Incretins in Diabetes: Physiology, Pharmacology and Mythology

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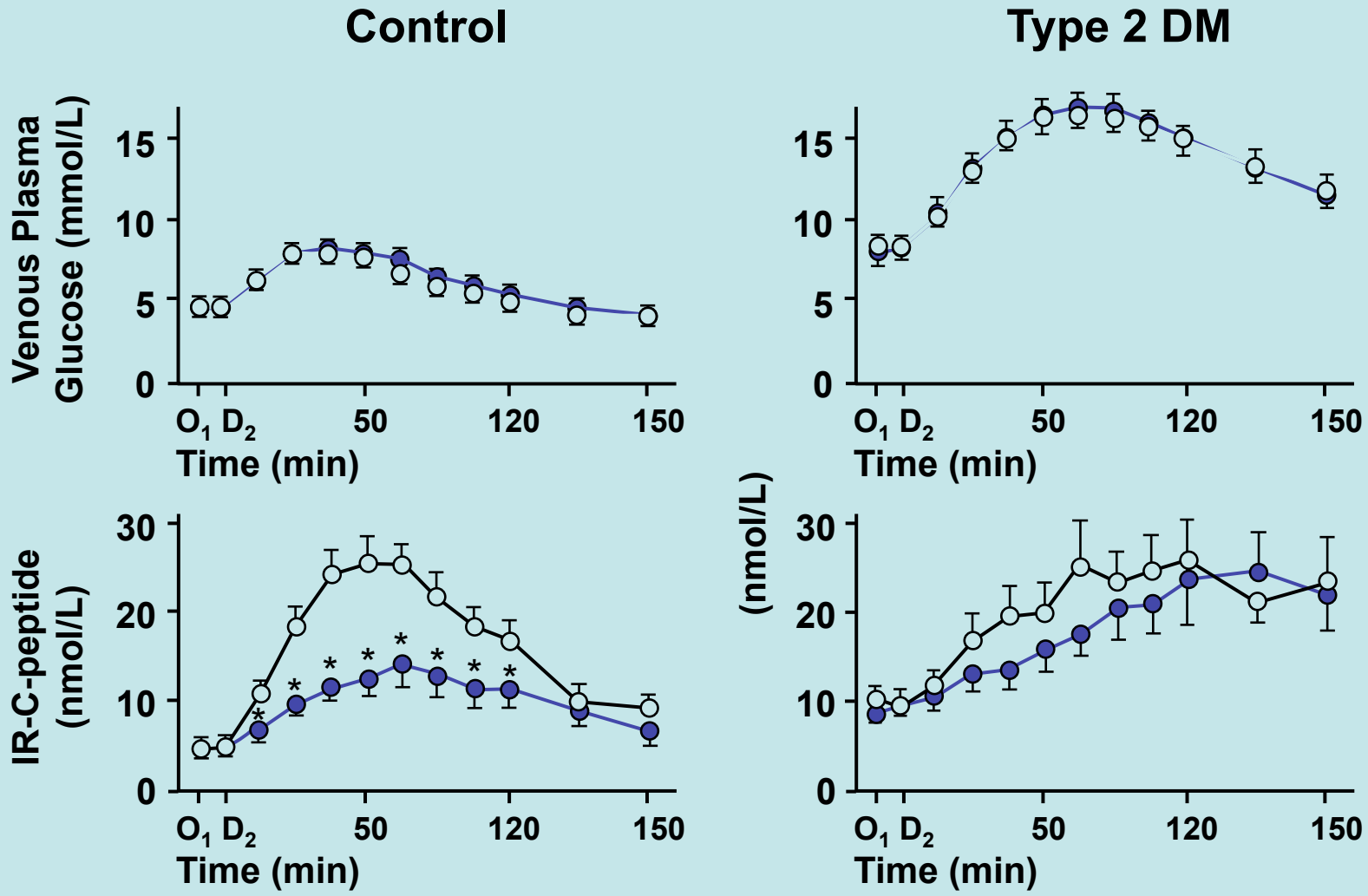
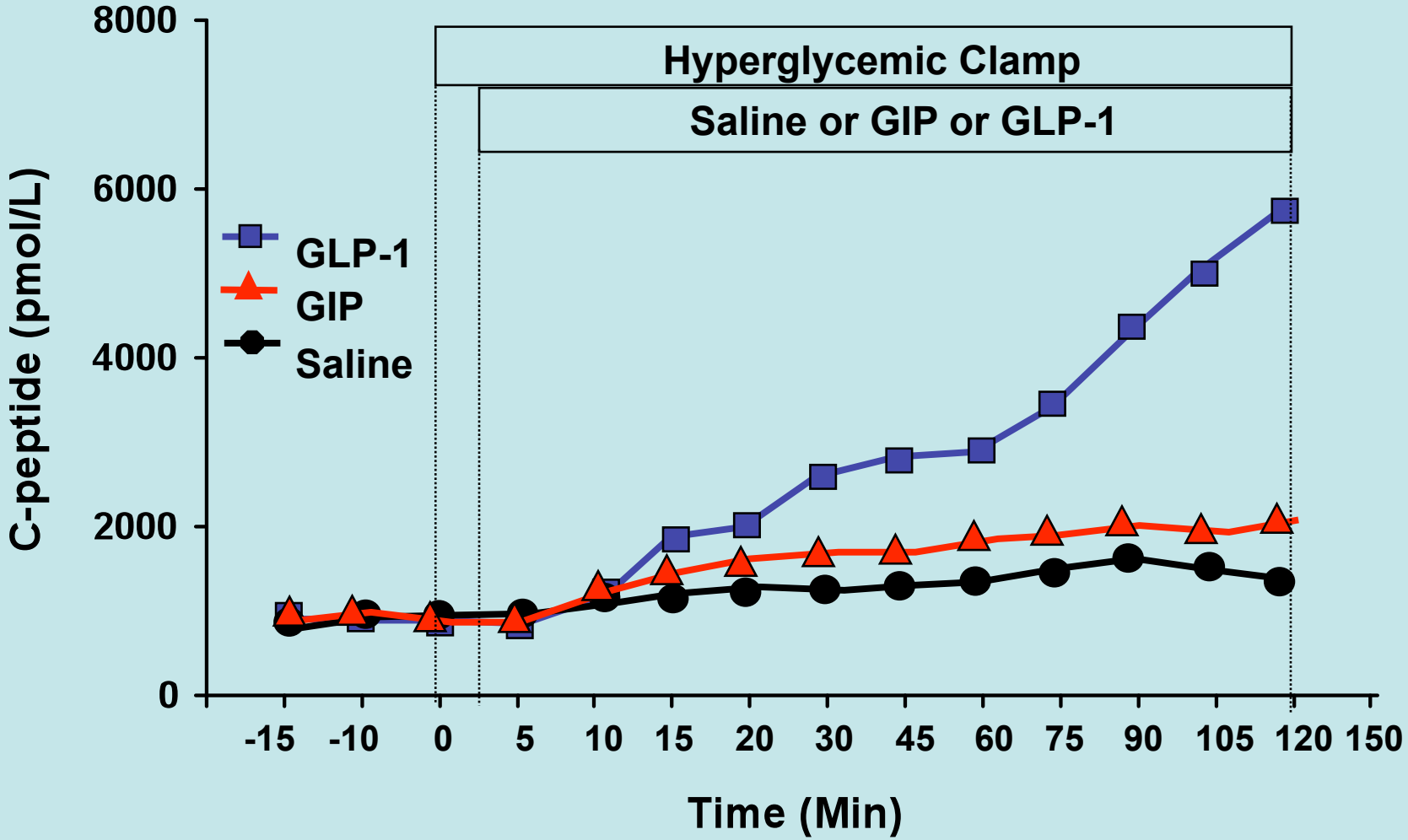
The Incretin Effect in T2DM



