



New insights in the pathophysiology of type 2 diabetes mellitus

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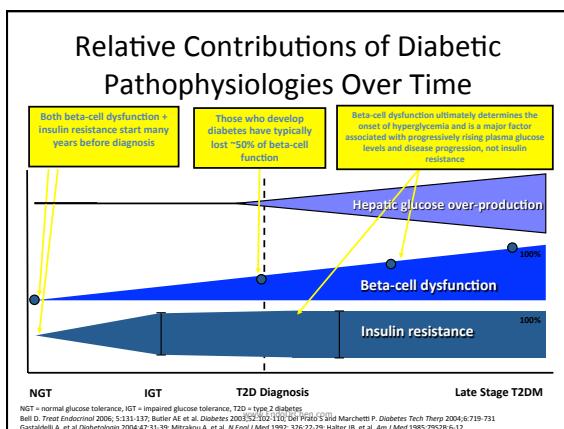
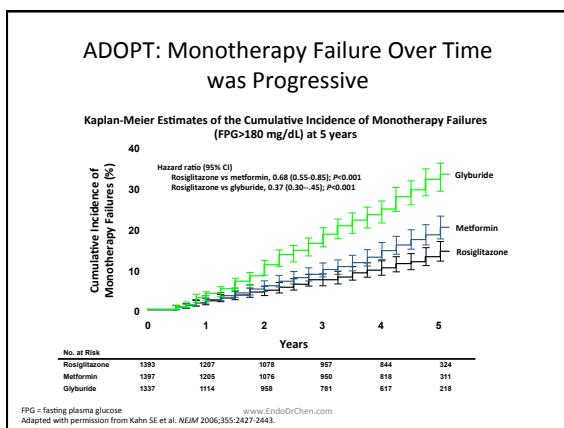
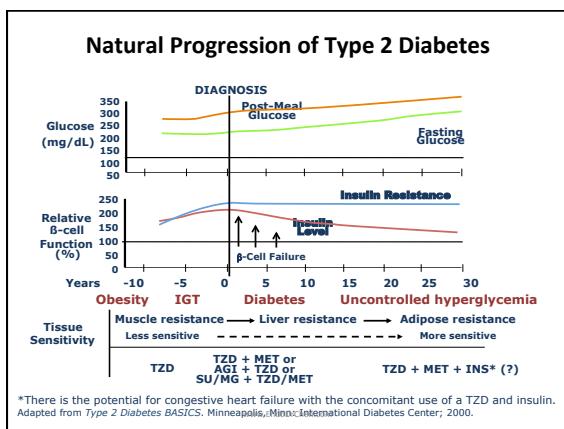
Agenda

- Pathophysiology of type 2 diabetes mellitus
 - Insulin resistance
 - Beta cell dysfunction
 - Alpha cell dysfunction
 - Increased hepatic glucose production
 - Increased renal glucose reabsorption
 - Diminished incretin effect
- Role of incretins
- Pharmacology of incretins

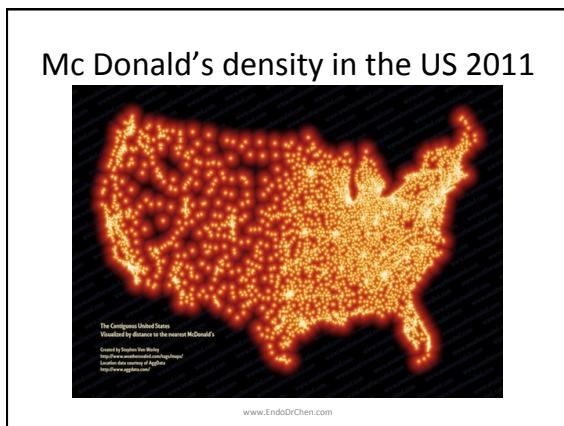
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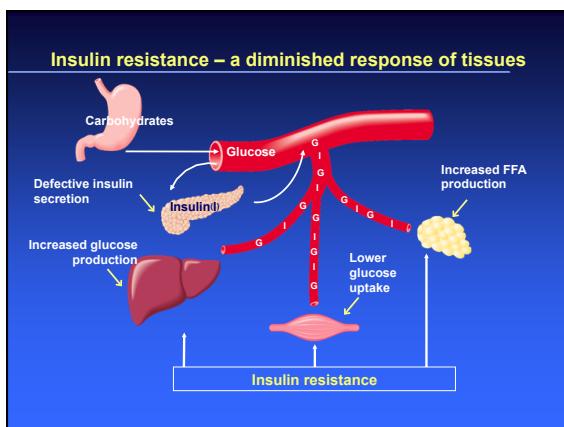
NATURAL HISTORY OF TYPE 2 DIABETES MELLITUS

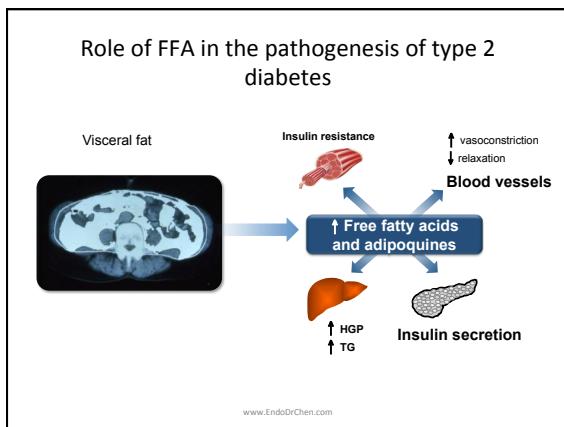
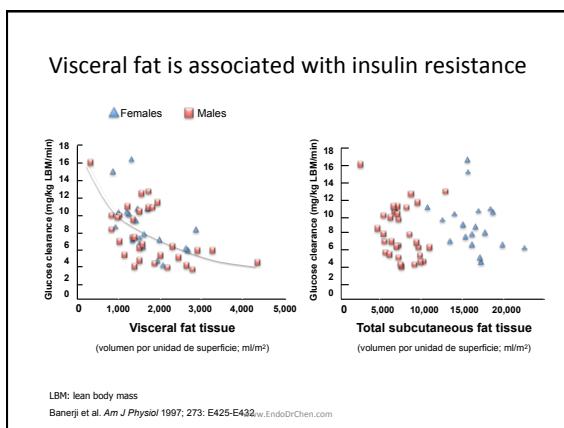
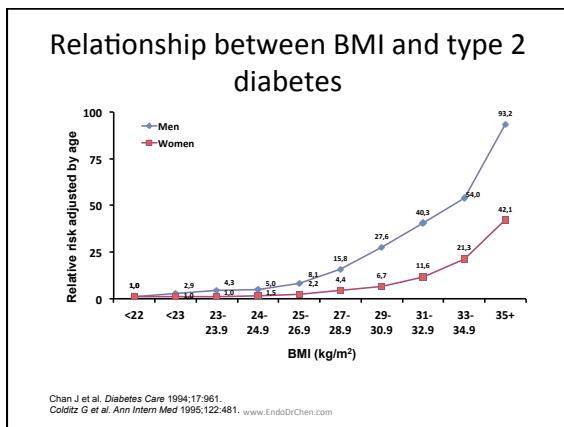
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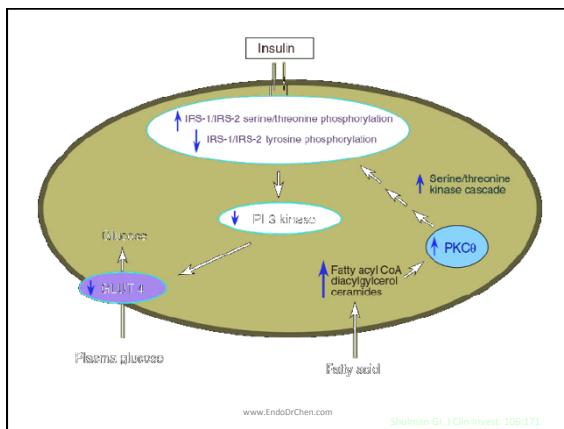


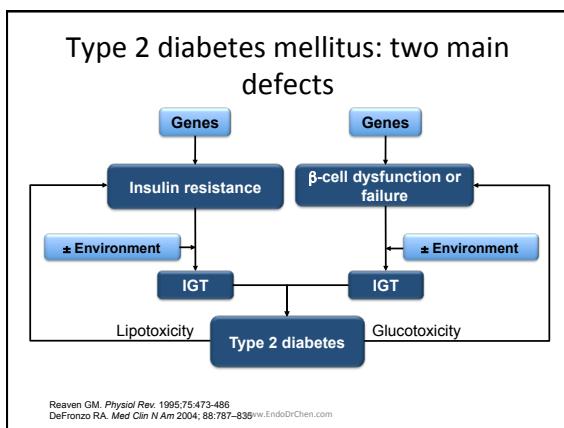




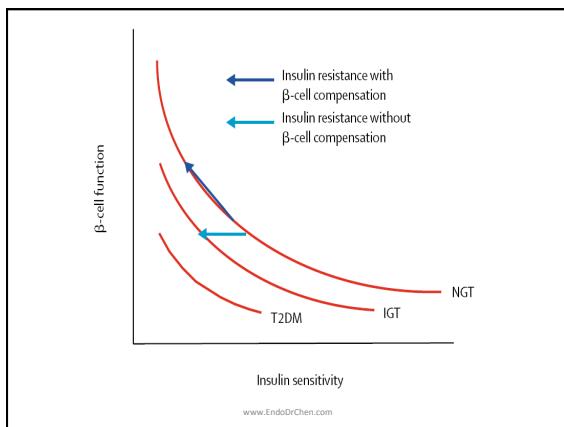
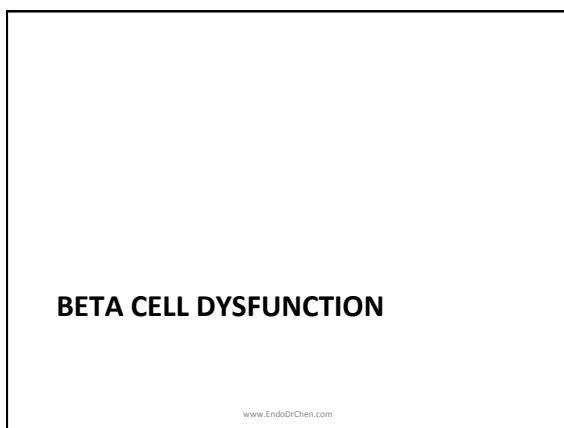
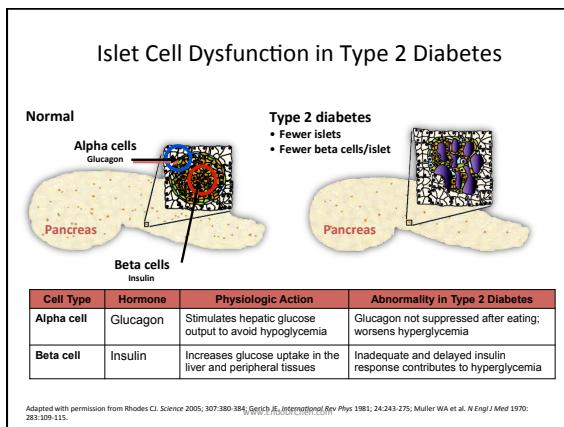


