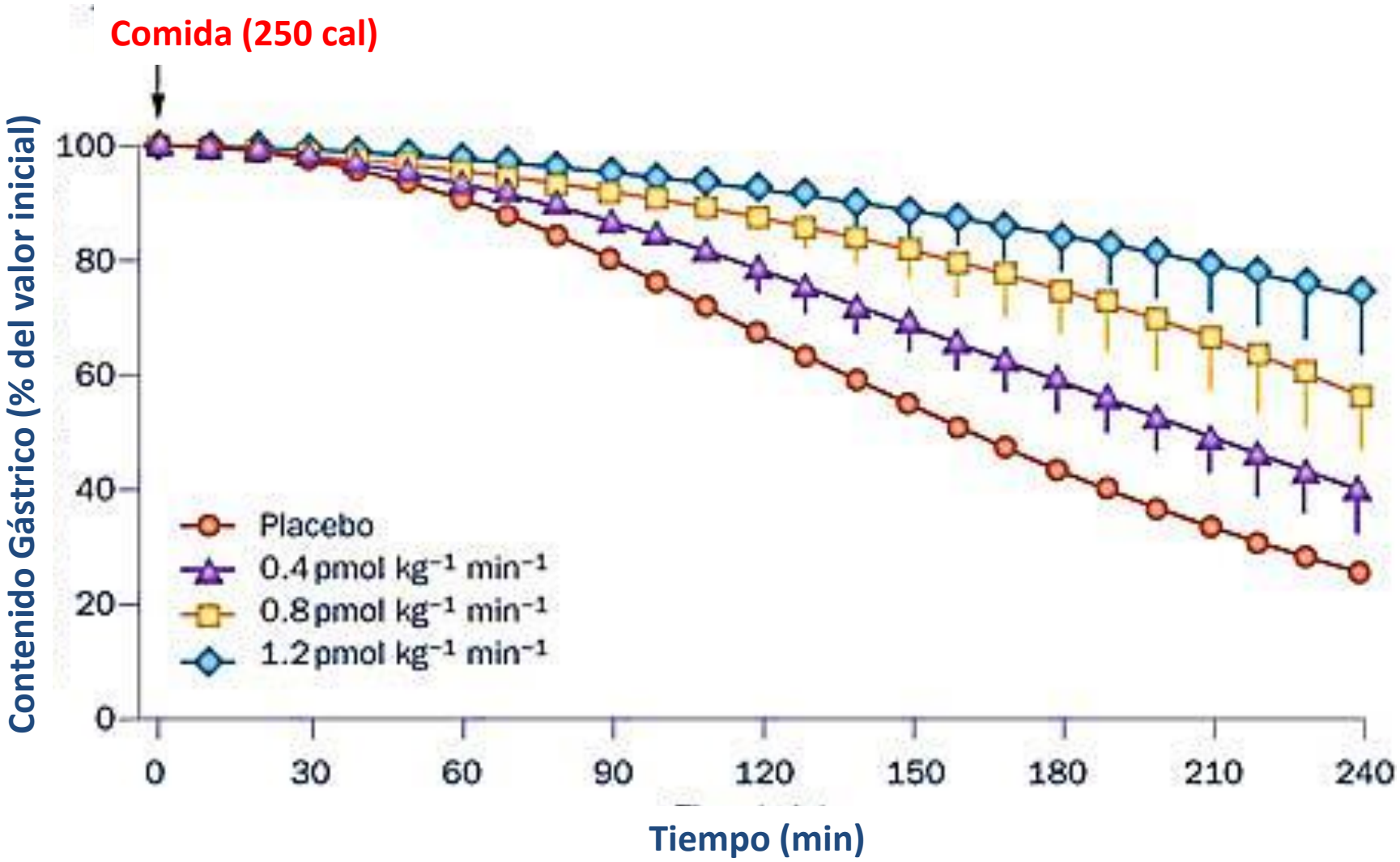
Meier, J. J. et al. J. Clin. Endocrinol. 88, 2716–2725 (2003).

GLP-1: Múltiples Efectos Fisiológicos

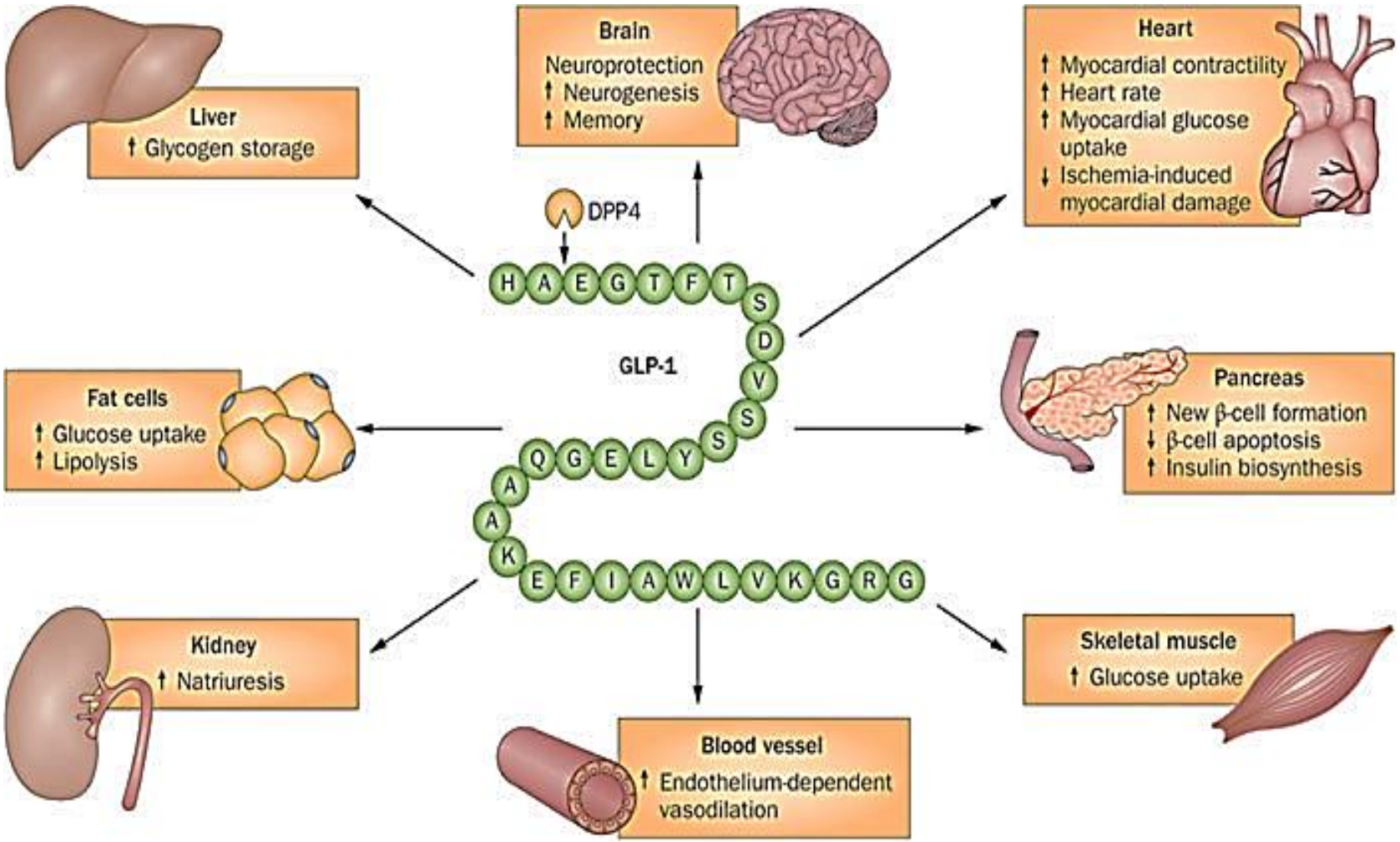


Adapted from Baggio & Drucker. *Gastroenterol* 2007;132;2131–57

Tasa de Vaciamiento Gástrico durante la administración IV de 0.4, 0.8, or 1.2 pmol·kg^{-1}·min **de GLP-1 o Placebo en pacientes con Diabetes mellitus tipo 2 tras Ingesta de Comida**



