nefrodiabetologia.net

# Insulin therapy and novel agents in DM treatment

Krzysztof Wróblewski MD, PhD

- Dept. of Internal Medicine and Nephrodiabetology,
- Medical University of Lodz

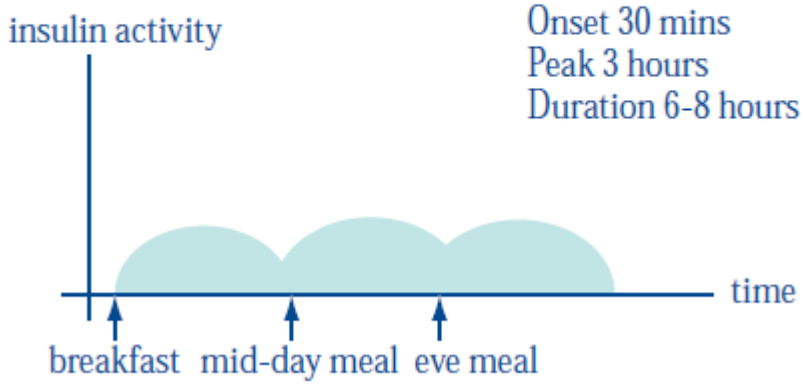
UNIWERSYTET MEDYCZNY W ŁODZI

# A physiological approach to insulin therapy

- long-acting basal insulin given once daily + rapid-acting bolus insulin given preprandially to cover mealtime glucose fluctuations.
  - Many patients find starting such an intensive regimen daunting.
- short- and long-acting insulins are sometimes mixed (including premixed commercial formulations) and used twice daily
- Another option – single injection of basal insulin to the oral agent regimen and adjust slowly as needed to include prandial insulin.

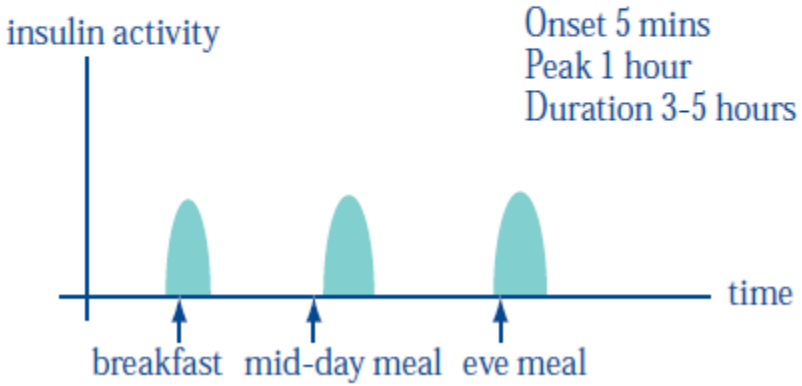
## Short-acting meal-time insulin

Product names include Actrapid, Humulin S and Insuman Rapid.



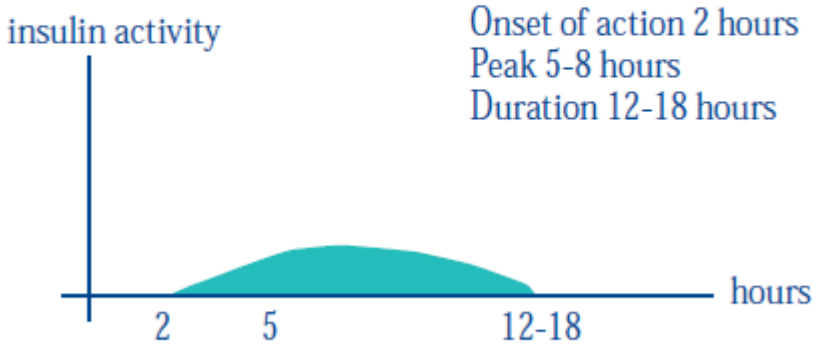

## Rapid-acting meal-time insulin (analogues)

Product names include NovoRapid and Humalog (insulin lispro).



