




**Pharmacologic modulation of incretins**

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**HOW CAN WE INCREASE INCRETIN EFFECTS IN TYPE 2 DIABETICS?**

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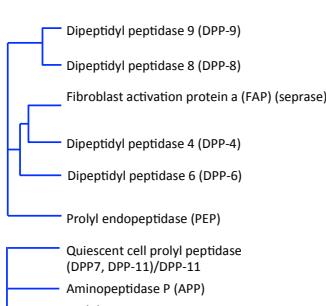
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**DPP-4 is a member of specific peptidases with proline**



DPP-4 gene family

Other proline specific peptidases

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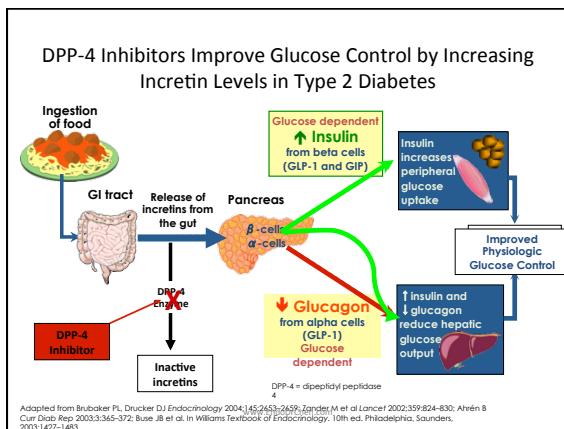
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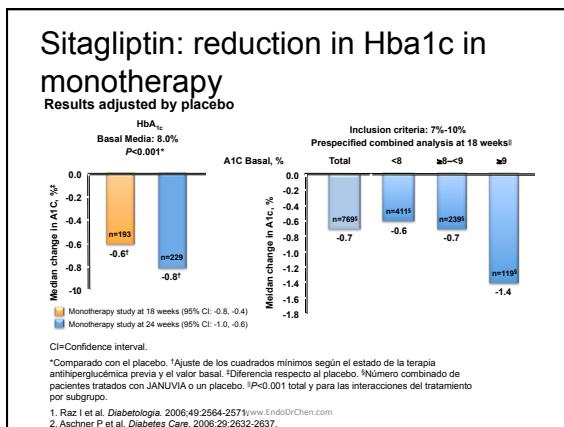
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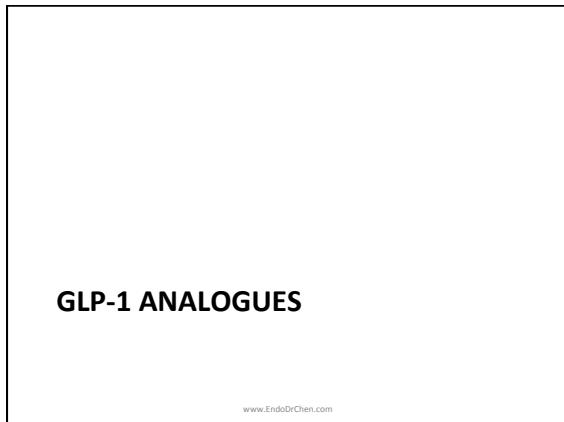


### DPP-4 inhibitors

- Oral agents: sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin
- Very well tolerated
- No effects in body weight