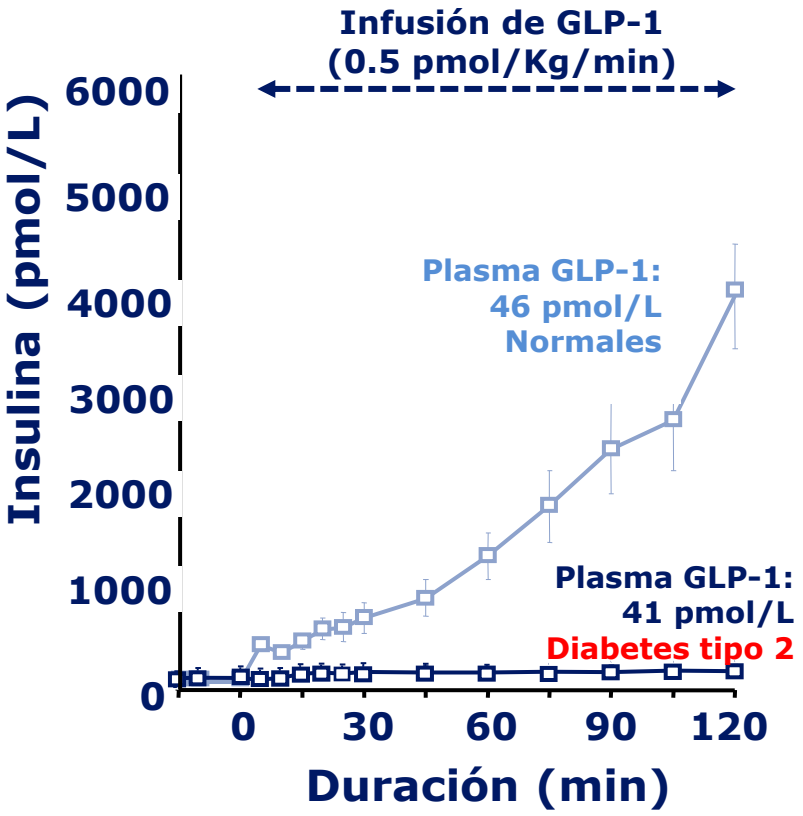
Acciones Fisiológicas de la Incretina Nativa



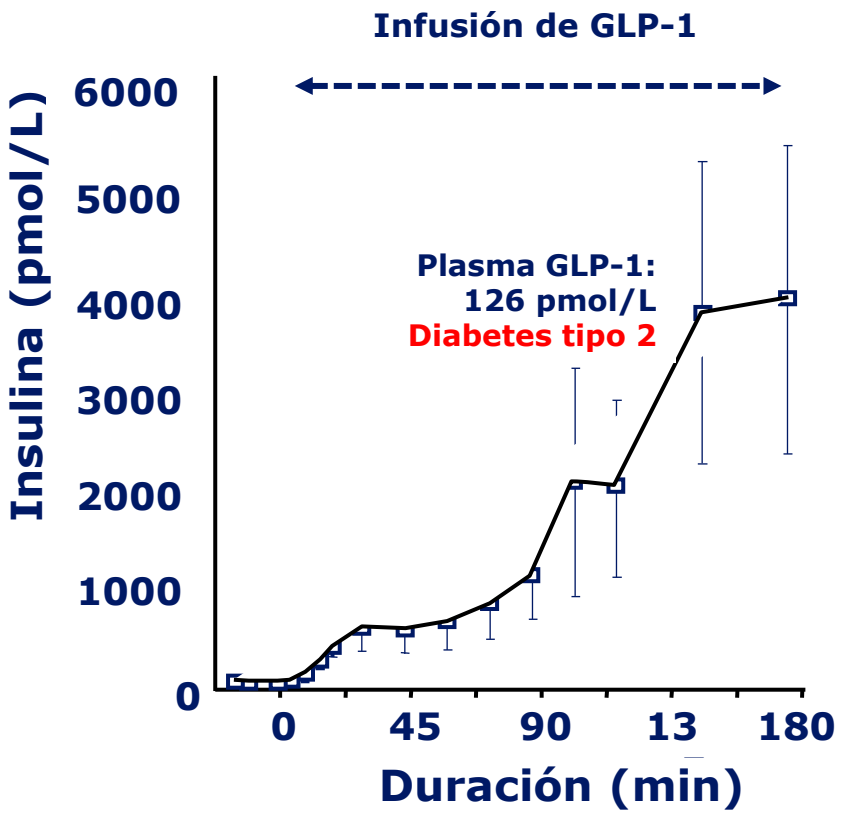
Juris J. Meier. Nature Reviews Endocrinology 8, 728-742 (December 2012)
Vilsbøll T & Garber AJ. *Diabetes Obes Metab* 2012;14(suppl 2):41–49;
Baggio LL & Drucker DJ. *Gastroenterology* 2007;132:2131–2157

La Respuesta Insulínica a niveles Fisiológicos de GLP-1 está disminuida … pero se restablece a dosis Farmacológicas

Niveles Fisiológicos de GLP-1[1]
(15 mM clamp hiperglicémico)

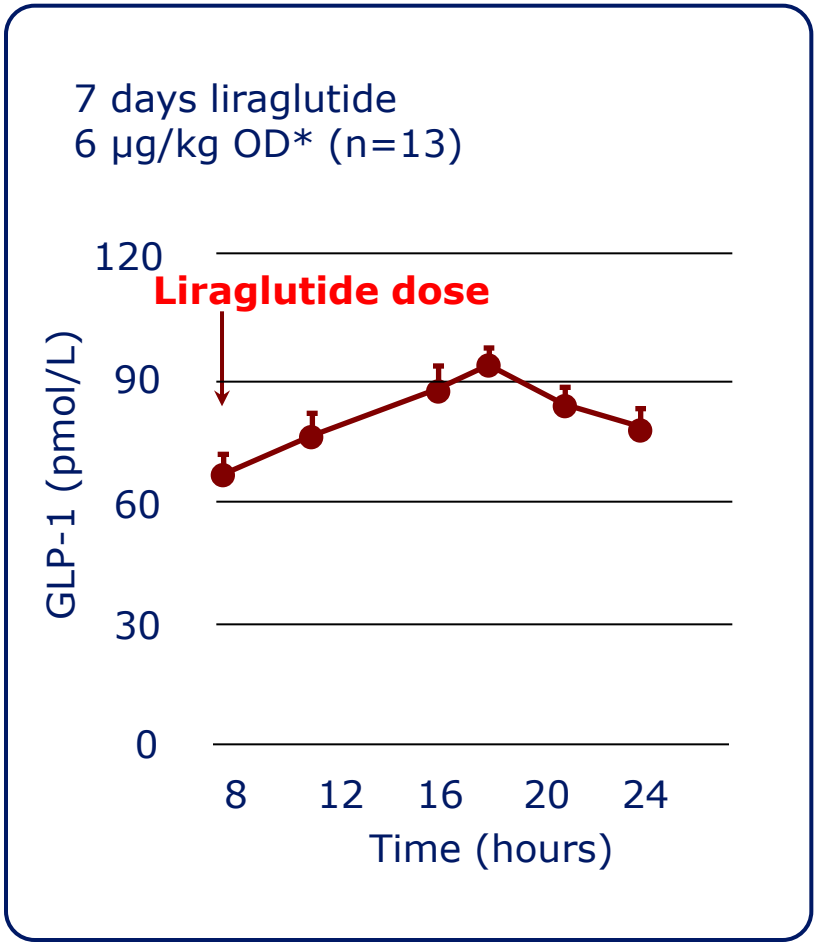


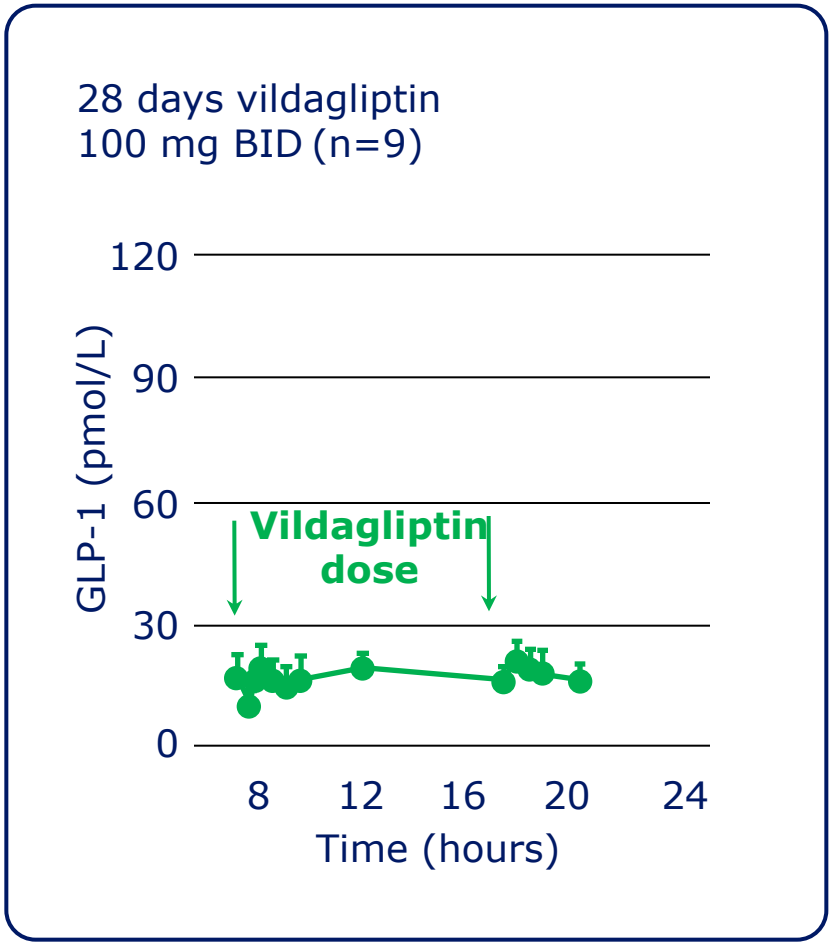
Niveles Farmacológicos de GLP-1[2]
(15 mM clamp hiperglicémico)