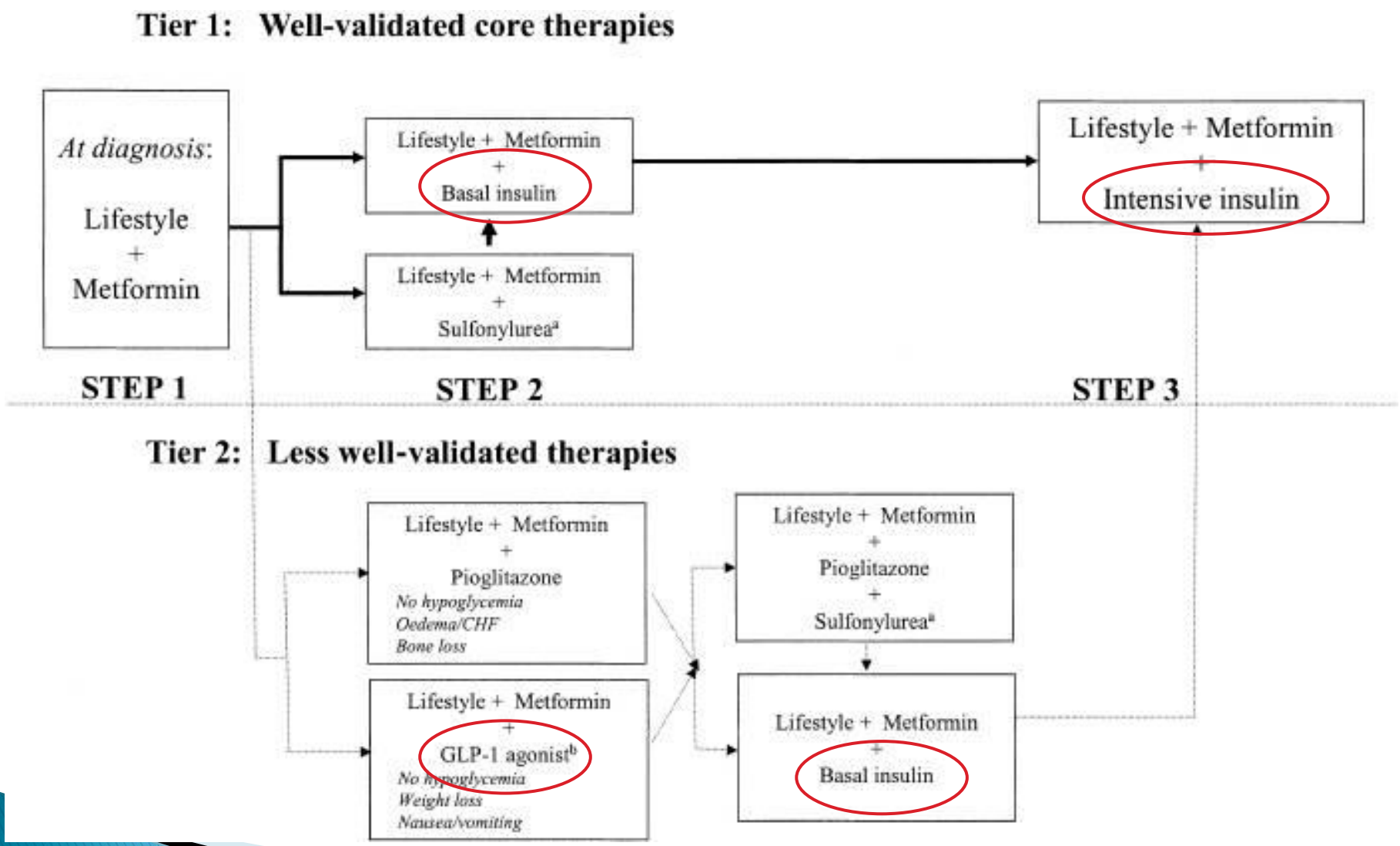
## Intermediate-acting basal insulin with peak

Product names include Insulatard, Humulin I and Insuman Basal.




## Long-acting peakless basal analogues

Lantus and Levemir are currently the only products in this category.