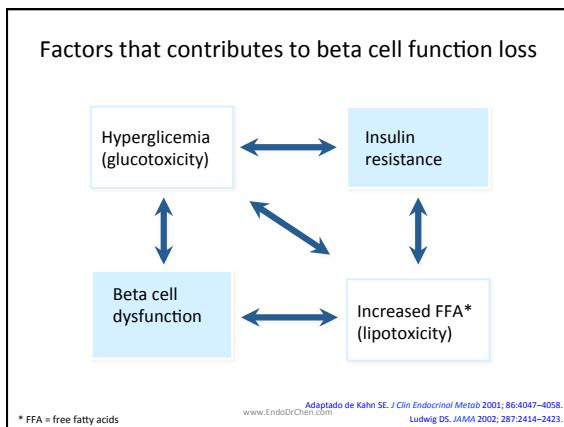
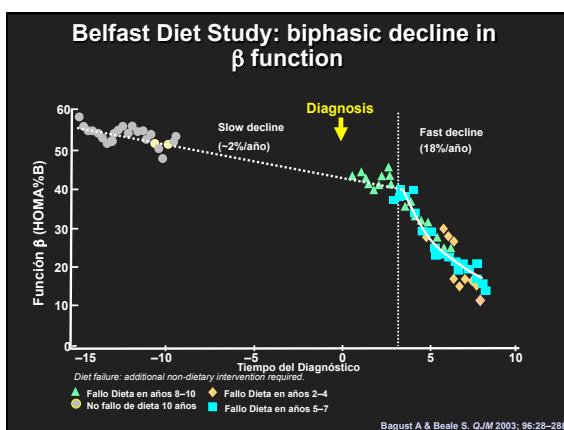
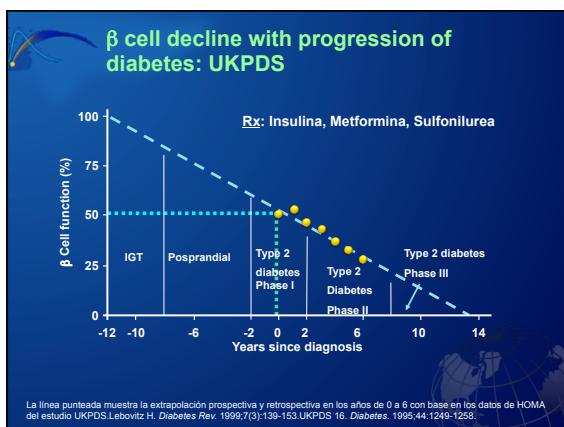


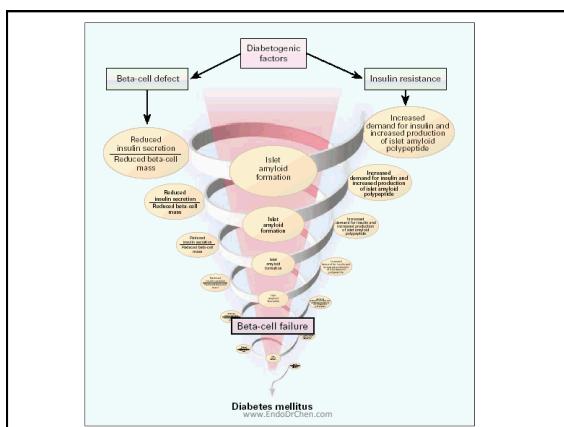
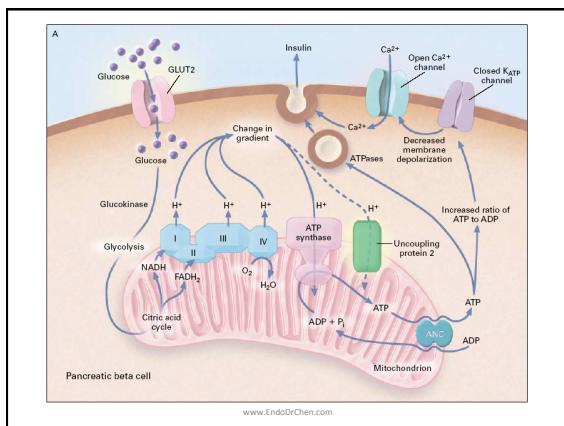
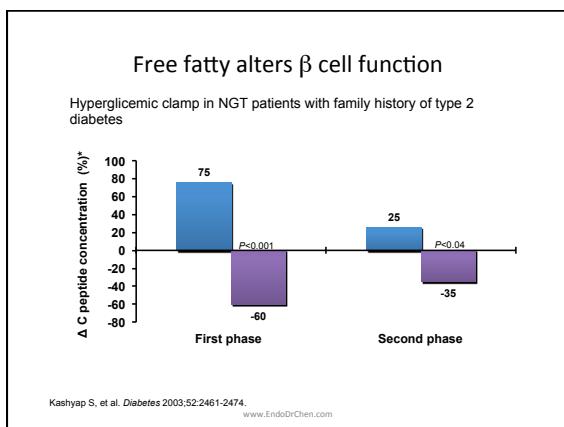


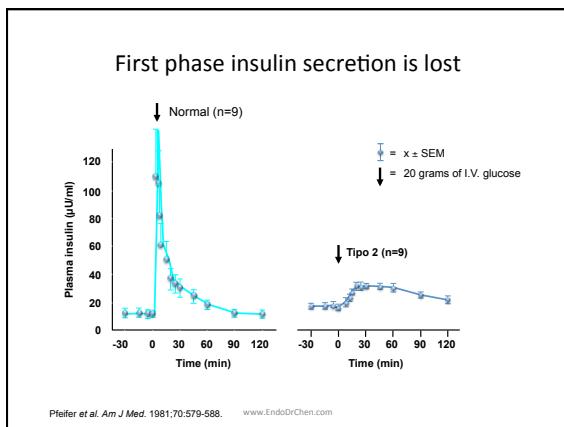
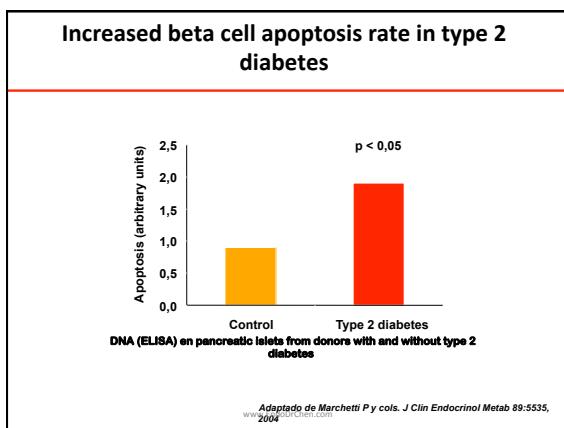
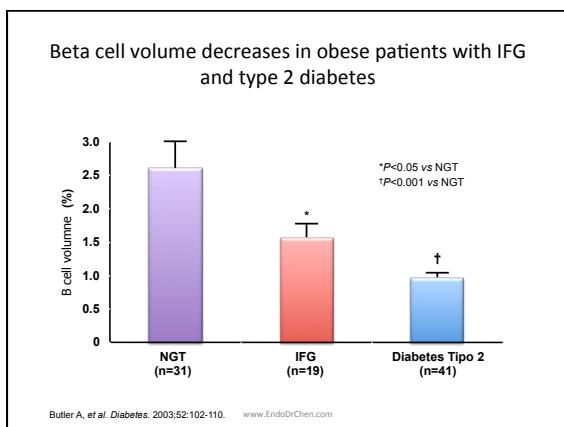