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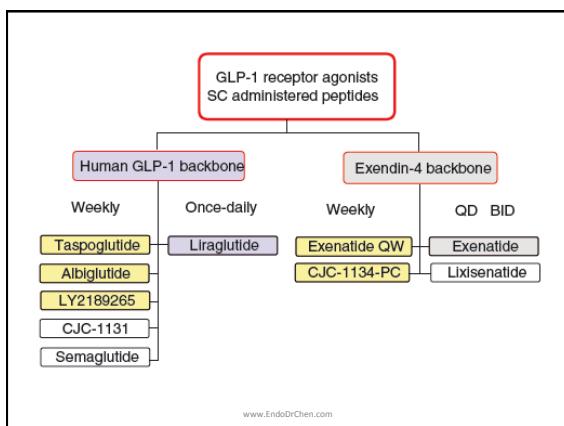
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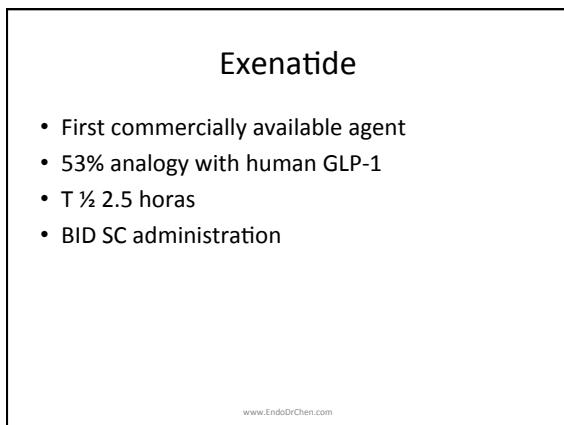
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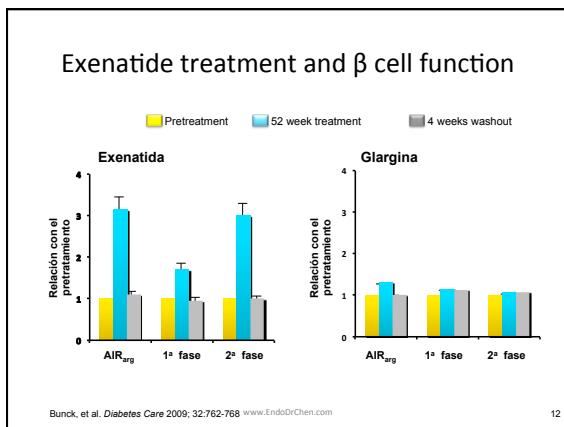
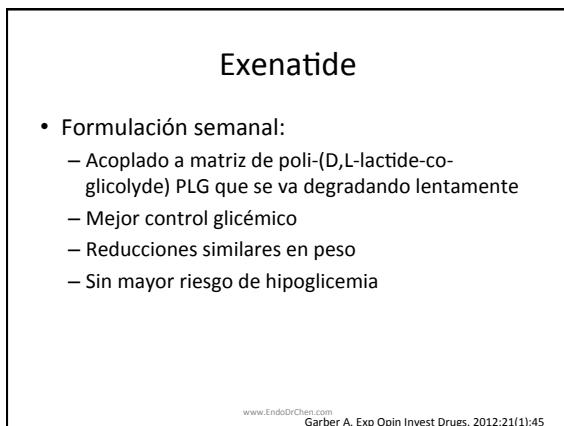
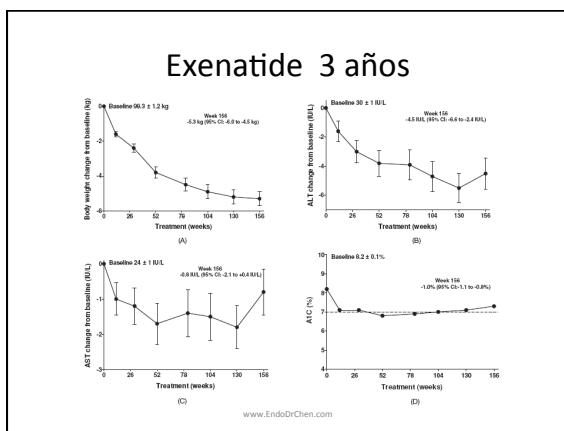
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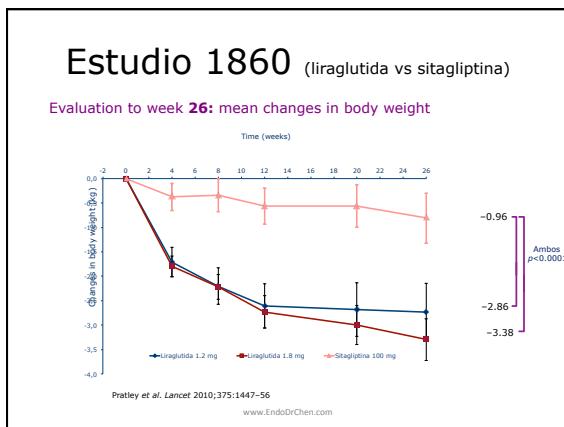
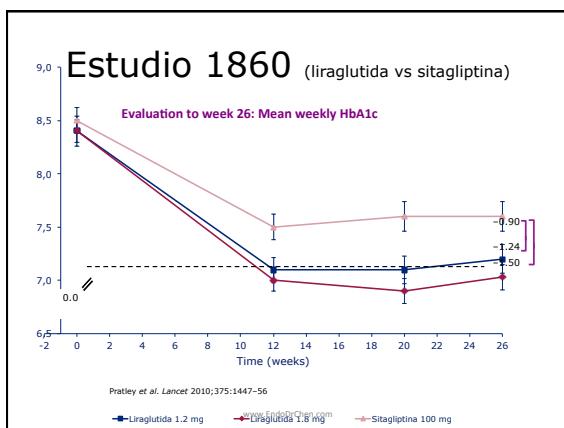
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**Liraglutide**