Tier 1: Well-validated core therapies
At diagnosis:
Lifestyle
+
Metformin
Lifestyle + Metformin
+
Basal insulin
Lifestyle + Metformin
+
Sulfonylurea[a]
Lifestyle + Metformin
+
Intensive insulin
STEP 1
STEP 2
STEP 3
Tier 2: Less well-validated therapies
Lifestyle + Metformin
+
Pioglitazone
No hypoglycemia
Oedema/CHF
Bone loss
Lifestyle + Metformin
+
GLP-1 agonist[b]
No hypoglycemia
Weight loss
Nausea/vomiting
Lifestyle + Metformin
+
Pioglitazone
+
Sulfonylurea[a]
Lifestyle + Metformin
+
Basal insulin

- T1DM – 0.5 to 1.0 U/kg per day, in multiple doses, approx. 40 to 50% of the insulin should be given as basal insulin.
- T1DM – 0.3 to 0.4 U/kg per day

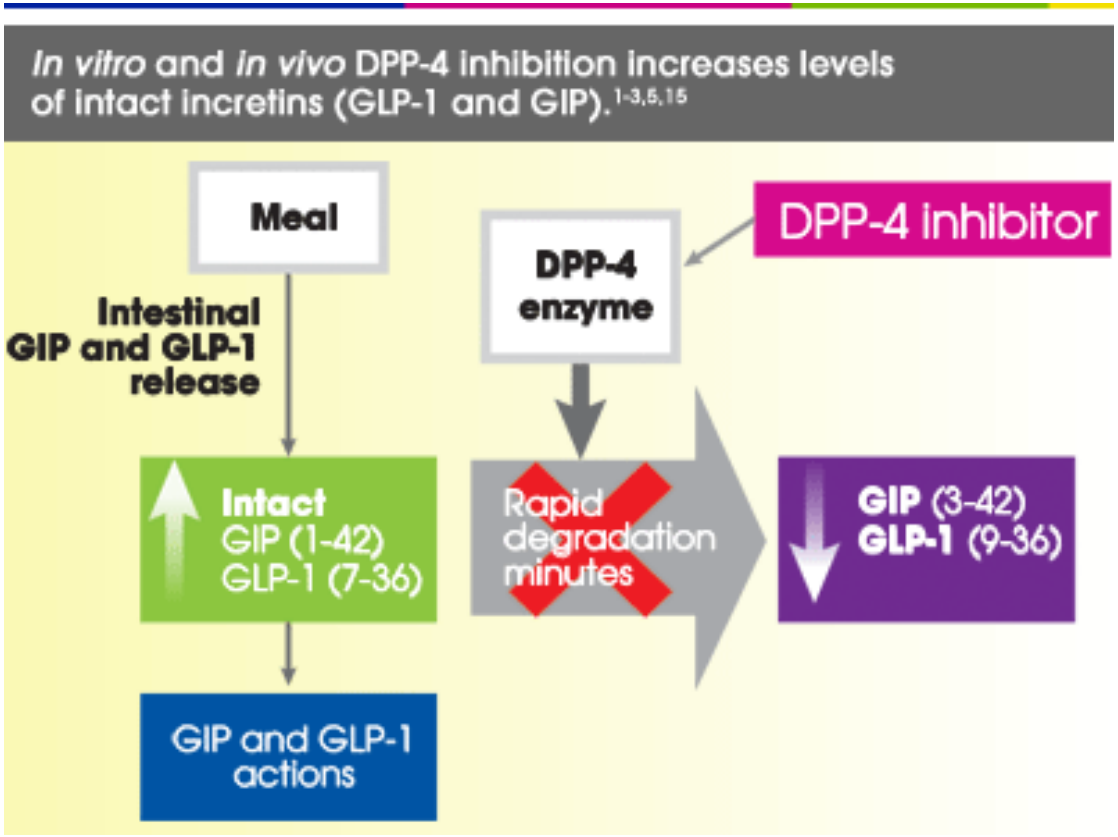
- Total Daily Insulin Requirement (in units) = 0.55 X Total Weight (kg)

