V Reunión de Diabetes y Obesidad

SEMI

LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

Novedades en Inhibidores de DPP-4

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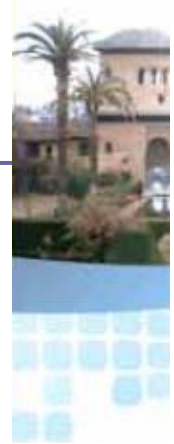
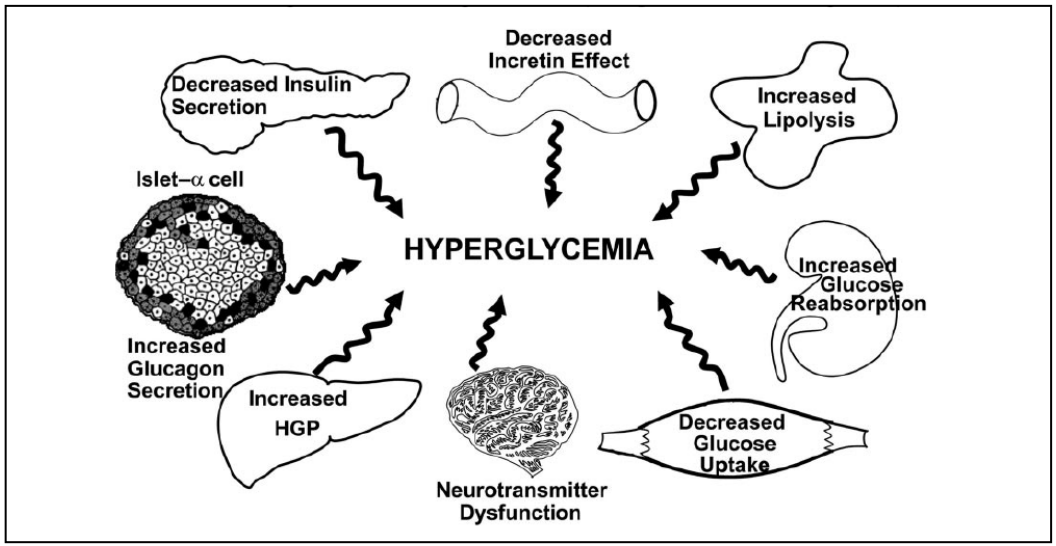
(Santa Cruz de Tenerife)

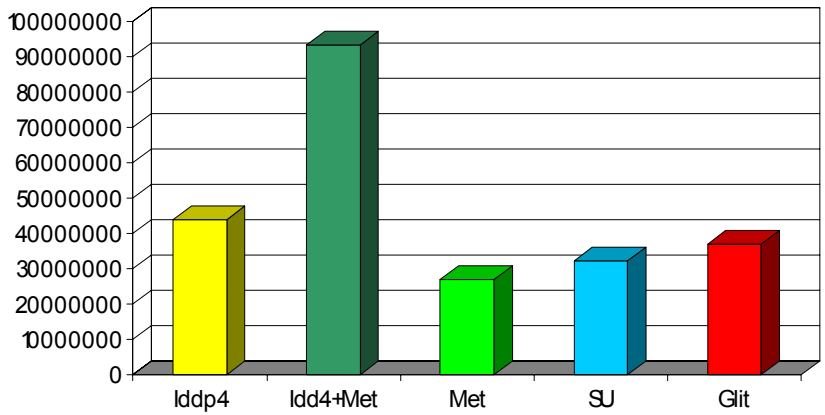
ada, 28 de enero de 2011

¿cómo evaluamos el éxito?





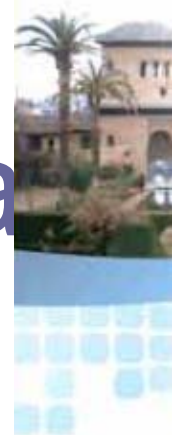
70th American Diabetes Association scientificsessions
JUNE 25-29, 2010 • ORLANDO, FL



Gasto €

Inhibidores de la DPP-4 (iDPP4)