- 97% homology to human GLP-1
- Chemical structure with a fatty acid which increases its half life

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Garber A. Exp Opin Invest Drugs. 2012;21(1):45



## DURATION-6

- Exenatide weekly vs liraglutide
- Hba1c
  - -1.48% liraglutide
  - -1.26% exenatide
- Greater weight loss with liraglutide (-3.6 vs -2.7 kg)

[www.EndoDrChen.com](http://www.EndoDrChen.com) Buse JB. EASD 2011. Abstract 75.

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## DURATION-6

- Higher incidence of subcutaneous nodules with exenatide weekly (10%) compared to liraglutide (1%)

[www.EndoDrChen.com](http://www.EndoDrChen.com) Garber A. Exp Opin Invest Drugs. 2012;21(1):45

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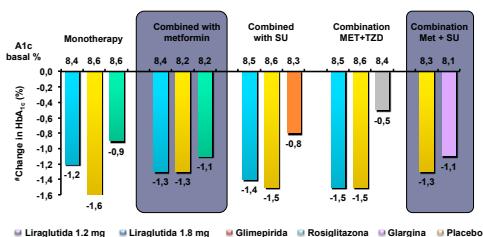


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## Reduction in Hba1c with liraglutide



Significativo \*vs. el comparador; #Cambio en HbA1c a partir del valor basal en la población global (LEAD 4,5) agregado al fallar la dieta y ejercicio (LEAD 3); o agregado a monoterapia previa con hipoglucemiantes orales (LEAD 2,1).