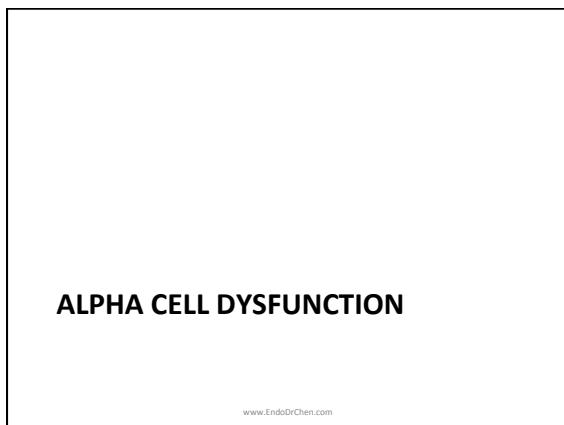


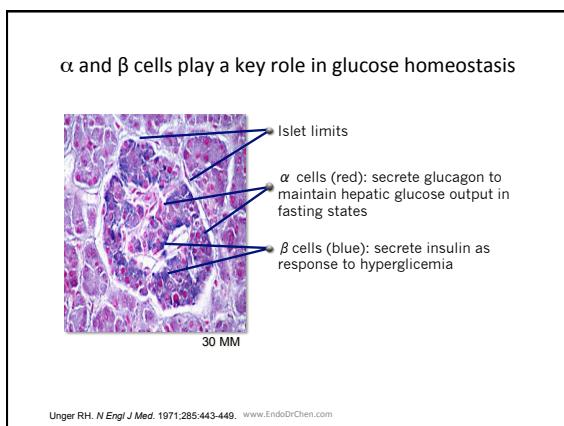


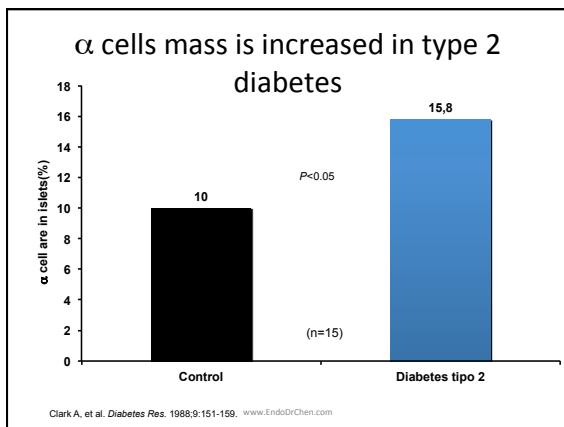


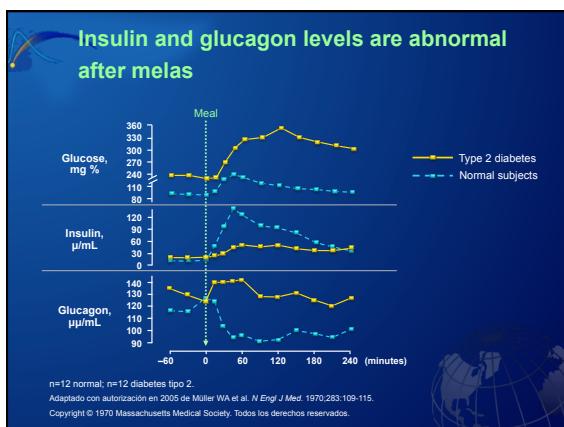
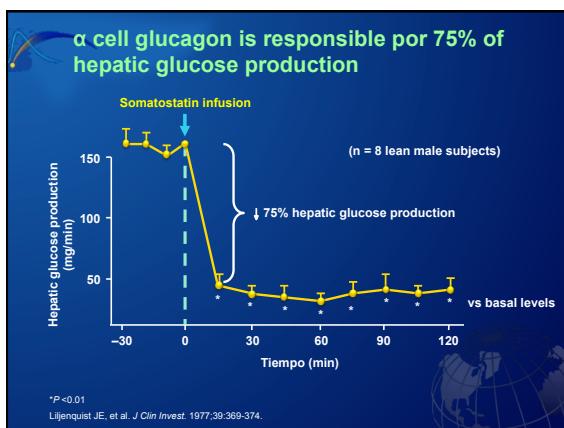
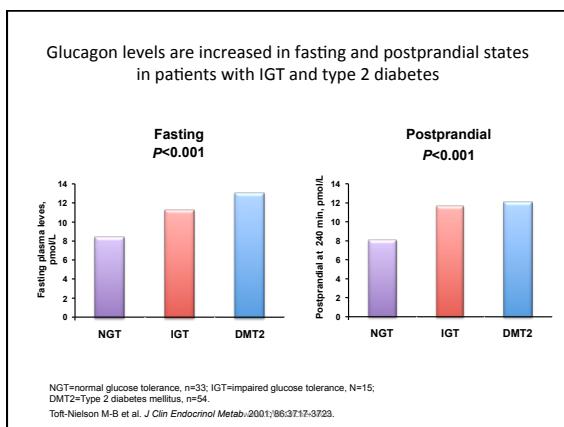


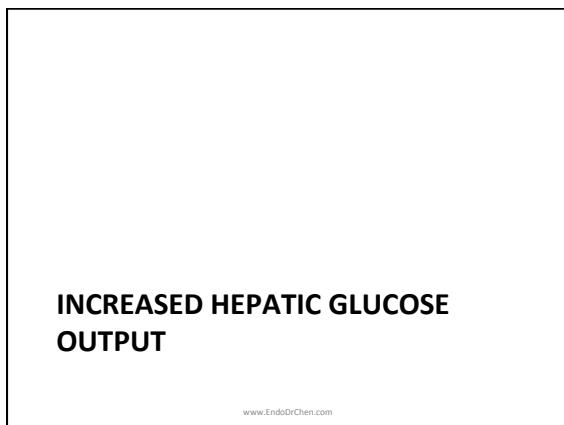


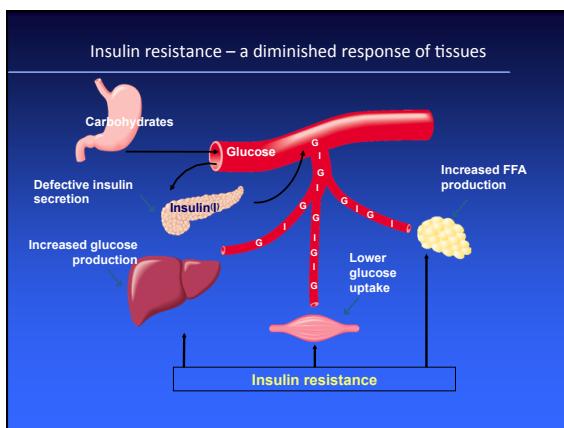


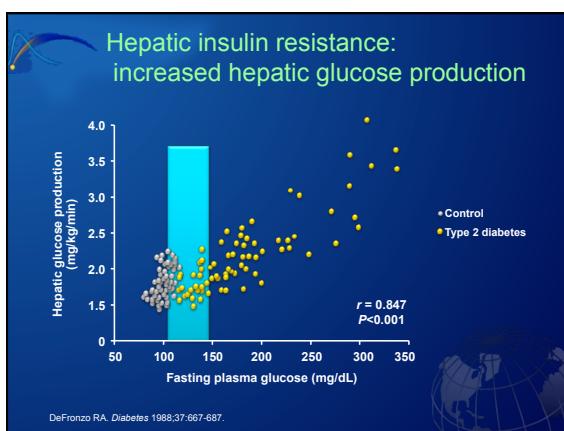


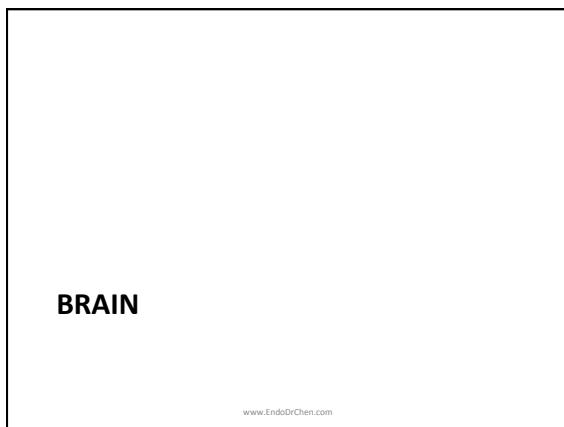
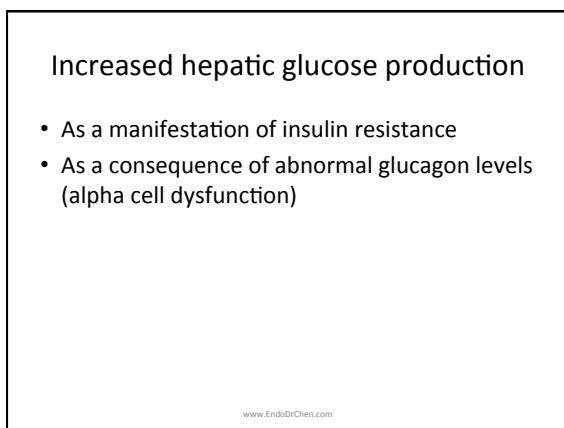
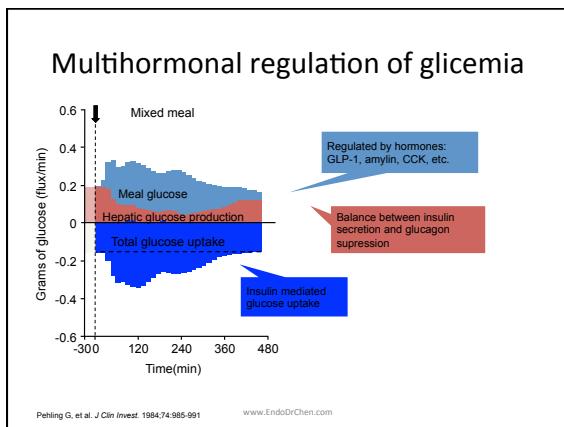