Novedades en Fisiología



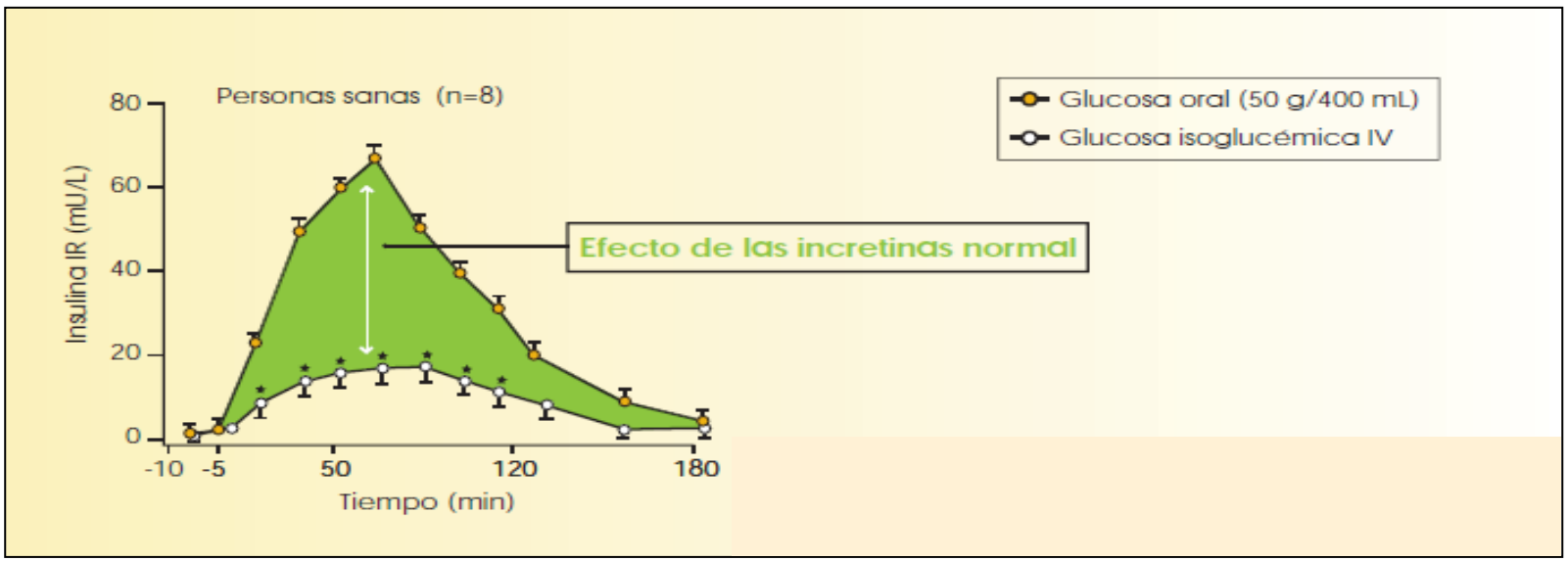
Homeostasis de la Glucosa

1. Glucemia en ayunas
2. Glucemia postprandial
   - Velocidad de vaciamiento gástrico
   - Efecto incretina

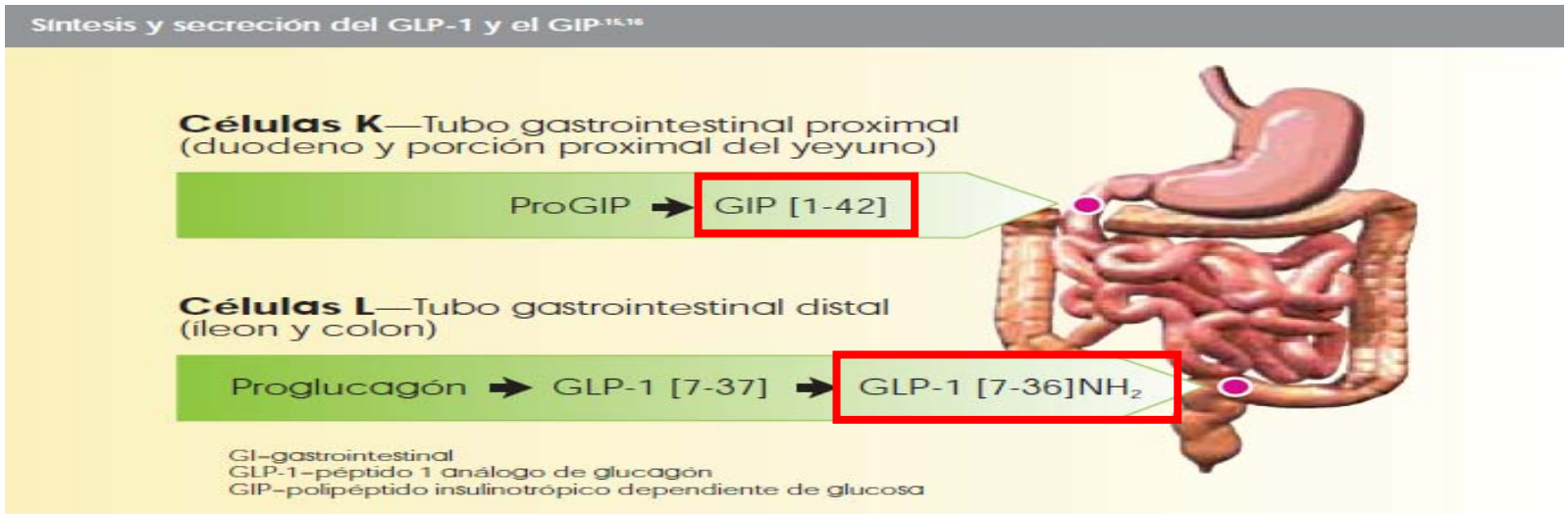
35%

rápido= ▲ glucemia

lento= ▼ glucemia



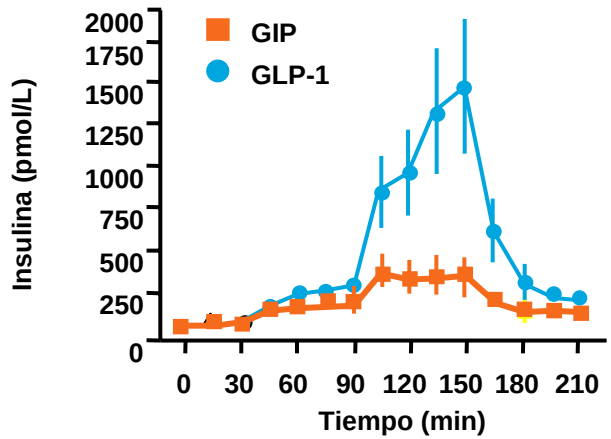
Efecto Incretina



- 65% de la respuesta insulínica postprandial
- Acción aditiva de GIP y GLP-1

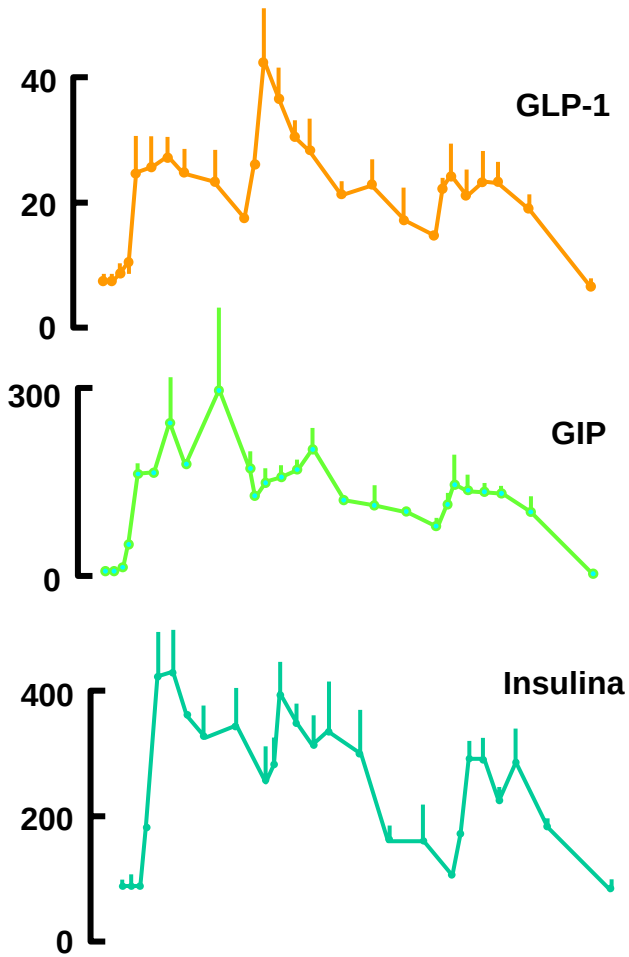
¿MÁS IMPORTANTE?

Localización de células K y L



Liberación de Incretinas

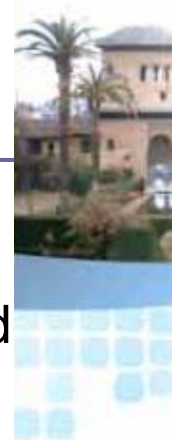
- En respuesta a la ingesta de carbohidratos digeribles y lípidos
- Acción
  - Inicio de secreción: 10-15 min.
  - Pico
    - GIP: 150-300 pmol / L
    - GLP-1: 25-40 pmol / l
  - Duración de acción 180 min.
- Efectos
  - GIP: INSULINOTRÓPICO
  - GLP-1
    - INSULINOTRÓPICO
    - Disminuye secreción de glucagón
    - Retrasa vaciamiento gástrico
    - Inhibe el apetito
- Rápida inactivación por DPP-4



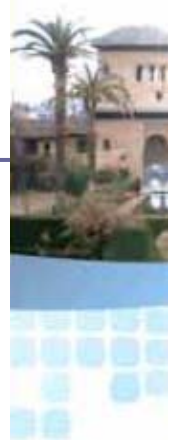
DPP-4 (Antígeno CD26 células T)

- Glicoproteína de membrana ampliamente representada e implicada en un gran número de procesos fisiológicos

- Localización: células endoteliales y epiteliales del lecho vascular, riñón, intestino, páncreas endocrino, tracto gastrointestinal, sistema biliar, timo, ganglios linfáticos, útero, placenta, próstata, miocardio, cerebro, glándulas suprarrenales, sudoríparas, salivares y mamarias



- Acción
  - Separación del extremo N-Terminal de diferentes oligopéptid inactivándolos
- Sustratos
  - Familia del Glucagón (GLP-1 y GIP)
  - Familia del Polipéptido Pancreático (Neuropéptido Y y Péptido YY)
  - Citokinas
  - RANTES (regulated on activation, normal T cell expressed and secreted)
  - Sustancia P



INGESTA

Liberación intestinal de GIP

Liberación intestinal De GLP-1

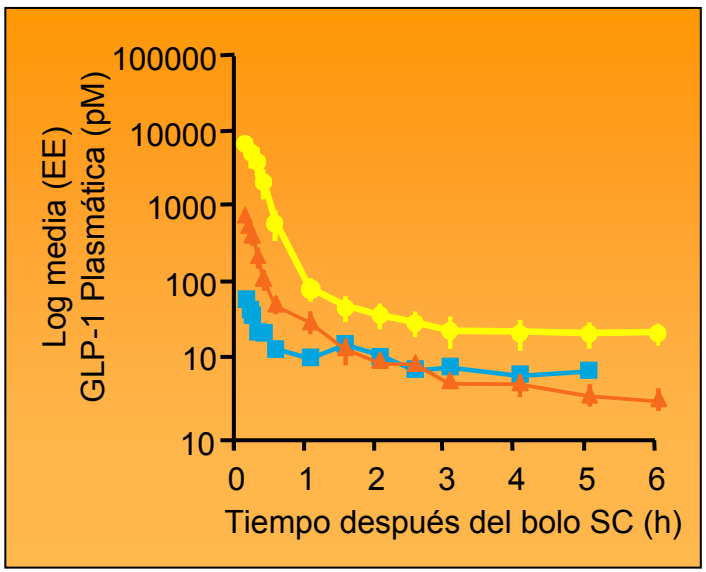
GIP (1-42) Activo

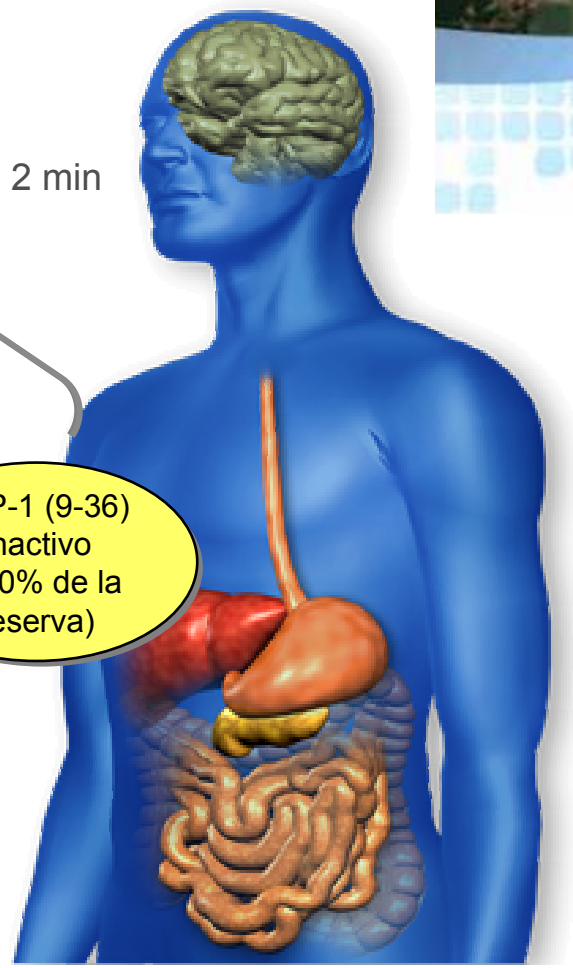
GLP-1 (7-36) Activo

$t_{1/2}$ = 1 a 2 min

DPP-4

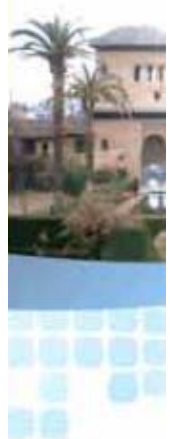
GLP-1 (9-36) Inactivo (> 80% de la reserva)



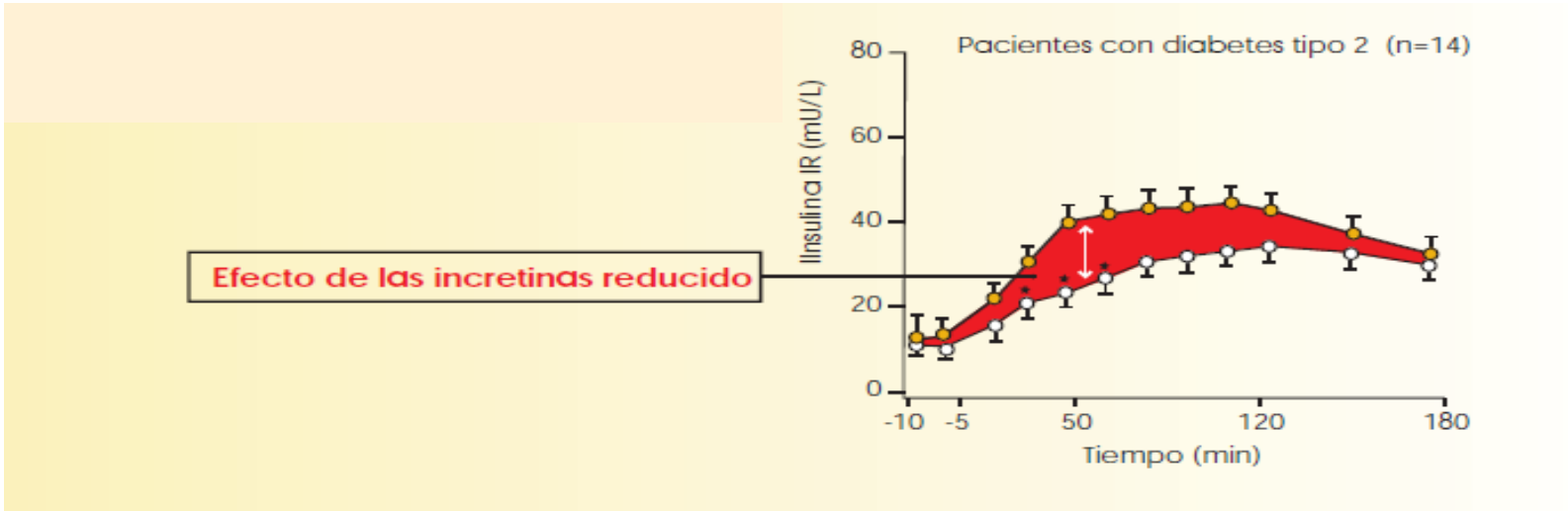


Drucker DJ. Diabetes Care 2003;26:2929–2940.