Generally,

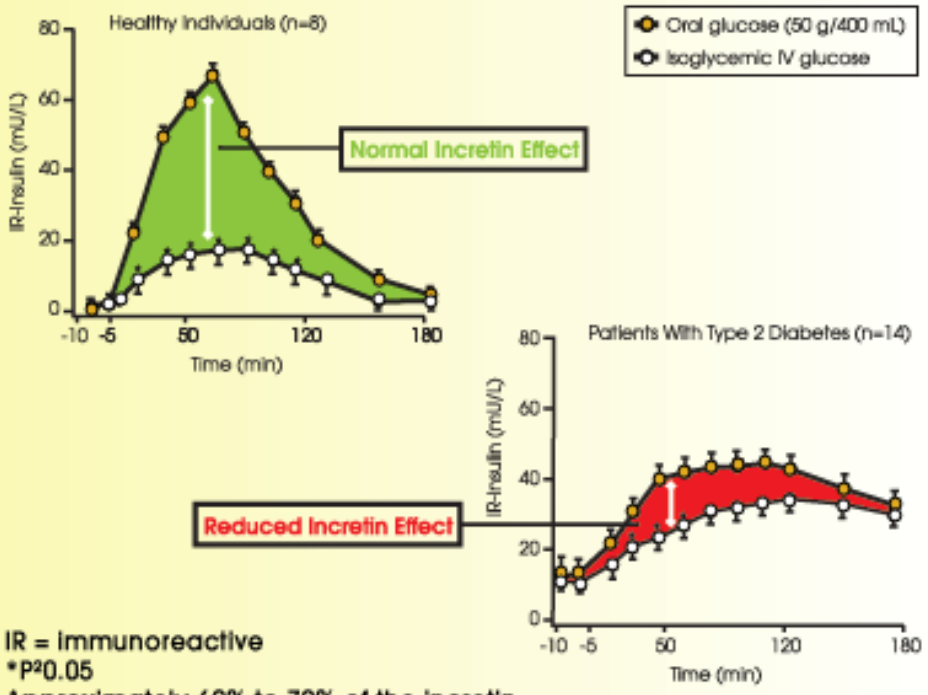
- **1 unit of insulin is needed to drop the glycemia by 50 mg/dl.**
- can range from **15-100 mg/dl** or more, depending on individual insulin sensitivities, and other circumstances.

# The 1500/1800 Rule:

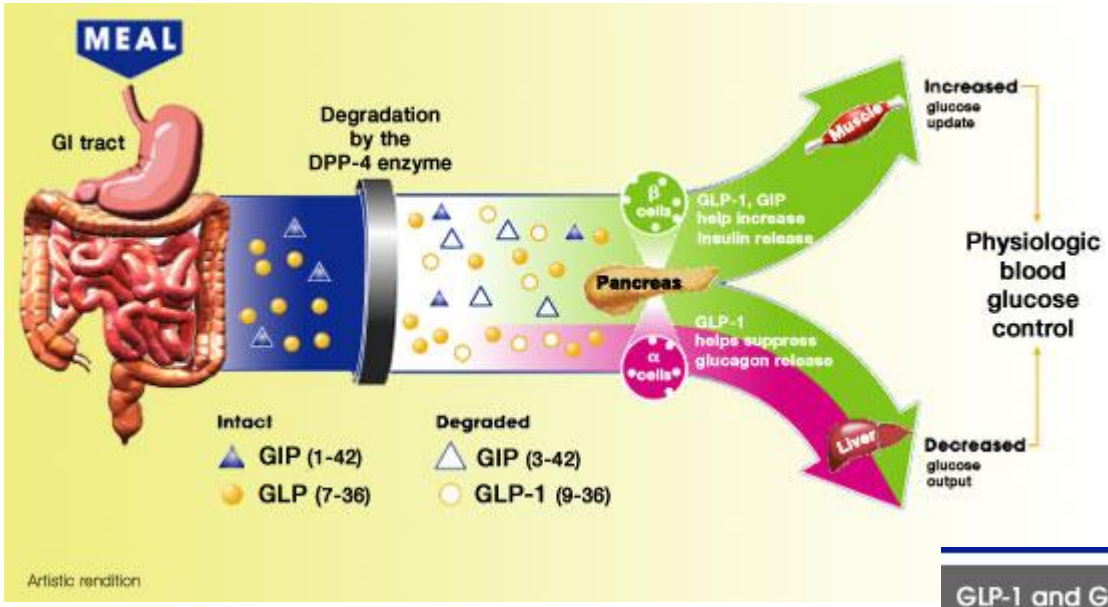
- For Type 1 diabetes and most Type 2s
- Estimates the point drop in mg/dl per unit of insulin analogs
- 1800/TDD = point drop per unit of
- Example:
  - If a Total Daily Dose of insulin = 30 units
  - 1800/30 uts/day = a 60 mg/dl drop per unit of insulin analog


