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Málaga

Lixisenatida

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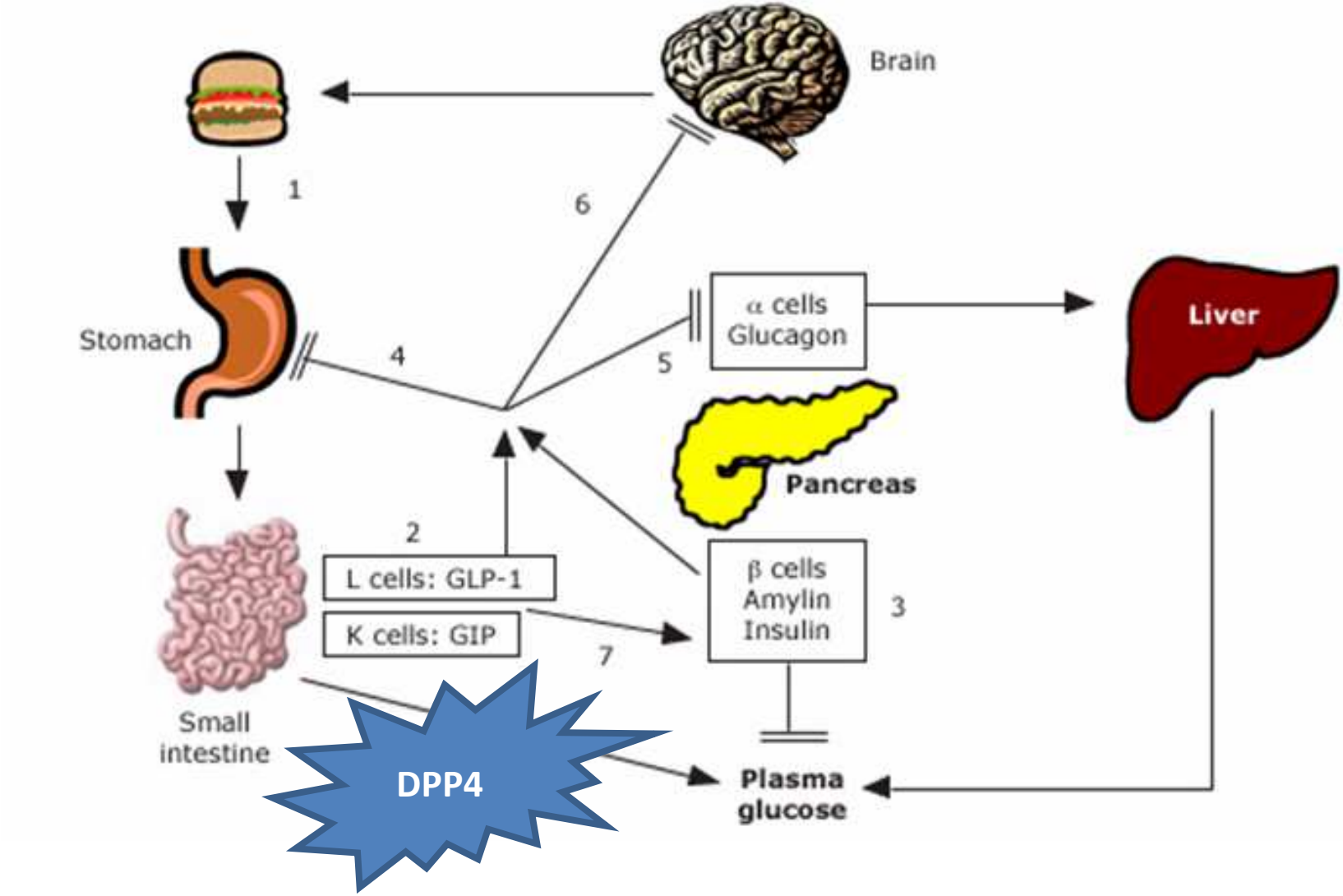
Indice

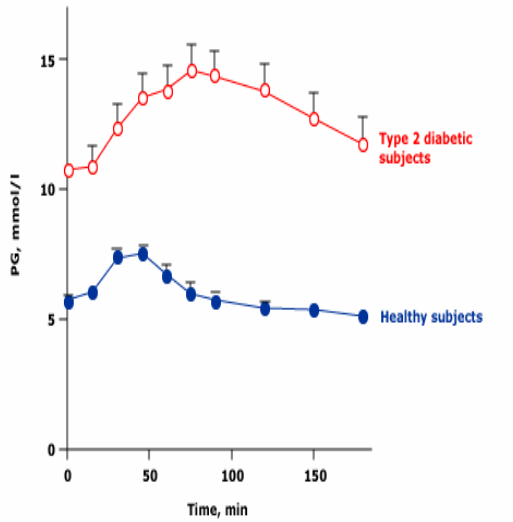
- Efecto incretina
- Diferencias entre iDPP-4 y agonistas GLP-1
- Tipos de agonistas GLP-1
- Lixisenatida en DM2 de corta evolución
- Lixisenatida en DM2 de larga evolución
- Resumen