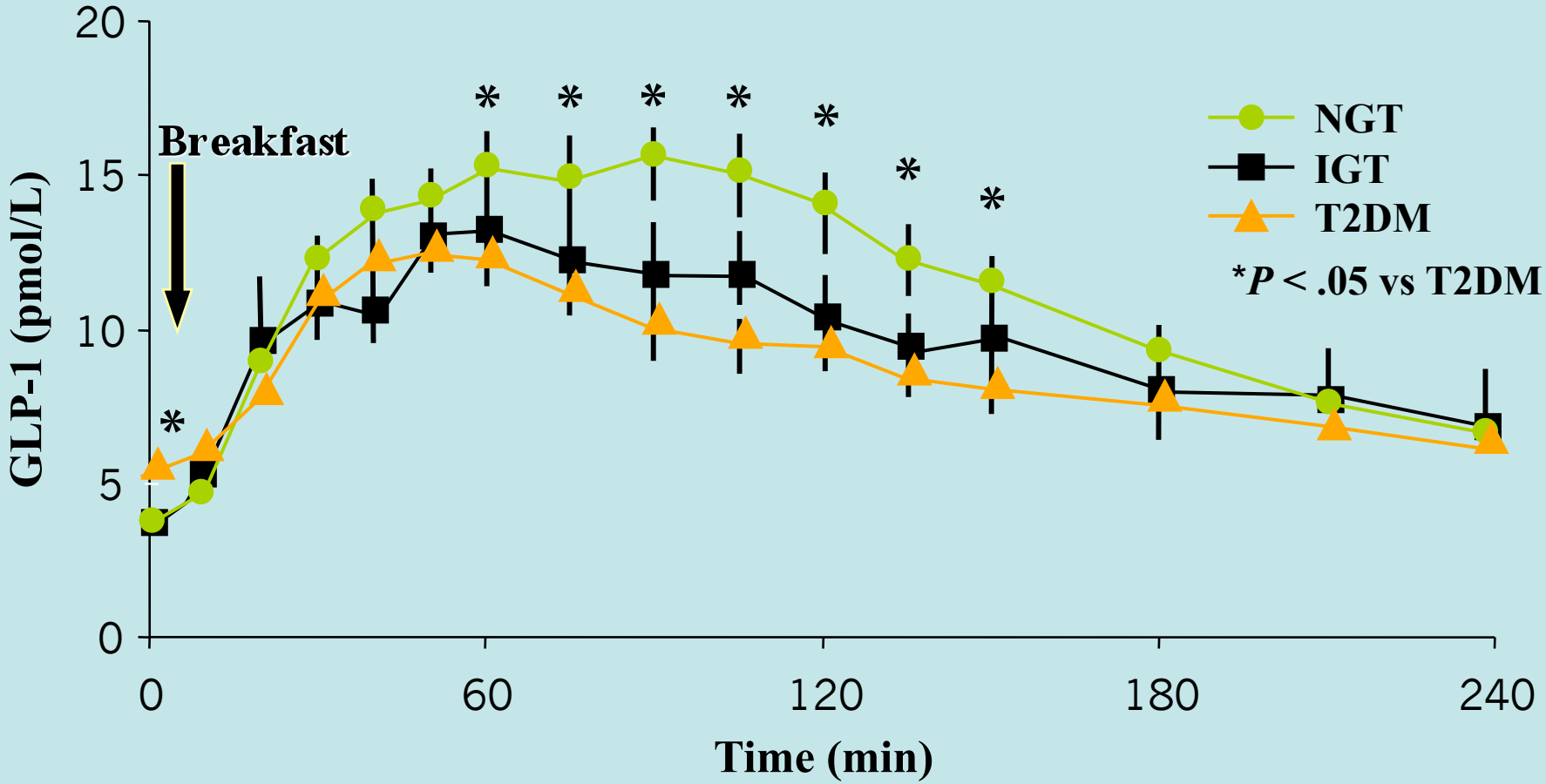
Nauck M, et al. *Diabetologia.* 1986;29:46-52. Copyright © 1986 Springer-Verlag.

Effectiveness of Incretins to Stimulate Insulin Secretion in Patients With T2DM



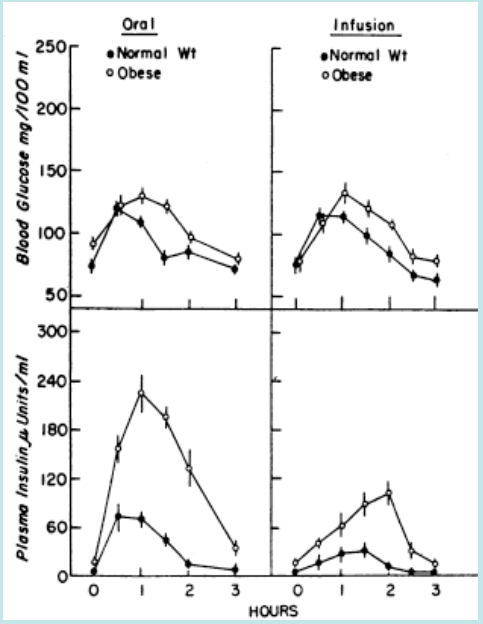
Data from Vilsboll T, et al. *Diabetologia.* 2002;45:1111-1119.

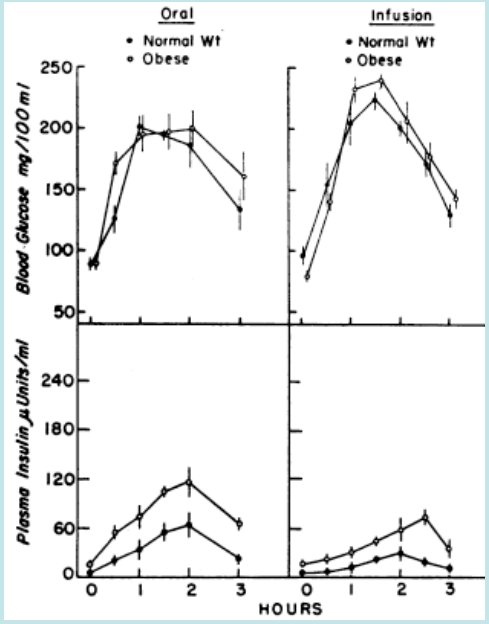
Release of GLP-1 Is Impaired in Patients With T2DM



Toft-Nielsen MB, et al. *J Clin Endocrinol Metab.* 2001

The “original” incretin effect in Diabetes



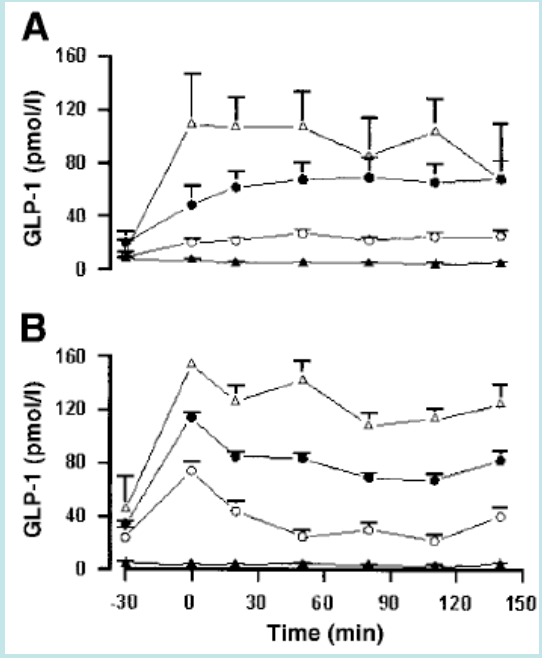


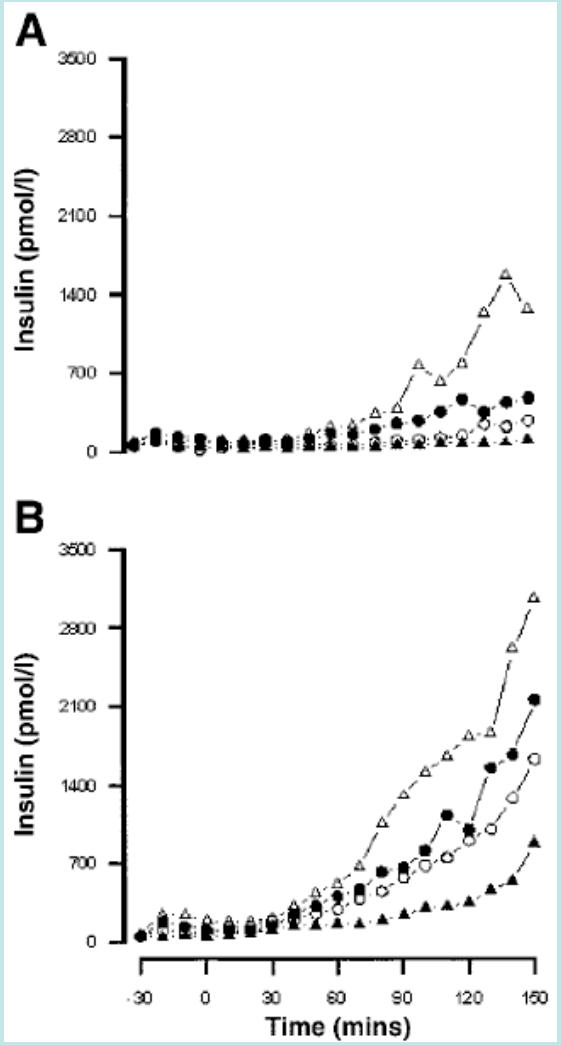
Insulinogenic effectiveness of the alimentary and glycemic components of glucose-stimulated insulin secretion

