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# Oral T2DM therapy

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UNIWERSYTET MEDYCZNY W ŁODZI

## Currently available antihyperglycemic therapies for T2DM in the United States

| ORAL TREATMENTS, BY CLASS | Generic name(s) | Trade name(s) | Available as generic | Date of FDA approval |
|---|---|---|---|---|
| Sulfonylurea[a] | Glipizide | Glucotrol[b] | Yes | May 1984 |
| | Glyburide | DiaBeta, Glynase, Micronase | Yes | May 1984 |
| | Glimepiride | Amaryl | Yes | Nov 1995 |
| Biguanide | Metformin hydrochloride | Glucophage[c] | Yes | Mar 1995 |
| α-Glucosidase inhibitor | Acarbose | Precose | No | Sep 1995 |
| | Miglitol | Glyset | No | Dec 1996 |
| Thiazolidinedione (TZD) | Rosiglitazone | Avandia | No | Jun 1999 |
| | Pioglitazone | Actos | No | Jul 1999 |
| Meglitinide (glinide) | Repaglinide | Prandin | No | Dec 1997 |
| | Nateglinide | Starlix | No | Dec 2000 |
| DPP-4 inhibitor | Sitagliptin phosphate | Januvia | No | Oct 2006 |
| | Saxagliptin | Onglyza | No | Jul 2009 |
| Bile acid sequestrant | Colesevelam | Welchol | No | Jan 2008 |
| Sulfonylurea and biguanide | Glyburide and metformin | Glucovance | Yes | Jul 2000 |
| Biguanide and glitazone | Rosiglitazone maleate and metformin hydrochloride | Avandamet | No | Oct 2002 |
| Sulfonylurea and glitazone | Rosiglitazone maleate and glimepiride | Avandaryl | No | Nov 2005 |
| Biguanide and DPP-4 inhibitor | Sitagliptin and metformin hydrochloride | Janumet | No | Mar 2007 |

- **Metformin** – the only biguanide available
- decreases hepatic glucose output and lowers fasting glycemia
- metformin monotherapy lowers HbA1c levels by ~1.5 %
- well tolerated /gastrointestinal adverse effects/
- in monotherapy no hypoglycemia
- No hypoglycemia, in prediabetis

- Metformin interferes with vitamin B12 absorption but rarely associated with anemia
- The major nonglycemic effect – weight stability or modest weight loss /in contrast with other oral agents/
- beneficial effect on CVD outcomes (UKPDS study)
- risk of lactic acidosis extremely rare (less than 1/100,000 treated patients)
- Not to use if GFR <30 ml/min

- **Sulfonylureas** lower glycemia by enhancing insulin secretion.
- In terms of efficacy – similar to metformin, lowering HbA1C levels by ~1.5 %
- The major adverse side effect is hypoglycemia (less common in 2nd generation drugs)

- potential cause of increased CVD mortality (UGDP study /1970/, but **not confirmed** by UKPDS /1998/, ADVANCE /2008/)