Efecto incretina

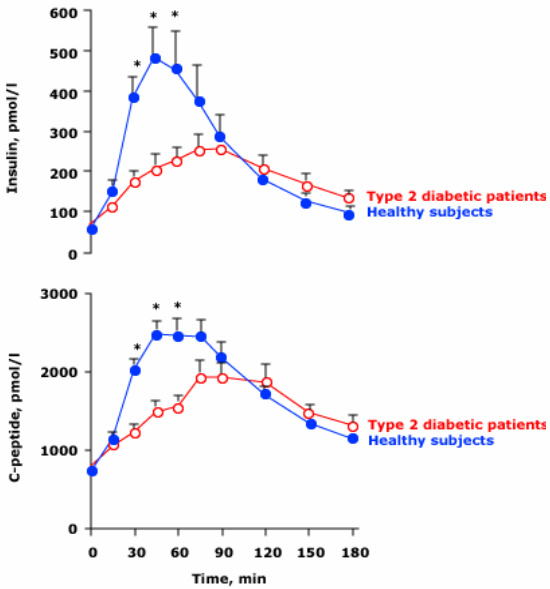


Efecto incretina en DM tipo 2

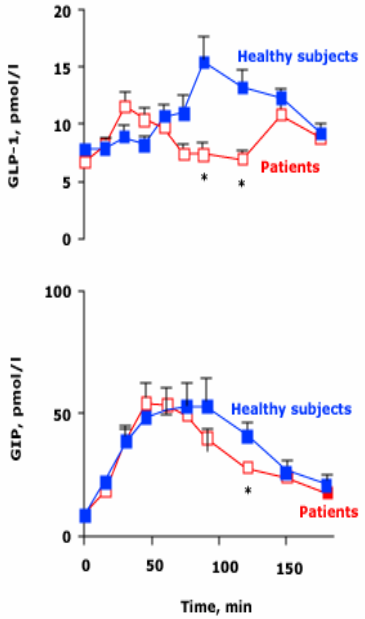
Plasma glucose concentrations during the 180 min period after meal ingestion



Increase in plasma concentrations of insulin (top) and c-peptide (bottom) for type 2 diabetic patients and healthy subjects after ingestion of a mixed breakfast meal



GLP-1 concentrations (top) and GIP concentrations (bottom) using NH2-terminal assays



Vilsboll T. Diabetes 2001;50:609

Inh. DPP4 vs. Análogos GLP-1

Inh DPP4

- Estimulación secreción insulina postprandial
- Inhibición secreción de glucagón

Análogos GLP-1

- Estimulación secreción insulina postprandial
- Inhibición secreción de glucagón
- Enlentecimiento vaciamiento gástrico

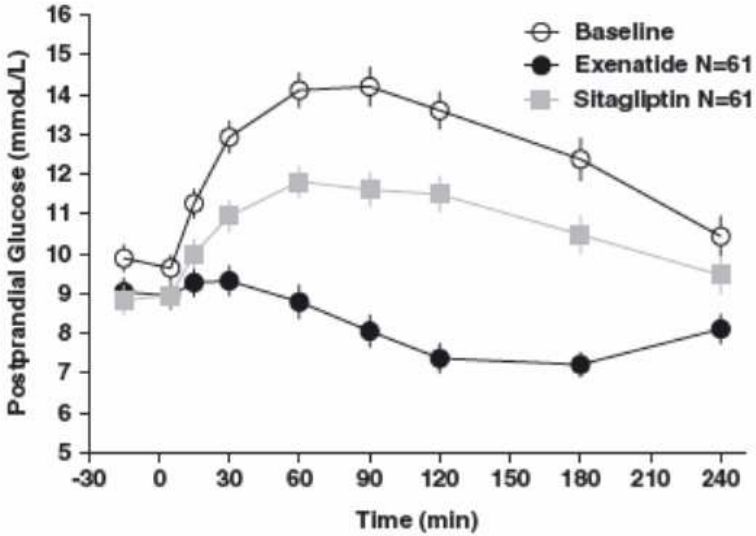


Figure 1. Mean (s.e.) postprandial plasma glucose concentration during a standard meal at baseline and after treatment with exenatide or sitagliptin. Exenatide was administered at T = −15 min. Sitagliptin was administered at T=−30 min. Standardized meal was given at T = 0 min. Adapted from