1. Højberg *et al*. *Diabetologia* 2009;52:199-207; 2. Vilsbøll *et al*. *Diabetologia* 2002;45:1111–9

Los niveles de GLP-1 con Análogos de su receptor son Farmacológicos y con inhibidores de DPP-4 son Fisiológicos

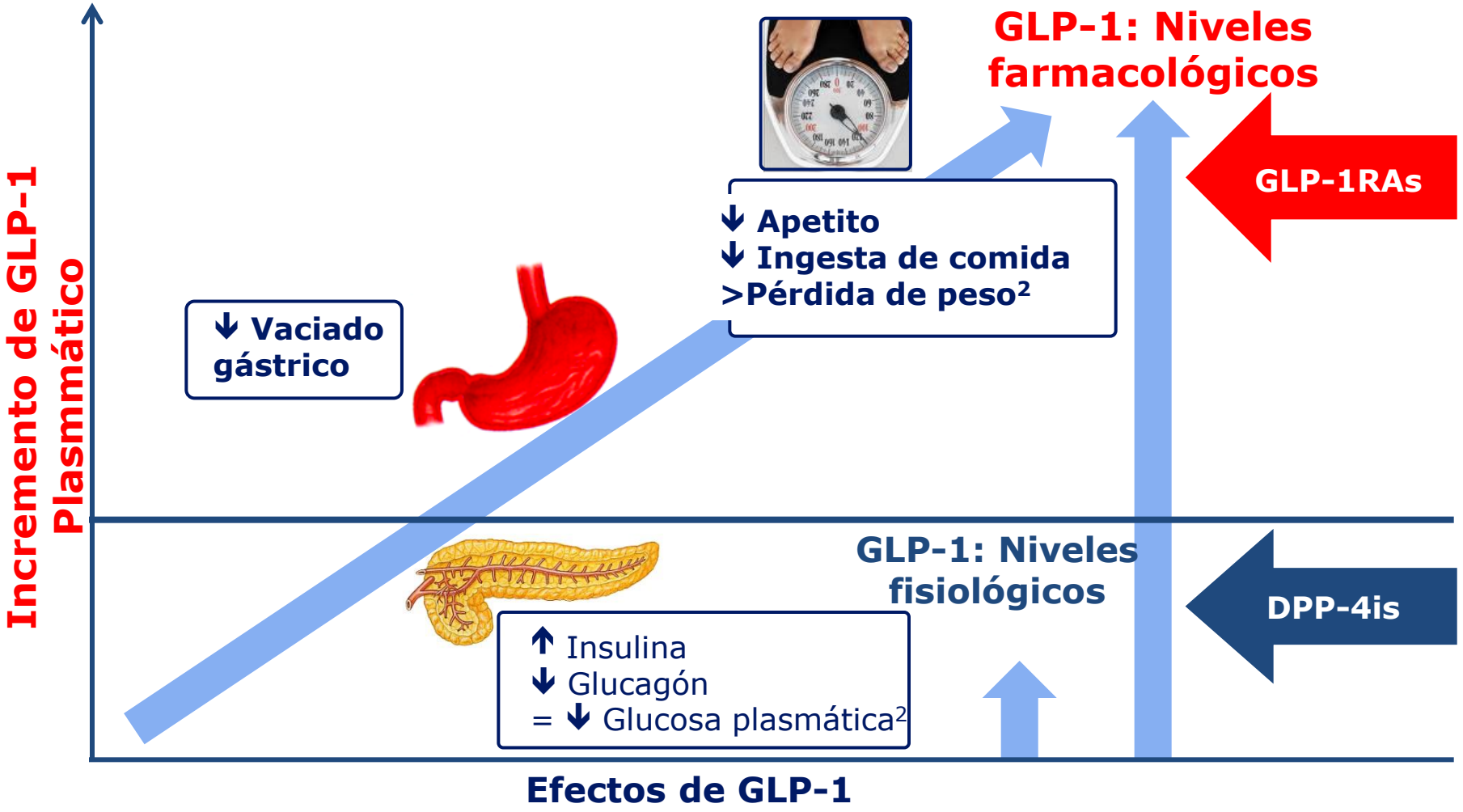




*GLP-1 levels for liraglutide calculated as 1.5% free liraglutide

Adapted from Degn *et al. Diabetes* 2004;53:1187–94;
Mari *et al. J Clin Endocrinol Metab* 2005;90:4888–94.

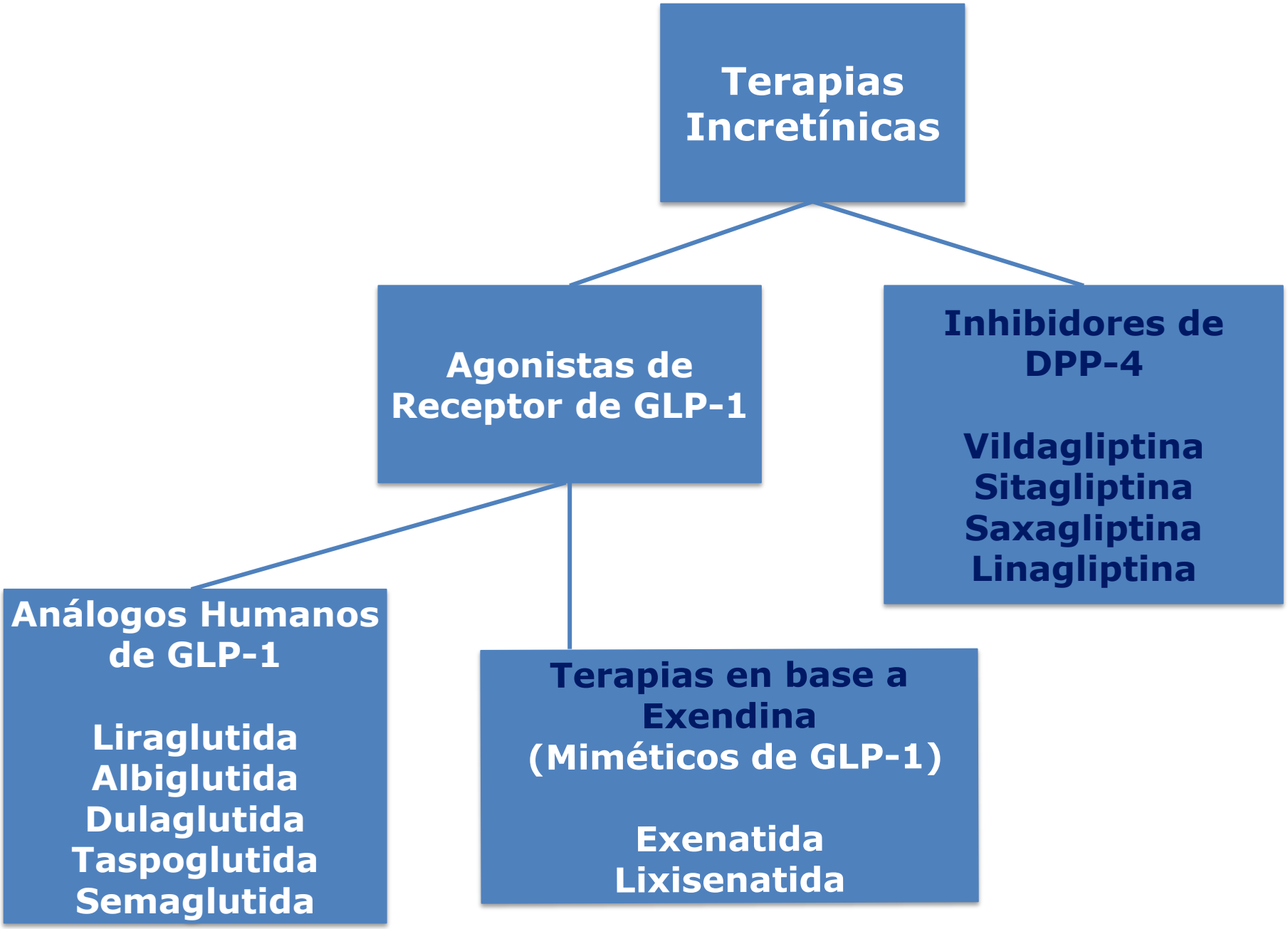
Beneficios fisiológicos adicionales se observan a niveles farmacológicos de GLP-1



DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; GLP-1RAs, glucagon-like peptide 1 receptor agonists

Adapted from Holst et al.[1]