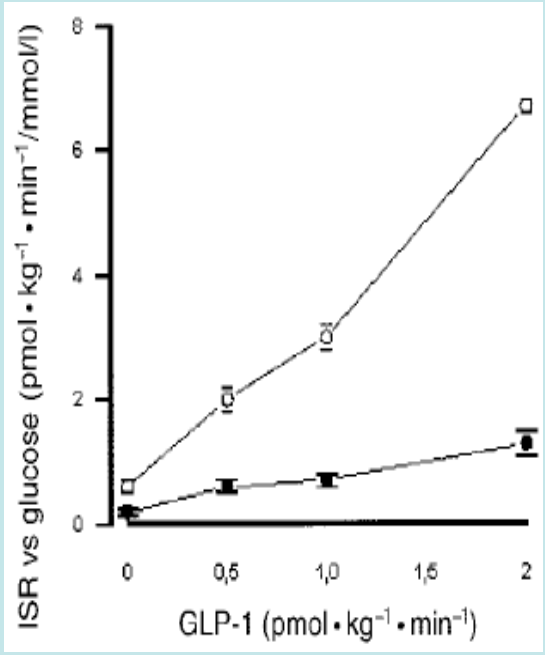
Subjects	Alimentary	Glycemic	
		“Normal profile”	“Diabetic profile”
		μU-min ml⁻¹/g of glucose	
Normal	54.9	65.5	64.1
Obese	170.6	210	226
Normal wt diabetics	33.5	27.1	46.5
Obese diabetics	65.2	107.2	68.9

M Perley, D Kipnis, JCI 1967

β-cell sensitivity to GLP-1 in T2DM and non-DM

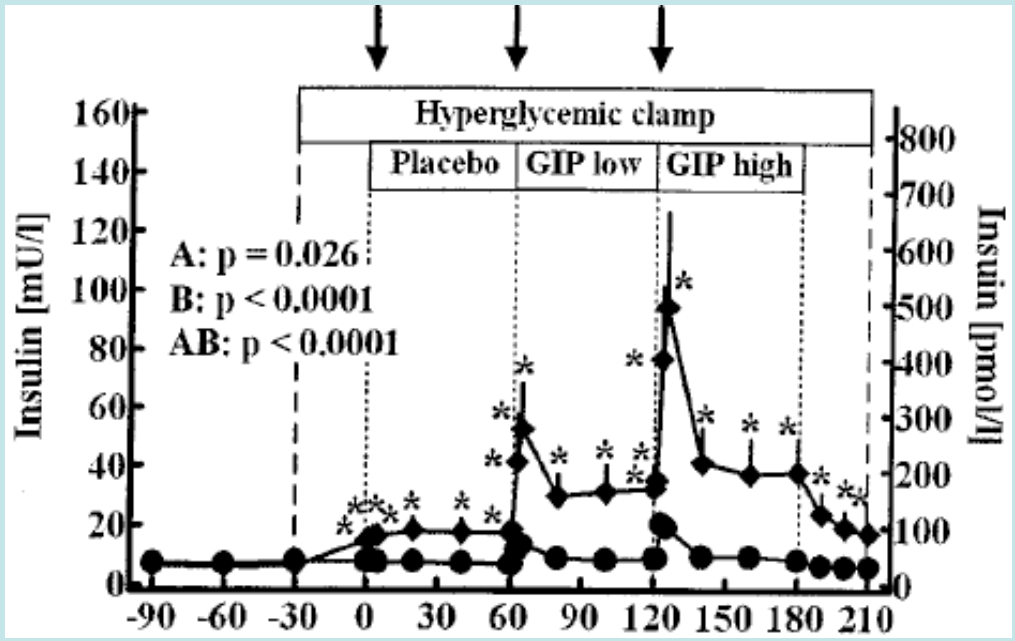


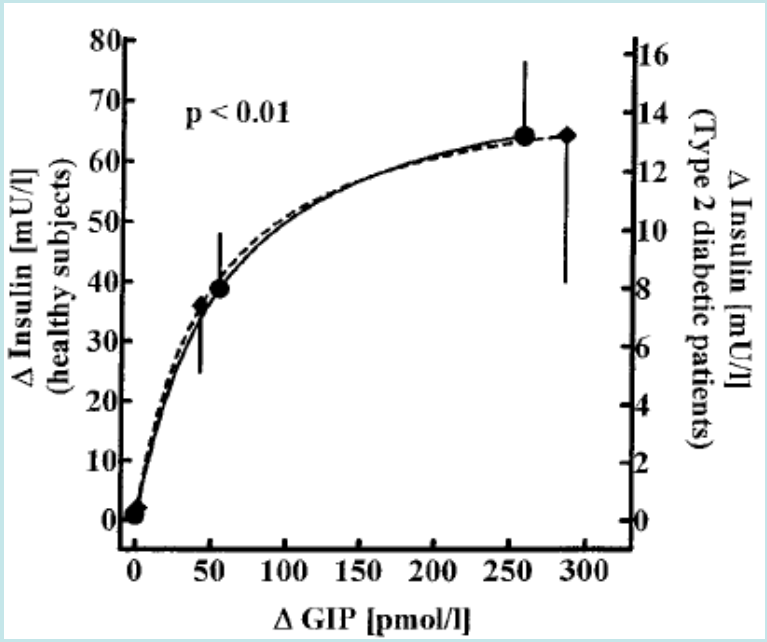




L Kjems et al, Diabetes 2003

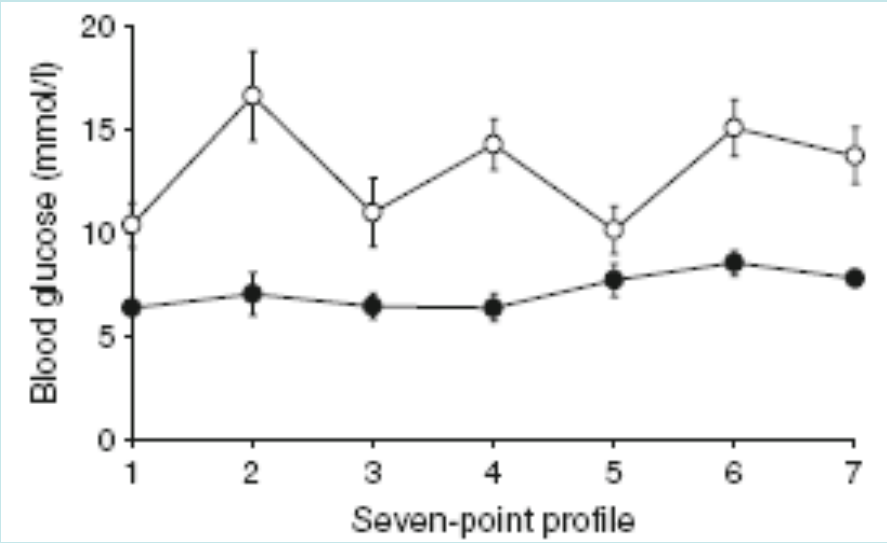
β-Cell sensitivity to GIP in T2DM and non-DM