De Fronzo RA. Curr Med Res Opin. 2008; 14:2943

Inh. DPP4 vs. Análogos GLP-1

Inh DPP4

- Estimulación secreción insulina postprandial
- Inhibición secreción de glucagón

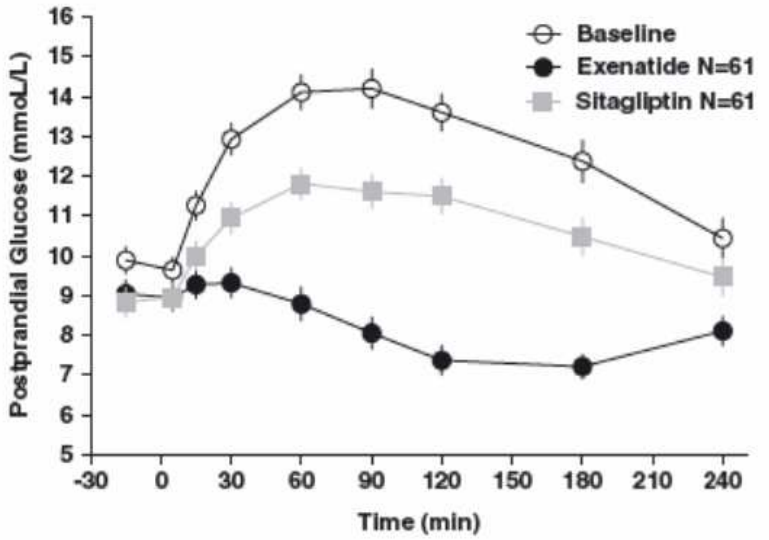
Análogos GLP-1

- Estimulación secreción insulina postprandial
- Inhibición secreción de glucagón
- Enlentecimiento vaciamiento gástrico

Ingesta calórica
+ 130 cal/d vs. – 134 cal/d

Peso
NS vs. -2-3 Kg

Descenso HbA1c
0.74 % vs. 0.9 a 1.0%



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De Fronzo RA. Curr Med Res Opin. 2008; 14:2943

Agonistas GLP-1

Acción corta

Derivados de Exendina-4

- Exenatida
  - $T_{1/2} \approx$ 2-4 h.
- Lixisenatida
  - $T_{1/2} \approx$ 2-6 h.
  - Afinidad R x4

Acción Larga (Análogos GLP-1)

Derivados de GLP-1 humano

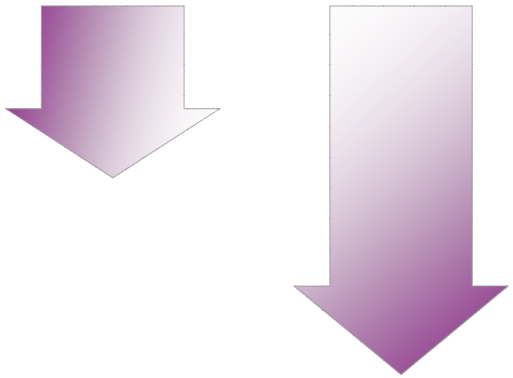
- Liraglutida
  - $T_{1/2} \approx$ 13 h.
- Exenatida LAR
  - $T_{1/2} \approx$ 2 sem.
- Albiglutida
- Dulaglutida
- Taspoglutida

Análogos GLP-1

Acción corta
Derivados de Exendina-4
EFECTO PRANDIAL
Exenatida, Lixisenatida

Efecto sobre la GPA

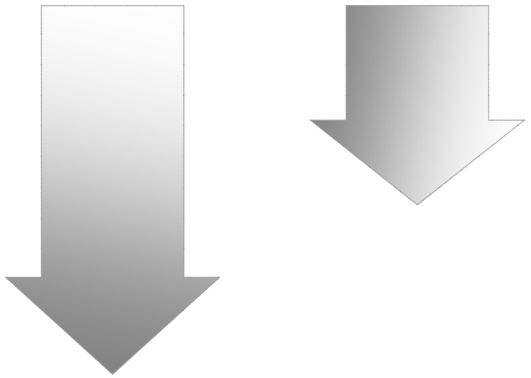
Efecto sobre la GPP



Acción larga
Derivados de GLP-1
EFECTO BASAL
Liraglutida, Exenatida LAR, Albiglutida

Efecto sobre la GPA

Efecto sobre la GPP



Fineman MS, et al. *Diabetes Obes Metab.* 2012;14(8):675-688.