Novedades en Fisiopatología



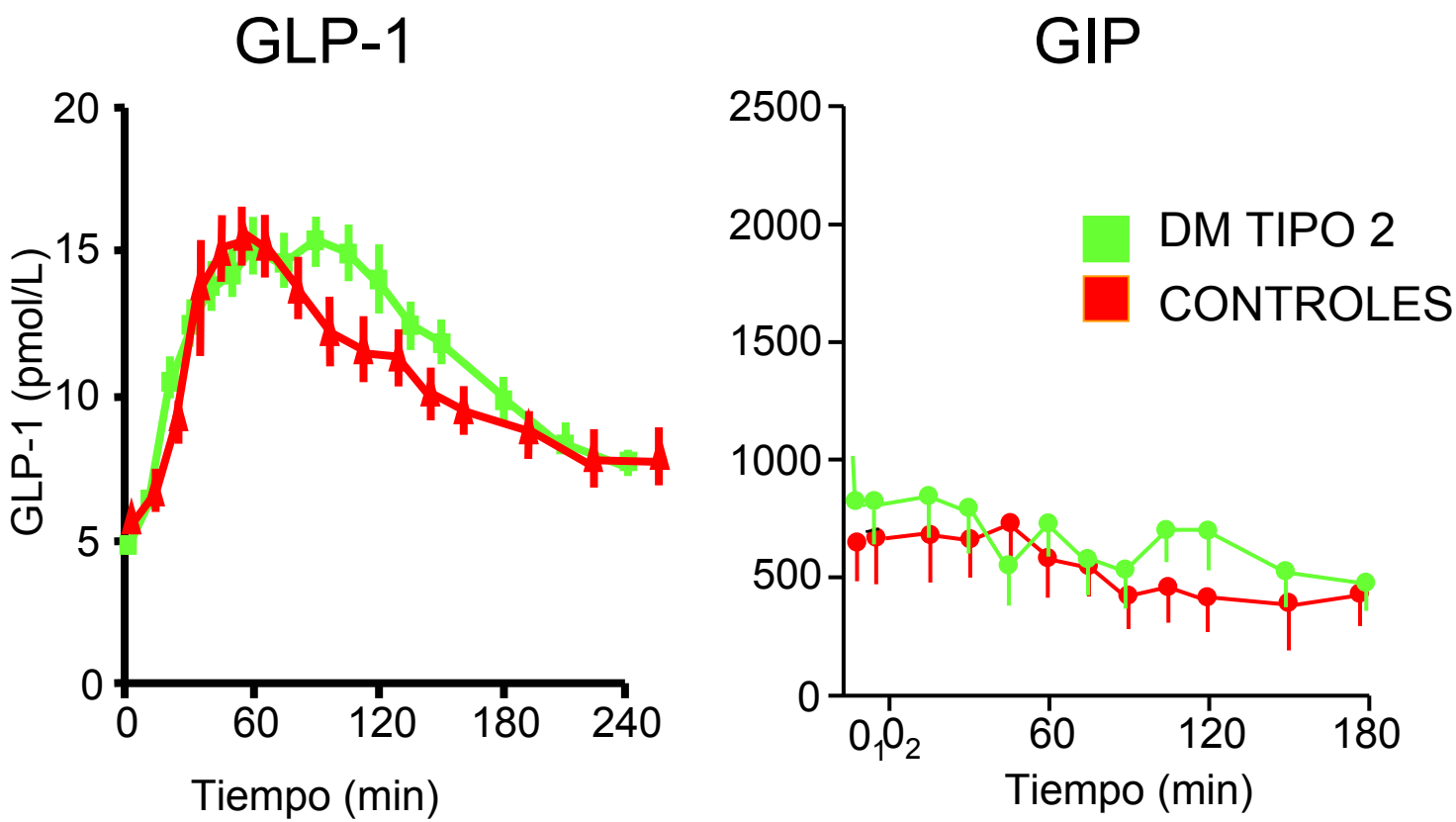
Incretinas en la Diabetes tipo 2



- El efecto Incretina está reducido en la diabetes 2
- No está reducido en situaciones de riesgo de diabetes
- Está reducido en todos los tipos de diabetes

J.J. Meier / Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 433–441

Incretinas en la Diabetes tipo 2



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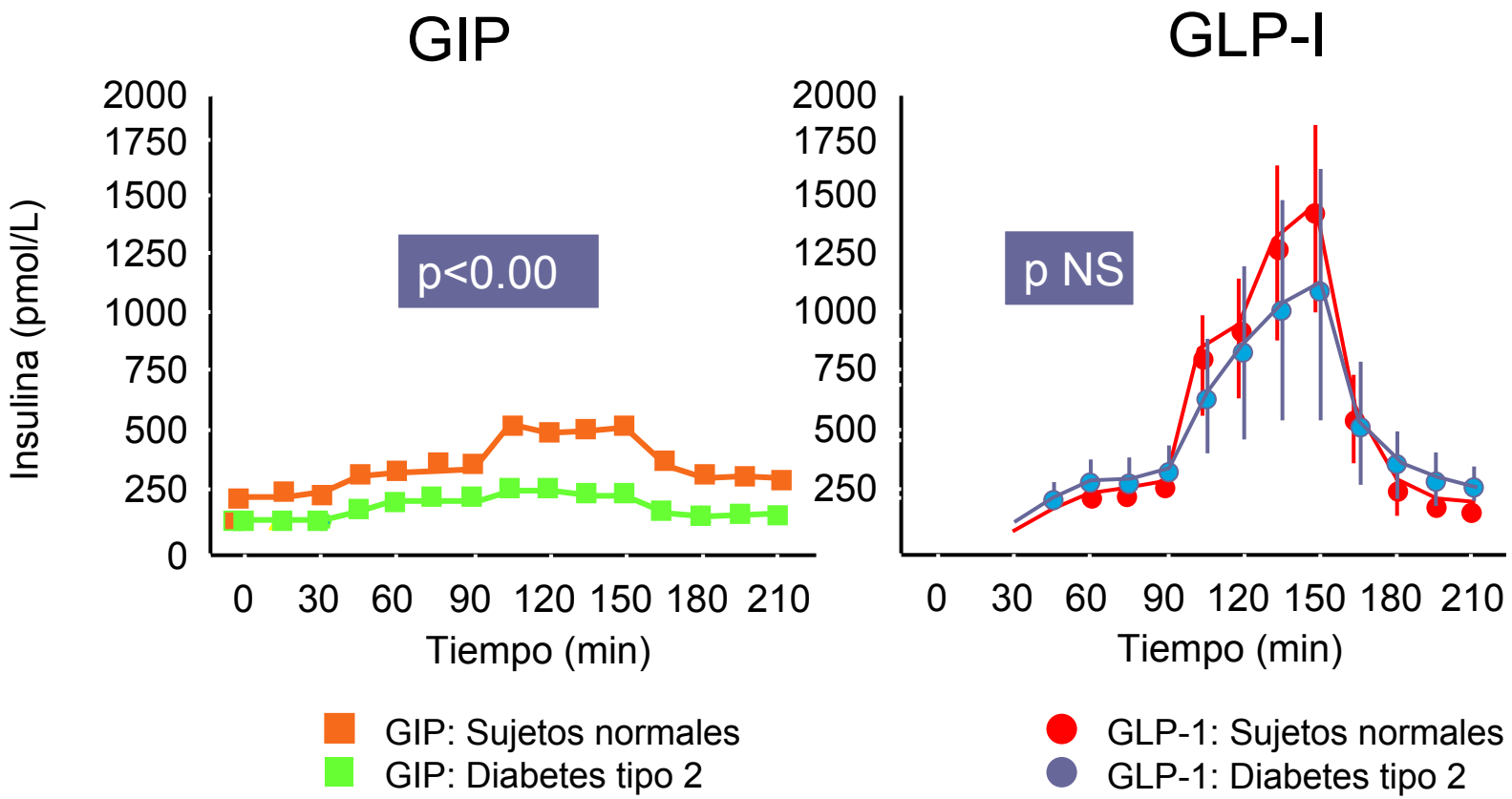

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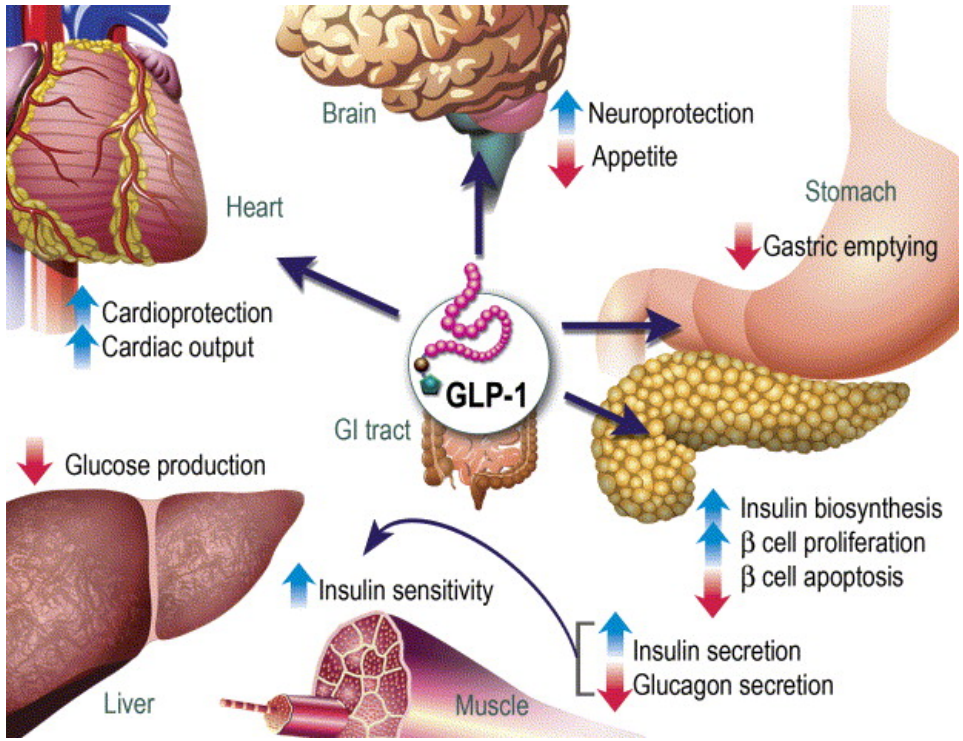
Incretinas en la Diabetes tipo 2

- GIP
  - Niveles no disminuidos
  - Acción insulinotrópica reducida
- GLP-1
  - Niveles no disminuidos
  - Acción insulinotrópica conservada

ALTERACIÓN FUNDAMENTAL EN LA DIABETES TIPO 2
ACCIÓN INSULINOTRÓPICA DE GIP

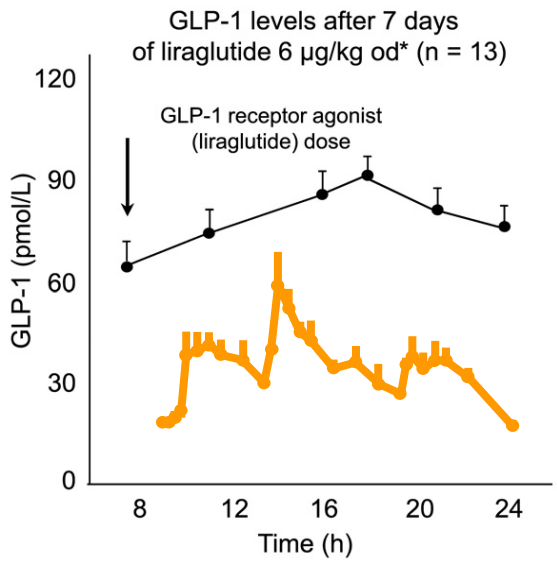
Efectos de GLP-1 en la diabetes tipo 2

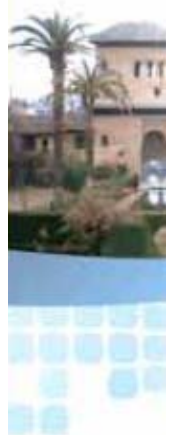


MEJORA

Control glucémico
Función célula β
Peso
FRCV

INFUSIÓN I. V.
Dosis +++ fisiológicas





Novedades en Inhibidores de DPP-4

1. Eficacia
2. Mecanismo de Acción
3. Seguridad

Eficacia (1)