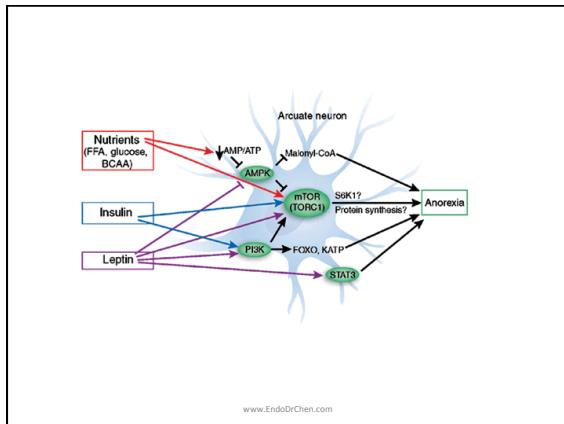


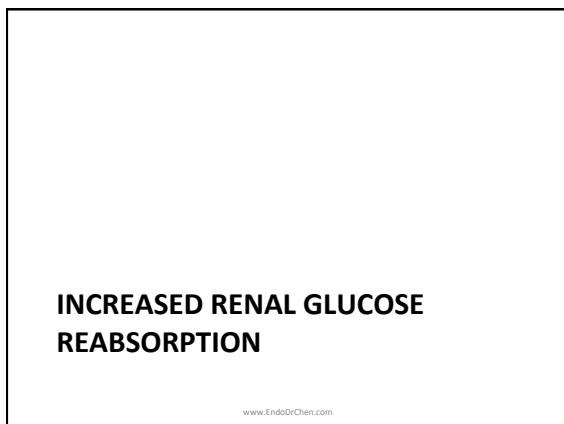


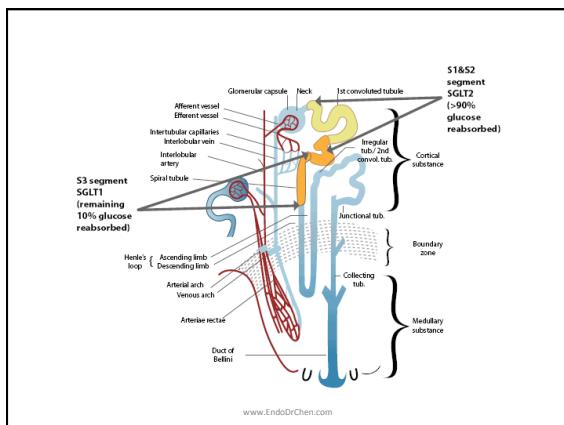


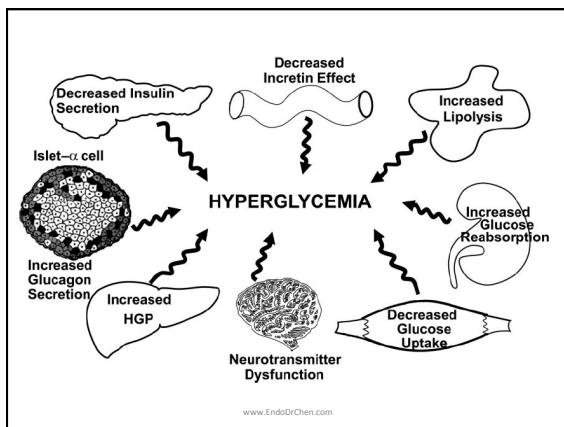
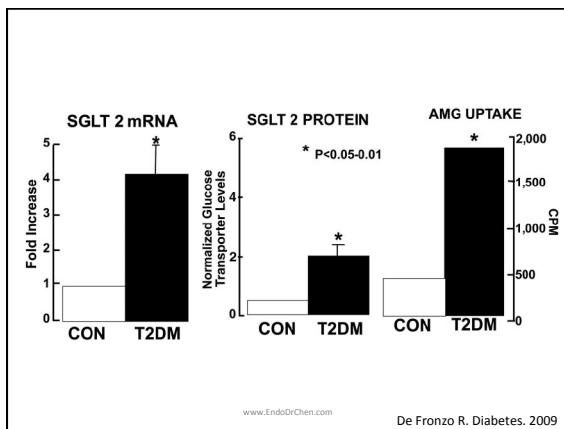


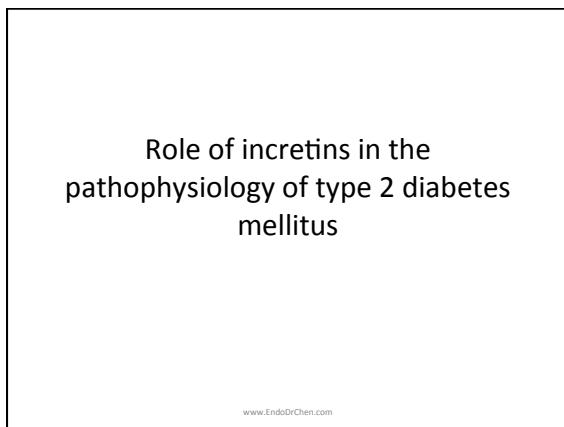


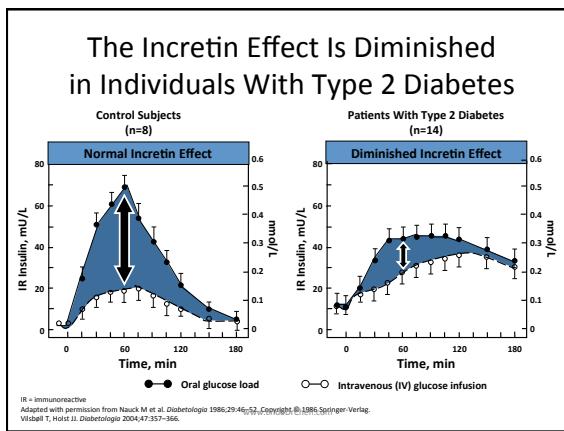


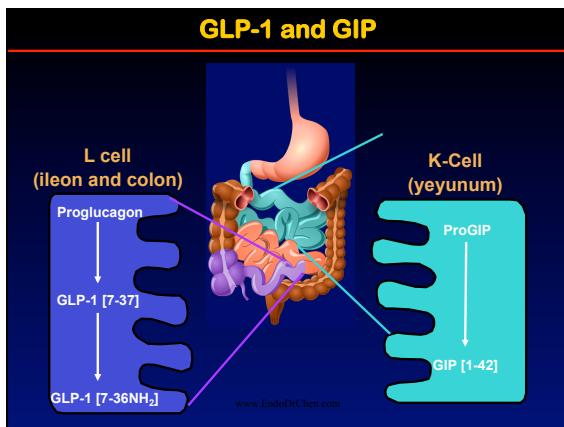












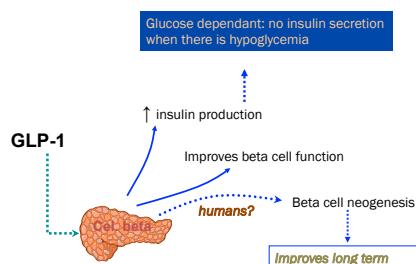
GIP

- Normal levels in type 2 diabetes
- Diminished effect stimulating insulin secretion
- Pharmacologic modulation does not increase insulin secretion

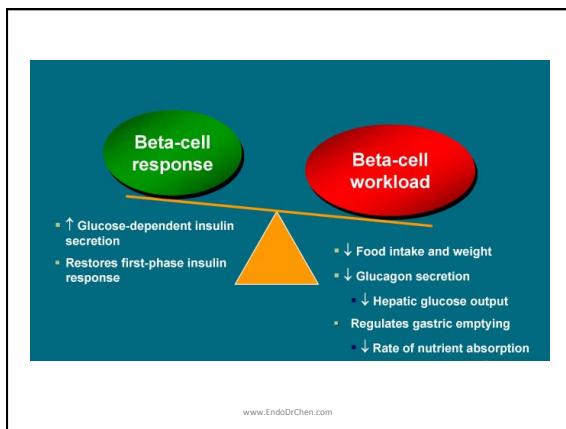
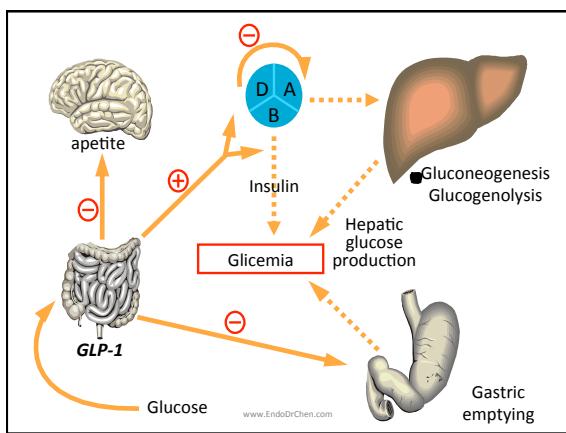
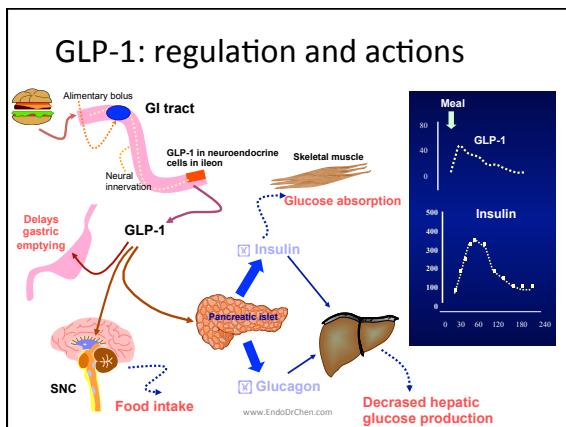
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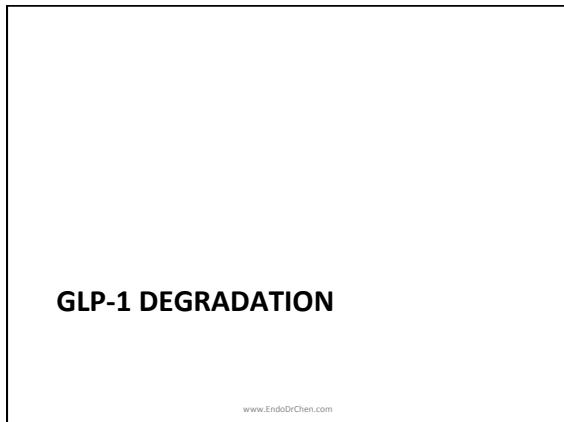
GLP-1