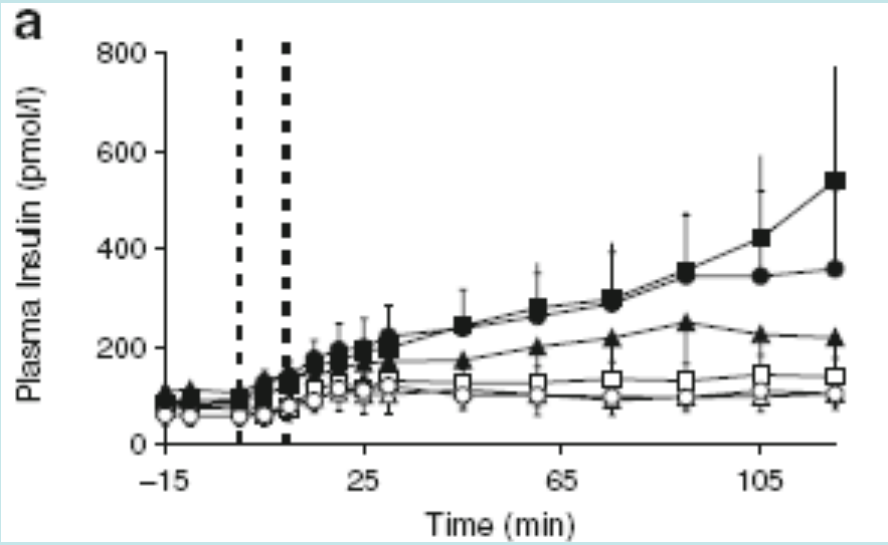




J Meier et al, Diabetes 2004

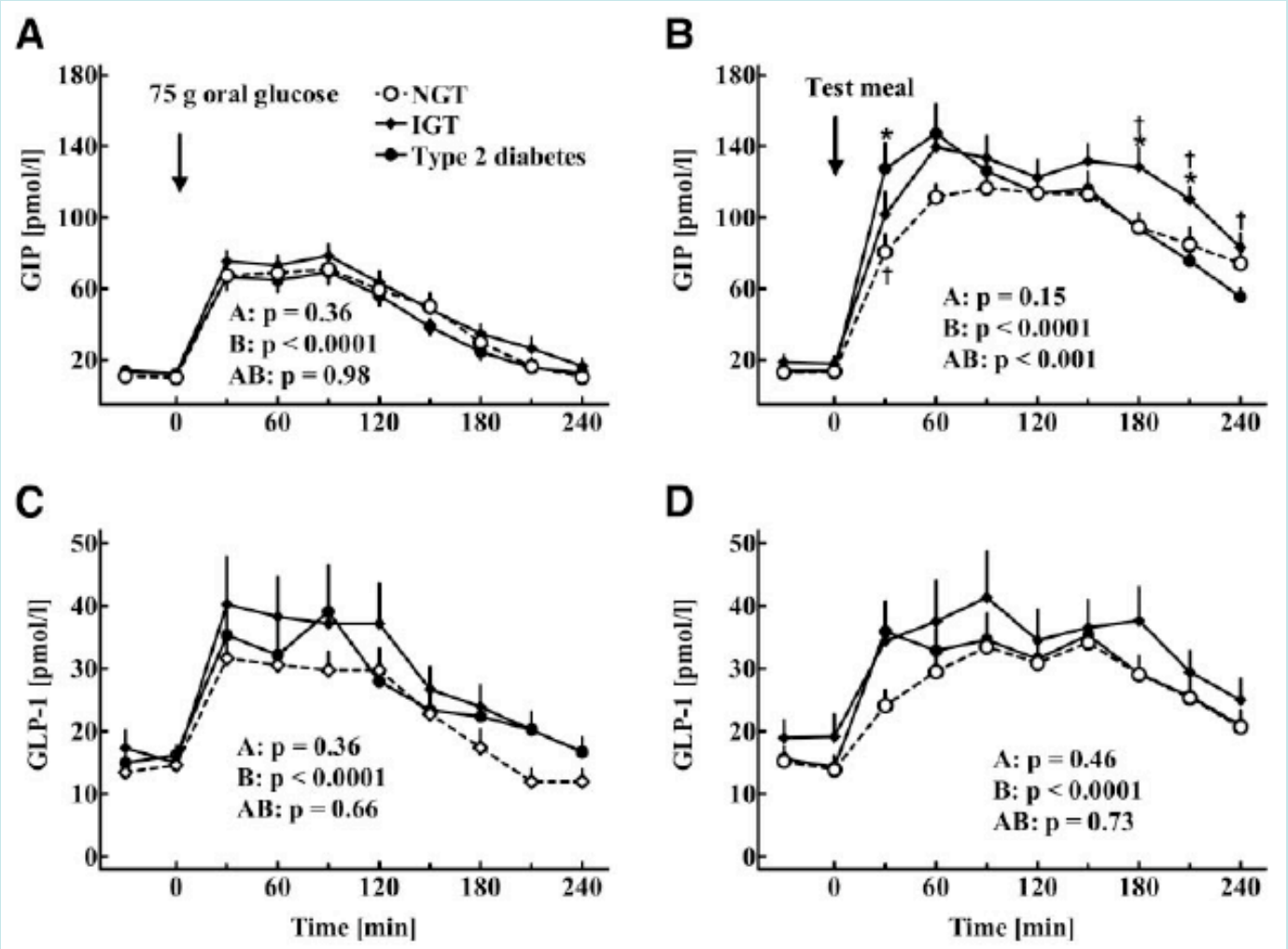
Improved responsiveness to incretins following improved glycemic control in T2DM





P Hojberg et al, Diabetologia, 2008

Incretin secretion in T2DM revisited



K Vollmer et al, Diabetes, 2008

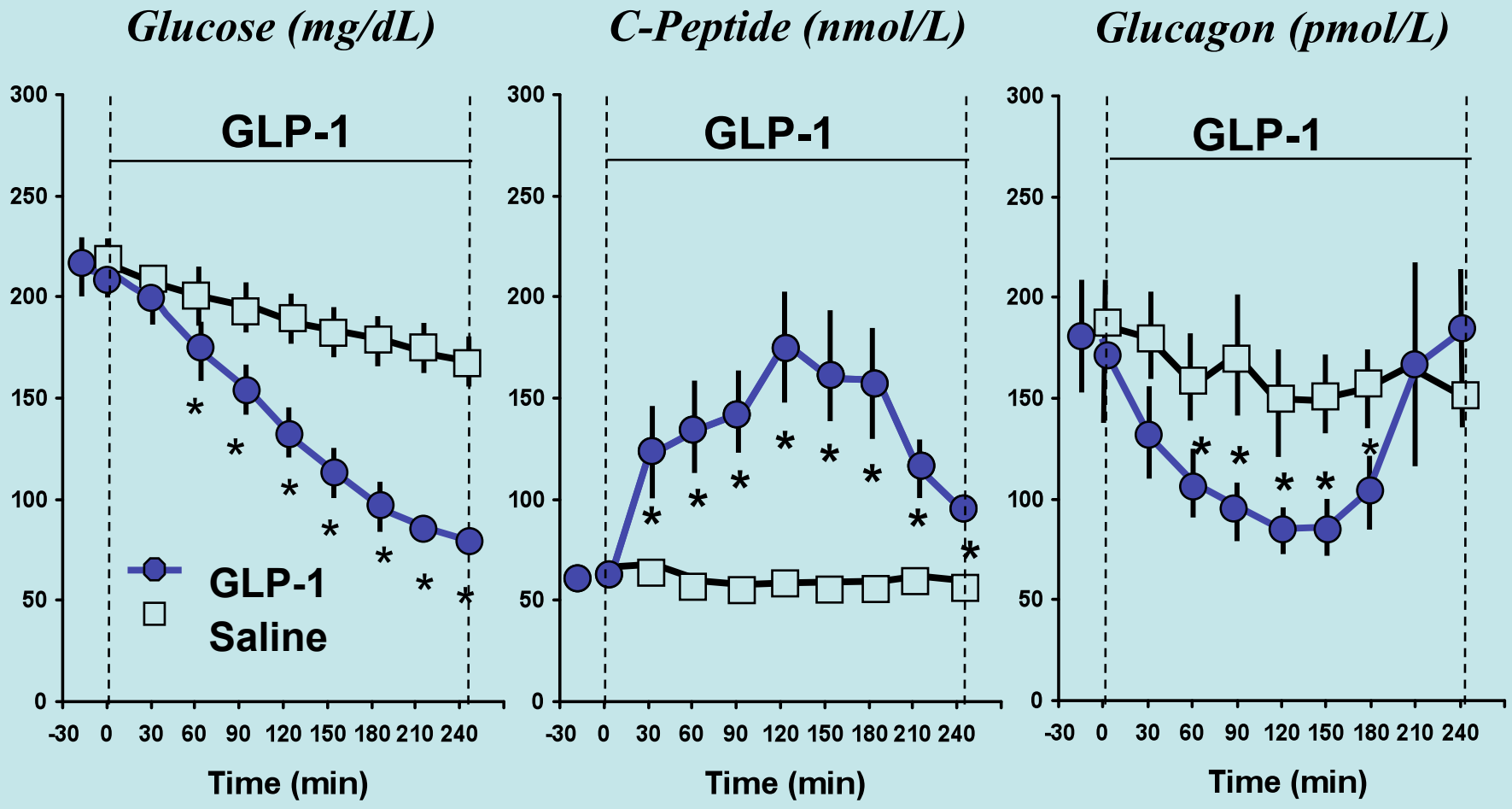
Incretin secretion in states of abnormal glucose metabolism