1. Holst JJ et al. *Trends Mol Med* 2008;14:161–168; 2. Flint A et al. *Adv Ther* 2011;28:213–226


Terapias Incretínicas
Agonistas de Receptor de GLP-1
Inhibidores de DPP-4
Vildagliptina
Sitagliptina
Saxagliptina
Linagliptina
Análogos Humanos de GLP-1
Liraglutida
Albiglutida
Dulaglutida
Taspoglutida
Semaglutida
Terapias en base a Exendina (Miméticos de GLP-1)
Exenatida
Lixisenatida

Estructura de GLP-1 Humano Nativo

Degradación Enzimática por DPP-4

7 9

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Lys Ala Ala Gln Gly Glu Leu Tyr Ser Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly

36

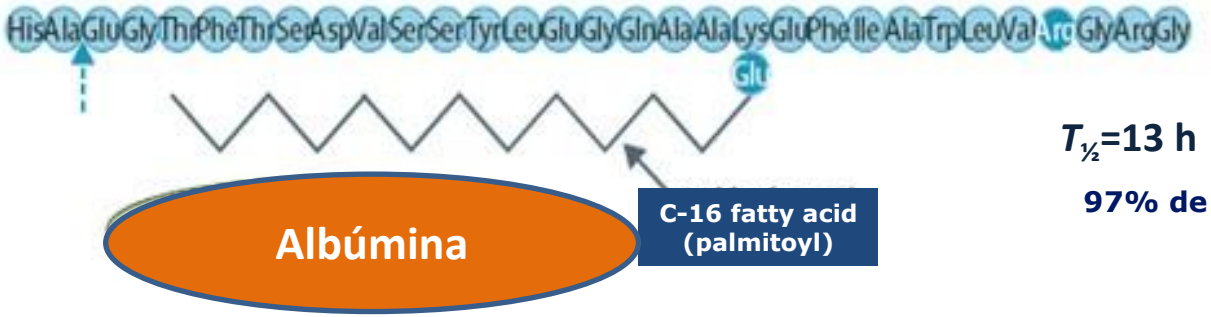
$T_{½}$=1.5–2.1 min

Exenatide

$T_{½}$= 2.4 h

53% de homología con el GLP-1 humano
Saliva de Gila *monster(Heloderma suspectum)*

Liraglutida

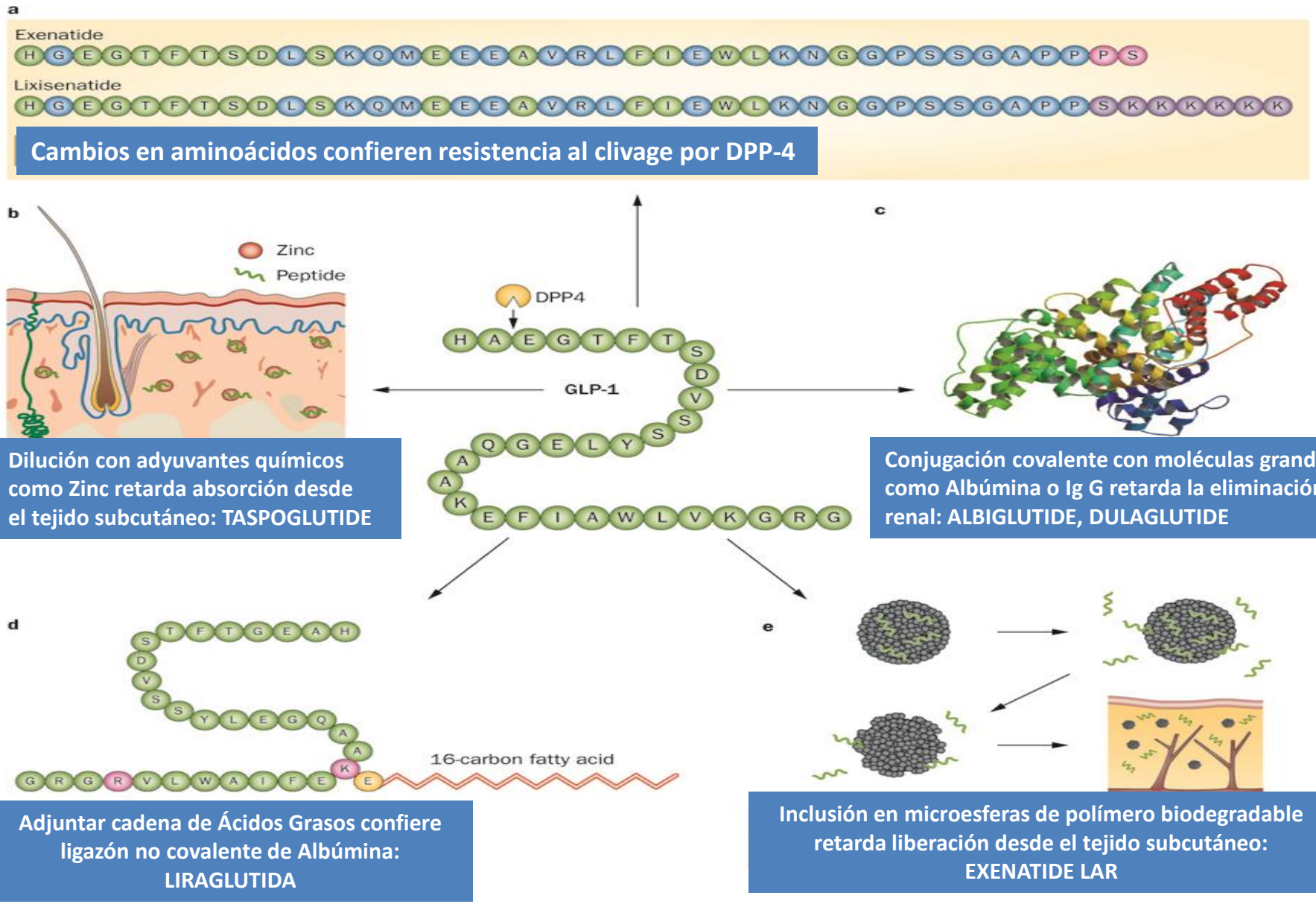


$T_{½}$=13 h

97% de homología con el GLP-1 humano

Knudsen *et al. J Med Chem* 2000;43:1664–9; Degn *et al. Diabetes* 2004;53:1187–94

Estrategias para desarrollar Agonistas del Receptor de GLP-1 con Efecto Prolongado



Meier, J. J. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2012.140

Incretinas Aprobadas por la (FDA) y la (EMA)

Drug	Incretin-Based Mechanism	Approval Date	
		FDA	EMA
Exenatide	GLP1 agonist	April 28, 2005	November 20, 2006
Sitagliptin	DPP4 inhibitor	October 16, 2006	March 21, 2007
Vildagliptin	DPP4 inhibitor	(Not approved by the FDA)	September 26, 2007
Saxagliptin	DPP4 inhibitor	July 31, 2009	October 1, 2009
Liraglutide	GLP1 agonist	January 25, 2010	June 30, 2009
Linagliptin	DPP4 inhibitor	May 2, 2011	August 24, 2011
Exenatide extended-release	GLP1 agonist	January 27, 2012	June 17, 2011
Alogliptin	DPP4 inhibitor	January 25, 2013	September 19, 2013
Lixisenatide	GLP1 agonist	(Not approved by the FDA)	February 1, 2013

* GLP1 denotes glucagon-like peptide 1, an incretin; DPP4 denotes dipeptidyl peptidase 4, an exopeptidase that inactivates the incretins.