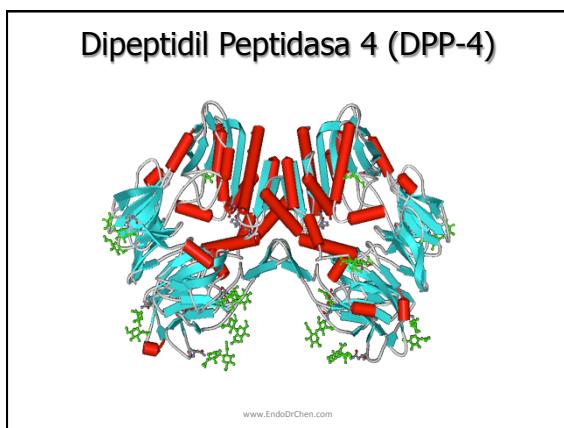
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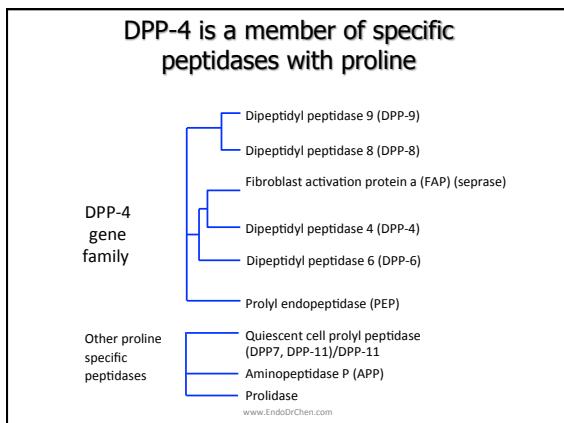
GLP-1: beta cell effects

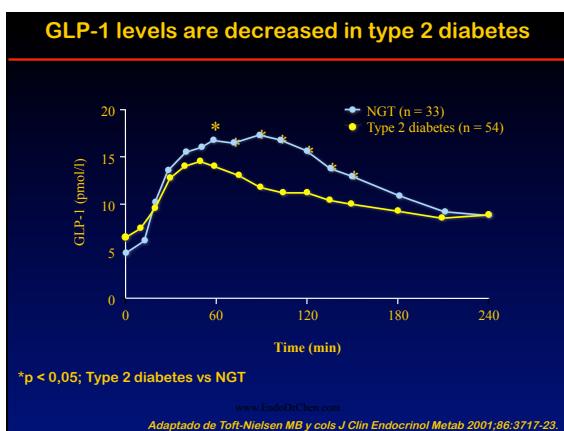
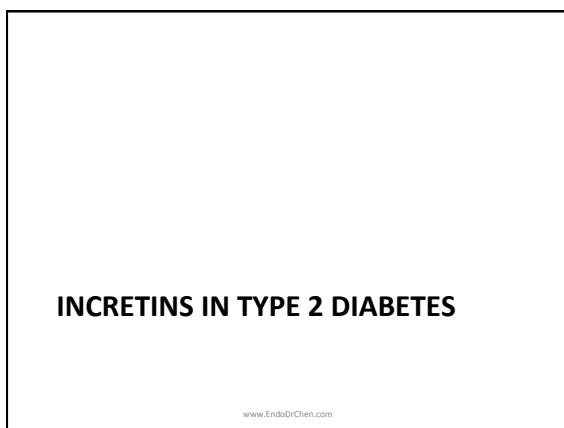
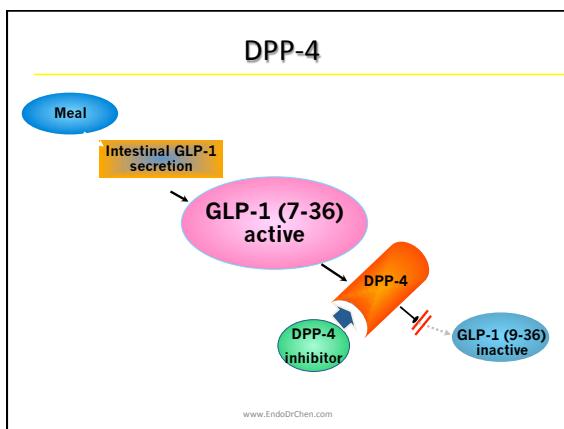
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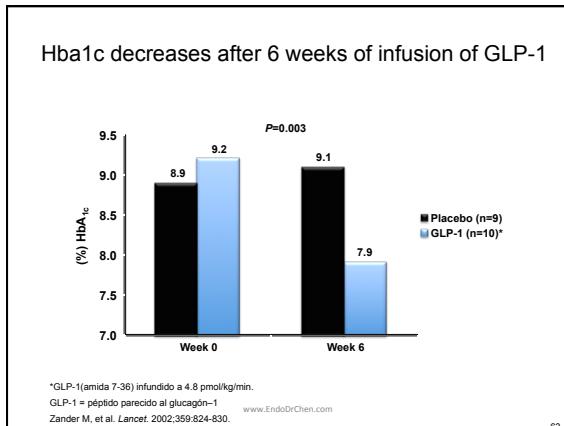
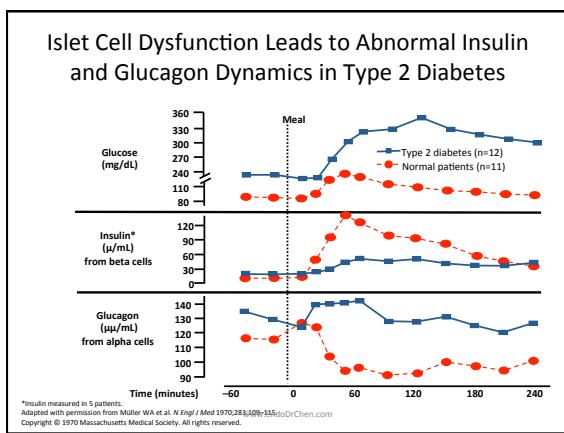
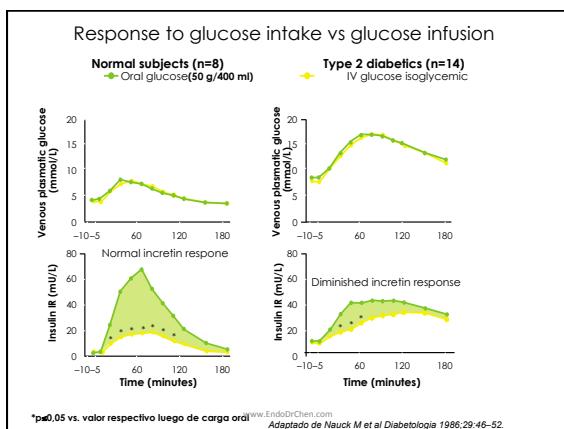


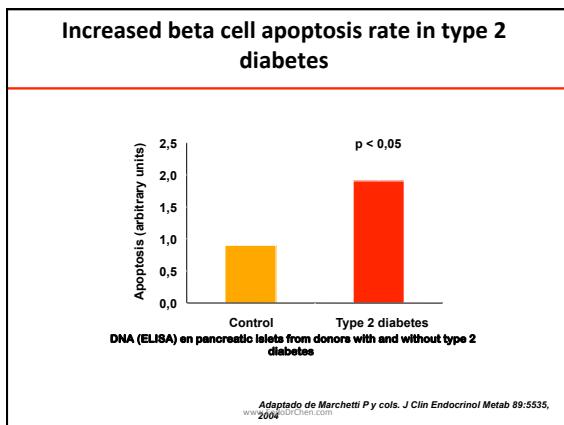
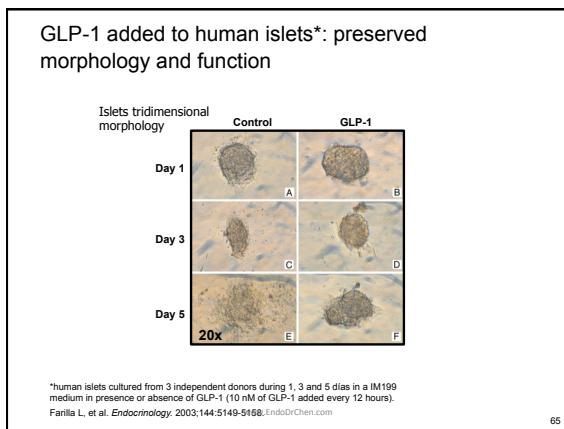
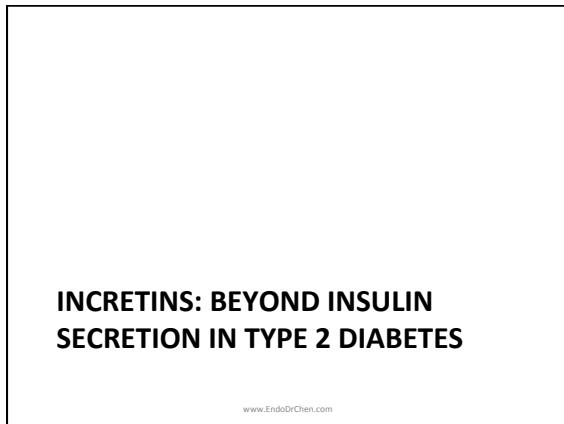