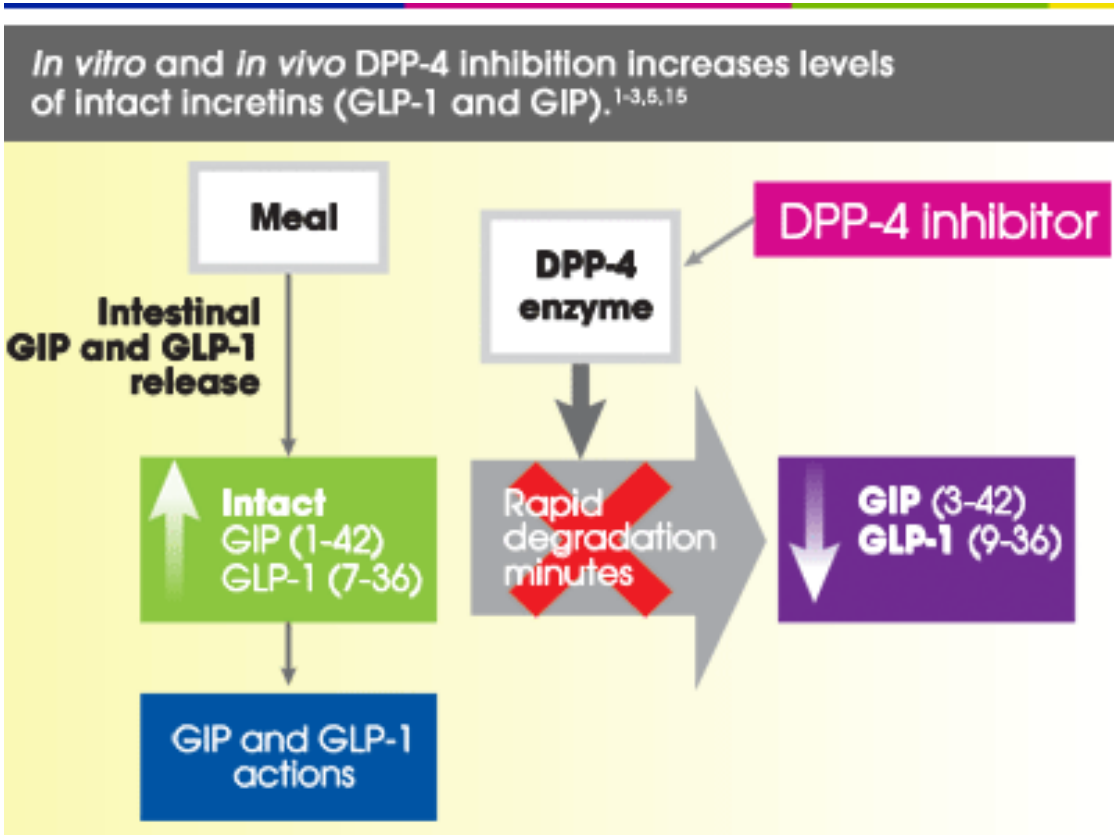
- glycemic benefits fully realized at **half-maximal doses**, higher doses should be avoided.

- **α-Glucosidase inhibitors** reduce the rate of digestion of polysaccharides in the proximal small intestine
- primarily lower postprandial glucose levels without hypoglycemia
- less effective in than metformin or the sulfonylureas, reducing HbA1c levels by 0.5–0.8 %
- malabsorption and weight loss do not occur, however, increased gas production and gastrointestinal symptoms /thus discontinued by 25–45% of participants/

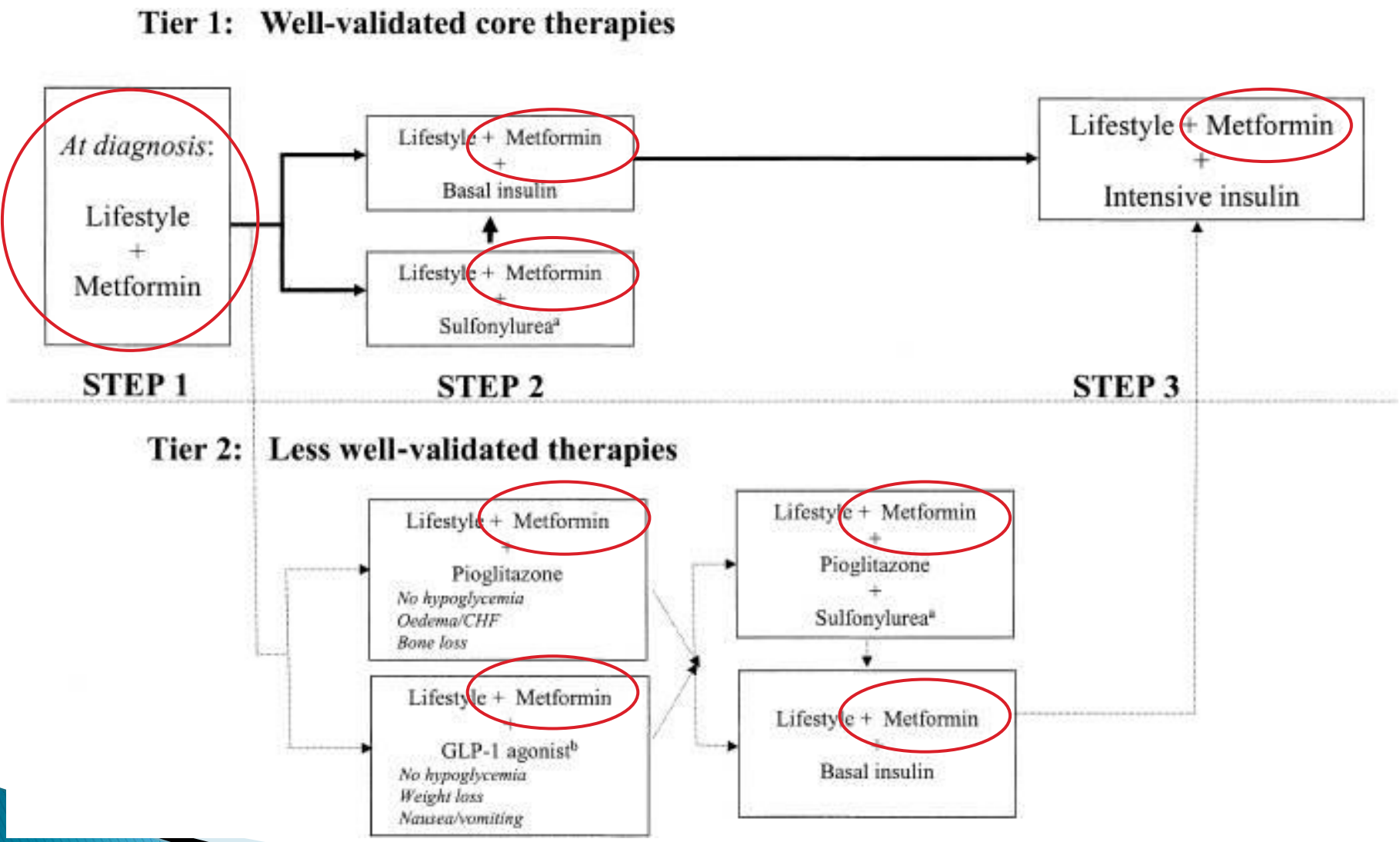
- **Thiazolidinediones (TZDs or glitazones)** – peroxisome proliferator-activated receptor γ modulators
- increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers")
- effectiveness of TZDs in monotherapy 0.5-1.4 % reduction HbA1c
- more durable effect on glycemic control compared with sulfonylureas