*In vitro* and *in vivo* DPP-4 inhibition increases levels of intact incretins (GLP-1 and GIP).[1-3,5,15]
Meal
Intestinal GIP and GLP-1 release
DPP-4 enzyme
DPP-4 inhibitor
Intact GIP (1-42) GLP-1 (7-36)
Rapid degradation minutes
GIP (3-42) GLP-1 (9-36)
GIP and GLP-1 actions

## The incretin effect is reduced in type 2 diabetes[2]

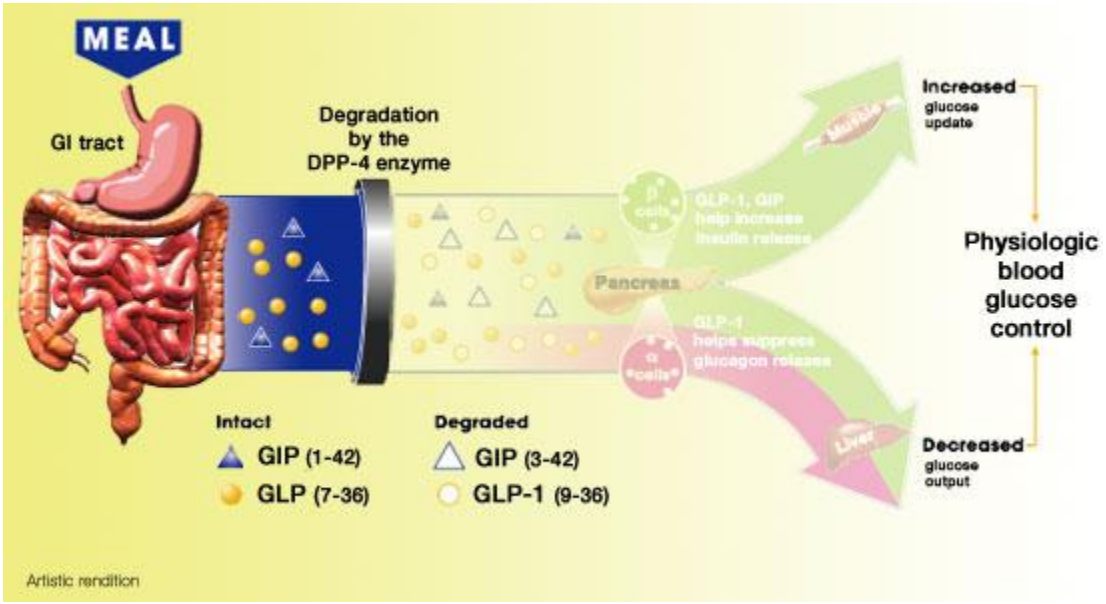


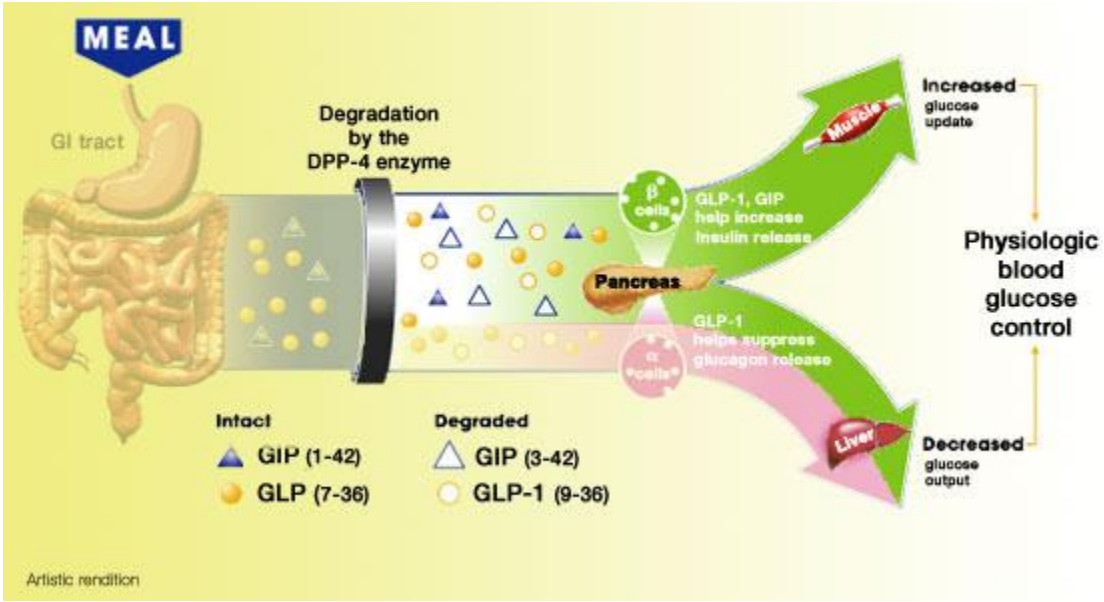

IR = immunoreactive
*P²0.05
Approximately 60% to 70% of the incretin effect is related to GLP-1 and GIP.[1,9]
Adapted from Nauck M et al.[2]