FDA: Food and Drug Administration
EMA: European Medicines Agency

Egan AG et al. N Engl J Med 2014;370:794-797. **(Febrero 2014)**

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Incretinas

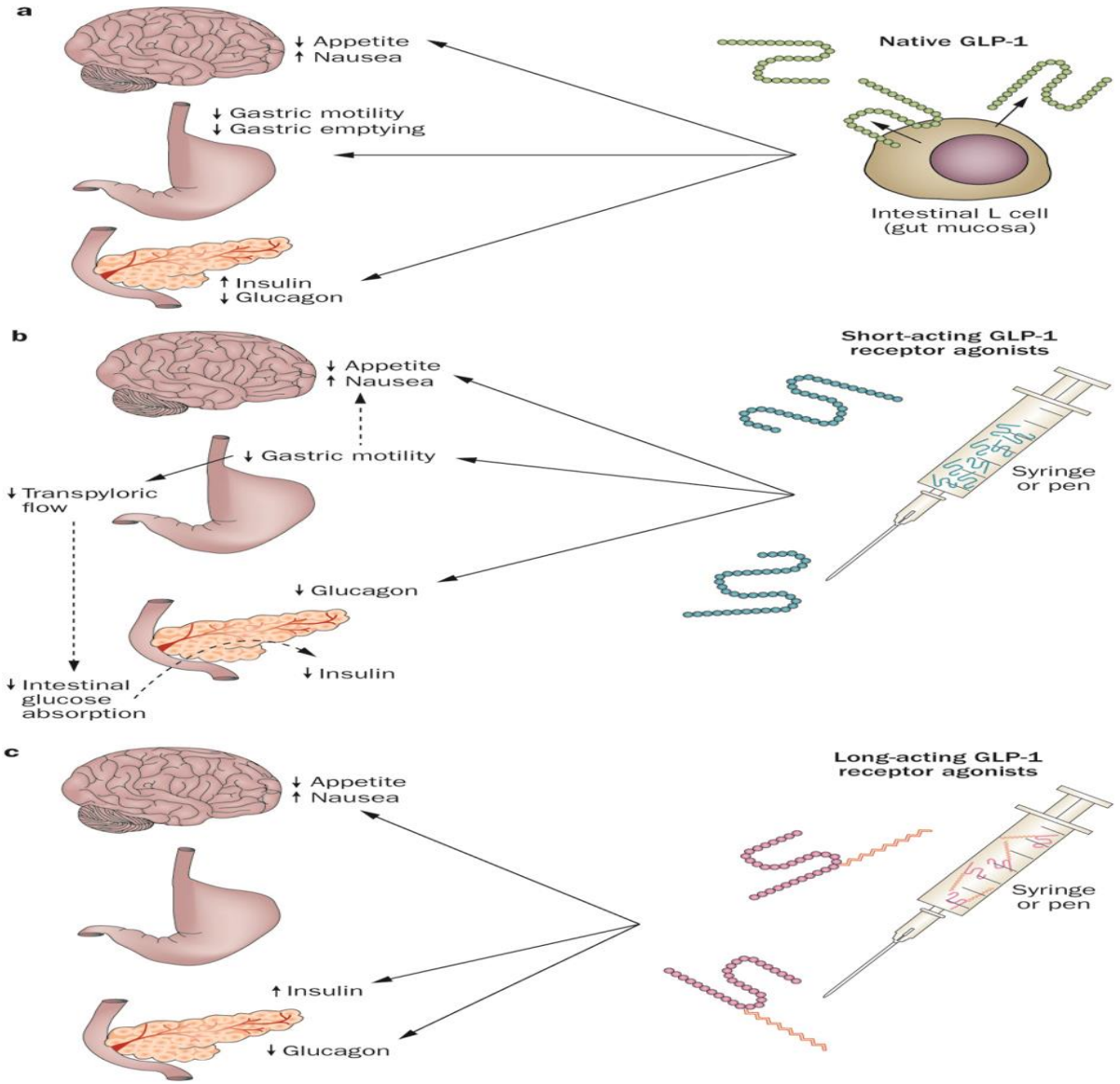
Compuesto	Nombre comercial	Presentación	Dosis Inicial (mcg/día)	Dosis Máxima (mg/día)	Duración de Efecto (horas)
Exenatida	Byetta	5 mg 10 mg	5 mcg/12 h	10 mgr/12 h	12
Liraglutida	Victoza	1.2 mg 1.8 mg	0.6mg/24h	1.8	24
Lixisenatida	Lyxumia	20 mcg	10 mcg/24h	20 mcg	24
Exenatide LAR	Bydureon	2 mg	2 mg/ semana	2mg/ semana	168

Comparación de Análogos del Receptor de GLP-1 de Corta vs Larga Duración

PARÁMETRO	ANÁLOGO GLP-1 ACCIÓN CORTA	ANÁLOGO GLP-1 ACCIÓN LARGA
COMPUESTO	EXENATIDE LIXISENATIDE	LIRAGLUTIDA EXENATIDE LAR ALBIGLUTIDA DULAGLUTIDA
vida 1/2	2-5 horas	12 horas- varios días
Glicemia en ayunas	Leve Reducción	Fuerte Reducción
Hiperglicemia Post Prandial	Fuerte Reducción	Leve Reducción
Secreción de Insulina en Ayunas	Leve Estimulación	Fuerte Estimulación
Secreción de Insulina Post Prandial	Disminuida	Leve Estimulación
Secreción de Glucagon	Disminuida	Disminuida
Tasa de Vaciado Gástrico	Lenta	Sin Efecto
Presión Arterial	Disminuida	Disminuida
Frecuencia Cardiaca	Leve Incremento (0-2 latidos/min)	Moderado Incremento (2 a 5 latidos/min)
Reducción de Peso	1-5 kg	2-5 kg
Náusea	20-50% Mejora en meses	20-40% Mejora en ≈ 4-8 semanas

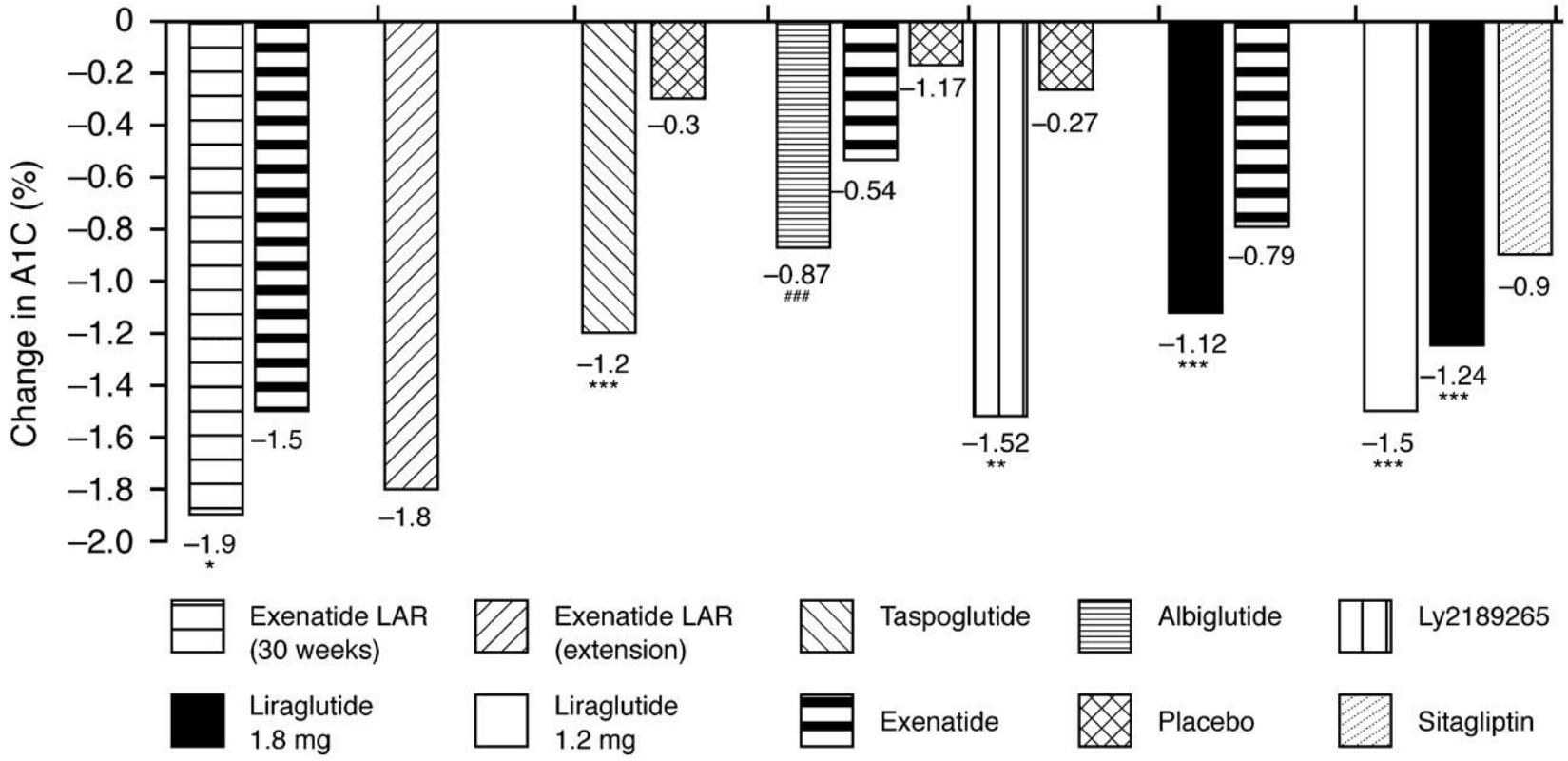
Meier, J. J. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2012.140

Efectos Fisiológicos GLP-1 y Modelos Propuestos de Acción para GLP-1 Nativa, Análogos de Receptor de GLP-1 de Corta y Larga Acción en Estado Post-Prandial