A Meta-Analysis of Placebo-Controlled Clinical Trials Assessing the Efficacy and Safety of Incretin-Based Medications in Patients with Type 2 Diabetes

Walid K.H. Fakhoury Corinne LeReun Donna Wright

Pharmacology 2010;86:44–57
DOI: 10.1159/000314690

Dipeptydil peptidase-4 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials

M. Monami*, I. Iacomelli, N. Marchionni, E. Mannucci

Nutrition, Metabolism & Cardiovascular Diseases (2010) 20, 224–235

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

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JAMA, April 14, 2010—Vol 303, No. 14 (Reprinted)

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IMS Health, London, UK

Pharmacology 2010;86:44–57
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Articles included in the review (n = 38)
- –Exenatide = 8
- –Liraglutide = 7
- –Sitagliptin = 12
- –Vildagliptin = 11

Table 2. Unadjusted results of HbA_{1c} comparing each study treatment with placebo

Change from baseline in HbA_{1c} levels: metaregression	Number of RCTs	WMD	95% CI	p value
Exenatide	8	–0.75	–0.83 to –0.67	<0.001
Liraglutide	7	–1.03	–1.16 to –0.90	<0.001

RCT = Randomized controlled trial.

Table 3. Unadjusted results of weight comparing each study treatment with placebo

Metaregression	WMD	95% CI	p value
Exenatide	–1.10	–1.32 to –0.88	<0.001
Liraglutide	–0.82	–1.92 to 0.27	0.142

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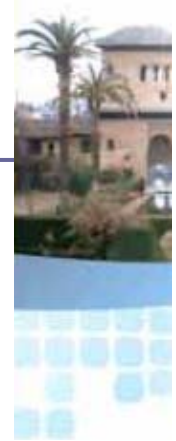

TOTAL n=41

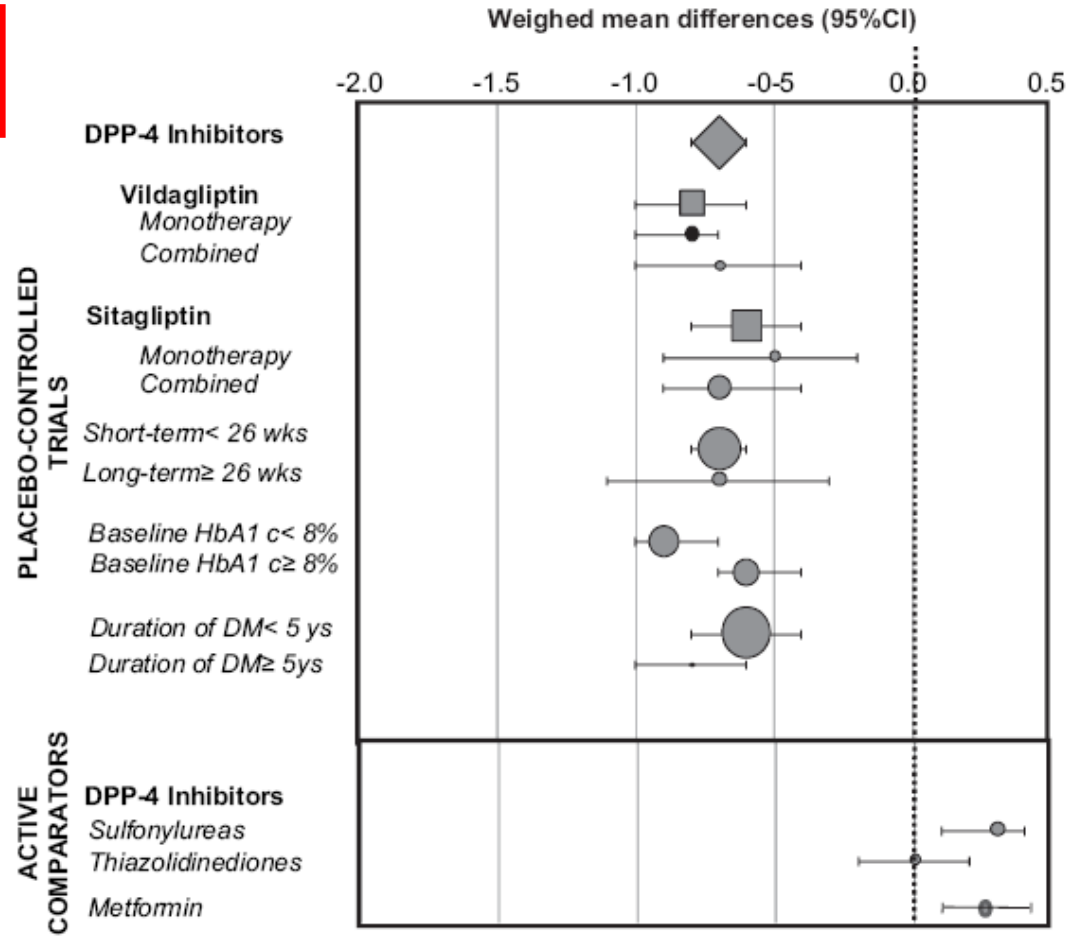

Figure 2 Standardized differences (with 95% CI) of mean HbA1c at endpoint.

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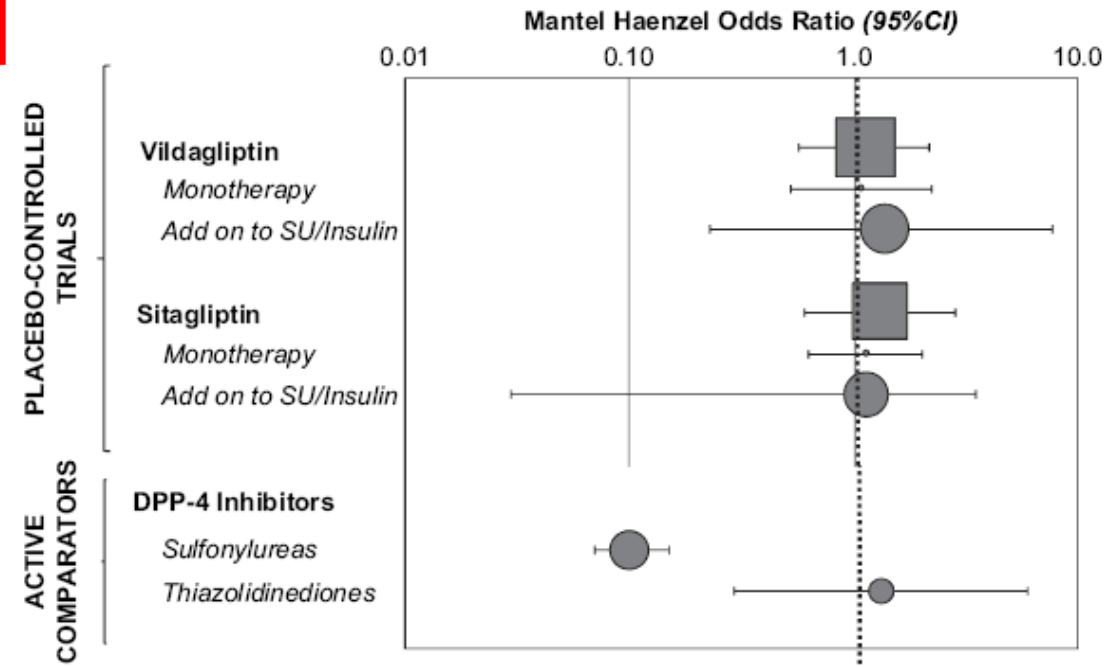

Figure 3 Mantel–Haenszel odds ratio (with 95% CI) for any hypoglycemia (logarithmic scale).

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

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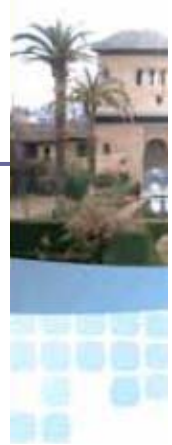
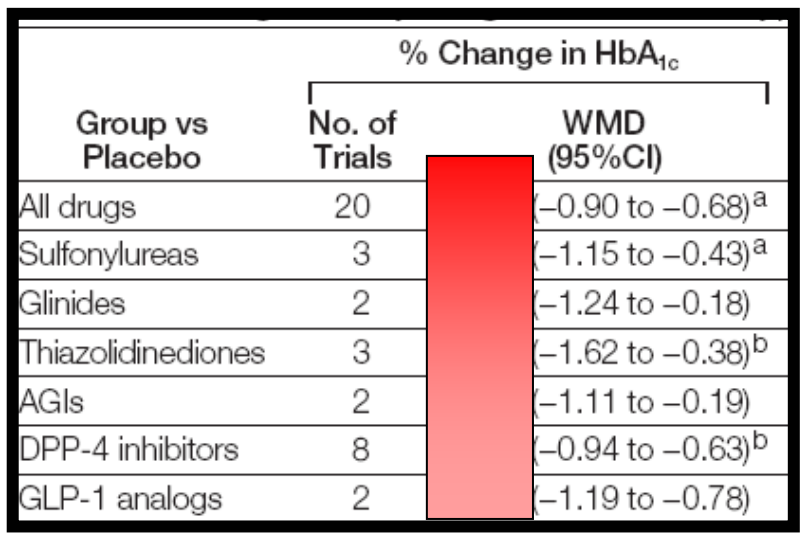


27 Articles included in meta-analysis

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

	% Change in HbA_{1c}		HbA_{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
Group vs Placebo	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)	No. of Trials	WMD (95%CI)	No. of Trials	RR (95%CI)
All drugs	20	−0.79 (−0.90 to −0.68)[a]	10	2.56 (1.99 to 3.28)[b]	12	0.14 (−1.37 to 1.65)[a]	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	−0.79 (−1.15 to −0.43)[a]	1	3.38 (2.02 to 5.83)	2	1.99 (0.86 to 3.12)	3	2.63 (0.76 to 9.13)[a]
Glinides	2	−0.71 (−1.24 to −0.18)	1	3.20 (1.47 to 7.58)	2	0.91 (0.35 to 1.46)	2	7.02 (1.45 to 43.21)
Thiazolidinediones	3	−1.00 (−1.62 to −0.38)[b]	1	1.69 (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	−0.65 (−1.11 to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.79 (−0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.99 (−1.19 to −0.78)	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.
[a] $I^2 \geq 75\%$.
[b] $I^2 = 50\%$-75%.