1. T2DM: decreased, normal, increased
2. IGT: Normal, decreased
3. GDM: Normal
4. First degree relatives of DM: Normal
5. Men with hx of LBW: Normal
6. Chronic pancreatitis: Normal

The incretins in T2DM

1. Diabetes is not likely to be an incretin deficiency state.
2. The insulin response to incretins is reduced, but it is unclear whether this is a defect specific to GIP and GLP-1, or simply a function of general β-cell dysfunction.
3. The incretin effect may be related to hyperglycemia
   - mild DM with normal response
   - correction of hyperglycemia improves the responses to GIP and GLP-1

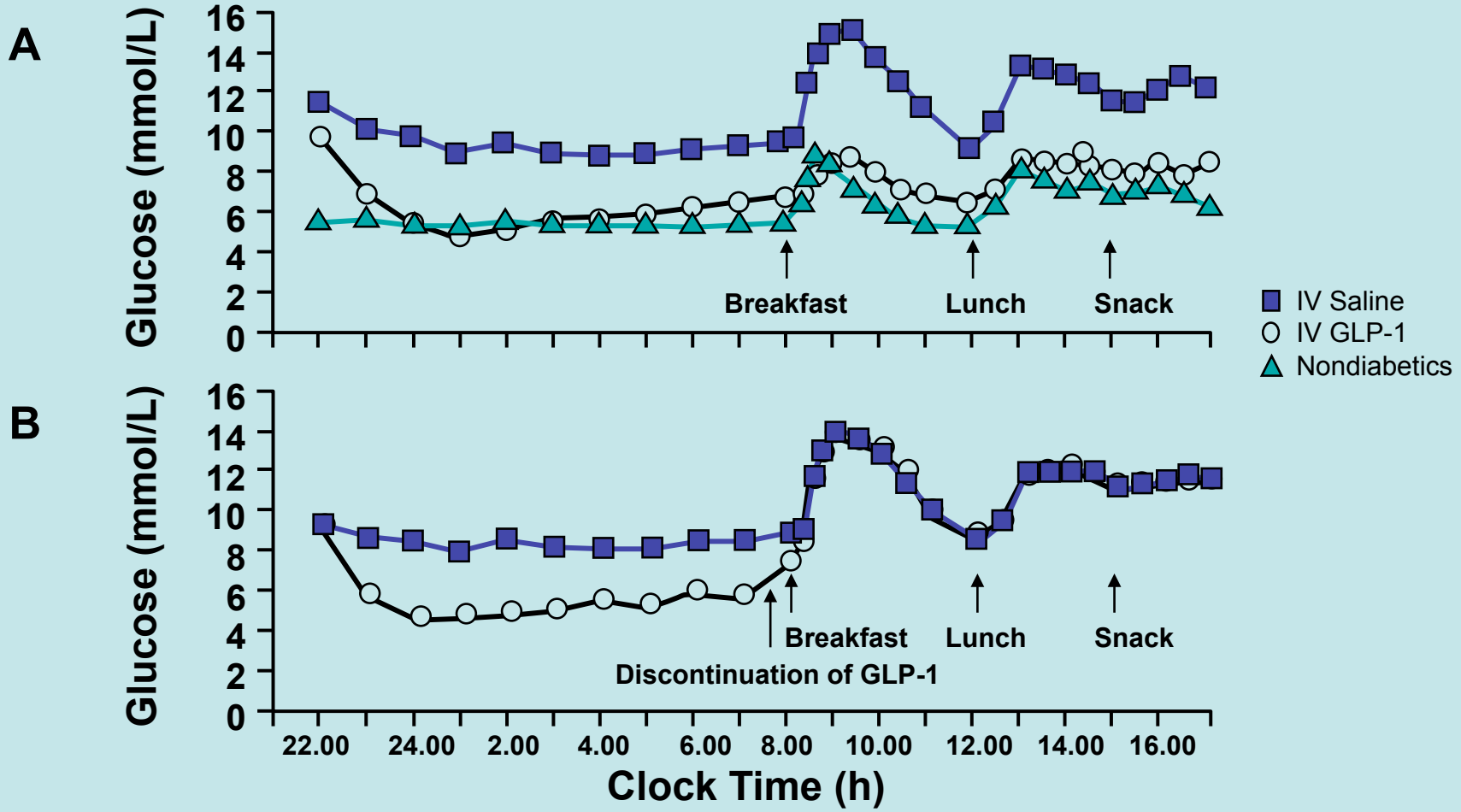
Effect of GLP-1 on Fasting Hyperglycemia in Patients With T2DM



Adapted from Nauck MA, et al. *Diabetologia.* 1993;36:741-744.