- The most common adverse effects:
  - weight gain
  - fluid retention with peripheral edema and a 2x increased risk for congestive heart failure
- Rosiglitazone – 30–40% increase in risk for myocardial infarction but pioglitazone was associated with a 16% reduction in death and myocardial infarction,

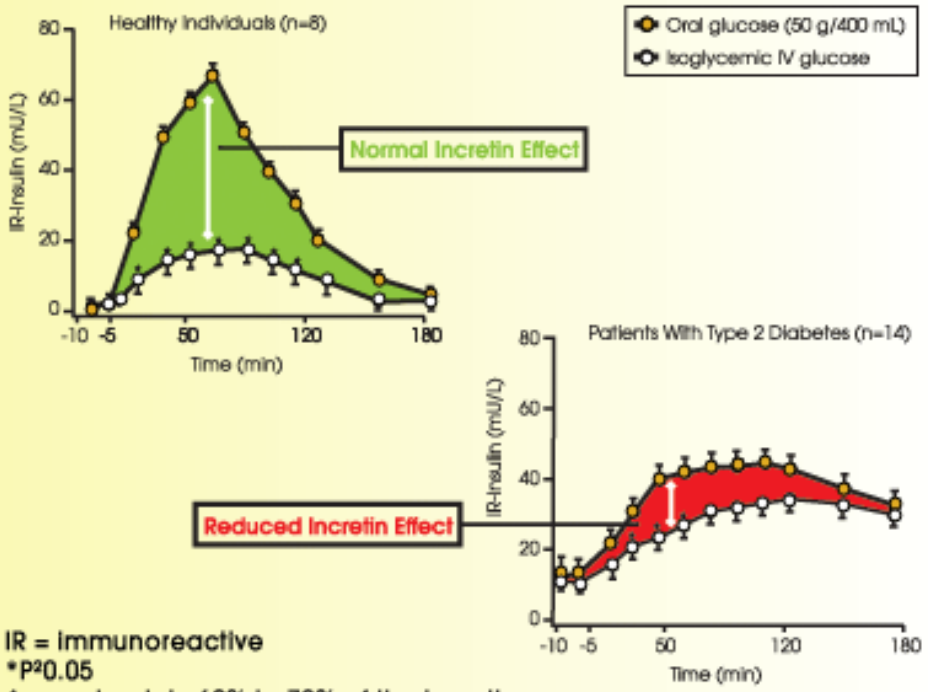
- **DPP-4 inhibitors** – small molecules that enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion
- In clinical trials performed to date, DPP-4 inhibitors lower A1Clevels 0.6-0.9 %
- weight neutral and relatively well tolerated
- nohypoglycemia when used as monotherapy