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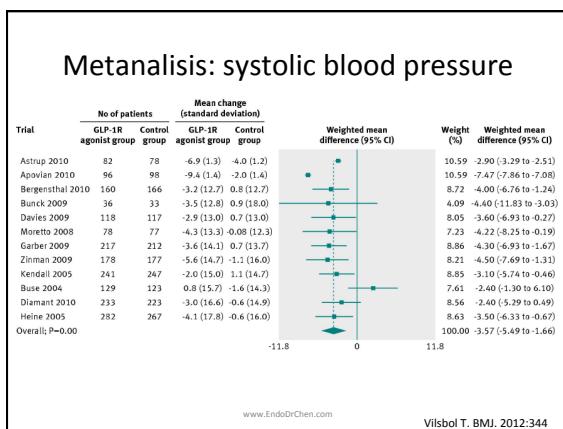
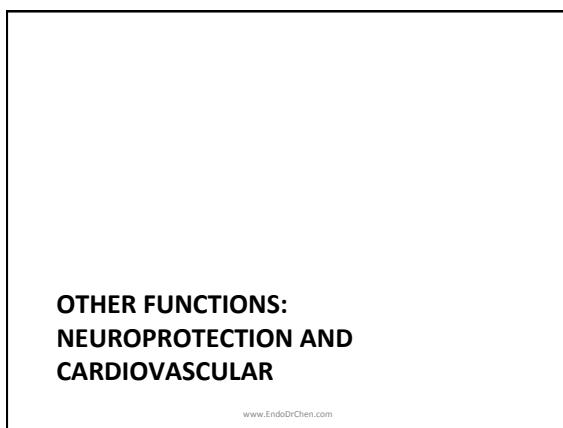
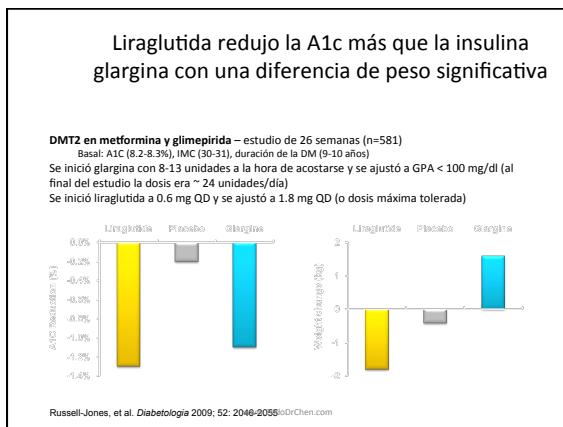
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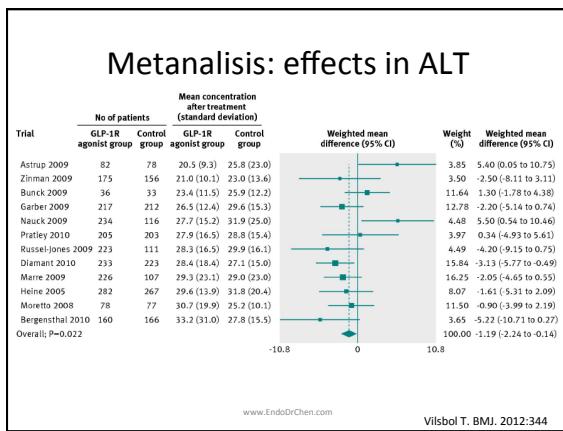
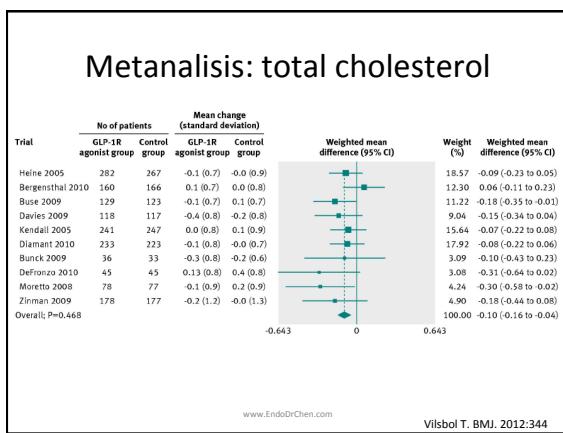
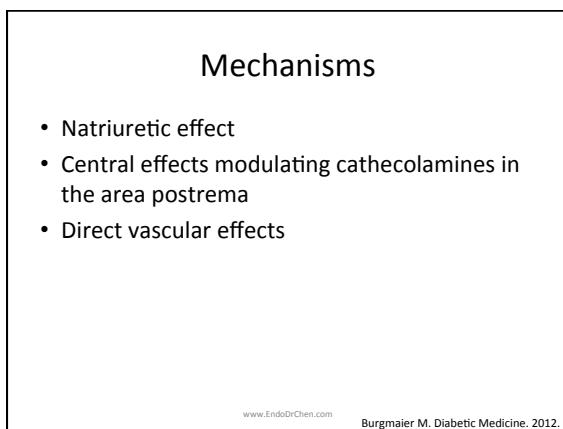