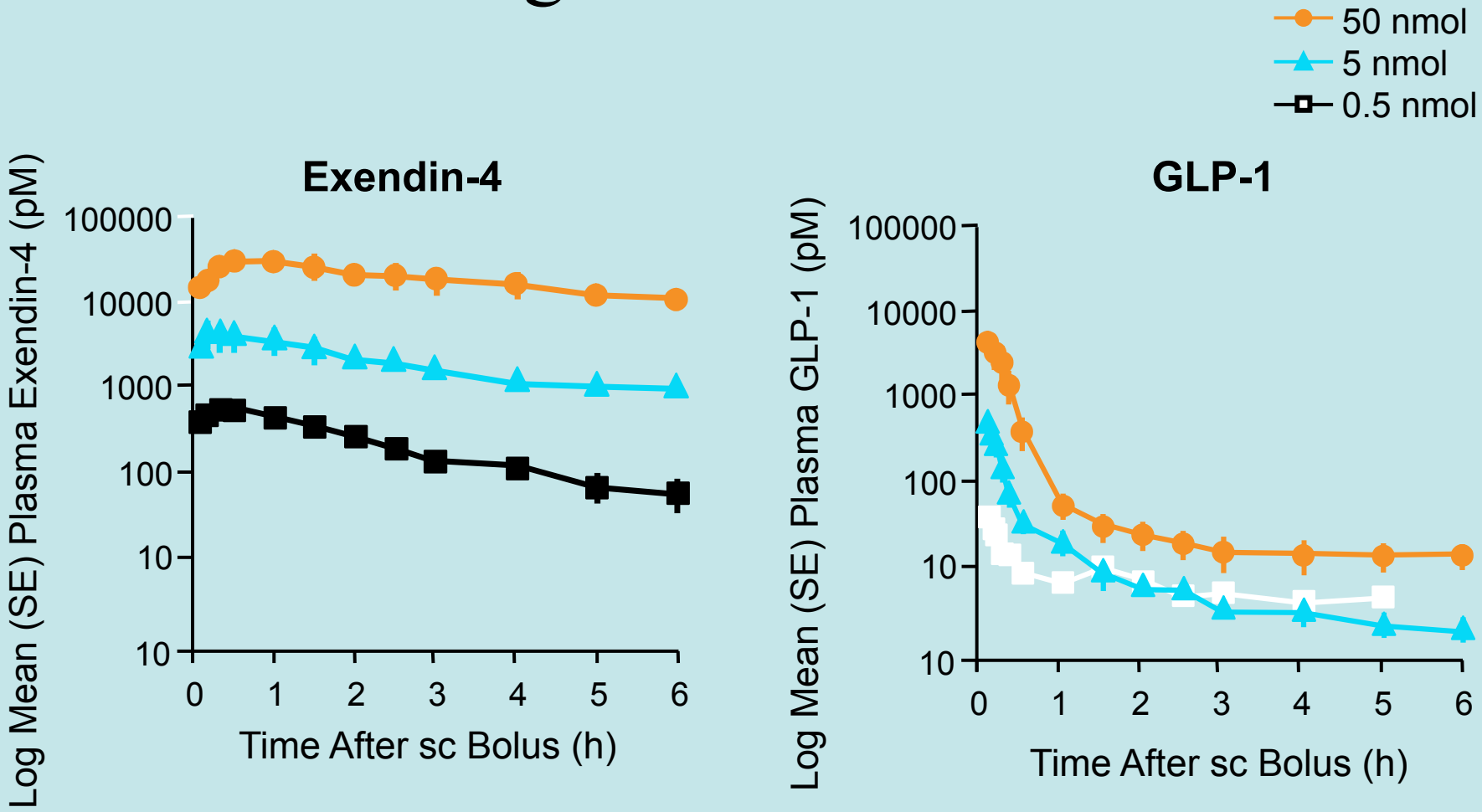
*$P<0.05$

Normalization of Fasting and Postprandial Glucose With IV GLP-1 in T2DM



Rachman J, et.al. *Diabetologia.* 1997;40:205-211. Copyright © 1997 Springer-Verlag.

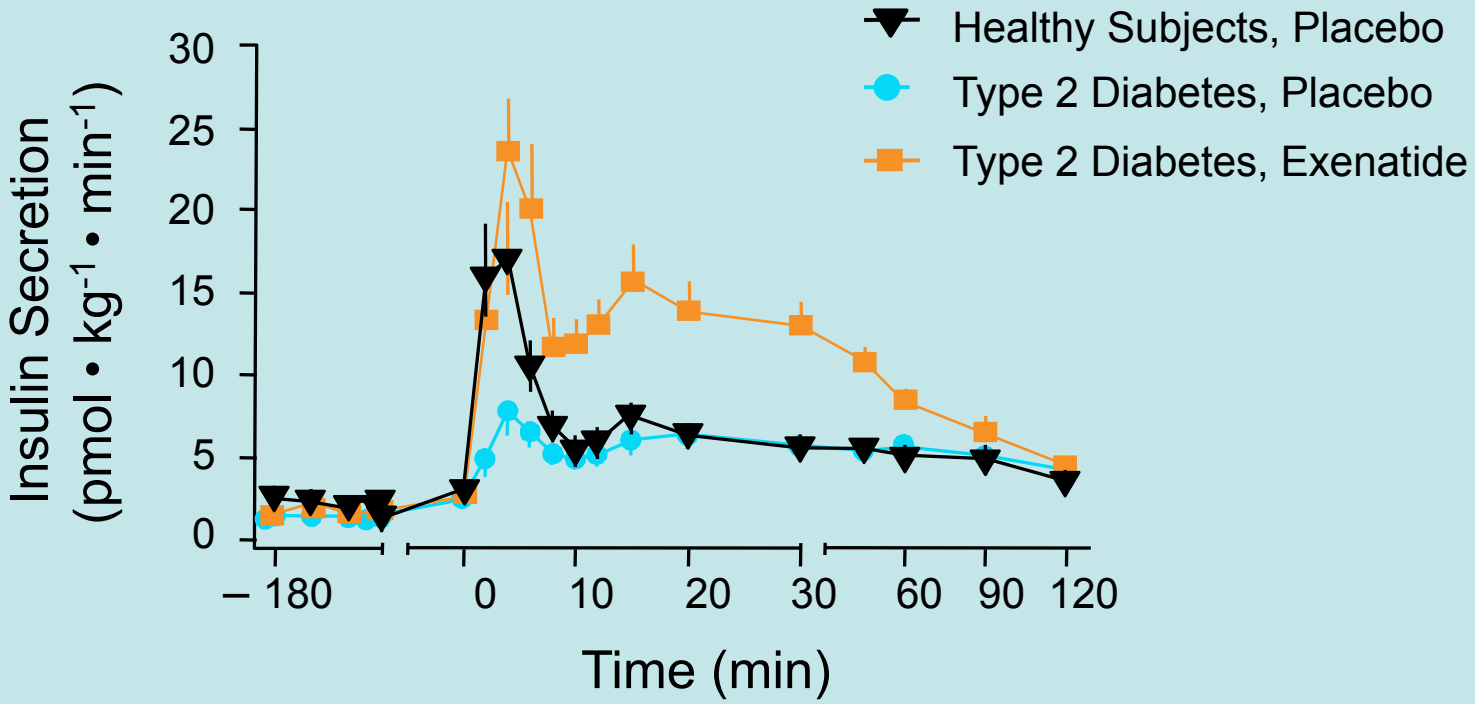
Exendin-4 Remains in the Circulation Longer Than GLP-1



N = 4-7 (rats).
P < .05.

Adapted from Parkes D, et al. *Drug Dev Res.* 2001;53:260-267.

Acute Exenatide Infusion Restored First-Phase Insulin Response



First- (0-10 min) and second- (10-120 min) phase insulin increased in exenatide-treated patients compared with placebo-treated T2DM, $P < .0002$.

Second-phase insulin increased in exenatide-treated patients compared with healthy controls, $P < .0029$.

Values are mean (SE).

N = 25.

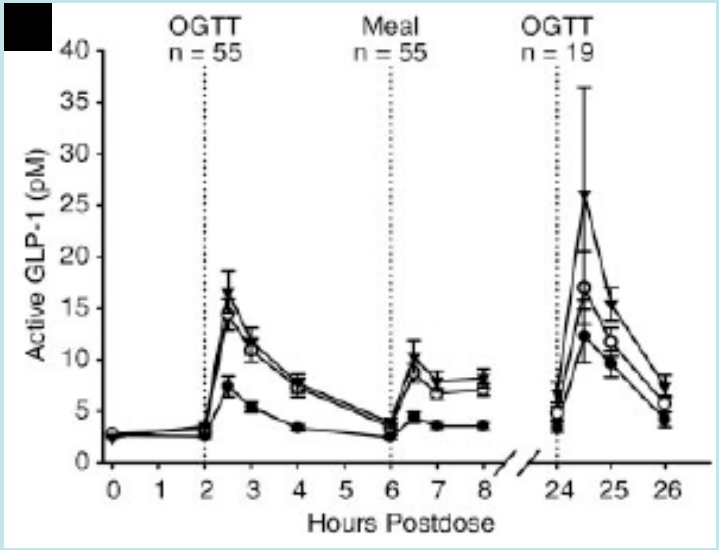
Fehse F, et al. *J Clin Endocrinol Metab*. 2005;90:5991-5997.

Pharmacologic effects of GLP-1r agonists in T2DM

1. Stimulation of glucose-stimulated insulin secretion
2. Suppression of glucagon
3. Delayed gastric emptying
4. Reduced food intake and weight loss