Meier, J. J. (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2012.140

Variación de HbA1c con Agonistas del Receptor de GLP-1

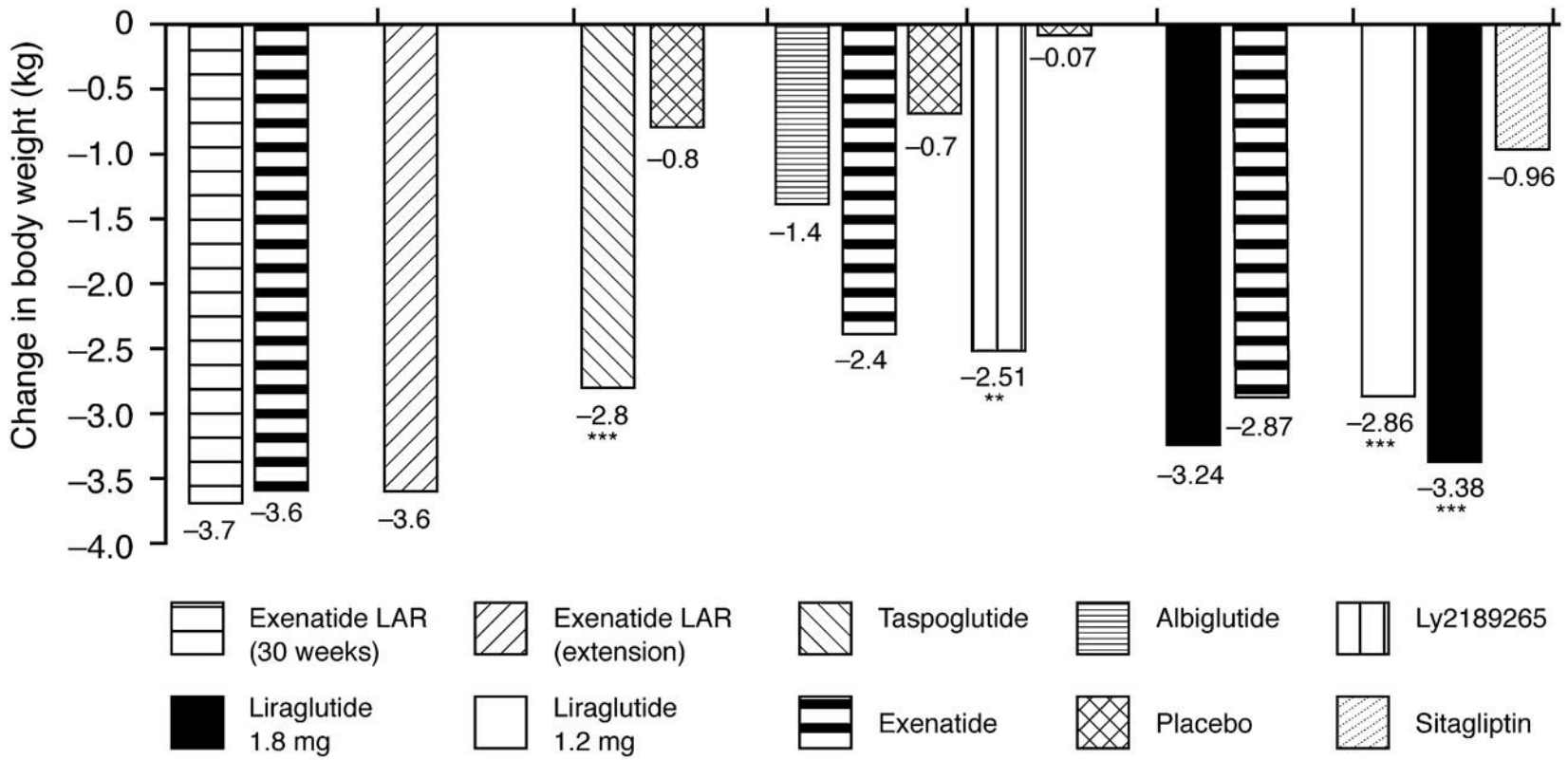


Change in A1C with long-acting GLP-1 receptor agonists across the clinical trials (24,32,36–39,41). *P < 0.01 vs. comparator; **P < 0.001; ***P < 0.0001; ###P < 0.0001 vs. placebo.

Garber A J Dia Care 2011;34:S279-S284

American Diabetes Association.

Variación de Peso con Agonistas del Receptor de GLP-1

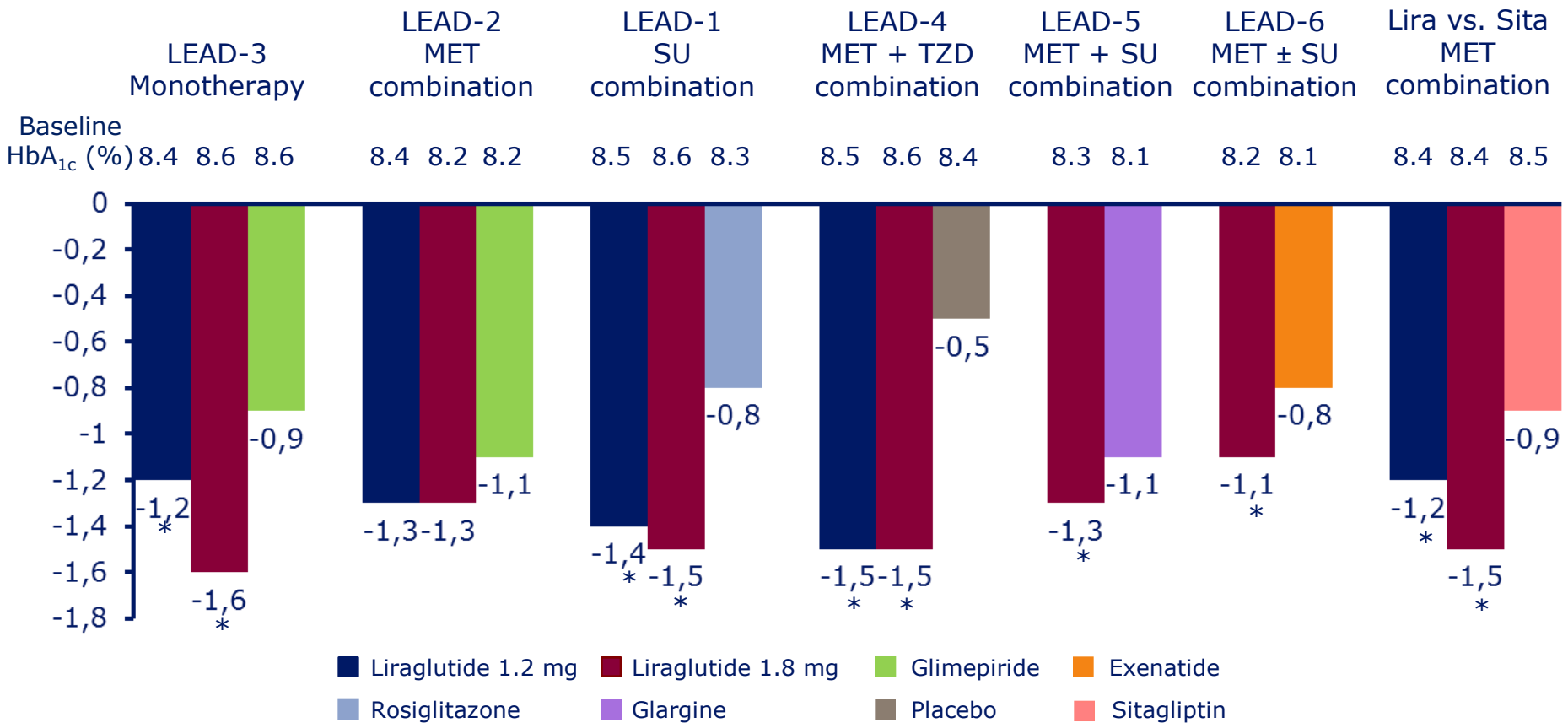


Change in body weight with long-acting GLP-1 receptor agonists across the clinical trials (24,32,36–39,41). **P < 0.001; ***P < 0.0001.

Garber A J Dia Care 2011;34:S279-S284

American Diabetes Association.

