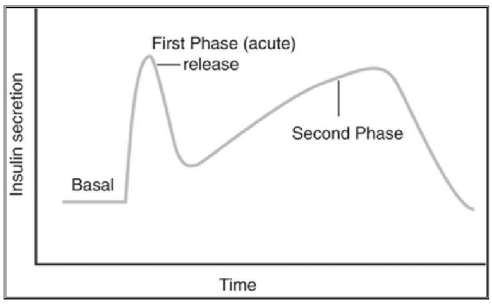
Management of Type 2 Diabetes

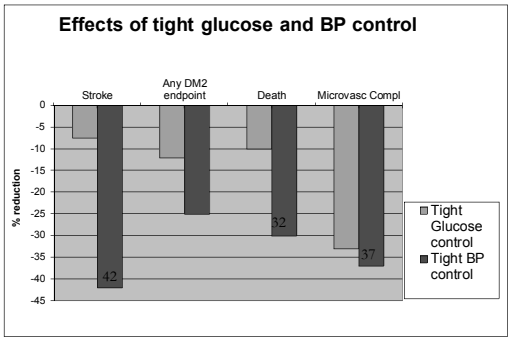
DG van Zyl

Insulin Secretion



Why Do We Bother to Achieve Good Control in DM2

The Importance of BP and Glucose Control



Current guideline recommendations Glycaemia

			SEMDSA 2009
HbA_{1c} [b,c]	<7.0%	<6.5%	< 7%
Fasting plasma glucose	5.0–7.2 mmol/L	<6.0 mmol/L	4 – 7 mmol/L
Postprandial plasma glucose[d]	<10.0 mmol/L	<7.8 mmol/L	5 – 8 mmol/L

[a] Targets for non-pregnant patients only.
[b] A different HbA_{1c} goal may be indicated in specific patient populations.
[c] Measured using a Diabetes Control and Complications Trial (DCCT)-aligned HbA_{1c} assay.
[d] Measured 1–2 hours after the beginning of the meal.

[1] American Diabetes Association. Diabetes Care 2005; 28: S4–36.
[2] IDF Clinical Guidelines Task Force. Global guideline for type 2 diabetes. Brussels: International Diabetes Federation, 2005.

Pharmacotherapy: Common Principles

- Combining drugs is usually more effective than stopping one agent and introducing another
- Adding a second agent is usually better than increasing the dosage of one that is already near maximum dosage
- Secondary failure of 2 drug combinations should be expected eventually

Common Principles (Cont)

- 3 drug combinations may be useful although clinical trial evidence is lacking
- Failure of 2 oral drug combinations usually calls for the use of insulin, alone or in combination with oral agents
- In patient with severe hyperglycaemia insulin may be started from the beginning until glucotoxicity resolves. It can then be reduced or even withdrawn.

Clinical Effects of Anti-hyperglycemic Agents

Name	Average HbA1c reduction	Patient best suited
Acarbose	0.5 – 1	High postprandial glucose
Metformin	1 – 2	Obese patients
Meglitinides	1 – 2	High postprandial glucose
Sulph/urias	1 – 2	Recently Dx type 2 diabetes
Glitazones	0.5 – 1.5	Obese or insulin resistant

Stepped Care: Type 2 Diabetes

Step 1: Nutrition therapy, exercise, lifestyle changes

Training in self-management and self-monitoring of blood glucose

Step 2: Add oral agents

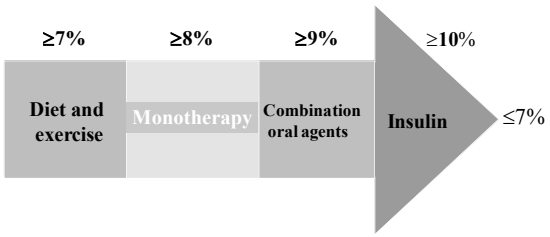
- mono-therapy
- combination therapy

Step 3: Add or change to insulin

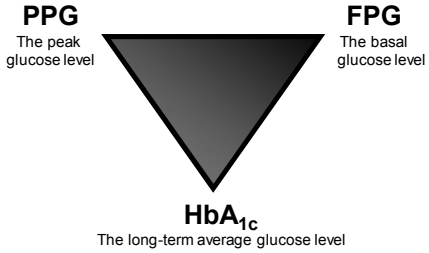
Step 4: Intensify insulin therapy

Old Approach

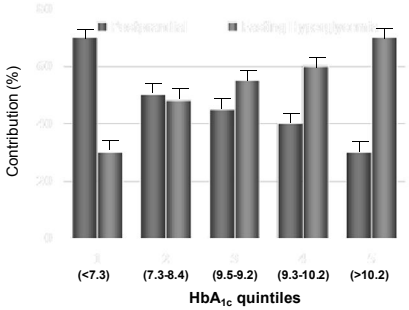
Diabetes Treatment by Hba_1c Level



For Optimal Management We Should Target……



PPG Contributes Up to 75% of Glucose Load



Monnier L, et al. *Diabetes Care* 2003;26.