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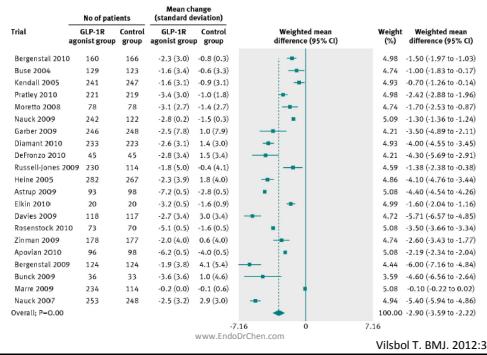


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## Metanalisis: changes in body weight



## Other risk factors modulation

- Inhibition of lymphocytic chemotaxis
- Reduction in monocytes adhesion
- Reduction in plaque inflammation
- Reduction in hsCRP and PAI-1
- Improvement of endothelial dysfunction

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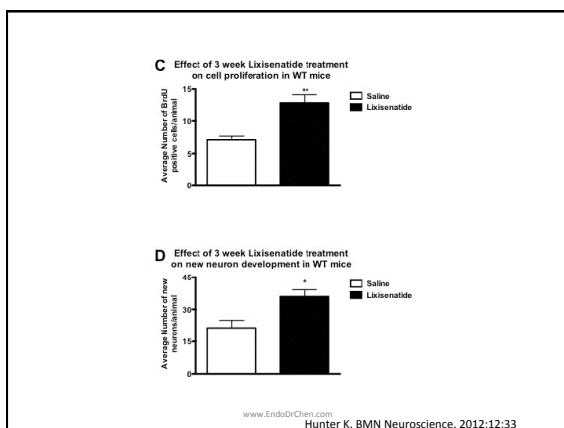
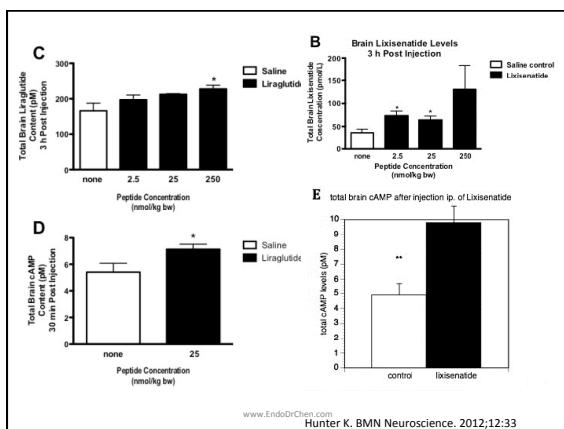
Burgmaier M. Diabetic Medicine. 2012.

## Neurogenesis

- There is a correlation between Alzheimer disease and T2DM
- Neurons express GLP-1 receptors
- In animal models, liraglutide reduces amyloid plaque formation in the brain