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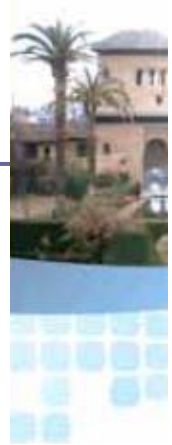

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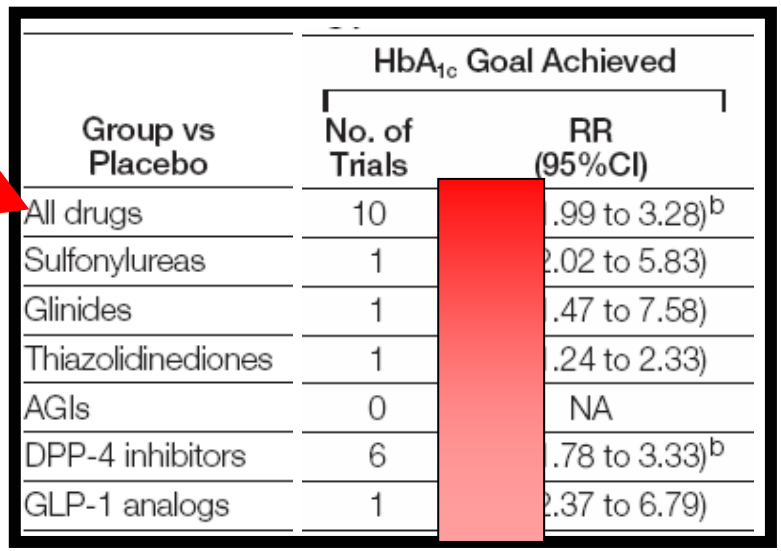

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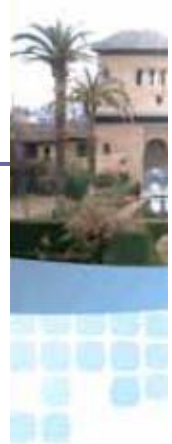

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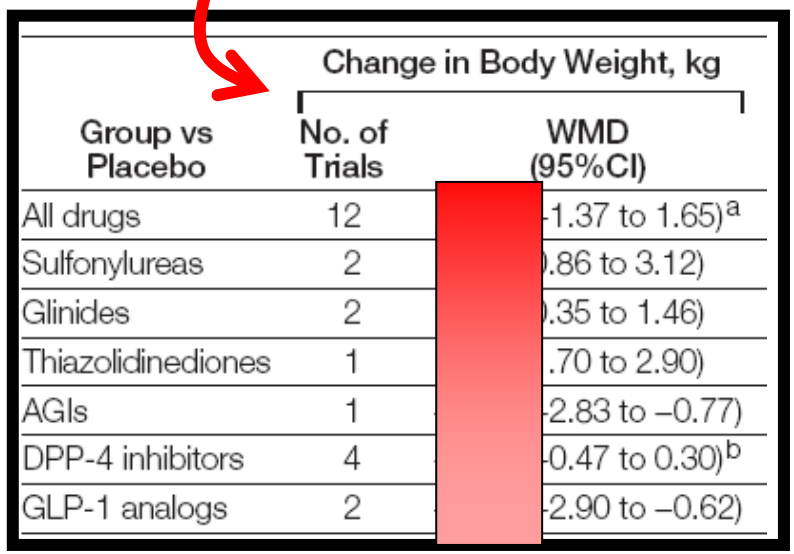
AGIs	2	−0.65 (−1.11 to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.70 (−0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.90 (−1.19 to −0.78)	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.
[a] $I^2 \geq 75\%$.
[b] $I^2 = 50\%$-75%.

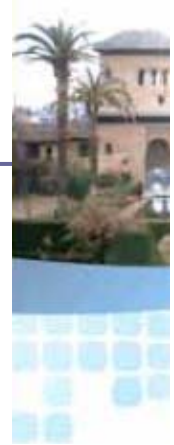


Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes

Olivia J. Phung, PharmD
Jennifer M. Scholle, PharmD
Mehak Talwar, BS
Craig I. Coleman, PharmD

JAMA, April 14, 2010—Vol 303, No. 14 (Reprinted)

SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA



27 Articles included in meta-analysis

Table 2. Results of Traditional Meta-analysis Comparing Noninsulin Antidiabetic Drugs With Placebo on Change in HbA_{1c}, HbA_{1c} Goal Achieved, Change in Body Weight, and Overall Hypoglycemia

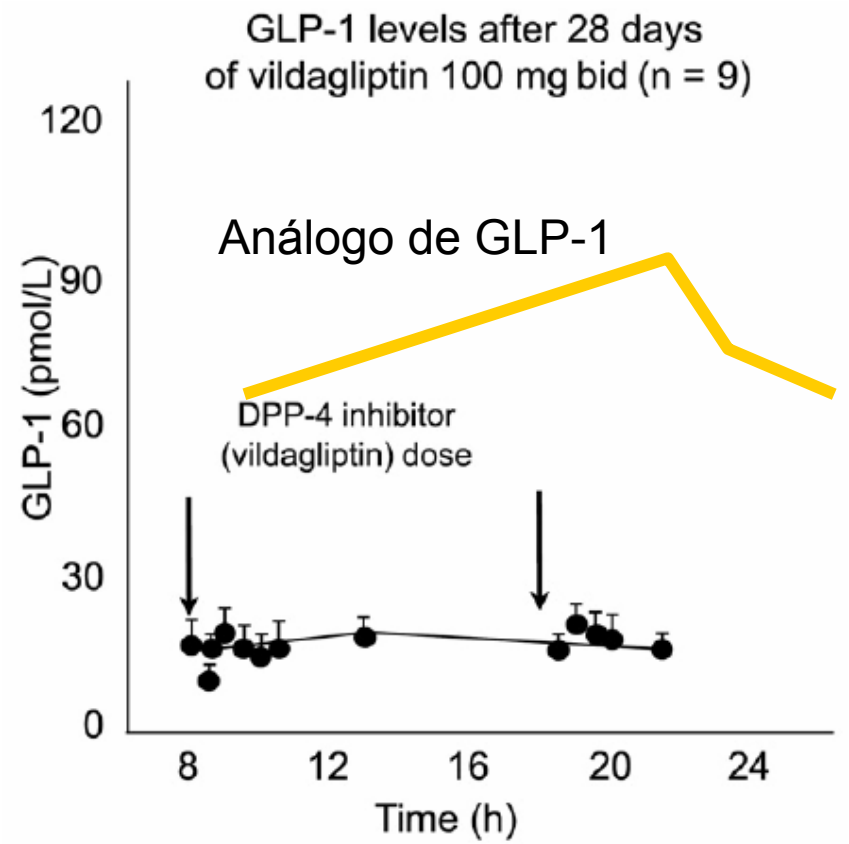
	% Change in HbA_{1c}		HbA_{1c} Goal Achieved		Change in Body Weight, kg		Overall Hypoglycemia	
Group vs Placebo	No. of Trials	WMD (95% CI)	No. of Trials	RR (95% CI)	No. of Trials	WMD (95% CI)	No. of Trials	RR (95% CI)
All drugs	20	−0.70 (−0.90 to −0.69)[a]	10	2.56 (1.99 to 3.28)[b]	12	0.14 (−1.37 to 1.65)[a]	19	1.43 (0.89 to 2.30)
Sulfonylureas	3	−0.70 (−1.15 to −0.43)[a]	1	3.38 (2.02 to 5.83)	2	1.00 (0.86 to 3.12)	3	2.63 (0.76 to 9.13)[a]
Glinides	2	−0.71 (−1.24 to −0.18)	1	3.20 (1.47 to 7.58)	2	0.01 (0.35 to 1.46)	2	7.02 (1.45 to 43.21)
Thiazolidinediones	3	−1.00 (−1.62 to −0.38)[b]	1	1.69 (1.24 to 2.33)	1	2.30 (1.70 to 2.90)	2	2.04 (0.50 to 8.23)
AGIs	2	−0.65 (−1.11 to −0.19)	0	NA	1	−1.80 (−2.83 to −0.77)	2	0.60 (0.08 to 4.55)
DPP-4 inhibitors	8	−0.70 (−0.94 to −0.63)[b]	6	2.44 (1.78 to 3.33)[b]	4	−0.09 (−0.47 to 0.30)[b]	8	0.67 (0.30 to 1.50)
GLP-1 analogs	2	−0.90 (−1.19 to −0.78)	1	3.96 (2.37 to 6.79)	2	−1.76 (−2.90 to −0.62)	2	0.94 (0.42 to 2.12)

Abbreviations: AGIs, α-glucosidase inhibitors; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; NA, not applicable; RR, relative risk; WMD, weighted mean difference.
[a] $I^2 \geq 75\%$.
[b] $I^2 = 50\%$-75%.

Group vs Placebo	Overall Hypoglycemia No. of Trials	RR (95% CI)
All drugs	19	.89 to 2.30)
Sulfonylureas	3	.76 to 9.13)[a]
Glinides	2	.45 to 43.21)
Thiazolidinediones	2	.50 to 8.23)
AGIs	2	.08 to 4.55)
DPP-4 inhibitors	8	.30 to 1.50)
GLP-1 analogs	2	.42 to 2.12)

Mecanismo de acción (2)

- Previenen la inactivación de las incretinas



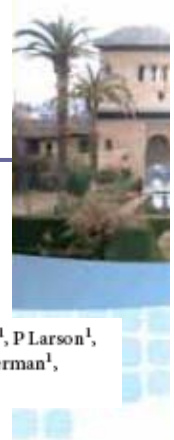
Dudas razonables

1. Incremento de GLP-1 activo ¿total?
2. Elevación poco significativa de GLP-1
3. Acción no totalmente específica

Teorías sobre el mecanismo de acción

- Efectos beneficiosos sobre la glucemia
  - Receptores de GLP-1 en SN parasimpático intestinal
  - Sensores de GLP-1 en sistema portal hepático
  - Acción de otras incretinas y neuropéptidos regulados por la DPP-4 (PACAP hipofisario)
  - Mejoría en la funcionalidad de la célula β
- Efecto neutro sobre el peso
  - Inactivación del Neuropéptido Y
- Ausencia de efecto sobre apetito y vaciamiento gástrico
  - Dosis dependiente