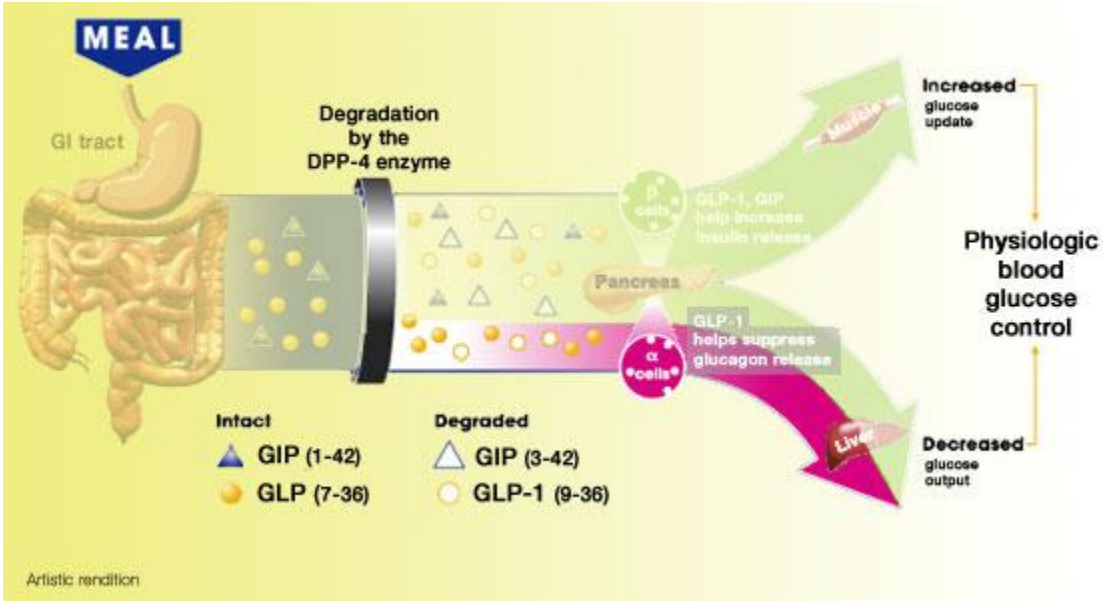



**GLP-1 and GIP Are the Two Major Incretins[2,3]**
Physiologic effects in glucose regulation

| GLP-1 | GIP |
|---|---|
| • Secreted by L cells in the distal gut (ileum and colon)[2,4] | • Secreted by K cells in the proximal gut (duodenum and proximal jejunum)[2,3] |
| • Stimulates glucose - dependent insulin release from beta cells[3,13] | • Stimulates glucose - dependent insulin release from beta cells[2,3] |
| • Suppresses hepatic glucose output by inhibiting glucagon response from alpha cells in a glucose - dependent manner[2,13] | |