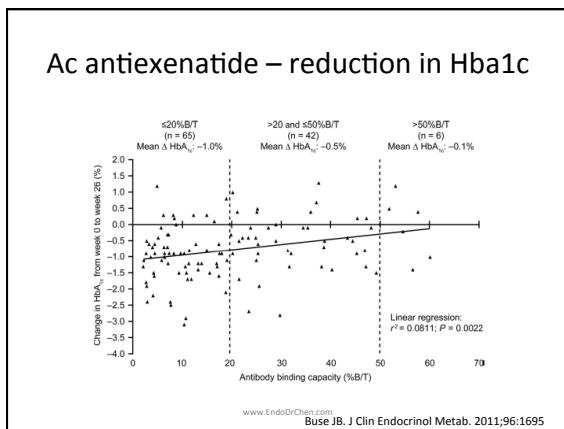
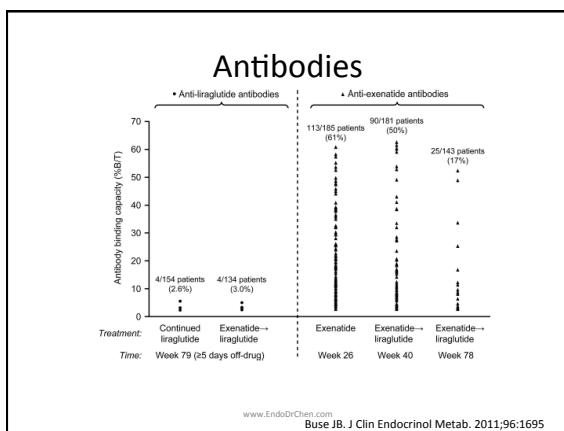
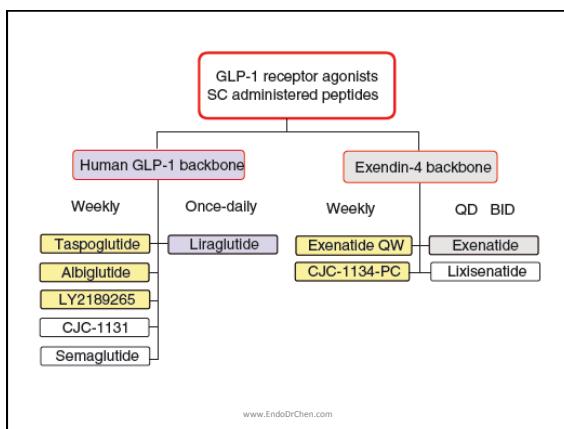
www.EndoDrChen.com

Hunter K. BMN Neuroscience. 2012;12:33

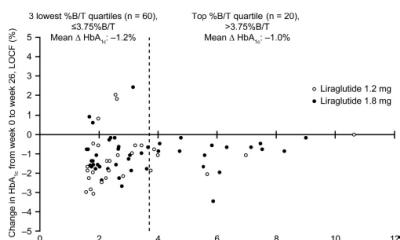


ARE ALL GLP-1 RECEPTOR AGONISTS THE SAME?

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### Ac antiliraglutide – reduction in Hba1c



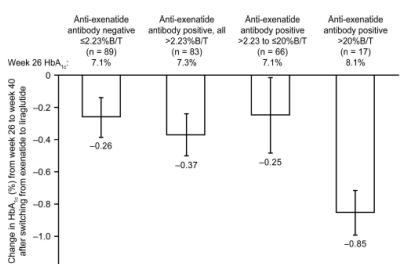
[www.EndoDrChen.com](http://www.EndoDrChen.com)  
Buse JB. J Clin Endocrinol Metab. 2011;96:1695