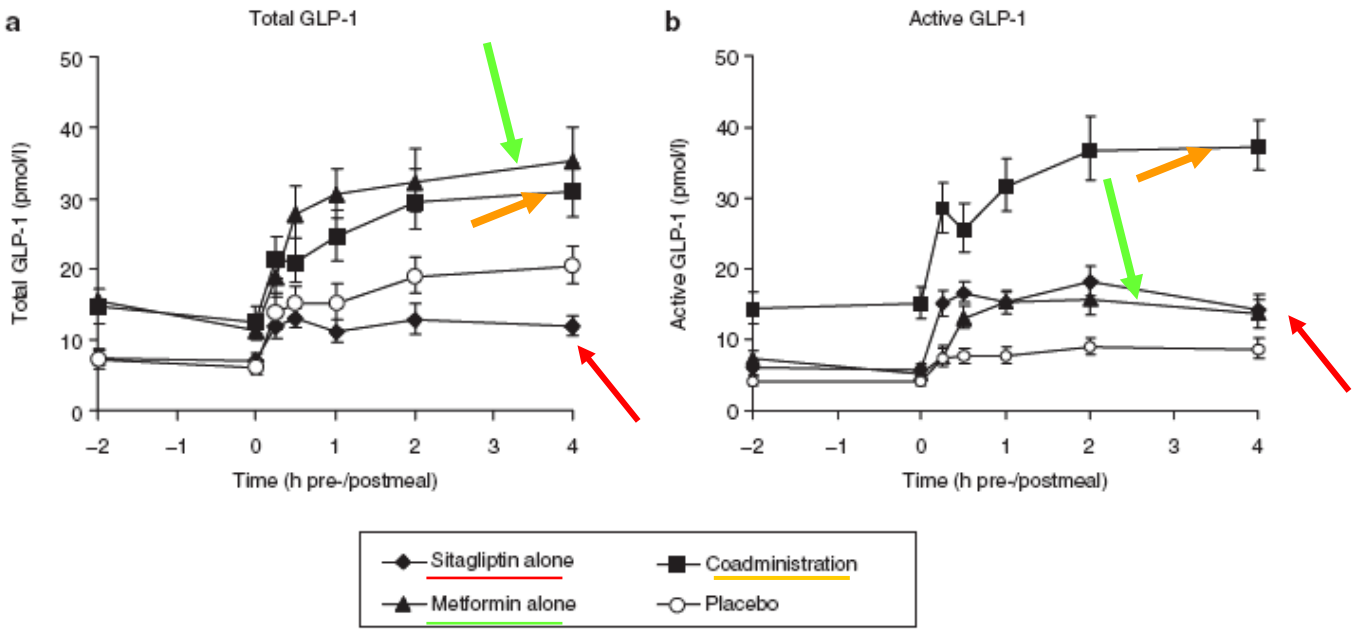
Acción sinérgica con METFORMINA



Dipeptidyl Peptidase-4 Inhibitors Administered in Combination With Metformin Result in an Additive Increase in the Plasma Concentration of Active GLP-1

EM Migoya[1], R Bergeron[2], JL Miller[1], RNK Snyder[1], M Tanen[1], D Hilliard[1], B Weiss[1], P Larson[1], M Gutierrez[3], G Jiang[1], F Liu[1], KA Pryor[1], J Yao[1], L Zhu[1], JJ Holst[4], C Deacon[4], G Herman[1], N Thornberry[1], J Amatruda[1], D Williams-Herman[1], JA Wagner[1] and R SinhaRoy[1]

Received 26 April 2010; accepted 30 June 2010; advance online publication 3 November 2010. doi:10.1038/clpt.2010.184



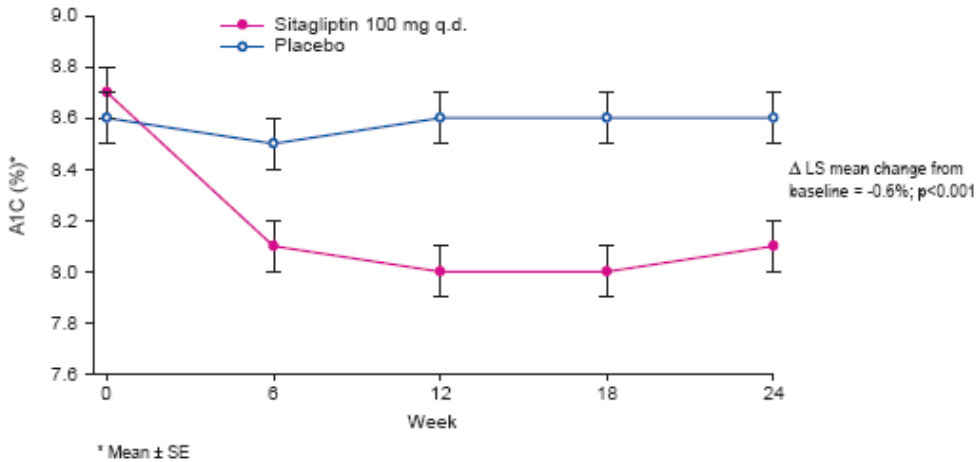
Acción aditiva con INSULINA

Sitagliptin, a Selective DPP-4 Inhibitor, Improves Glycemic Control when Added to Insulin, with or without Metformin, in Patients with Type 2 Diabetes

Tina Vilsbøll,[1] Julio Rosenstock,[2] Hannele Yki-Järvinen,[3] William T. Cefalu,[4] Yu Chen,[5] Edmund Luo,[5] Yan Ling,[5] Keith D. Kaufman,[5] John M. Amatruda,[5] Samuel S. Engel,[5] Leonid Katz[5]

[1]Gentofte Hospital, University of Copenhagen, Department of Internal Medicine F, Copenhagen, Denmark; [2]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX; [3]University of Helsinki, HUCH, Helsinki, Finland; [4]Louisiana State University, Pennington Biomedical Research Center, Baton Rouge, LA; [5]Merck Research Laboratories, Rahway, NJ

Figure 3. A1C over time



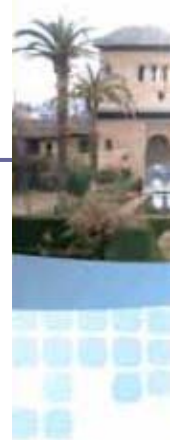
- When assessed by insulin stratum (long-acting, intermediate-acting or premixed) or metformin stratum, the A1C responses were similar to that observed for the entire cohort.
- The proportion of patients with an A1C <7% at Week 24 was significantly higher in the sitagliptin group compared to the placebo group (13% vs. 5%).

Summary

When added to stable-dose insulin therapy,

- Sitagliptin significantly reduced A1C, FPG, and postmeal glucose compared with placebo after 24 weeks.
- More patients achieved an A1C <7% with sitagliptin.
- The incidence of hypoglycemia was significantly increased with sitagliptin, with similar incidences of hypoglycemic episodes considered severe.
- No increase from baseline in body weight was observed in either treatment group.

Efectos no glucémicos



DPP-4 Inhibition by Sitagliptin Improves the Myocardial Response to Dobutamine Stress and Mitigates Stunning in a Pilot Study of Patients With Coronary Artery Disease

Philip A. Read, MA, MRCP; Fakhar Z. Khan, MA, MRCP; Patrick M. Heck, MB, MRCP; Stephen P. Hoole, MB, MRCP; David P. Dutka, DM, FRCP

(*Circ Cardiovasc Imaging*. 2010;3:195-201.)

Más efectos No glucémicos

Efecto en ancianos

Treatment of Elderly Patients With Type 2 Diabetes Mellitus: A Systematic Review of the Benefits and Risks of Dipeptidyl Peptidase-4 Inhibitors

Published online October 20, 2010.

Sherwyn L. Schwartz, MD

Seguridad (3)

Dipeptydil peptidase-4 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials

M. Monami*, I. Iacomelli, N. Marchionni, E. Mannucci

Table 5 Selected adverse events during treatment with DPP-4 inhibitors.

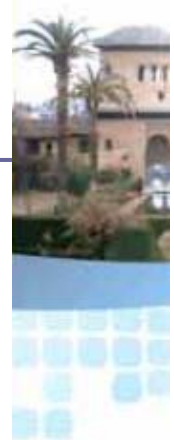
Adverse event	# Cases/# Patients		# Trials[a]	MH-OR [95% CI]	*p*
	ID	C			
Nausea					
DPP-4 Inhibitors	153/5795	119/3906	21	0.77 [0.57; 1.04]	0.09
Vomiting					
DPP-4 Inhibitors	47/4575	44/3119	14	0.73 [0.48; 1.12]	0.15
Diarrhea					
DPP-4 Inhibitors	249/6318	227	22	0.80 [0.56; 1.15]	0.23
Nasopharyngitis					
DPP-4 Inhibitors	566/7589	282/4132	27	1.04 [0.60; 1.68]	0.59
Urinary infections					
DPP-4 Inhibitors	104/2938	43/1904	10	1.36 [0.94; 1.97]	0.10
Upper respiratory infections					
DPP-4 Inhibitors	302/4902	173/3229	18	0.91 [0.74; 1.12]	0.40
Other infections					
DPP-4 Inhibitors	178/3059	118/1538	13	0.70 [0.55; 0.90]	0.005

RESEARCH ARTICLE Open Access

Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes

Debora Williams-Herman*, Samuel S Engel, Elizabeth Round, Jeremy Johnson, Gregory T Golm, Hua Guo, Bret J Musser, Michael J Davies, Keith D Kaufman and Barry J Goldstein

Williams-Herman *et al. BMC Endocrine Disorders* 2010, **10**:7
http://www.biomedcentral.com/1472-6823/10/7

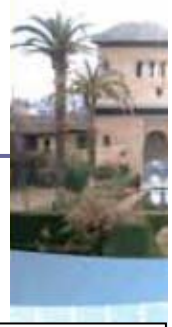


Infections and infestations SOC			
Bronchitis	4.2	3.8	0.4 (-0.4, 1.3)
Cellulitis	0.8	1.0	-0.2 (-0.6, 0.2)
Gastroenteritis	2.0	1.9	0.1 (-0.5, 0.7)
Gastroenteritis Viral	1.0	1.0	0.0 (-0.4, 0.5)
Influenza	4.5	5.2	-0.7 (-1.7, 0.2)
Nasopharyngitis	7.7	7.0	0.9 (-0.3, 2.1)
Pharyngitis	1.5	1.4	0.1 (-0.4, 0.6)
Sinusitis	2.7	2.7	0.1 (-0.6, 0.8)
Upper respiratory tract infection	8.6	9.0	-0.3 (-1.6, 1.0)
Urinary tract infection	4.1	4.2	-0.2 (-1.1, 0.6)
Viral infection	1.1	0.9	0.2 (-0.2, 0.7)

Table 10: Any malignancy adverse events

Adverse Event	n/patient-years of exposure (Incidence Rate per 100 Patient-years†)		
	Sitagliptin 100 mg	Non-exposed	Difference between Sitagliptin and Non-exposed (95% CI)*
Any malignancy	46/4690 (1.0)	40/3930 (1.0)	-0.0 (-0.5, 0.4)

¿ y la temible pancreatitis?