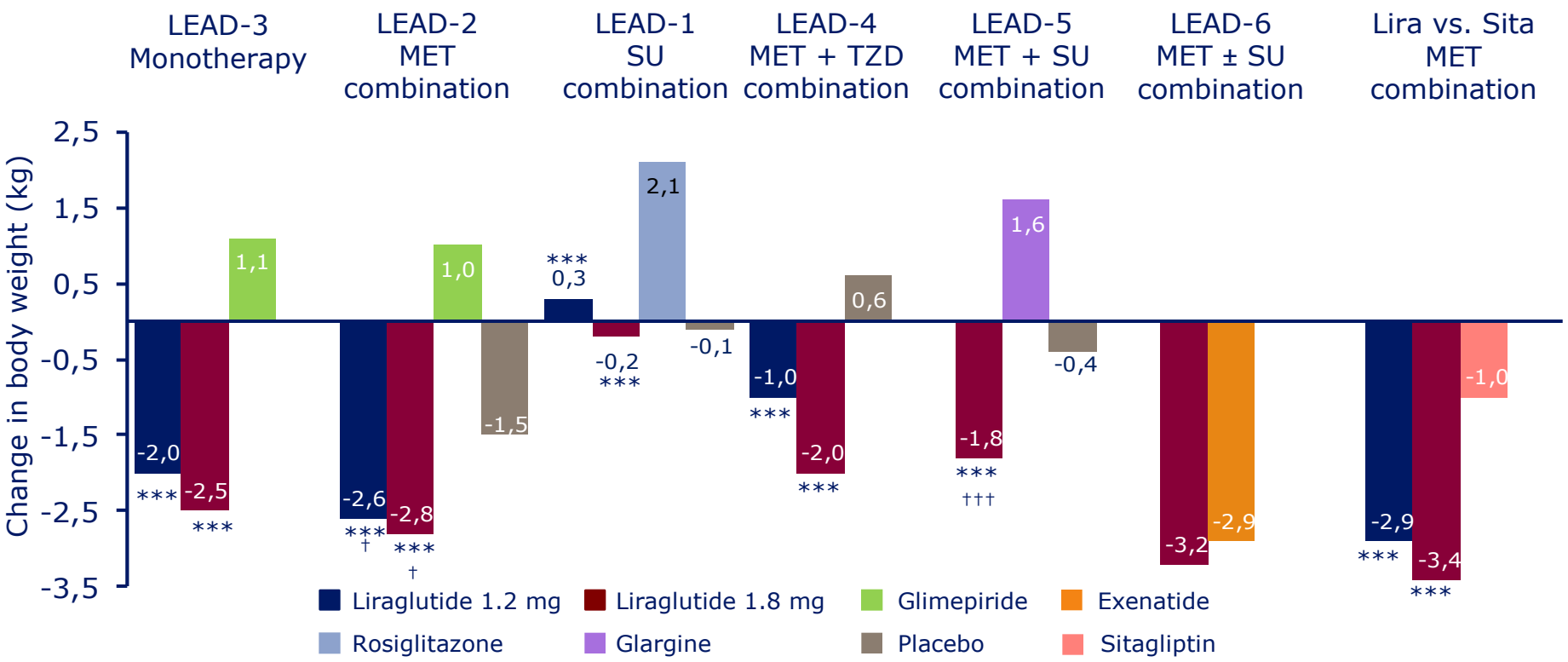
Programa LEAD: Efectos en HbA_{1c}



Significant *vs. comparator; change in HbA_{1c} from baseline for overall population (LEAD-4,-5); add-on to diet and exercise failure (LEAD-3); or add-on to previous oral anti-diabetic drug (OAD) monotherapy (LEAD-2,-1). HbA_{1c}, glycosylated haemoglobin; MET, metformin; Sita, sitagliptin; SU, sulphonylurea; TZD, thiazoladinedione.

Marre et al. *Diabet Med.* 2009;26;268–278 (LEAD-1); Nauck et al. *Diabetes Care.* 2009;32;84–90 (LEAD-2); Garber et al. *Lancet.* 2009;373:473–481 (LEAD-3); Zinman et al. *Diabetes Care.* 2009;32:1224–1230 (LEAD-4); Russell-Jones et al. *Diabetologia.* 2009;52:2046–2055 (LEAD-5); Buse et al. *Lancet.* 2009;374:39–47 (LEAD-6); Pratley et al. *Lancet.* 2010:375;1447–1456 (lira vs. sita).

Programa LEAD: Efectos en peso corporal



*p<0.01, ***p≤0.0001 vs. active comparator; †p≤0.01, †††p≤0.0001 vs. placebo. [Active comparators vs. placebo not shown.] Data from core trials.

Marre et al. *Diabet Med.* 2009;26;268–278 (LEAD-1); Nauck et al. *Diabetes Care.* 2009;32;84–90 (LEAD-2); Garber et al. *Lancet.* 2009;373:473–481 (LEAD-3); Zinman et al. *Diabetes Care.* 2009;32:1224–1230 (LEAD-4); Russell-Jones et al. *Diabetologia.* 2009;52:2046–2055 (LEAD-5); Buse et al. *Lancet.* 2009;374:39–47 (LEAD-6); Pratley et al. *Lancet.* 2010;375:1447–1456 (lira vs. sita).

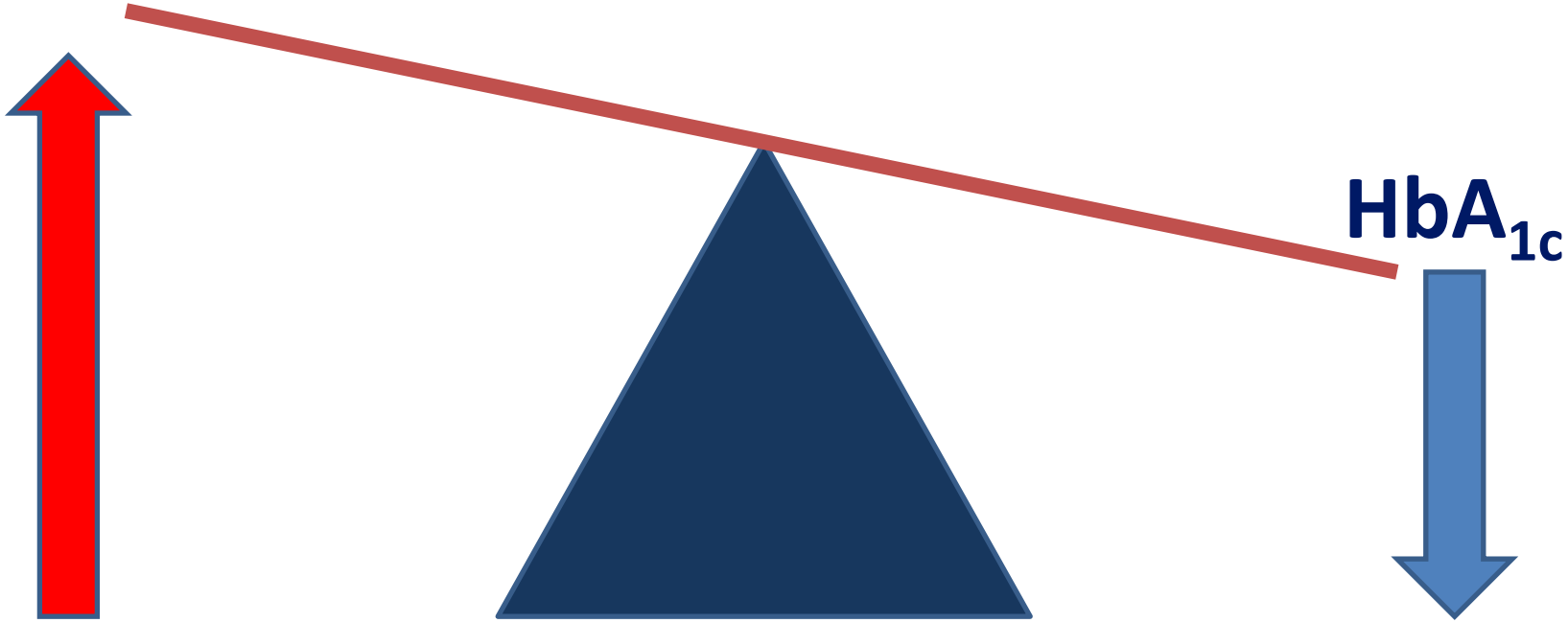
Eficacia y Tolerabilidad de Análogos de GLP-1

	LIRAGLUTIDA	EXENATIDE LAR	TASPOGLUTIDA	ALBIGLUTIDA	LY 2189265
Variación en Hb A1C (%)	−1.1 to −1.6	−1.9	−1.2	−0.9	−1.5
Variación de Peso (kg)	−0.2 to −3.2	−3.7	−2.8	−1.4	−2.5
Variación en PA Sistólica (mmHg)	−2.3 to −6.7	−4.7	No reportado	−5.8	−5.1
Náusea (%)	7–29	26.4	52	25.8	13
Vómito (%)	4.4–17	10.8	22	12.9	No reportado