*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

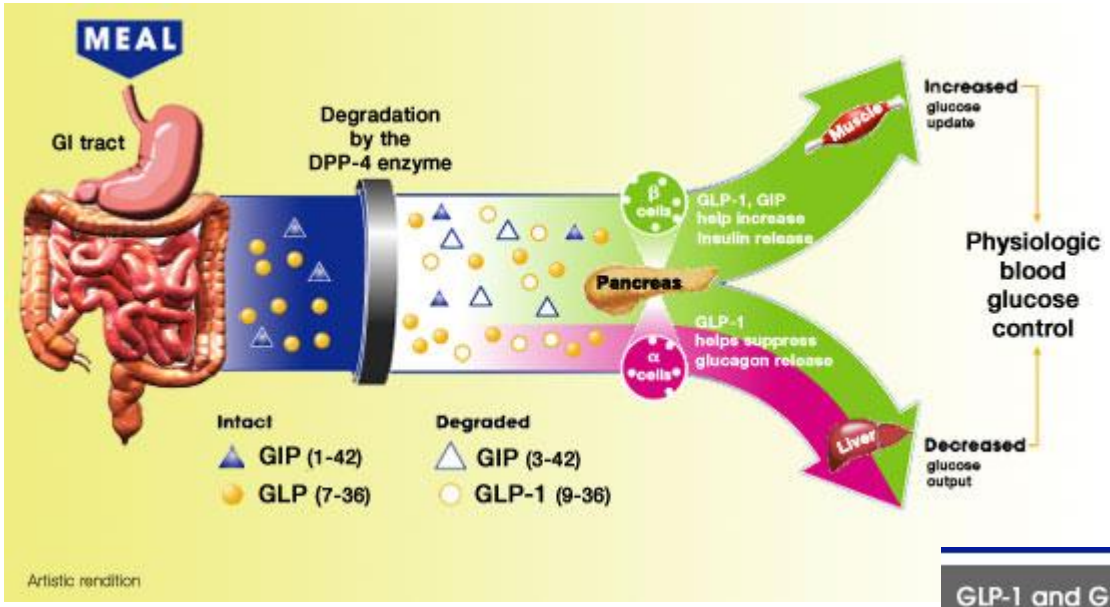
- Step 1: lifestyle intervention and metformin.
- Step 2: addition of a second medication.
- Step 3: further adjustments.


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

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



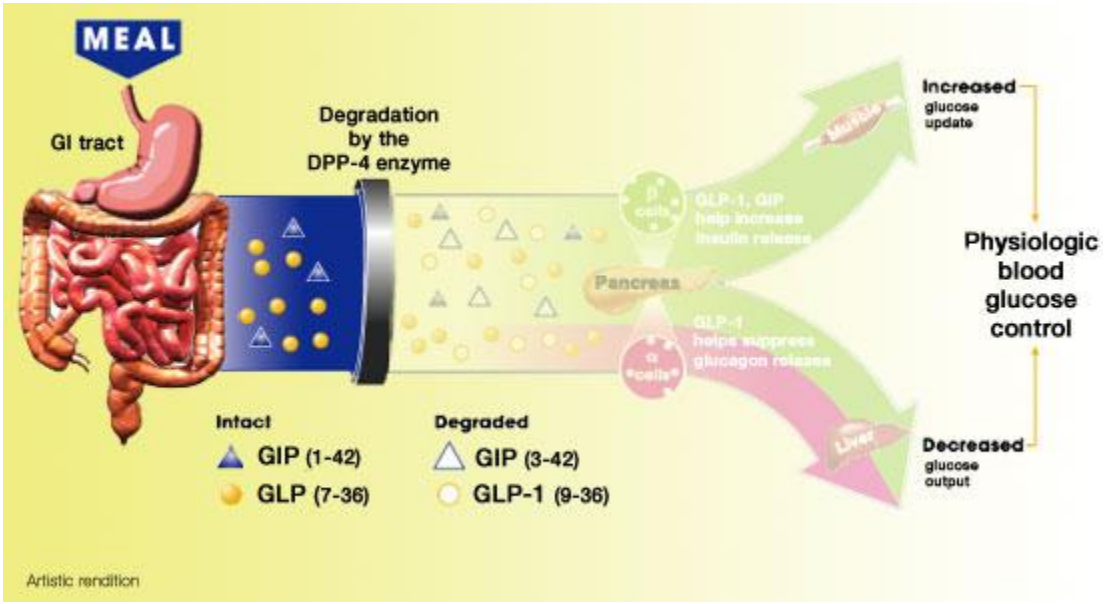

IR = immunoreactive
*P²0.05
Approximately 60% to 70% of the incretin effect is related to GLP-1 and GIP.[1,9]
Adapted from Nauck M et al.[2]