GPA = glucosa plasmática en ayunas; GPP = glucosa plasmática postprandial

Contribución GBA y GPP sobre HbA1c

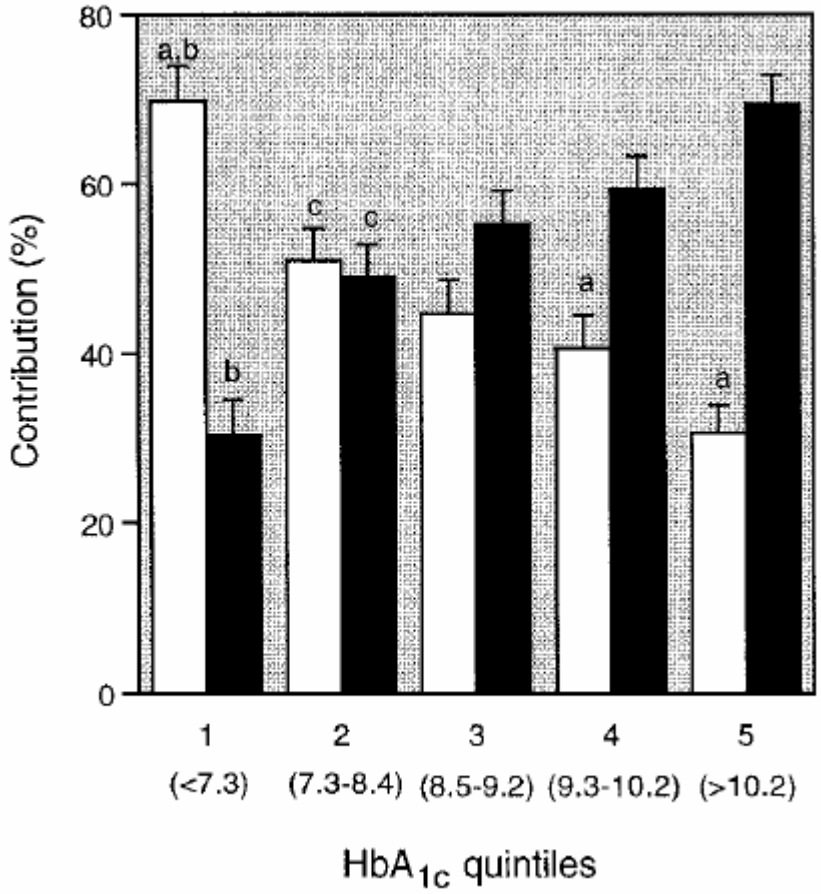
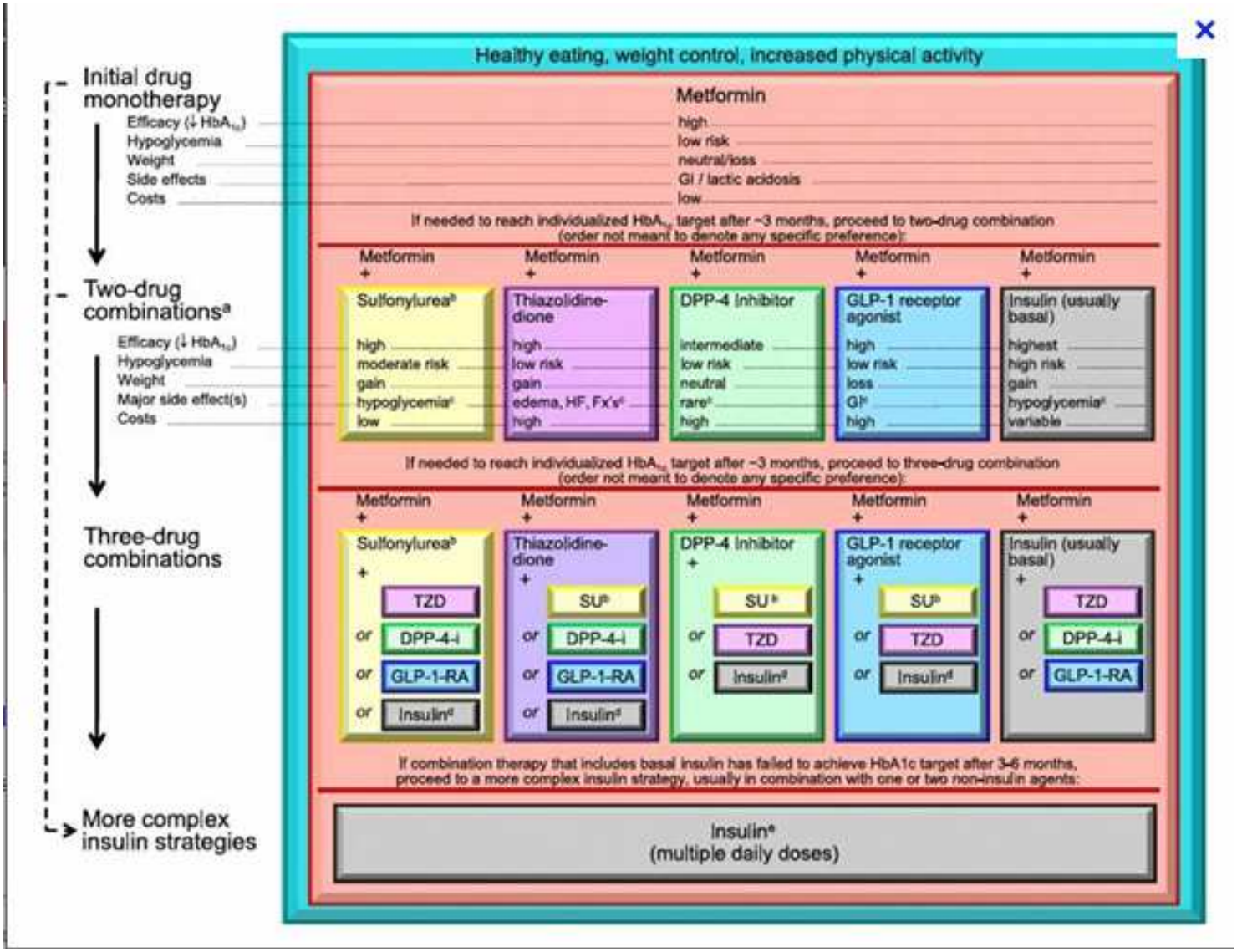