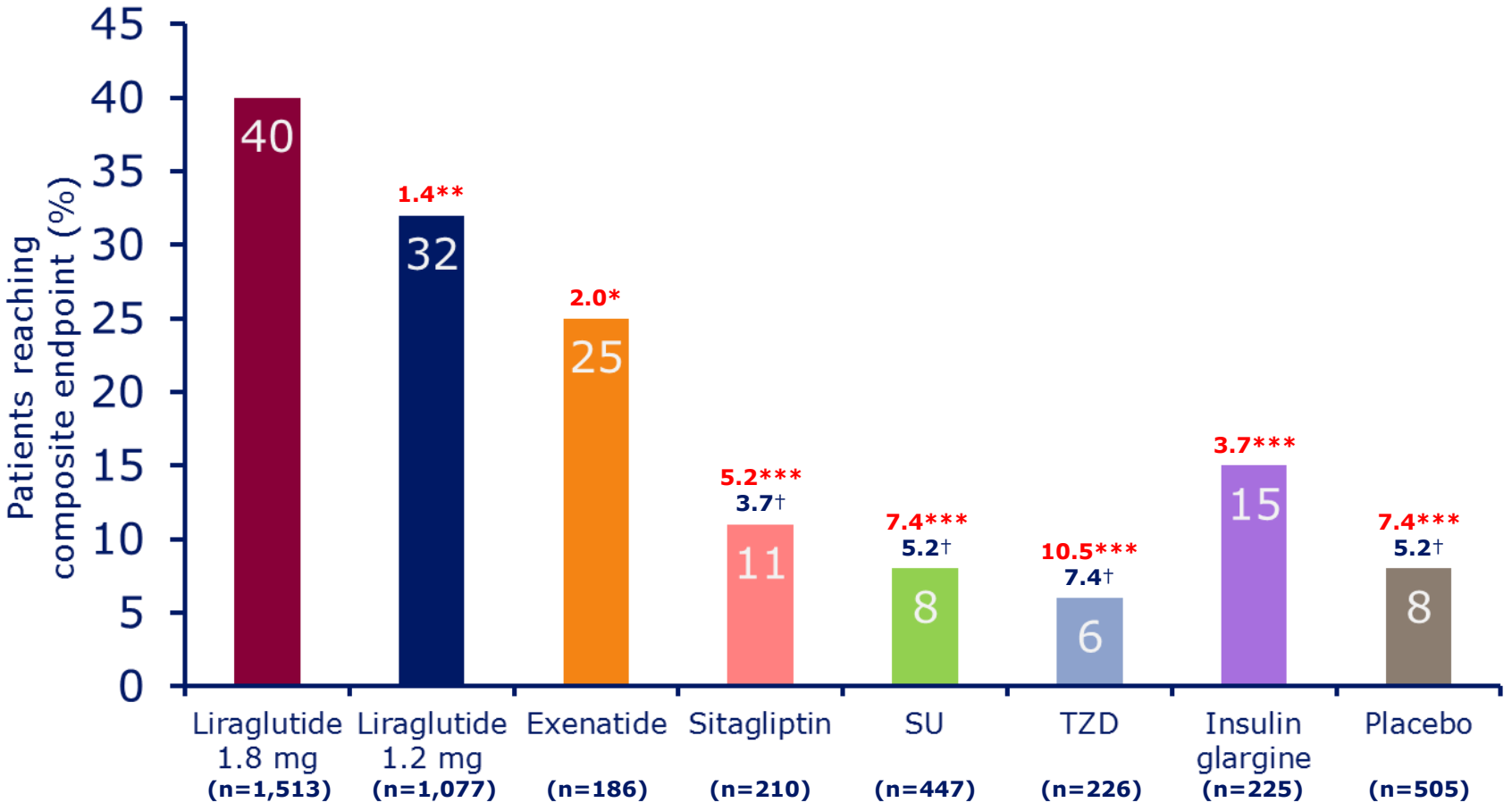
Garber Alan J. Diabetes Care May 2011 vol. 34 no. Supplement 2 S279-S284

El Reto en el Control de la Glucosa

Hipoglucemia/
Ganancia de Peso

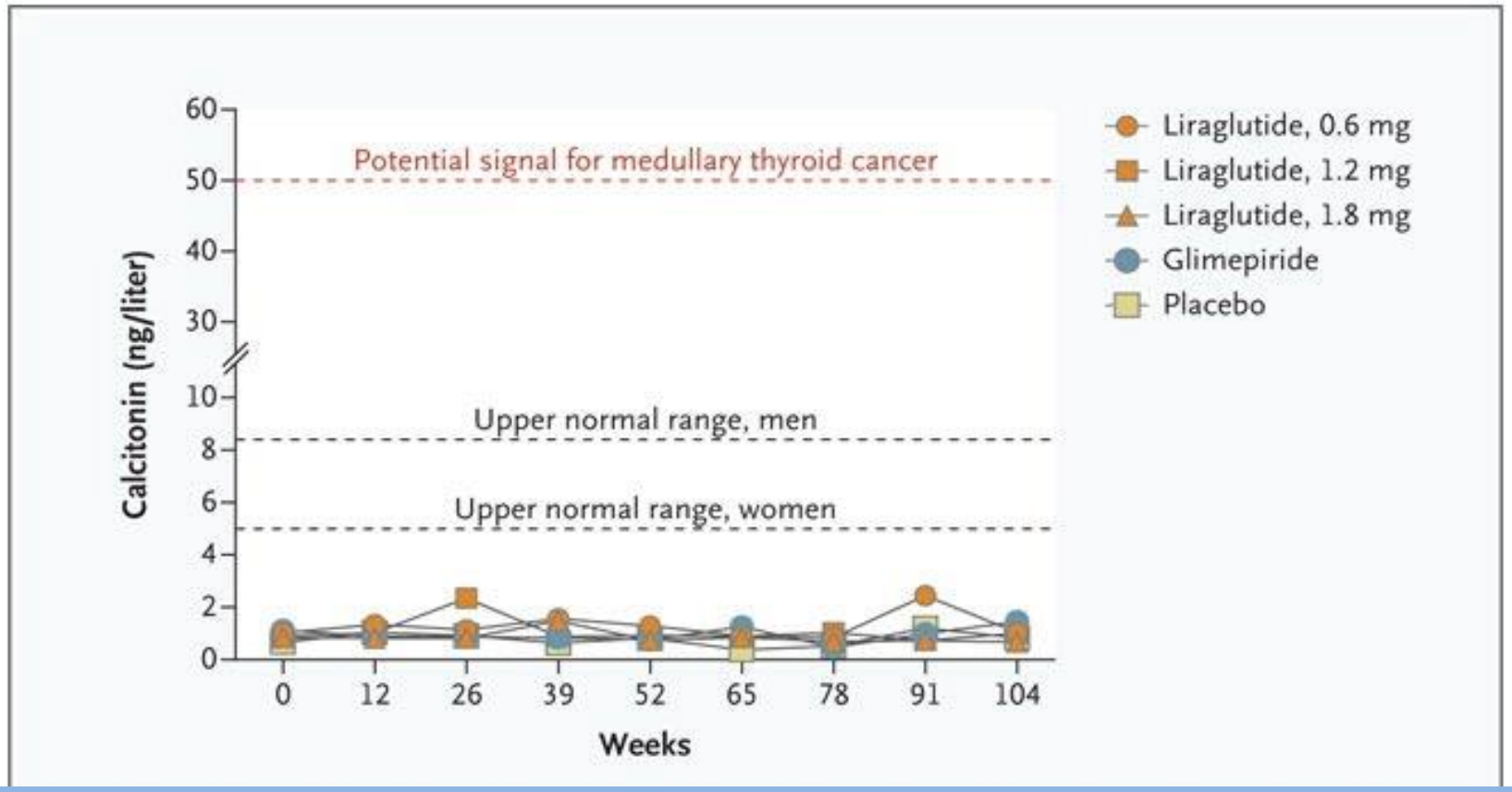


Variable Compuesta: HbA_{1c}<7.0%, sin ganancia de peso, sin hipoglicemia



HbA_{1c}, glycosylated haemoglobin; SU, sulphonylurea; TZD, thiazolidinedione.
Odds ratio of achieving composite endpoint with liraglutide 1.8 mg is superior, with *p<0.01; **p<0.001, ***p<0.0001.
Odds ratio of achieving composite endpoint with liraglutide 1.2 mg is superior, with †p<0.0001.
Zinman et al. *Diabetes Obes Metab.* 2012;14:77–82.

Riesgo de Carcinoma Medular de Tiroides



Promedio de Valores de Calcitonina en 1079 Pacientes en un Estudio de 2 años donde se agregó Liraglutide, Glimepiride o Placebo a personas con Terapia Inicial con Metformina

Parks M, Rosebraugh C. N Engl J Med 2010;362:774-777.

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Incretinas
Riesgo de Pancreatitis

- **Butler PC, Elashoff M, Elashoff R, Gale EA (2013) A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? Diabetes Care 36:2118–2125**

- **Nauck MA (2013) A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. Diabetes Care 36:2126–2132**
- **Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB (2013) Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med 173:534–539**
- **Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC (2011) Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology 141:150–156**
- **Egan AG, Blind E, Dunder K et al (2014) Pancreatic safety of incretin-based drugs—FDA and EMA assessment. N Engl J Med 370:794–797**
- **Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E (2014) Glucagon-like peptide-1 receptor agonists and pancreatitis: a meta-analysis of randomized clinical trials. Diabetes Res Clin Pract 102:269–275**
- **White WB, Cannon CP, Heller SR et al (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 369:1327–1335**
- **Scirica BM, Bhatt DL, Braunwald E et al (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369:1317–1326**
- **Meier JJ (2012) GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 8:728–742**
- **Pyke C, Heller RS, Kirk RK et al (2014) GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology 155:1280–1290**

La eficacia de los Análogos del Receptor de GLP-1 en el Tratamiento de Diabetes tipo 2 se refleja en:

- **Reducciones significativas de la HbA_{1c}**
- **Pérdida de peso significativa en la mayoría de los pacientes**
- **Bajo riesgo de Hipoglucemia**
- **Disminución leve en la Presión Arterial Sistólica**
- **Mejoraría modestamente el Perfil lipídico y Marcadores de riesgo cardiovascular**
- **Otros probables Efectos Pleiotrópicos**

Análogos de GLP-1 en el Tratamiento de la Diabetes