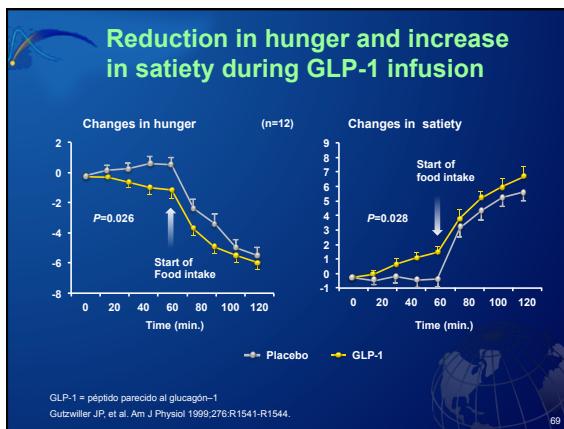
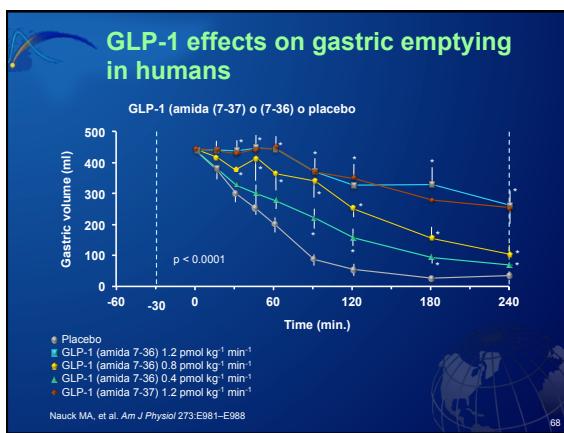
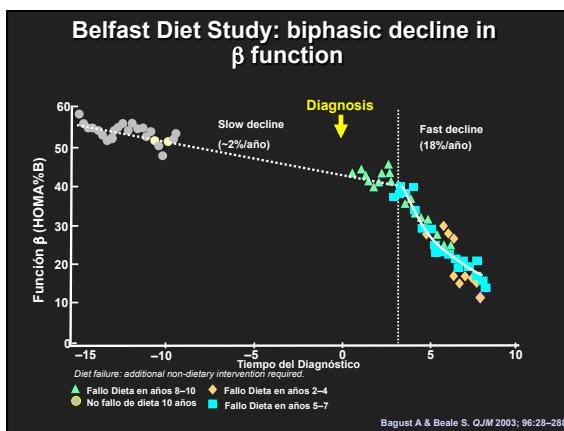


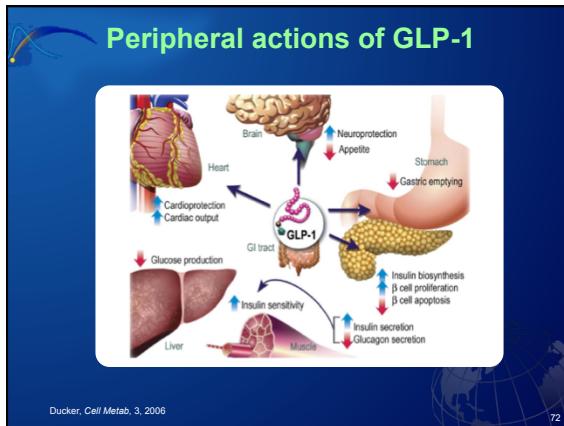
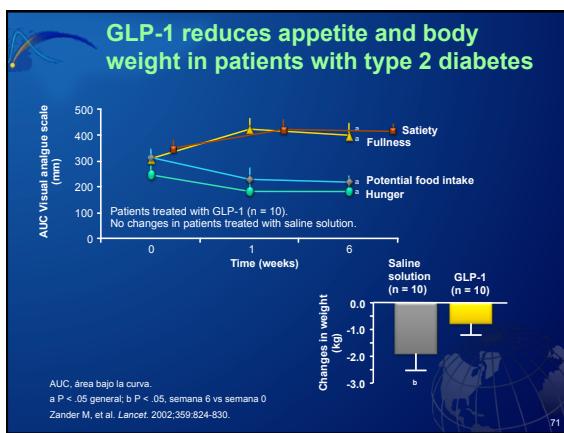
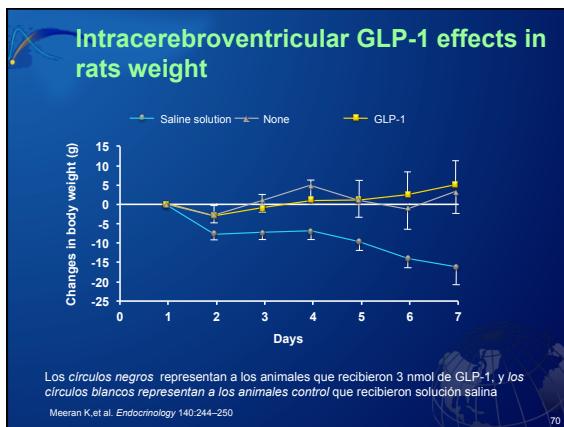


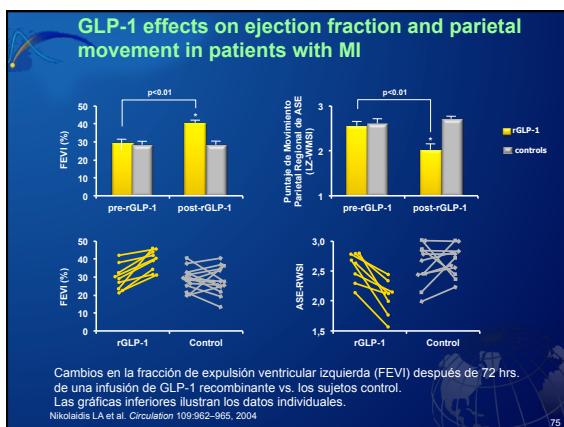
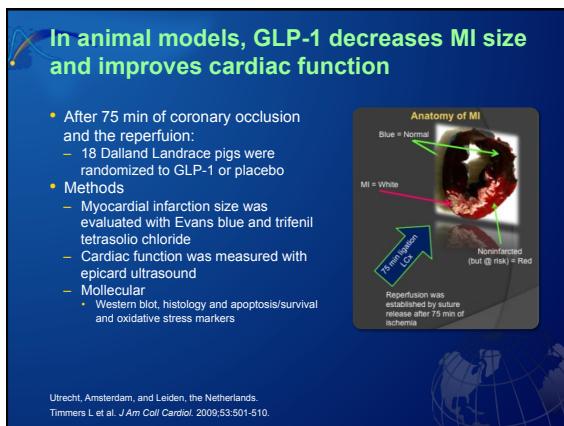
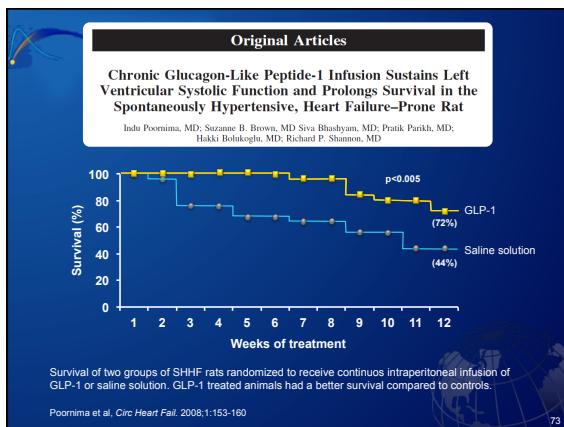


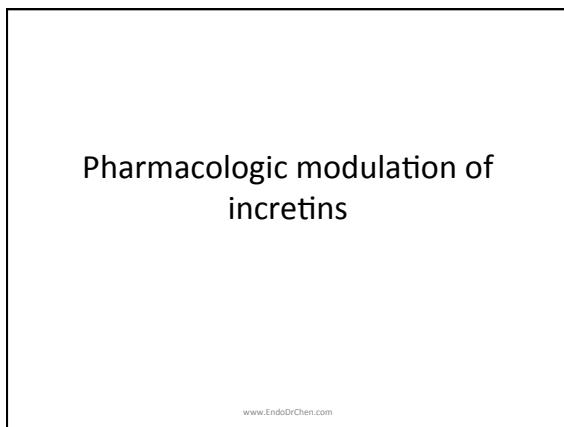
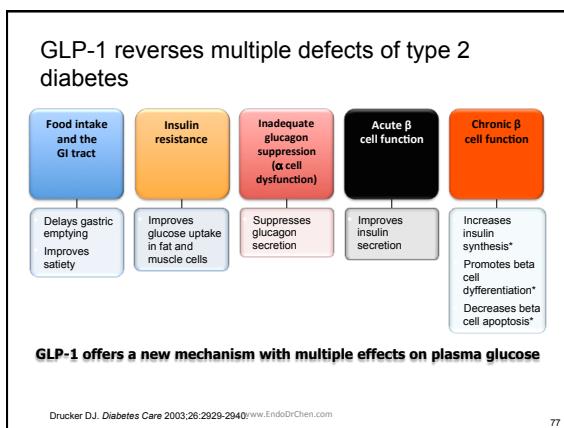
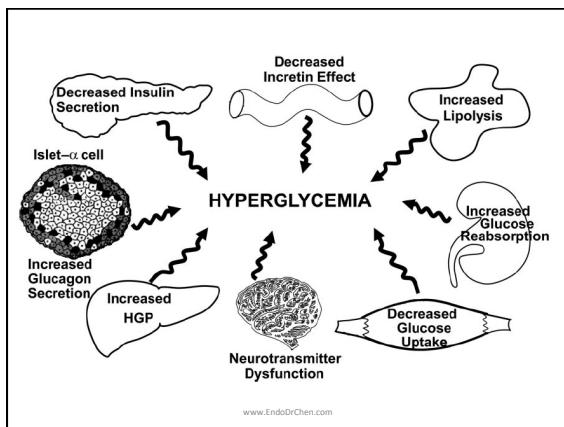








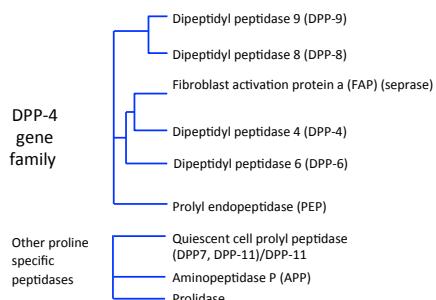




HOW CAN WE INCREASE INCRETIN EFFECTS IN TYPE 2 DIABETICS?