Figure 3—*Relative contributions of postprandial (□) and fasting (■) hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of* HbA_{1c}. a, *significant difference was observed between fasting and postprandial plasma glucose (paired* t *test);* b, *significantly different from all other quintiles (ANOVA);* c, *significantly different from quintile 5 (ANOVA).*

Monnier L. Diabetes Care. 2003;26:881-5

Algoritmo Tratamiento
Diabetes Mellitus Tipo 2

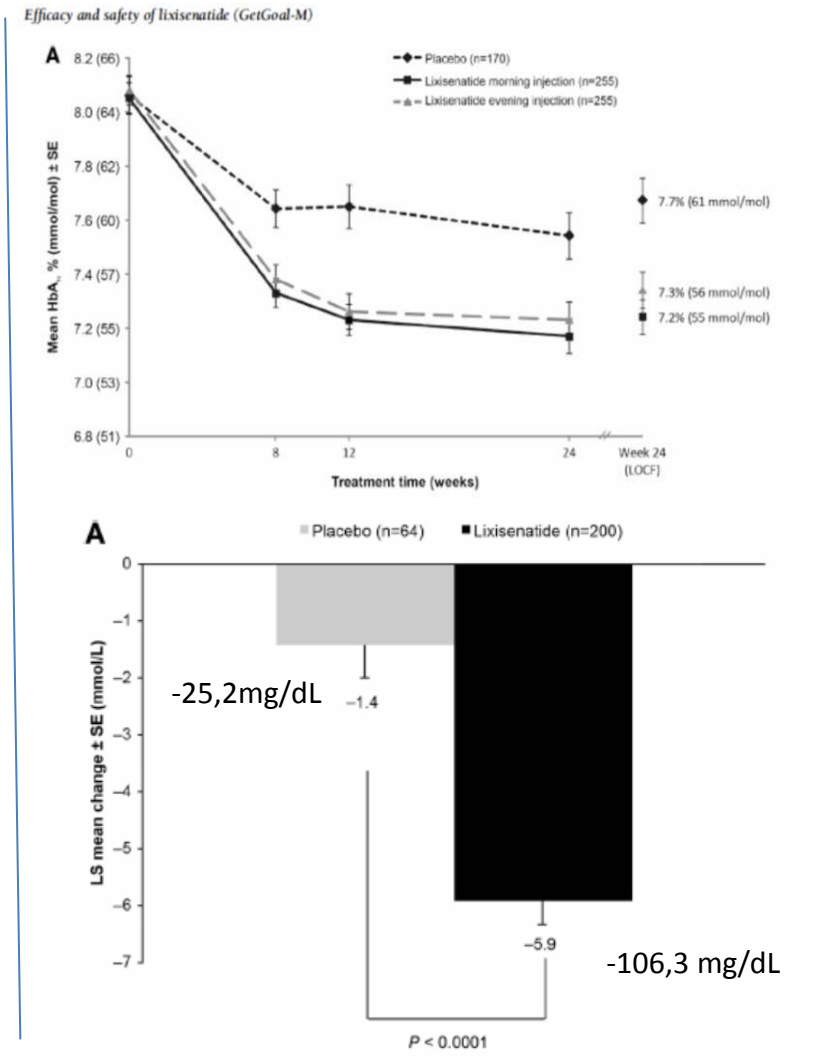


Lixisenatida
Diabetes Mellitus tipo 2 (corta evolución)