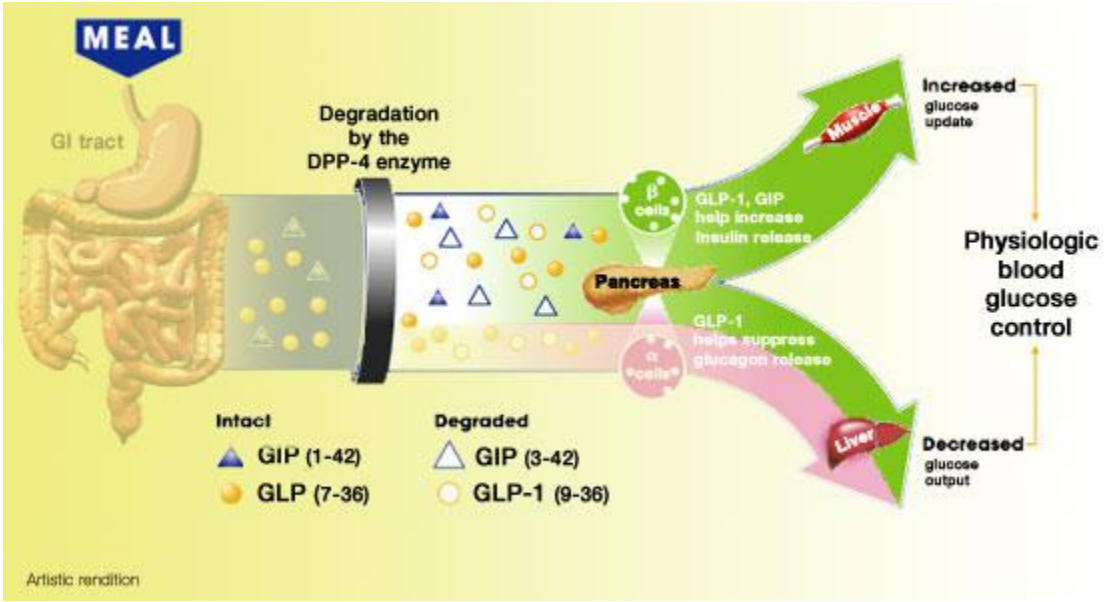


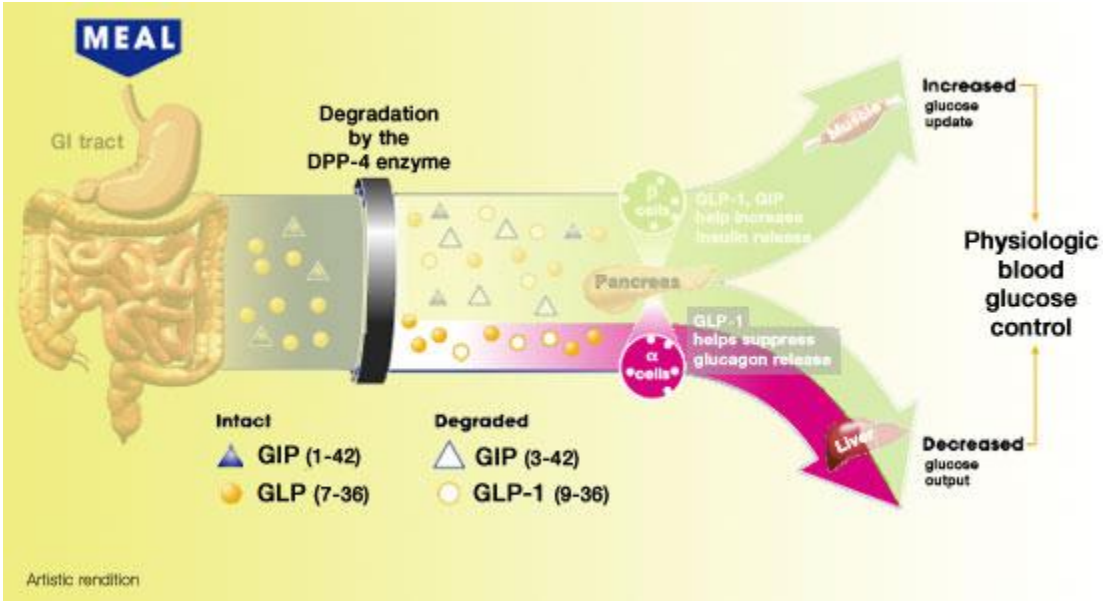

## GLP-1 and GIP Are the Two Major Incretins[2,3]

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