### Ac antiliraglutide

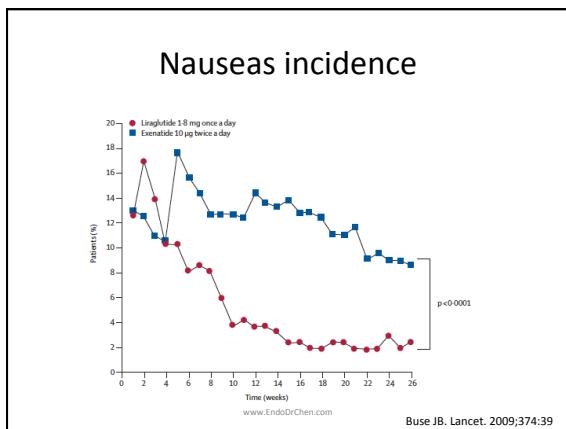
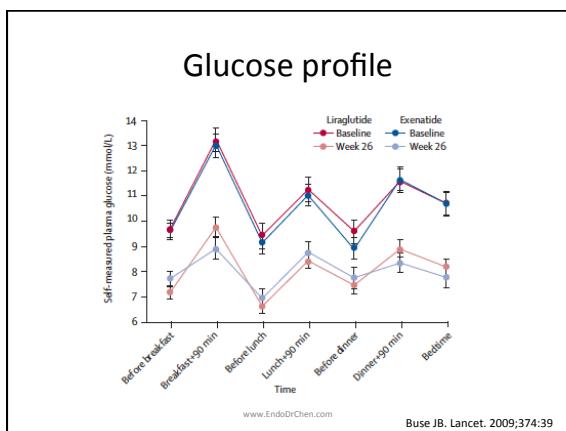
	Liraglutide 1.2 mg	Liraglutide 1.8 mg			
n	Baseline HbA <sub>1c</sub>	Δ HbA <sub>1c</sub>	n	Baseline HbA <sub>1c</sub>	Δ HbA <sub>1c</sub>
Anti-liraglutide antibody negative	337	8.5 (1.1)	534	8.4 (1.0)	-1.2 (1.1)
Anti-liraglutide antibody positive	32	8.9 (1.2)	48	8.3 (1.1)	-1.1 (0.9)
Anti-liraglutide antibody positive with GLP-1 cross-reacting effect	18	8.7 (0.9)	25	8.4 (1.0)	-1.2 (0.8)
Anti-liraglutide antibody positive with <i>in vitro</i> neutralizing effect	4	8.8 (0.9)	5	8.3 (1.0)	-1.6 (0.7)

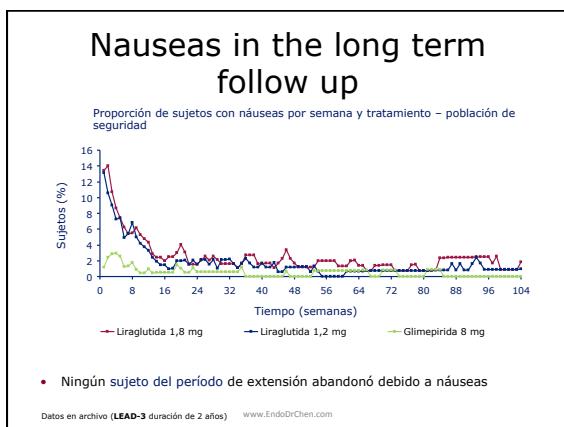
[www.EndoDrChen.com](http://www.EndoDrChen.com)  
Buse JB. J Clin Endocrinol Metab. 2011;96:1695

### Ac anti exenatide



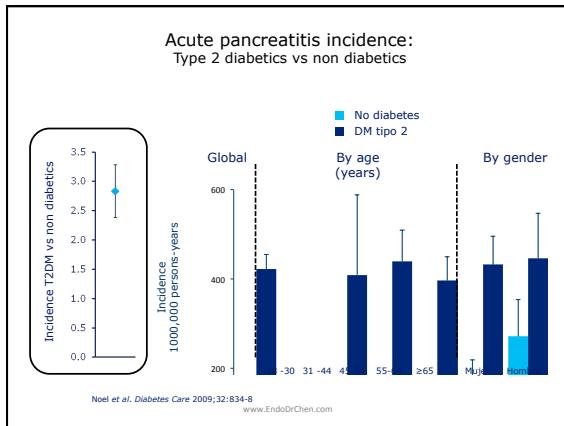
[www.EndoDrChen.com](http://www.EndoDrChen.com)  
Buse JB. J Clin Endocrinol Metab. 2011;96:1695