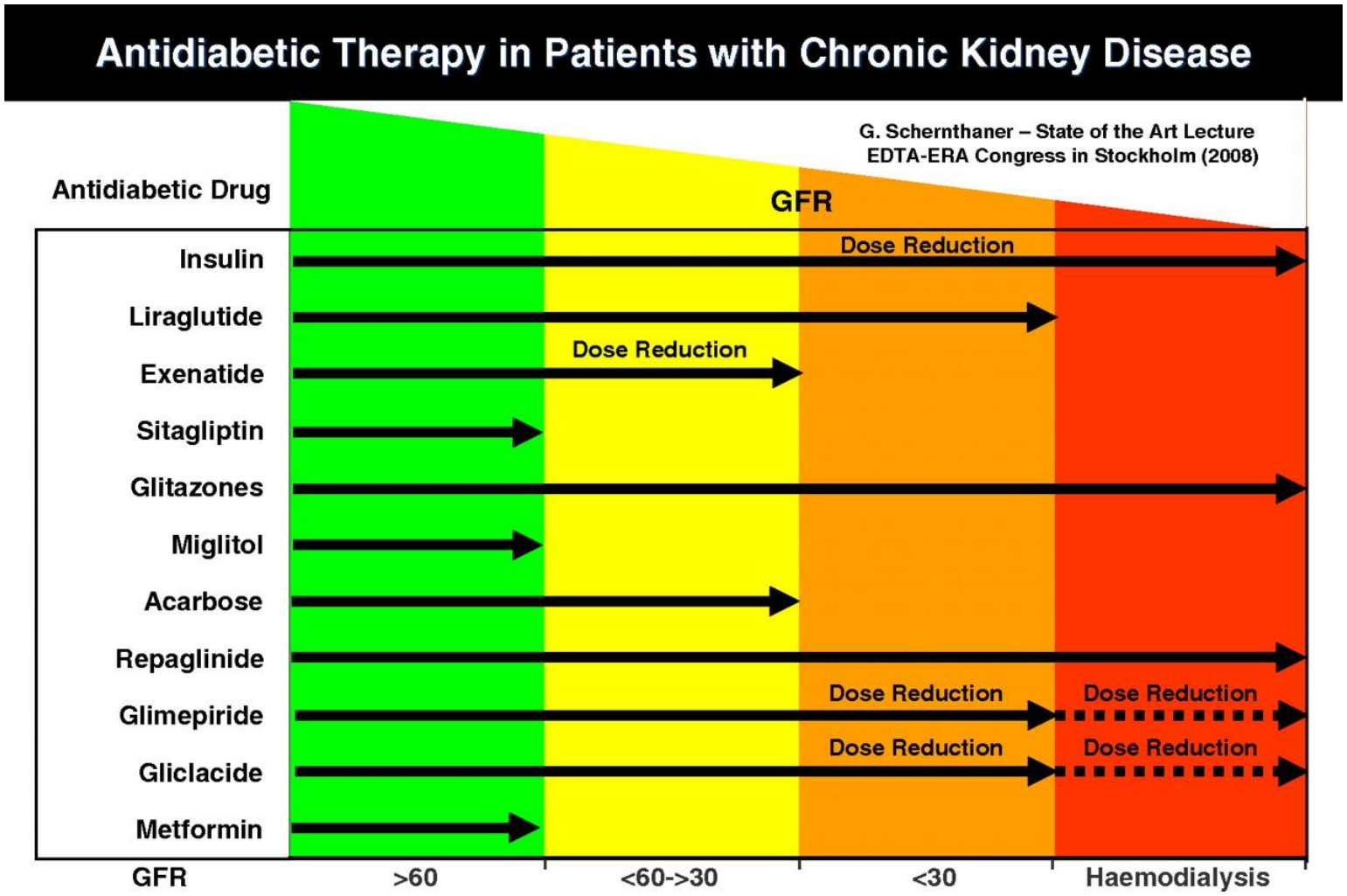

MEAL
GI tract
Degradation by the DPP-4 enzyme
Pancreas
GLP-1, GIP help increase insulin release
GLP-1 helps suppress glucagon release
Increased glucose update
Physiologic blood glucose control
Decreased glucose output
Intact
GIP (1-42)
GLP (7-36)
Degraded
GIP (3-42)
GLP-1 (9-36)
Artistic rendition


MEAL
GI tract
Degradation by the DPP-4 enzyme
β cells
GLP-1, GIP help increase insulin release
Pancreas
α cells
GLP-1 helps suppress glucagon release
Muscle
Increased glucose update
Liver
Decreased glucose output
Physiologic blood glucose control
Intact
GIP (1-42)
GLP (7-36)
Degraded
GIP (3-42)
GLP-1 (9-36)
Artistic rendition


MEAL
GI tract
Degradation by the DPP-4 enzyme
Pancreas
GLP-1 helps suppress glucagon release
Increased glucose update
Physiologic blood glucose control
Decreased glucose output
Intact
GIP (1-42)
GLP (7-36)
Degraded
GIP (3-42)
GLP-1 (9-36)
Artistic rendition

**INJECTABLE TREATMENTS, BY CLASS**

| | | | | |
|---|---|---|---|---|
| Regular insulin | Human insulin (regular) | Humulin R, Novolin R | Yes | Oct 1982 |
| Intermediate-acting insulin[d] | Human insulin (NPH insulin) | Humulin N, Novolin N | Yes | Oct 1982 |
| Human insulin combinations | Insulin regular and NPH insulin | Humulin 70/30 | Yes | Apr 1989 |
| Rapid-acting insulin analogues | Insulin lispro | Humalog | No | Jun 1996 |