Available drugs

Insulin Secretagogues

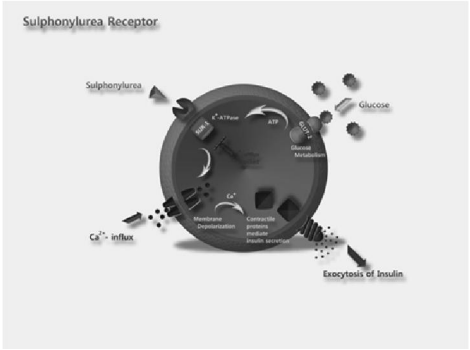
- Sulphonylurias
- Meglitinides

Increase the secretion of endogenous insulin, as long as pancreatic beta – cell function remains

Available Insulin Secretagogues

- **Sulphonylureas**
  - Glipizide (Minidiab)
  - Gliclazide (Diamicron)
  - Glimperide (Amaryl)
- **Meglitinides**
  - Repaglinide (Novonorm)
  - Nataglinide (Starlix)

Mechanism of Sulphonylurea Action



Take Note (Sulphonylureas)

- Alcohol and H2 blockers are competitive inhibitors of sulphonylurea metabolism
- Hypoglycaemia is the most serious complication of sulphonylurea use
- Pancreatic vs. Cardiac SUR

Meglitinides (Post-prandial Glucose Regulators)

- Bind to the SUR at a different site than Sulphonylureas
- Given at mealtimes and mimics the physiological insulin response
- Correlation between post-prandial hyperglycaemia and incidence of cardiovascular mortality (Honolulu heart study, Chicago heart study, DECODE and DIAS studies)
- No long term studies are available on Repaglanide use and cardiovascular risk. Studies using IMT as outcome however showed significant benefit

Available Insulin Sensitizing Agents

Biguanides (Metformin)

~~Thiazolidinediones (Pioglitazone, Rosiglitazone)~~

Biguanides (Metformin)

Mechanisms of action

- Decrease GNG (liver)
- Increase insulin mediated glucose uptake
- Reduce glucose absorption
- Increase splanchnic glucose utilisation
- Activate insulin receptors and GLUT-4

Advantages

- Weight loss, mild anorexic effect
- No hypoglycaemia
- Decrease thrombotic risk
  - ↓ platelet aggregation
  - ↓ PAI-1 levels
- Beneficial effect on lipid profile
  - ↓ LDL, ↓ Triglyserides, ↑ HDL
- Save in pregnancy (MiG study)

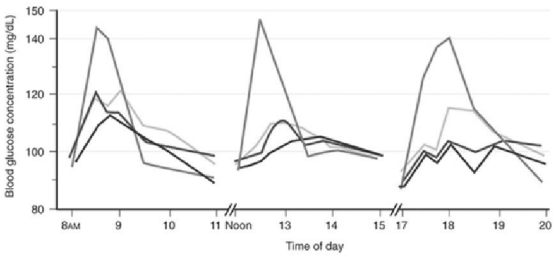
Alpha glucosidase inhibitors

- Slows the digestion of sucrose and starch and therefore delay absorption
- Slow post-meal rise in blood glucose

Side effects

- Flatulence, abdominal discomfort , diarrhoea
- As mono-therapy will *not* cause hypoglycaemia
- Hypoglycaemia when used with other medicine (e.g. a sulphonylurea)

Alpha glucosidase inhibitors



Alpha glucosidase inhibitors

Contraindications

- Intestinal diseases, such as Crohn's
- Autonomic neuropathy affecting the gastro-intestinal tract