Antonio Gonzalez-Perez, BPharm, MSc[1,2], Raymond G Schlienger, PhD, MPH[3] and
Luis A García Rodríguez, MD MSc[1]

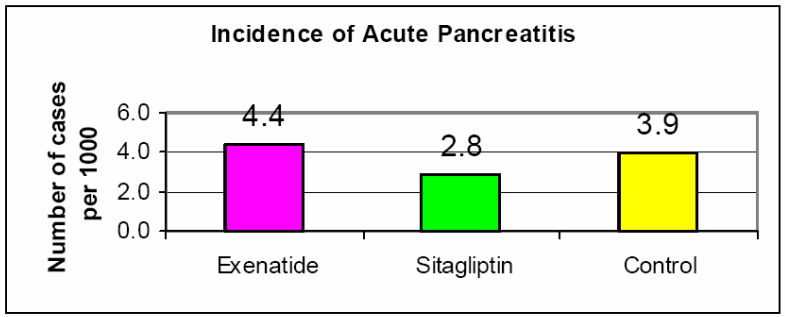


Table 3. Risk of acute pancreatitis and duration of current use of anti-diabetic drugs (nested case-control analysis)

	Cases (N=419)		Controls (N=5000)		OR**	95% CI
	n	%	n	%		
Insulin						
non use*	399	95.2%	4650	93.0%	1	(ref)
short-duration (<1 yr)	7	1.7%	82	1.6%	0.41	(0.17-1.00)
mid-duration (1-3 yrs)	5	1.2%	88	1.8%	0.34	(0.13-0.91)
long-duration (>3 yrs)	7	1.7%	158	3.2%	0.30	(0.13-0.68)
Metformin						
non use*	328	78.3%	4261	85.2%	1	(ref)
short-duration (<1 yr)	26	6.2%	213	4.3%	0.88	(0.53-1.47)
mid-duration (1-3 yrs)	31	7.4%	237	4.7%	0.93	(0.58-1.49)
long-duration (>3 yrs)	18	4.3%	205	4.1%	0.50	(0.28-0.91)
Sulphonylureas						
non use*	334	79.7%	4460	89.2%	1	(ref)
short-duration (<1yr)	13	3.1%	125	2.5%	0.81	(0.42-1.57)
mid-duration (1-3yrs)	25	6.0%	156	3.1%	1.20	(0.70-2.03)
long-duration (>3yrs)	31	7.4%	193	3.9%	1.66	(1.01-2.74)
Thiazolidinediones						
non use*	396	94.5%	4864	97.3%	1	(ref)
short-duration (<1 yr)	11	2.6%	57	1.1%	1.28	(0.61-2.68)
mid-duration (1-3 yrs)	7	1.7%	46	0.9%	1.19	(0.49-2.90)
long-duration (>3 yrs)	2	0.5%	14	0.3%	1.27	(0.23-6.89)
Other anti-diabetics						
non use*	412	98.3%	4962	99.2%	1	(ref)
short-duration (<1 yr)	1	0.2%	9	0.2%	1.24	(0.13-11.82)
mid-duration (1-3 yrs)	1	0.2%	8	0.2%	0.94	(0.11-8.14)
long-duration (>3 yrs)	2	0.5%	10	0.2%	1.85	(0.34-10.10)

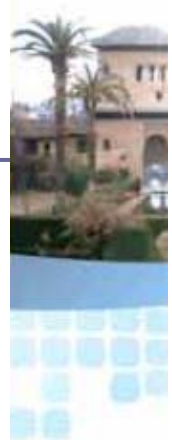
* Baseline category

** = adjusted for all variables included in the table plus those in the fully adjusted model of Table 2

Conclusiones sobre iDPP-4

- Argumentos a favor de su utilización
  - Eficacia en la reducción de glucemia basal, postprandial y A1c (no inferioridad, fundamentalmente en asociación con metformina)
  - No incremento de peso
  - Bajo riesgo de hipoglucemia
  - Seguridad confirmada
  - Potenciales efectos beneficiosos cardiovasculares
  - Potenciales efectos protectores sobre la célula β

Conclusiones sobre iDPP-4



- Argumentos en contra de su utilización
  - Coste del tratamiento
  - Recomendaciones algunos Estamentos Oficiales - Guías
  - Falta de estudios de eficacia y de seguridad a largo plazo

1. Lifestyle intervention (healthy eating, weight control,

TRIAL EVALUATING **CARDIOVASCULAR**

TECOS

OUTCOMES WITH **SITAGLIPTIN**

BW ↑	Costs Hypo BW ↑	Costs BW ↑ CV safety	ø Hypo Weak GI-AE	etc.

Posicionamiento de los iDPP4

1. Como 2º escalón tras no consecución de objetivos (A1c < 6,5%) con metformina en fases iniciales
2. Pacientes que no deberían presentar hipoglucemias
   - Condición específica de salud
   - Trabajo
   - Edad
3. Pacientes con hiperglucemias postprandiales en tratamiento con insulina basal

No deben ser “retrasadores de la insulinización”

Inhibidores de la DPP-4 (iDPP4)

¡¡ Los iDPP4 son diferentes !!

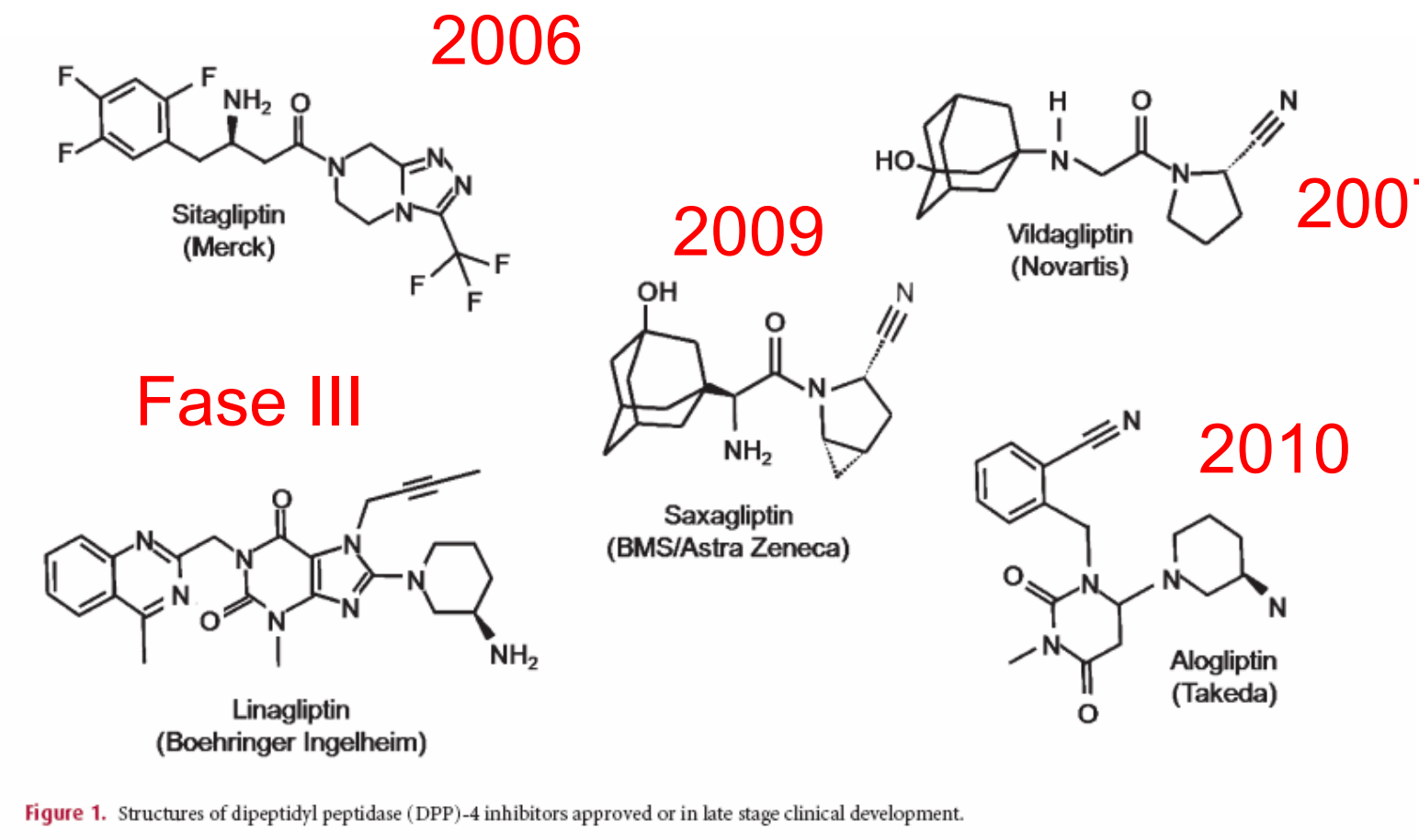


Figure 1. Structures of dipeptidyl peptidase (DPP)-4 inhibitors approved or in late stage clinical development.

Química

Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

C. F. Deacon

Department of Biomedical Sciences, University of Copenhagen, Panum Institute, Copenhagen N, Denmark

- Clasificación química
  - iDPP4 péptido miméticos
    - Sitagliptina (SiT)
    - Vildagliptina (VIL)
    - Saxagliptina (SAX)
  - iDPP4 no péptido miméticos
    - Alogliptina (ALO)
    - Linagliptina (LIN)
- Interacción con DPP4
  - No Covalente: SIT, ALO y LIN
  - Covalente en 2 pasos: VIL Y SAX

Diabetes, Obesity and Metabolism 13: 7–18, 2011.

Inhibitor	Chemistry
Sitagliptin [7–9]	β-amino acid-based
Vildagliptin [10–12]	Cyanopyrrolidine
Saxagliptin [13,14]	Cyanopyrrolidine
Alogliptin [15,16]	Modified pyrimidinedione
Linagliptin [17,18]	Xanthine-based

Eficacia inhibidora

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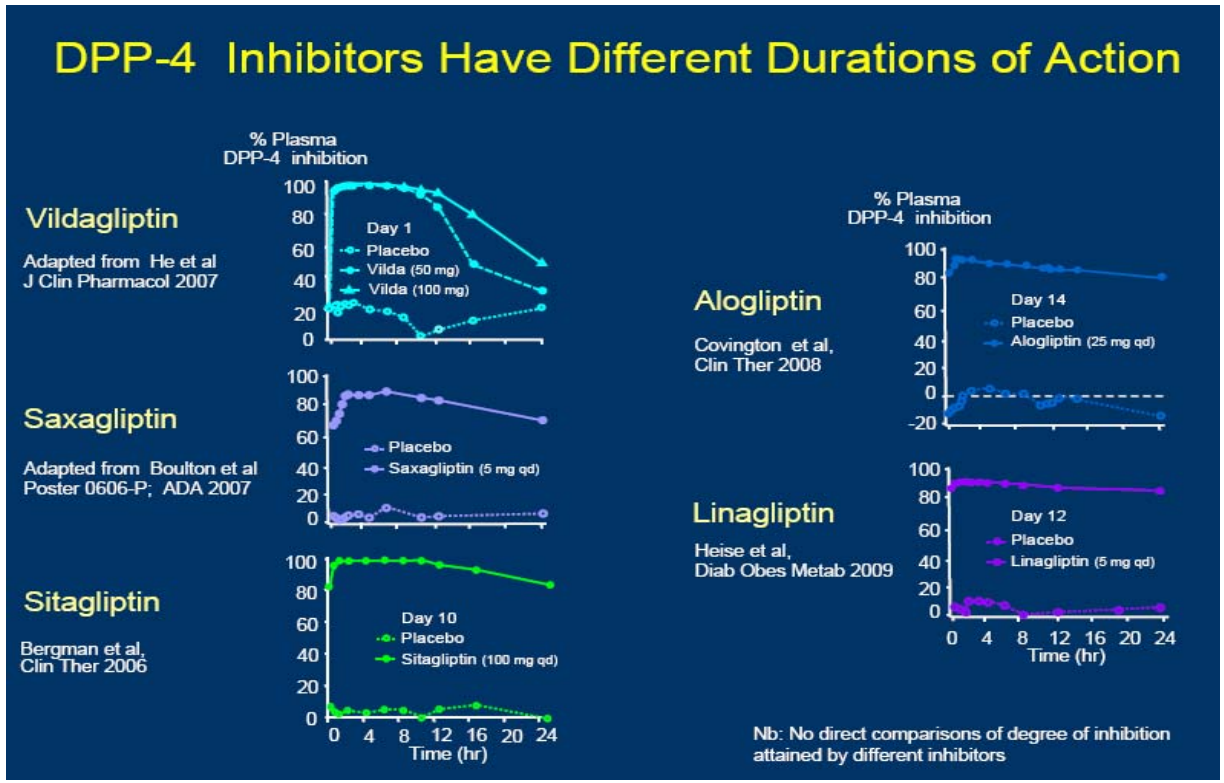
C. F. Deacon