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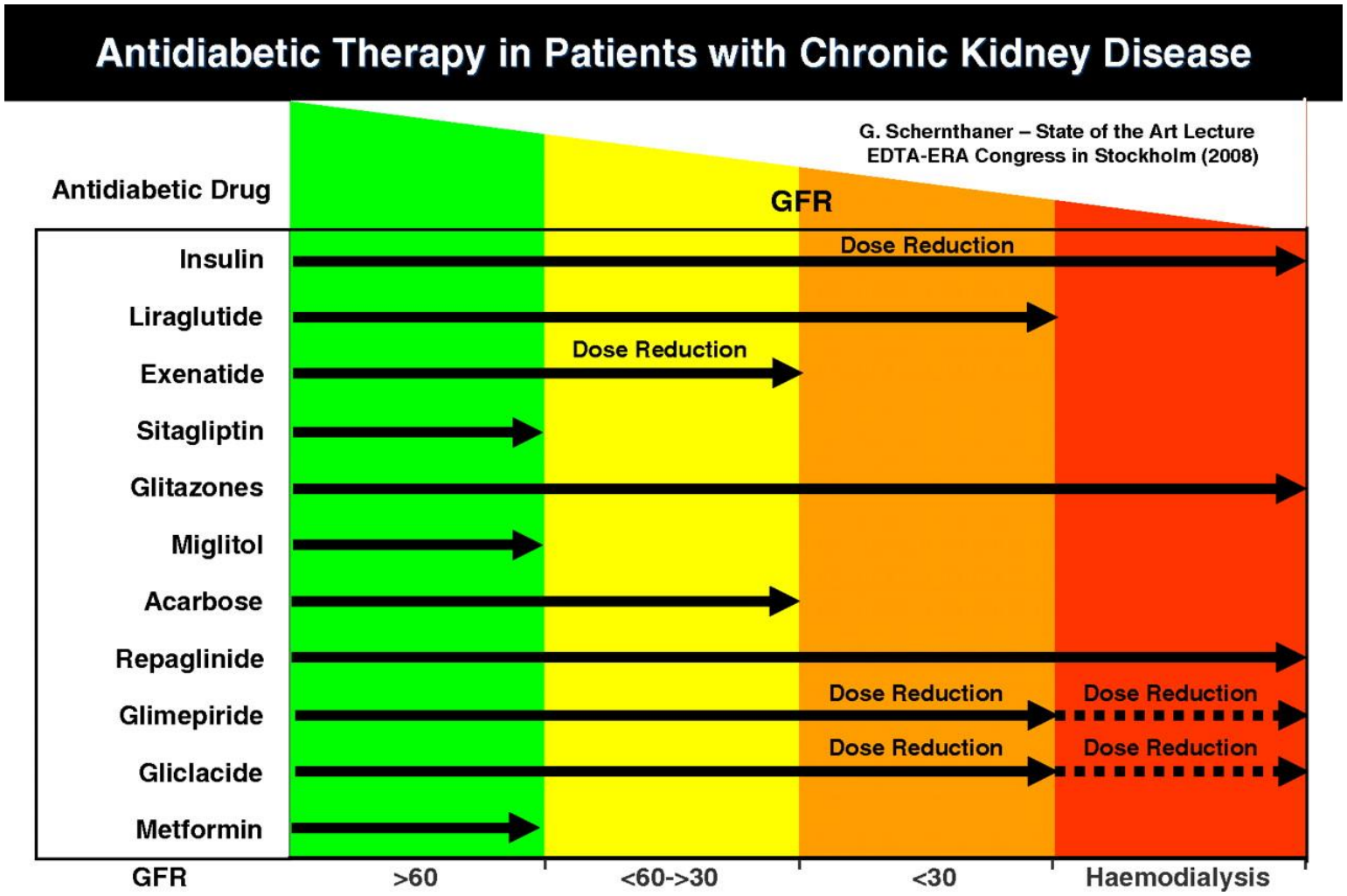


Schernthaner, G. et al. Nephrol. Dial. Transplant. 2010 25:2044-2047