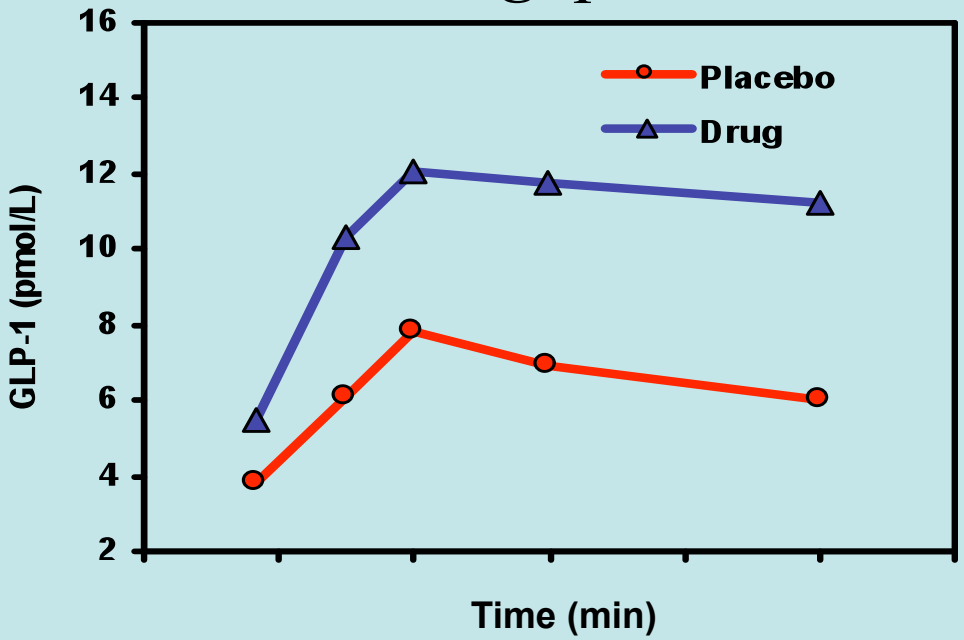
Effect of DPP-IV inhibition of plasma GLP-1 levels

Sitagliptin



G Herman, et al, JCEM, 2006

Vildagliptin

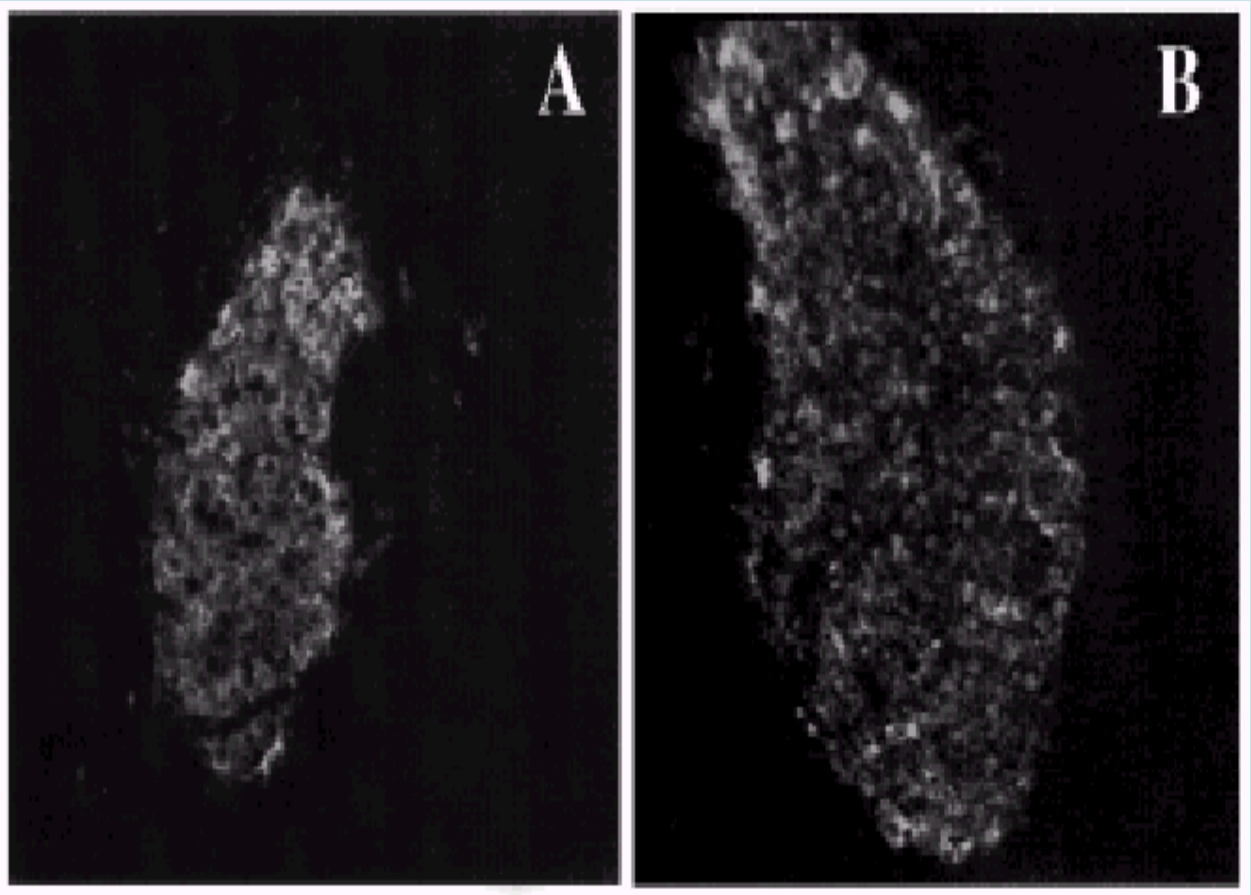


Ahren B, et al. J Clin Endocrinol Metab. 2004

Effects of DPP-4 Inhibition on glucose metabolism in T2DM

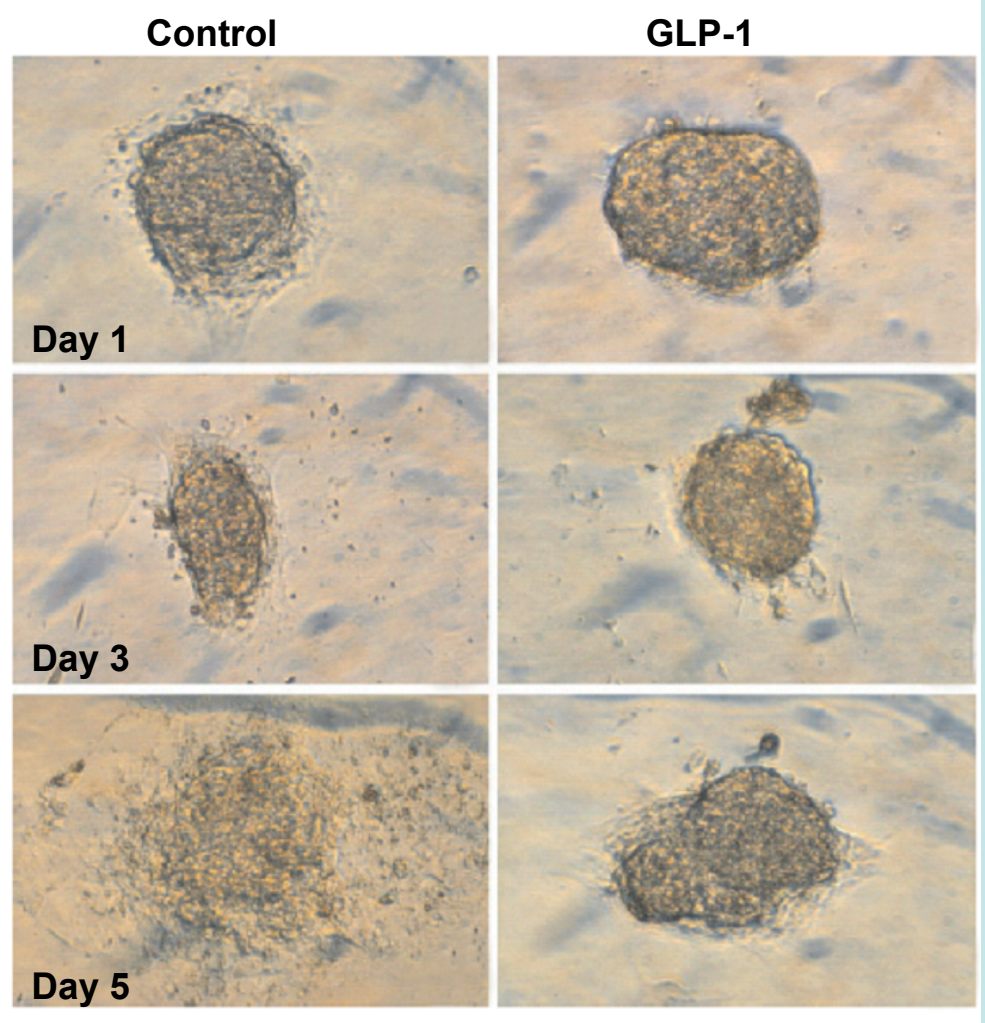
1. Improved insulin secretion
2. Inhibition of glucagon release
3. Improved meal tolerance
4. Reduced HbA1c