Table 1—*Demographic and baseline characteristics (safety population)*

Demographic variable	Lixisenatide morning injection (n = 255)	Lixisenatide evening injection (n = 255)	Combined placebo (n = 170)
Sex (male/female), %	38.4/61.6	44.7/55.3	47.6/52.4
Race (Caucasian/Black/Asian/other), %	86.7/2.7/8.6/2.0	89.4/2.4/7.8/0.4	91.2/2.4/6.5/0
Age, years	54.5 ± 9.2	54.8 ± 10.4	55.0 ± 9.4
Duration of diabetes, years	6.2 ± 5.3	6.2 ± 5.4	5.9 ± 4.7
Weight, kg	90.1 ± 21.0	89.0 ± 20.7	90.4 ± 20.1
BMI, kg/m^2	33.2 ± 6.9	32.5 ± 5.8	33.1 ± 6.5
HbA_{1c}, %	8.0 ± 0.9	8.1 ± 0.9	8.1 ± 0.9
HbA_{1c}, mmol/mol	64 ± 9.8	65 ± 9.8	65 ± 9.8
FPG, mmol/L	9.4 ± 2.2	9.3 ± 2.3	9.5 ± 2.3
Duration of metformin use, years	3.7 ± 3.3	3.7 ± 3.9	3.3 ± 3.5
Daily metformin dose, mg	1,969 ± 447	1,943 ± 406	2,001 ± 440

Data are presented as mean ± SD unless otherwise indicated.



BO AHRÉN. Diabetes Care. 2013 Sep;36(9):2543-50

Lixisenatida
DM tipo 2 (corta evolución)

Table 2—*Adverse events*

Type of AE	Lixisenatide morning injection (*n* = 255)	Lixisenatide evening injection (*n* = 255)	Combined placebo (*n* = 170)
Any AE, *n* (%)	177 (69.4)	177 (69.4)	102 (60.0)
Any serious AE, *n* (%)	5 (2.0)	8 (3.1)	2 (1.2)
Death	0	0	0
Discontinuation due to AE, *n* (%)	18 (7.1)	14 (5.5)	2 (1.2)
Gastrointestinal disorders (any), *n* (%)	93 (36.5)	105 (41.2)	44 (25.9)
Nausea, *n* (%)	58 (22.7)	54 (21.2)	13 (7.6)
Vomiting, *n* (%)	24 (9.4)	34 (13.3)	5 (2.9)
Diarrhea, *n* (%)	27 (10.6)	27 (10.6)	15 (8.8)
Symptomatic hypoglycemia*, *n* (%)	6 (2.4)	13 (5.1)	1 (0.6)
Severe hypoglycemia†	0	0	0

BO AHRÉN. Diabetes Care. 2013 Sep;36(9):2543-50

Lixisenatida vs. Exenatida

Estudio de No-inferioridad
El límite superior (IC 95%) de Diferencia de HbA1c se fijó en < 0.4%

Table 1—*Demographic and baseline characteristics (safety population)*

Demographic variable	Lixisenatide 20 µg QD (*n* = 318)	Exenatide 10 µg BID (*n* = 316)	All (*n* = 634)
Male/female, %	47.5/52.5	59.2/40.8	53.3/46.7
Caucasian/Black/Asian/other race, %	93.1/2.5/0.9/3.5	92.4/3.2/1.3/3.2	92.7/2.8/1.1/3.3
Age (years), mean ± SD	57.3 ± 9.2	57.6 ± 10.7	57.4 ± 9.9
Duration of diabetes (years), mean ± SD	6.8 ± 5.5	6.8 ± 4.9	6.8 ± 5.2
Weight, mean ± SD (kg)	94.0 ± 19.6	96.1 ± 22.5	95.0 ± 21.13
BMI (kg/m^2), mean ± SD	33.7 ± 6.3	33.5 ± 6.5	33.6 ± 6.4
HbA_{1c} (%), mean ± SD	8.03 ± 0.8	8.02 ± 0.8	8.02 ± 0.8
FPG, mg/dL (mean ± SD, mmol)	9.7 ± 2.0 (174.6 ± 36.0)	9.7 ± 2.3 (174.6 ± 41.4)	9.7 ± 2.1 (174.6 ± 37.8)
PAGI-QOL total score	0.59 ± 0.7	0.56 ± 0.7	0.58 ± 0.7
Daily metformin dose (mg), mean ± SD	2,020 ± 459	2,058 ± 453	2,039 ± 456

BID, twice daily; PAGI-QOL, Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life; QD, once daily.