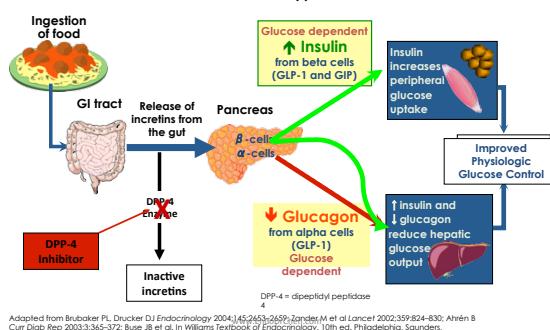
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DPP-4 is a member of specific peptidases with proline



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DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



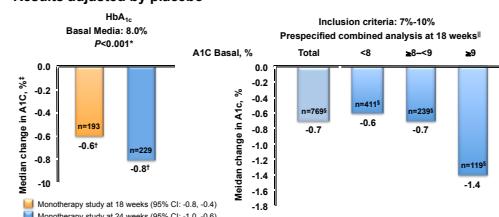
DPP-4 inhibitors

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

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Sitagliptin: reduction in Hba1c in monotherapy

Results adjusted by placebo



Inclusion criteria: 7%-10%
Prespecified combined analysis at 18 weeks^c
Total n=769^d
<8% n=411^e
≥8-<9% n=239^f
≥9% n=119^g

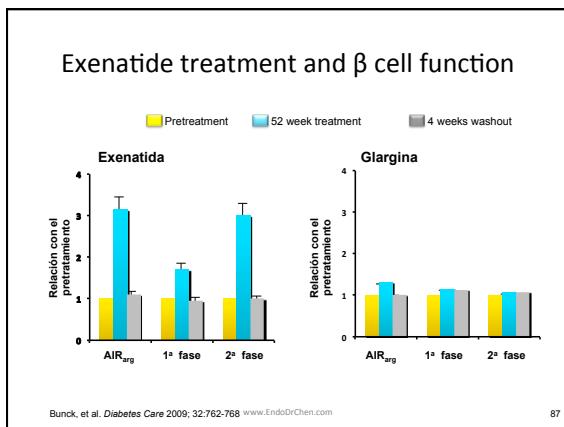
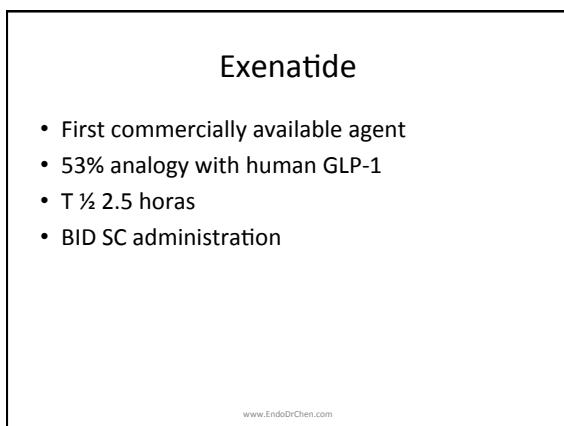
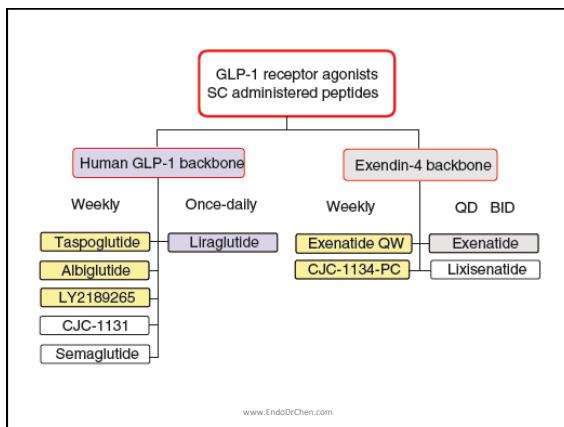
Ci=Confidence interval.

^aComparado con el placebo. ^bAjuste de los cuadros mínimos según el estado de la terapia antihiperglucémica previa y el valor basal. ^cDiferencia respecto al placebo. ^dNúmero combinado de pacientes tratados con JANUVIA o un placebo. ^eP=0.001 total y para las interacciones del tratamiento por subgrupo.

^fRaz I et al. *Diabetologia*. 2006;49:2564-2571. ^gAschner P et al. *Diabetes Care*. 2006;29:2632-2637.

GLP-1 ANALOGUES

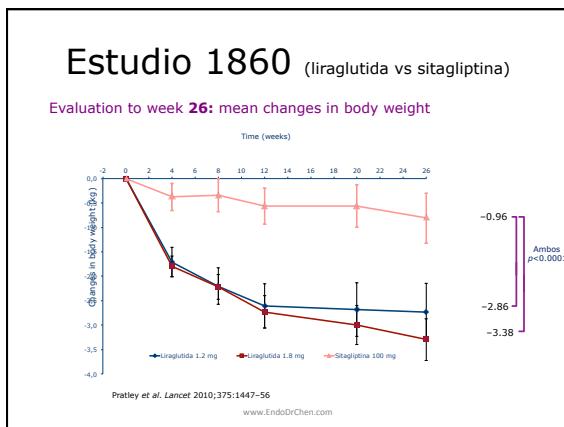
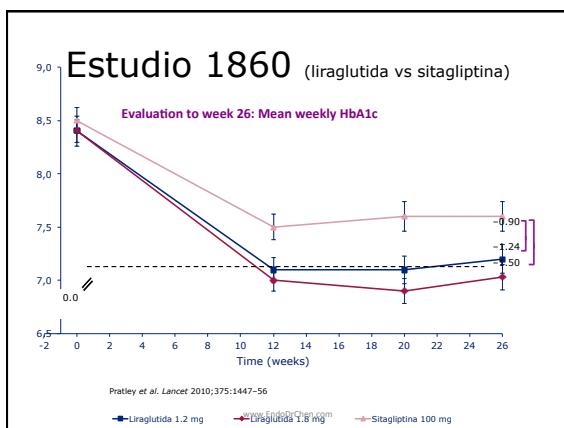
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Liraglutide

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

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

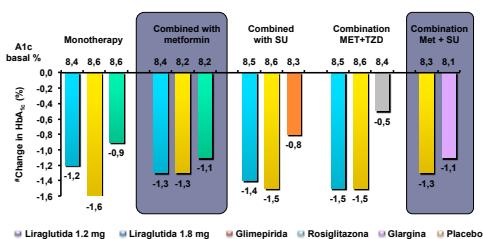


DURATION-6

- Exenatide weekly vs liraglutide
- Hba1c
 - 1.48% liraglutide
 - 1.26% exenatide
- Greater weight loss with liraglutide (-3.6 vs -2.7 kg)
- Higher incidence of subcutaneous nodules with exenatide weekly (10%) compared to liraglutide (1%)

www.EndoDrChen.com Buse JB. EASD 2011. Abstract 75.

Reduction in Hba1c with liraglutide

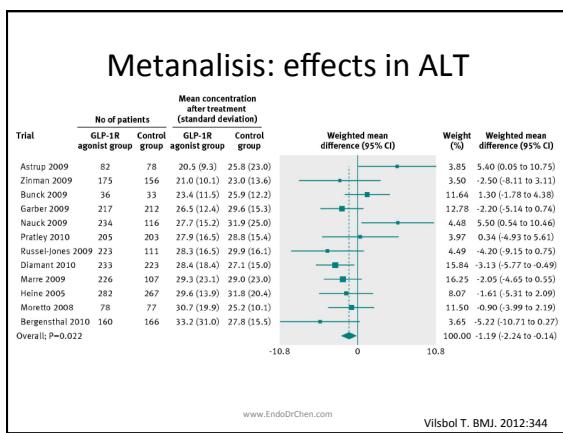
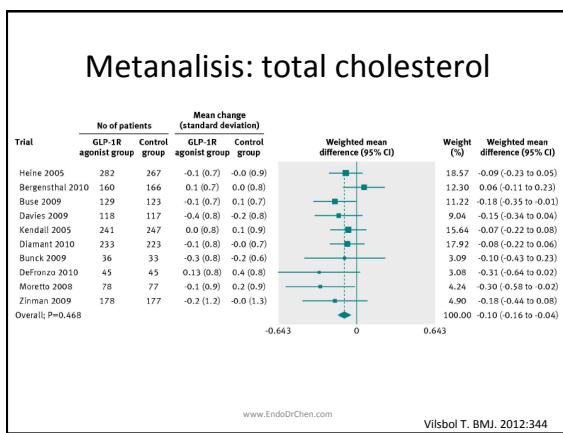
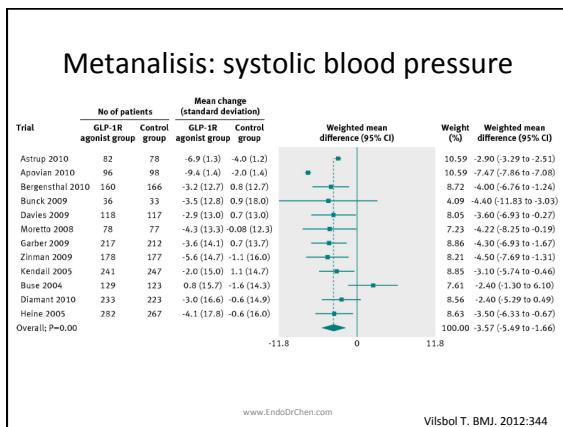