Stimulation of Islet Growth With a GLP-1 Analogue in Mice



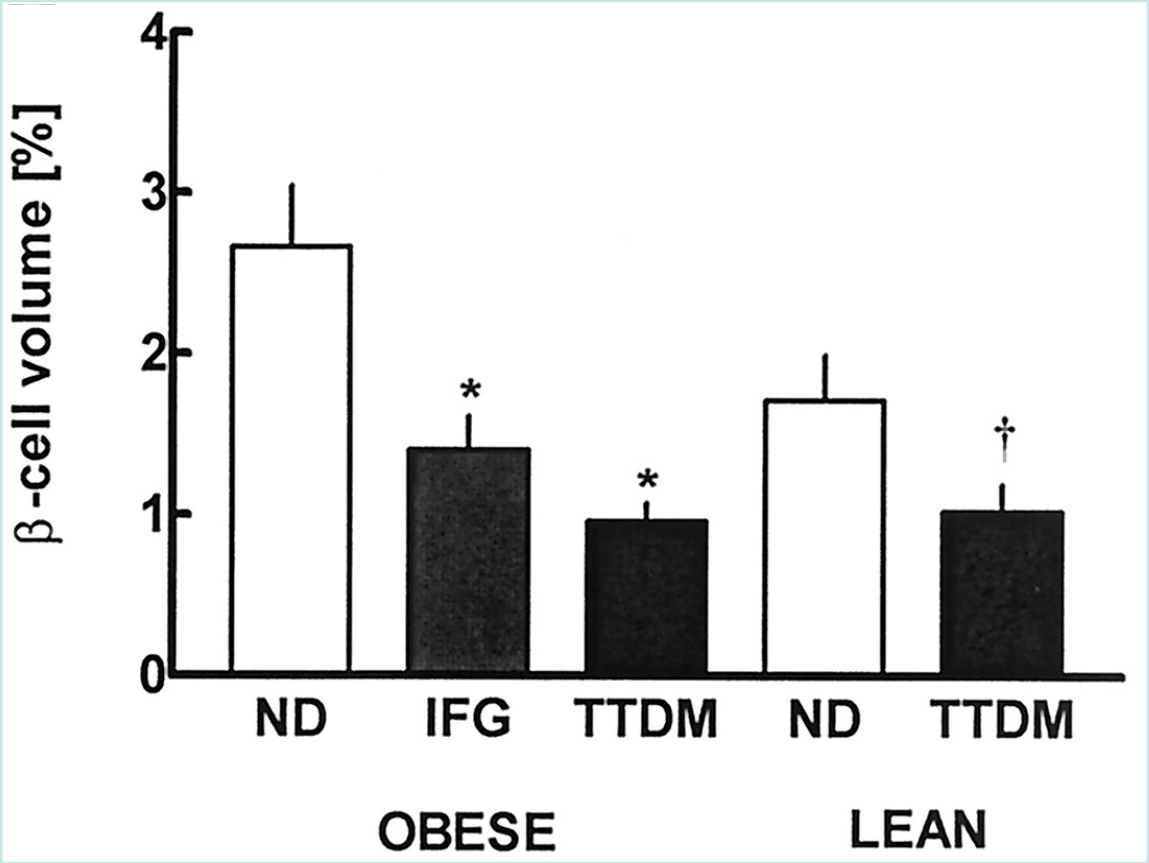
GLP-1 Preserves Human Islet Morphology *In Vitro*

- Pancreatic islets cultured in the absence of GLP-1 lost organization after 5 days
- By Day 5, 45% of islets in control cultures had lost their 3-D structure
- Only 15% of GLP-1–treated islets lost their 3-D structure in 5 days ($P < .01$ vs control)



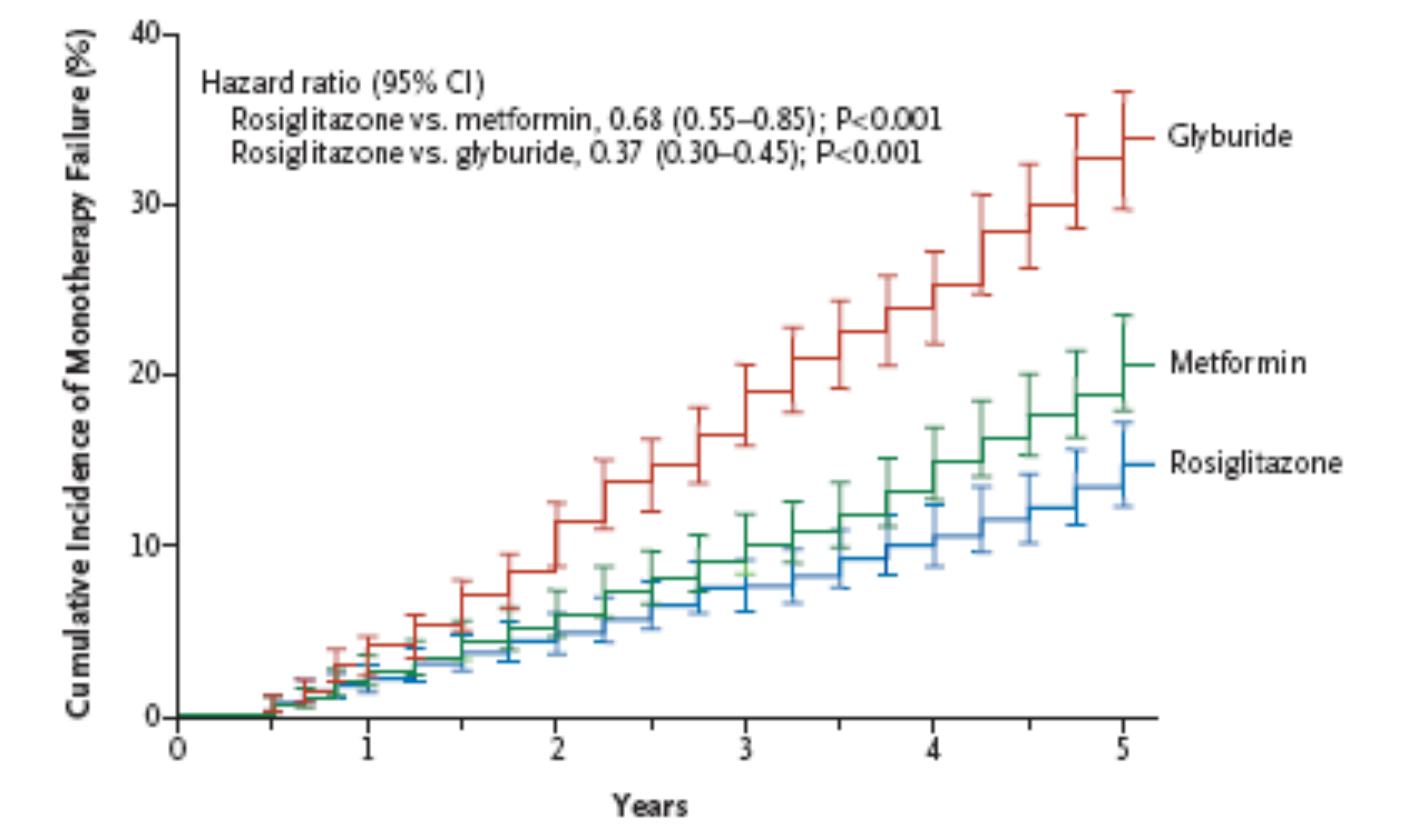
Farilla L, et al. *Endocrinology.* 2003;144:5149-5158.

Evidence that Type 2 DM is Associated with a Significant Decrease in β-cell Mass



Butler AE, et al. *Diabetes*. 2003;52:2304-2314.

Durability as a new index of drugs for T2DM



Kahn SE et al, NEJM, 2006

Summary

1. The incretin effect may be defective in T2DM.
2. Incretin secretion is not a major abnormality in T2DM but diabetic β-cells have reduced sensitivity to GIP and GLP-1.
3. Pharmacologic levels of GLP-1r agonists reduce blood glucose and cause weight loss.
4. DPP-4 inhibition reduces blood glucose but the mechanism of action is not clear.
5. The full extent to which the GLP-1 system can be utilized to treat human disease is not yet complete.