ROSENSTOCK J. Diabetes Care 2013; Oct;36(10):2945-51

Lixisenatida vs. Exenatida

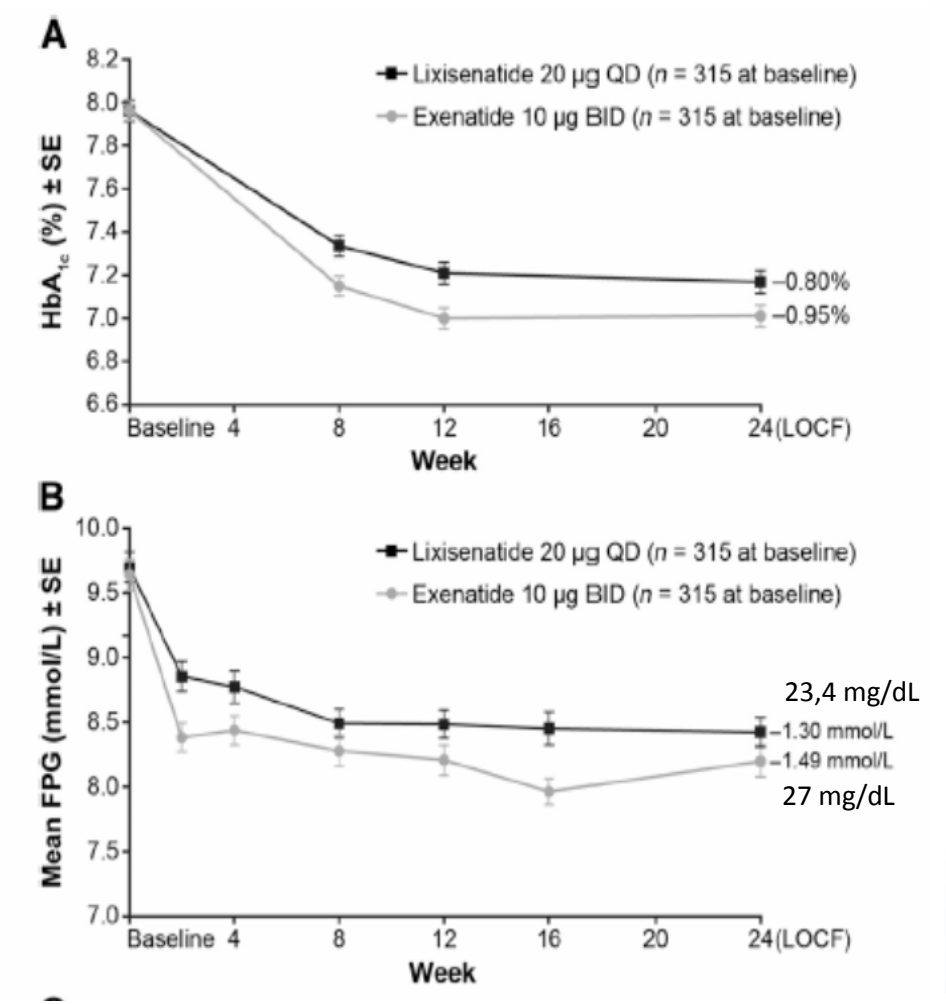


Table 2—*Safety profile during the 24-week, double-blind treatment period*

AE N (%)	Lixisenatide 20 µg QD (n = 318)	Exenatide 10 µg BID (n = 316)
Any AE	221 (69.5)	228 (72.2)
Any serious AE	9 (2.8)	7 (2.2)
Death	1 (0.3)	1 (0.3)
AE leading to discontinuation	33 (10.4)	41 (13.0)
Gastrointestinal disorders (any)	137 (43.1)	160 (50.6)
Preferred AE term (≥10% in either group)		
Nausea	78 (24.5)	111 (35.1)
Vomiting	32 (10.1)	42 (13.3)
Diarrhea	33 (10.4)	42 (13.3)
Symptomatic hypoglycemia	8 (2.5), 8 events	25 (7.9), 48 events
Severe hypoglycemia	0	0

BID, twice daily; QD, once daily.