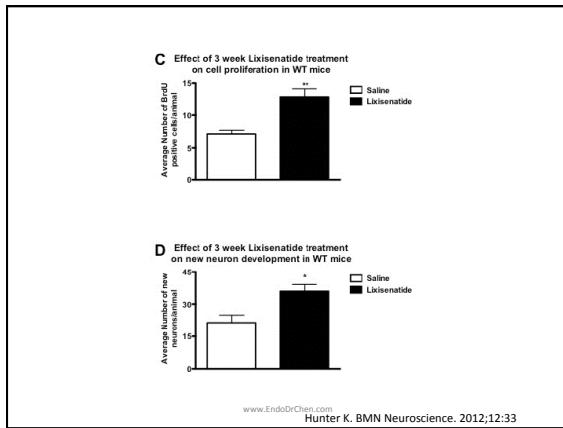
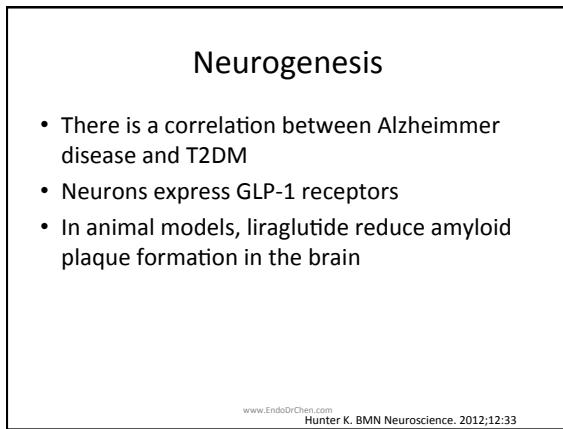
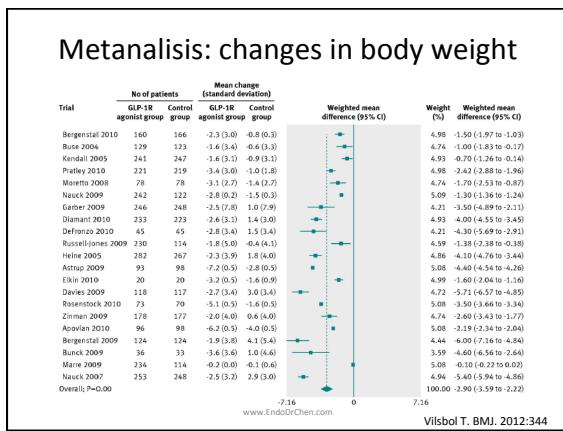
Significativo *vs. el comparador; #Cambio en HbA1c a partir del valor basal en la población global (LEAD 4.5) agregado al fallar la dieta y ejercicio (LEAD 3); o agregado a monoterapia previa con hipoglucemiantes orales (LEAD 2.1).

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OTHER FUNCTIONS: NEUROPROTECTION AND CARDIOVASCULAR

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ARE ALL GLP-1 RECEPTOR AGONISTS THE SAME?

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Human GLP-1 backbone

- Weekly
- Taspoglutide
- Albiglutide
- LY2189265
- CJC-1131
- Semaglutide

Exendin-4 backbone

- Once-daily
- Liraglutide
- Exenatide QW
- CJC-1134-PC

Weekly

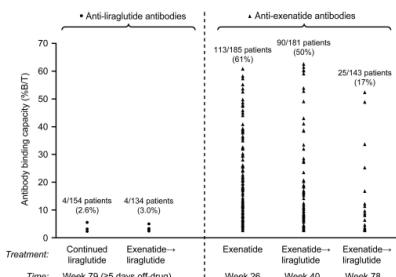
QD BID

Exenatide

Lixisenatide

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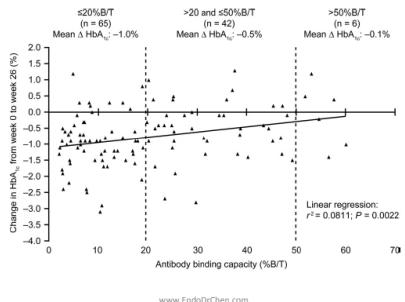
Antibodies



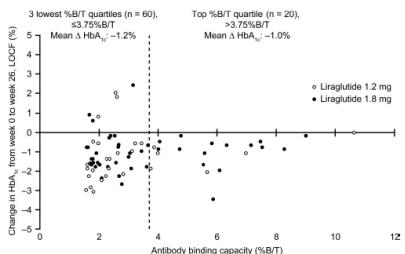
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Buse JB. J Clin Endocrinol Metab. 2011;96:1695

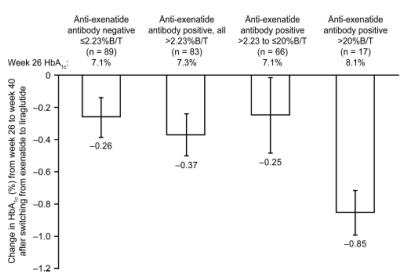
Ac antixenatide – reduction in Hba1c

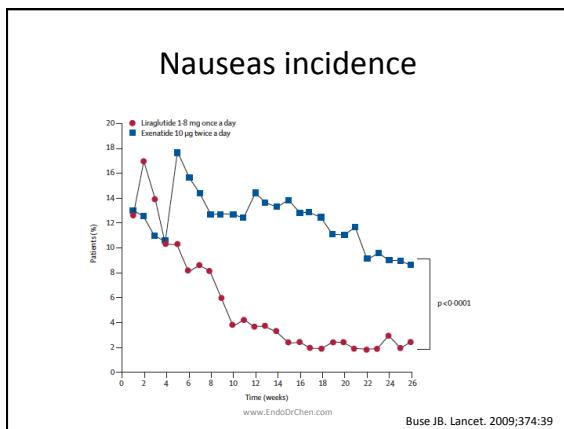
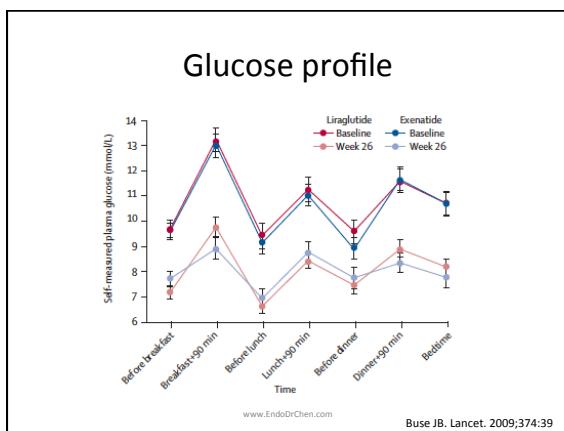


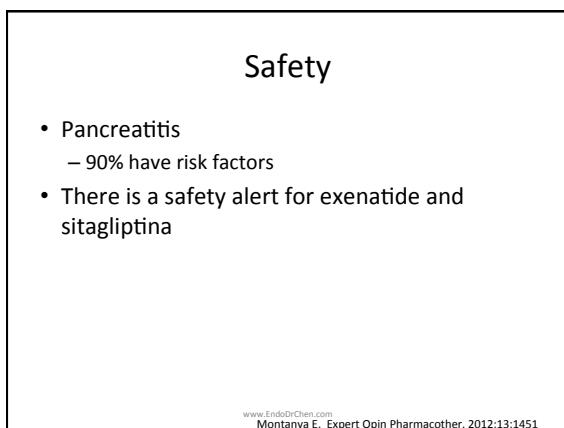
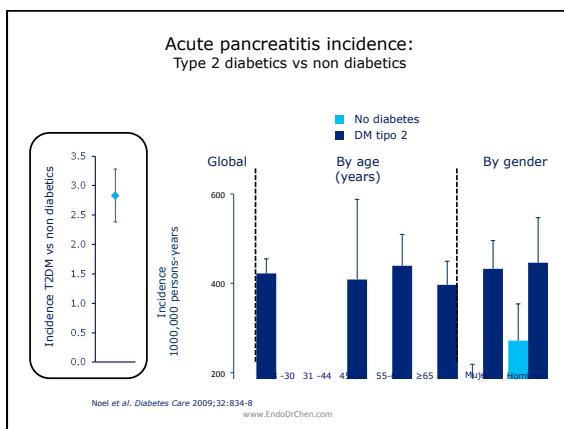
Ac antiliraglutide – reduction in Hba1c



Ac anti exenatide





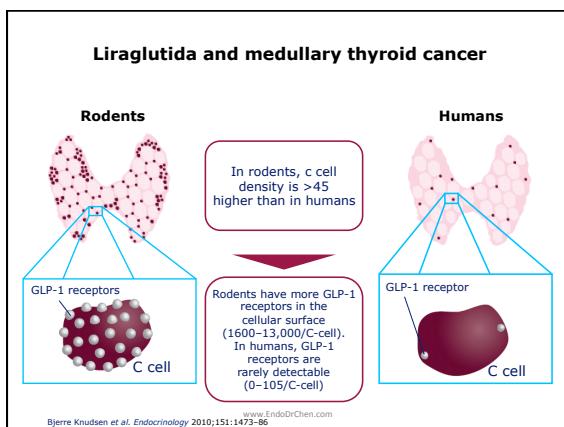


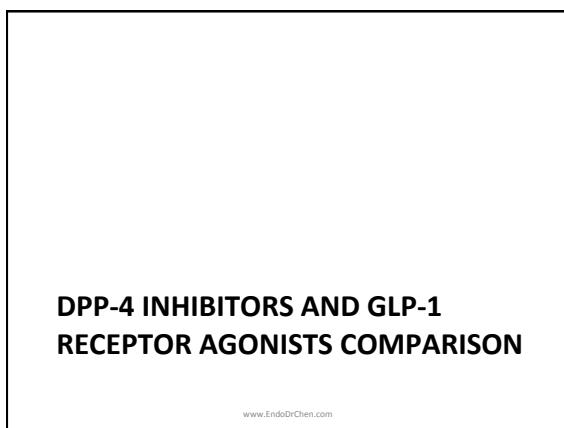
Incidence of pancreatitis in studies with liraglutide that have ended by February 28 2011

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

* number of cases / 1000 patient years of exposure
In a diabetic population with an incidence of 1.5–4.5/1000 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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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 tasoglutide)
- Less associated hypoglycemia
- Larger increase in heart rate

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Conclusiones

- Multiple pathophysiologic defects in type 2 diabetes
- GLP-1 may explain some of these defects
- GLP-1 receptor agonists are a promising therapy for type 2 diabetes

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QUESTIONS...
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