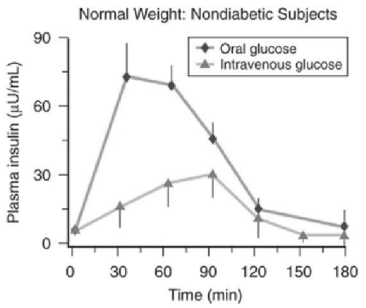
Must be taken just before a meal

Incretins

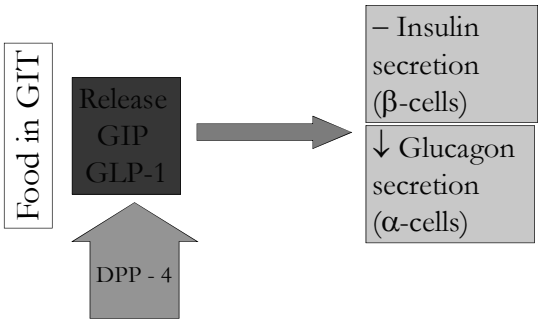
Gastric Inhibitory peptide

Glucagon like peptide-1

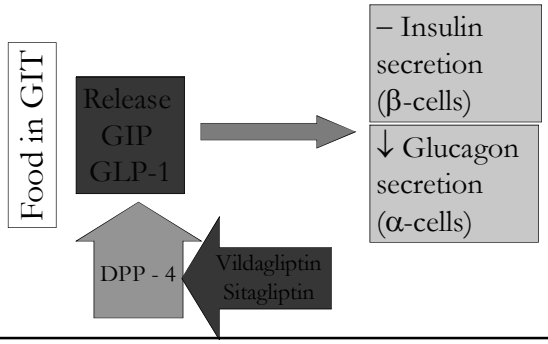
The Incretin effect



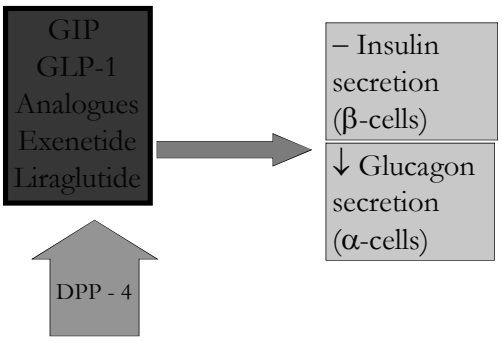
Incretin Physiology



DPP-4 enzyme inhibitors



Incretin analogues



Incretin Drugs

- GLP-1 analogues:
  - Exenatide (Bayetta): Given twice daily as subcutaneous injection
  - Liraglutide: Currently in phase III development. Given as a once daily subcutaneous injection
- DPP-IV inhibitors:
  - Vildagliptin: Taken orally once daily
  - Sitagliptin: Taken orally once daily
  - Saxagliptin: Taken orally once daily
  - Linagliptin: Taken orally once daily

GLP-1 (incretin mimetic agent)

- Improves beta-cell responsiveness to increasing glucose levels
- Decreases glucagon secretion
- Slows gastric emptying
- Results in a feeling of fullness
- Must be injected subcutaneously twice a day, within 30-60 minutes before a meal
- Reduces HbA_{1c} by ~1%

GLP-1 (incretin mimetic agent)

Side effects

- Nausea
- Weight loss
- Diarrhoea
- Risk of hypoglycaemia when used with a sulphonylurea

GLP-1 (incretin mimetic agent)

Contraindications

- End-stage kidney disease or renal impairment
- Pregnancy
- Severe gastrointestinal disease

Insulin in Type 2 Diabetes

When to Start Insulin in Type 2 Diabetic Patients

- Timely initiation of insulin therapy optimises blood glucose control and therefore improves prognosis
- HbA1C routinely > 7% indicates patient may benefit from insulin; three-monthly HbA1C monitoring is recommended

When to Start Insulin in Type 2 Diabetic Patients

- After OAD failure, combination insulin + OAD can improve glycaemic control with less weight gain than insulin alone
- Some patients may benefit from insulin therapy as soon as diet becomes inadequate

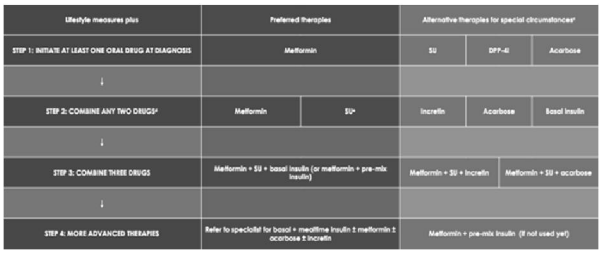
Indications for Insulin Therapy in Type 2 Diabetes

- Persistent hyperglycemia with oral agents
- Uncontrolled weight loss
- Latent autoimmune diabetes in adults (LADA)
- Advanced renal or hepatic disease
- Allergic reactions to oral agents
- Intercurrent events: MI, CVA, acute illness, surgery
- Women planning pregnancy
- Gestational diabetes

Early Insulin Initiation: Why Is It Important?

- Type 2 diabetes is a disease of insulin resistance and insulin deficiency
- Beta cell decline is inevitable
- Insulin is the most powerful drug we have
- Starting early means fewer years of poor control

SEMDSA Algorithm



Conclusion

- Remember: management of diabetes type 2 is more than just treating blood glucose.
- The number of drugs significantly increased from 2 classes of drugs 15 years ago to 8 classes at the moment (excluding insulins) with a few novel ones on the way.