CONCLUSIONS—Add-on lixisenatide once daily in type 2 diabetes inadequately controlled with metformin demonstrated noninferior improvements in HbA_{1c}, with slightly lower mean weight loss, lower incidence of hypoglycemia, and better gastrointestinal tolerability compared with exenatide twice daily.

ROSENSTOCK J. Diabetes Care 2013; Oct;36(10):2945-51

Análogos GLP-1* + Insulina Basal

- 2 escenarios:

- **Metformina+ Análogo GLP-1 + Insulina basal**

- Metformina + Insulina basal + Análogo GLP-1

*Exenatida, Lixisenatida, Liraglutida

Revisión Sistemática
Análogos GLP-1+ Insulina

Table 1 Characteristics of trials included in the systematic review

Parameter	References				
	Arnolds et al[19]	Riddle et al[20]	Buse et al[17]	Morrow et al[21]	Seino et al[22]
Design	R, OL, PG, SC 4 weeks n = 48	R, DB, PC, PG 24 weeks n = 34	R, DB, PC, PG, MC 30 weeks n = 259	OL, CO 36 days n = 33	R, DB, PC, PG, MC 24 weeks n = 311
Age (years)	57	55	59	50	58
Male (%)	60	NR	57	70	NR
Race, white (%)	NR	NR	78	79	0
Diabetes duration (years)	6	9	12	7	14
Body mass index (kg/m^2)	32	33	33	33	25
Baseline FPG (mmol/L)	5.3	NR	8.1	9.7	7.7
Baseline A1c (%)	8.1	7.8*	8.4	8.3	8.5
Intervention	Glargine (0.42 u/kg) + metformin + exenatide (5–10 µg BID)	Metformin + exenatide (5–10 µg BID) + glargine (0.50 u/kg)	Glargine + exenatide (10 µg BID) ± metformin and/or PIO	Liraglutide (1.8) + detemir (0.5 u/kg) ± metformin	Basal insulin ± SU + lixisenatide (20 µg QD)
Control (s)	Glargine (0.36 u/kg) + metformin + sitagliptin (100 mg QD) Glargine (0.42 u/kg) + metformin	Metformin + placebo + glargine (0.56 u/kg)	Glargine + placebo ± metformin and/or PIO	Liraglutide (1.8 mg) ± metformin Detemir (0.5 u/kg) ± metformin	Basal insulin ± SU + placebo
Sequence generation	No	No	Yes	NA	No
Concealment of allocation	No	No	No	NA	No
Blinding	No	Yes	Yes	No	Yes
Incomplete outcome data	No	No	No	No	No
Selective outcome reporting	No	No	Yes	No	No

Abbreviations: BID, twice daily; CO, crossover; DB, double blind; MC, multicenter; n, number; NR, not reported; NA, not applicable; OL, open label; PG, parallel group; PIO, pioglitazone; R, randomized; SC, single center; U, units; QD, once daily.

Berlie H. Diabetes, Metabolic Syndrome and Obesity, Targets and Therapy 212:5:165

Análogo GLP-1+Insulina Basal
DM tipo 2 fase avanzada

	Buse et al N= 259 Met+Glar+Placebo vs. Met+Glar+Exenatida	Seino et al N= 311 SU+Insulina basal+Placebo vs SU+Insulina Basal+Lixisenatida
Reducción HbA1c (%)	-1.04% vs. – 1.74%	+0.11% vs. -0.77%
HbA1c < 7%	35% vs. 60%	5.2% vs. 35.6%
HbA1c ≤ 6.5%	12% vs. 40%	1.3% vs. 17.8%
Incremento dosis insulina	20 u/dia vs. 13 u/dia	
Reducción GBA (mg/dL)	27 vs. 29	4.5 vs. 7.5
Reducción GPP 2 h. (mg/dL)	31 vs. 32	10 vs. 140
Reducción peso (Kg)	-1.1 vs. -1.8	+0.06 vs. - 0.38
TAS y TAD (Diferencia)	-4.4 mmHg y – 3.4 mmHg	
Frecuencia cardiaca	+ 3.0 lpm	

Buse JB. Ann Intern Med. 2011;154:103 .

Seino Y. Diab Obes Metab. 2012; 14:910

Lixisenatida
Resumen

- Agonista GLP-1 pacientes con DM2 e IMC> 30 Kg/m2
- Diabetes tipo 2, corta y larga evolución
- Control de glucemia prandial
- Dosis 10 ug/d sc x 2 semanas→ 20 ug/d
- Descenso HbA1c ~ 1%
- Insuficiencia renal 30-50 ml/min (datos limitados)
- Insuficiencia renal < 30 ml/min (no usar)
- Efectos adversos GI, pancreatitis, Ca medular tiroides
- No interacciones significativas