Type of adverse event	Placebo combined (n = 122)	Lixisenatide 2-step dose increase (n = 120)	Lixisenatide 1-step dose increase (n = 119)	Lixisenatide combined (n = 239)
Any TEAE	55 (45.1)	63 (52.5)	65 (54.6)	128 (53.6)
Any serious TEAE	5 (4.1)	1 (0.8)	0	1 (0.4)
Discontinuation as a result of a TEAE	1 (0.8)	5 (4.2)	3 (2.5)	8 (3.3)
Gastrointestinal disorders (any)	17 (13.9)	39 (32.5)	38 (31.9)	77 (32.2)
Nausea	5 (4.1)	29 (24.2)	24 (20.2)	53 (22.2)
Headache	14 (11.5)	10 (8.3)	9 (7.6)	19 (7.9)
Vomiting	0	9 (7.5)	8 (6.7)	17 (7.1)
Dizziness	3 (2.5)	9 (7.5)	4 (3.4)	13 (5.4)
Nasopharyngitis	4 (3.3)	6 (5.0)	5 (4.2)	11 (4.6)
Symptomatic hypoglycemia	2 (1.6)	3 (2.5)	1 (0.8)	4 (1.7)

[www.EndoDrChen.com](http://www.EndoDrChen.com)  
Fonseca VA. Diabetes Care. 2012;35:1225



## Safety

- Pancreatitis
  - 90% have risk factors
- There is a safety alert for exenatide and sitagliptina

www.EndoDrChen.com  
 Montanya E. Expert Opin Pharmacother. 2012;13:1451

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Incidence of pancreatitis in studies with liraglutide that have ended by February 28 2011

	Liraglutida	Active comparator
Safety analysis setd (n)	7653	1979
Total exposure (years)	5747.8	1536.1
Acute pancreatitis events	10	1
<b>Incidence of acute pancreatitis*</b>	<b>1.7</b>	<b>0.7</b>
Chronic pancreatitis events	3	0
<b>Incidence of chronic pancreatitis*</b>	<b>0.5</b>	<b>NA</b>

\* number of cases / 1000 patient years of exposure

In a diabetic population with an incidence of 1.5–0.5/1000 PYE, 9–26 cases of acute pancreatitis would be expected in the liraglutide group and 2–7 cases in the comparator group

Includes 1 event reported in the obesity development studies

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**Liraglutida and medullary thyroid cancer**

The diagram shows two panels: 'Rodents' and 'Humans'. In the 'Rodents' panel, a cluster of pink dots representing GLP-1 receptors is shown on a purple 'C cell'. A callout box states: 'In rodents, C cell density is >45 higher than in humans'. An arrow points down to the 'Humans' panel, which shows a single pink dot representing a GLP-1 receptor on a large purple 'C cell'. A callout box states: 'Rodents have more GLP-1 receptors in the cellular surface (1600–13,000/C-cell). In humans, GLP-1 receptors are rarely detectable (0–105/C-cell)'.

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Bjerre Knudsen et al. Endocrinology 2010;151:1473–86

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## DPP-4 INHIBITORS AND GLP-1 RECEPTOR AGONISTS COMPARISON

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Characteristic	DPP-4 inhibitors	GLP-1 agonists
Administration route	Oral	Parenteral
Effect in weight	Neutral	Reduction
Adverse events	Well tolerated in general	Nauseas, anorexia
Dosing	OD-bid	OD-bid-weekly
Extra pancreatic effects	No	Yes (CV, blood pressure, lipid profile)

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## WHY THE DIFFERENCE?

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## GLP-1 receptor agonists

GLP-1 agonists with > 24 hour duration seem to be associated with:

- Greater HbA1c lowering
- Greater FPG lowering
- Lesser PPG lowering
- Larger Increase in fasting insulin
- Larger decrease in fasting glucagon
- Equivalent weight loss
- Decreased effect on gastric emptying
- Less nausea (except taspoglutide)
- Less associated hypoglycemia
- Larger increase in heart rate

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**QUESTIONS...**  
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