Department of Biomedical Sciences, University of Copenhagen, Panum Institute, Copenhagen N, Denmark

Inhibitor	DPP-4 inhibition*
Sitagliptin [9,27]	Max ~97%; >80% 24 h postdose
Vildagliptin [12,25]	Max ~95%; >80% 12 h postdose
Saxagliptin [14,26]	Max ~80%; ~70% 24 h postdose
Alogliptin [28]	Max ~90%; ~75% 24 h postdose
Linagliptin [29]	Max ~80%; ~70% 24 h postdose

Diabetes, Obesity and Metabolism 13: 7–18, 2011.

Todos son Inhibidores Competitivos



Vida media

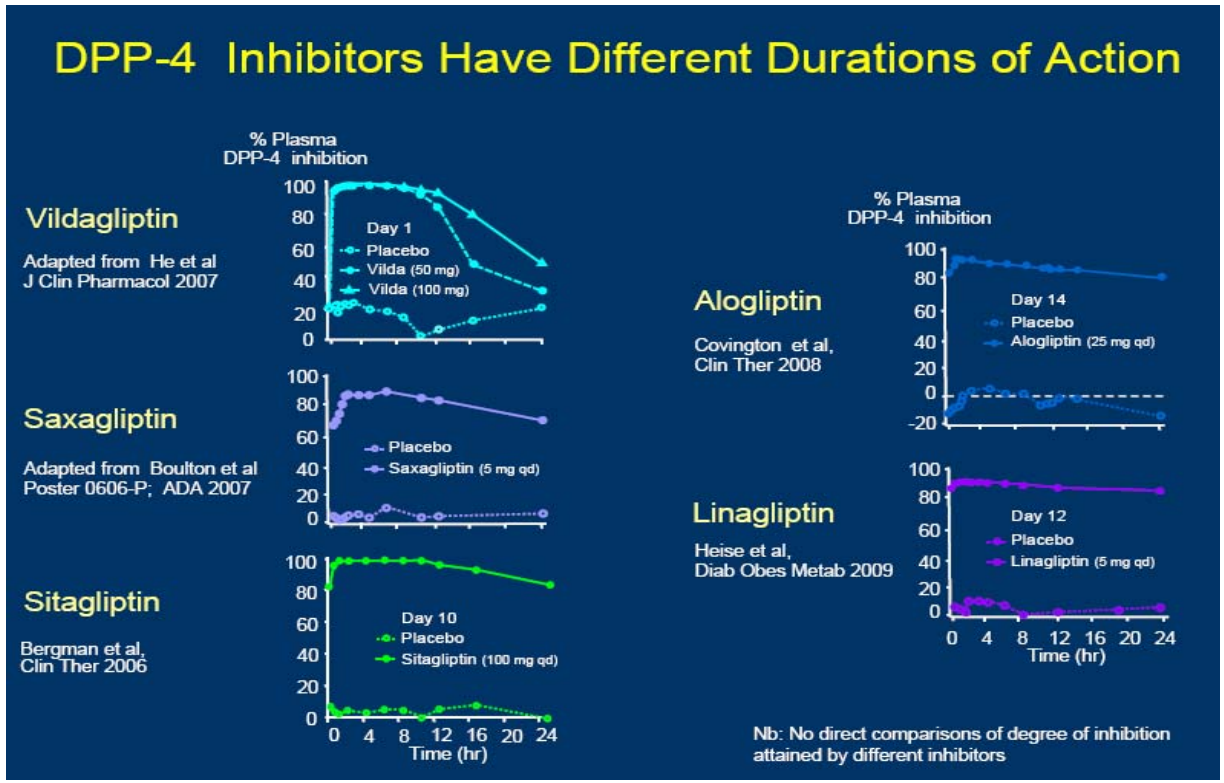
Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

C. F. Deacon

Department of Biomedical Sciences, University of Copenhagen, Panum Institute, Copenhagen N, Denmark

Inhibitor	Compound $t_{1/2}$ (h)
Sitagliptin [9,27]	8–24
Vildagliptin [12,25]	1½–4½
Saxagliptin [14,26]	2–4 (parent) 3–7 (metabolite)
Alogliptin [28]	12–21
Linagliptin [29]	10–40

Diabetes, Obesity and Metabolism 13: 7–18, 2011.



Selectividad

Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

C. F. Deacon

Department of Biomedical Sciences, University of Copenhagen, Panum Institute, Copenhagen N, Denmark

Diabetes, Obesity and Metabolism 13: 7–18, 2011.

Table 3. *In vitro* selectivity of dipeptidyl peptidase (DPP)-4 inhibitors (fold selectivity for DPP-4 vs. ‹

Inhibitor	Selectivity	QPP/DPP-2	PEP	FAPα	DPP-8	DPP-9
Sitagliptin [7]	High	>5550	>5550	>5550	>2660	>5550
Vildagliptin [10,20]	Moderate	>100 000	60 000	285	270	32
Saxagliptin [21]	Moderate	>50 000	Not reported	>4000	390	77
Alogliptin [15]	High	>14 000	>14 000	>14 000	>14 000	>14 000
Linagliptin [19]	Moderate	>100 000	>100 000	89	40 000	>10 000

QPP, quiescent cell proline dipeptidase; PEP, prolyl endopeptidase; FAPα, fibroblast activation protein-α.

¿INTERPRETACION DE LOS RESULTADOS?

Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

C. F. Deacon

Department of Biomedical Sciences, University of Copenhagen, Panum Institute, Copenhagen N, Denmark

Diabetes, Obesity and Metabolism 13: 7–18, 2011.

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Distribución, Metabolismo, Excreción

Diabetes, Obesity and Metabolism 13: 7–18, 2011.

- Unión a proteínas plasmáticas: 38% SIT, 10% VIL, 0-1% SAX, LIN 10
- Concentraciones mayores halladas en Intestino, riñón e hígado
- No atraviesan la BHE (VIL, SAX, LIN)
- Atraviesan barrera placentaria (SIT, VIL y SAX)

Inhibitor	Metabolism	Elimination route
Sitagliptin [7–9]	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin [10–12]	Hydrolysed to inactive metabolite (P_{450} enzyme independent)	Renal (22% as parent, 55% as primary metabolite)
Saxagliptin [13,14]	Hepatically metabolized to active metabolite (via P_{450} 3A4/5)	Renal (12–29% as parent, 21–52% as metabolite)
Alogliptin [15,16]	Not appreciably metabolized	Renal (>70% unchanged as parent)
Linagliptin [17,18]	Not appreciably metabolized	Biliary (>70% unchanged as parent); <6% via kidney

Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

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Dosificación y Utilización específica

Inhibitor	Dosing
Sitagliptin [9,27]	100 mg qd
Vildagliptin [12,25]	50 mg bid
Saxagliptin [14,26]	5 mg qd
Alogliptin [28]	25 mg qd
Linagliptin [29]	5 mg qd (anticipated)

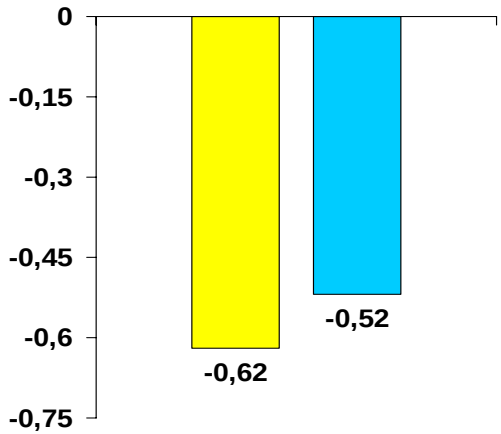
	Renal insufficiency*			Hepatic insufficiency	
Inhibitor	Mild (CrCl ≥50 ml/min)	Moderate (CrCl ≥30–<50 ml/min)	Severe/ESRD (CrCl <30 ml/min)	Mild/moderate	Severe
Sitagliptin (launched EU, USA)	√	Presently not recommended (EU) 1/2 dose (USA)†	Presently not recommended (EU) 1/4 dose (USA)†	√	Presently not recommended†
Vildagliptin‡ (launched EU)	√	Presently not recommended†	Presently not recommended†	Not recommended	Not recommended
Saxagliptin§ (launched EU, USA)	√	Presently not recommended (EU) 1/2 dose (USA)†	Presently not recommended (EU) 1/2 dose (USA)†	√ (Moderate: use with caution)	Presently not recommended†
Alogliptin (launched Japan)	√	1/2 dose	1/4 dose	√	Presently not recommended†
Linagliptin (not yet approved)	√ (likely)	√ (likely)	√ (likely)	Unknown Dose adjustment? / not recommended?	Unknown Dose adjustment? / not recommended?

Indicaciones actuales

	SITAGLIPTINA	VILDAGLIPTINA	SAXAGLIPTINA
Monoterapia	SI	No	No
Combinación con Metformina	SI	SI	SI
Combinación con SU	SI	SI	SI
Combinación con Glitazonas	SI	SI	SI
Triple terapia con Met + SU	SI	No	No
Triple terapia con Met +Glitaz	SI	No	No
Combinación con Insulina	SI	No	No

H2H: SIT vs. SAX

18 SEMANAS



Sitagliptin + Metformin

Saxagliptin + Metformin

Patients	Sitagliptin + metformin (n=398)	Saxagliptin + metformin (n=403)
	%	%
With AEs	47.2	47.1
With serious AEs	1.3	1.7
Discontinued due to serious AEs	–	0.5
With any hypoglycemic event	2.8	3.2
Influenza	5.8	5.7
Urinary tract infection	5.3	5.7


GRACIAS POR TU ATENCION