| | Insulin aspart | Novolog | No | Jun 2000 |
| | Insulin glulisine | Apidra | No | Apr 2004 |
| Long-acting basal insulin analogues | Insulin glargine | Lantus | No | Apr 2000 |
| | Insulin detemir | Levemir | No | Jun 2005 |
| Combinations (including analogues)[e] | Insulin lispro protamine and insulin lispro | Humalog Mix 75/25 and 50/50 | No | Dec 1999 |
| | Insulin aspart protamine and insulin aspart | Novolog Mix 70/30 | No | Nov 2001 |
| Amylin analogue | Pramlintide acetate | Symlin | No | Mar 2005 |
| GLP-1 receptor agonist | Exenatide | Byetta | No | Apr 2005 |




Schernthaner, G. et al. Nephrol. Dial. Transplant. 2010 25:2044-2047

- **Exenatide (Byetta)** – a synthetic version of exendin-4, a hormone found in the saliva of the *Gila monster* , with 53% homology to endogenous huGLP-1 – twice daily
  - Exenatide LAR (Bydureon) – based on Medisorb technology – once weekly
- **Liraglutide (Victoza)** – acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous huGLP-1 – once daily

- **Albiglutide** – long acting huGLP-1 analog (dimer combined with human albumin)
- **Taspoglutide** – amionoacids in 8th and 35th position replaced by isobutyric acid
  - September 2010 –Phase III clinical trials was halted due to a incidences of serious hypersensitivity reactions and gastrointestinal side effects.[