

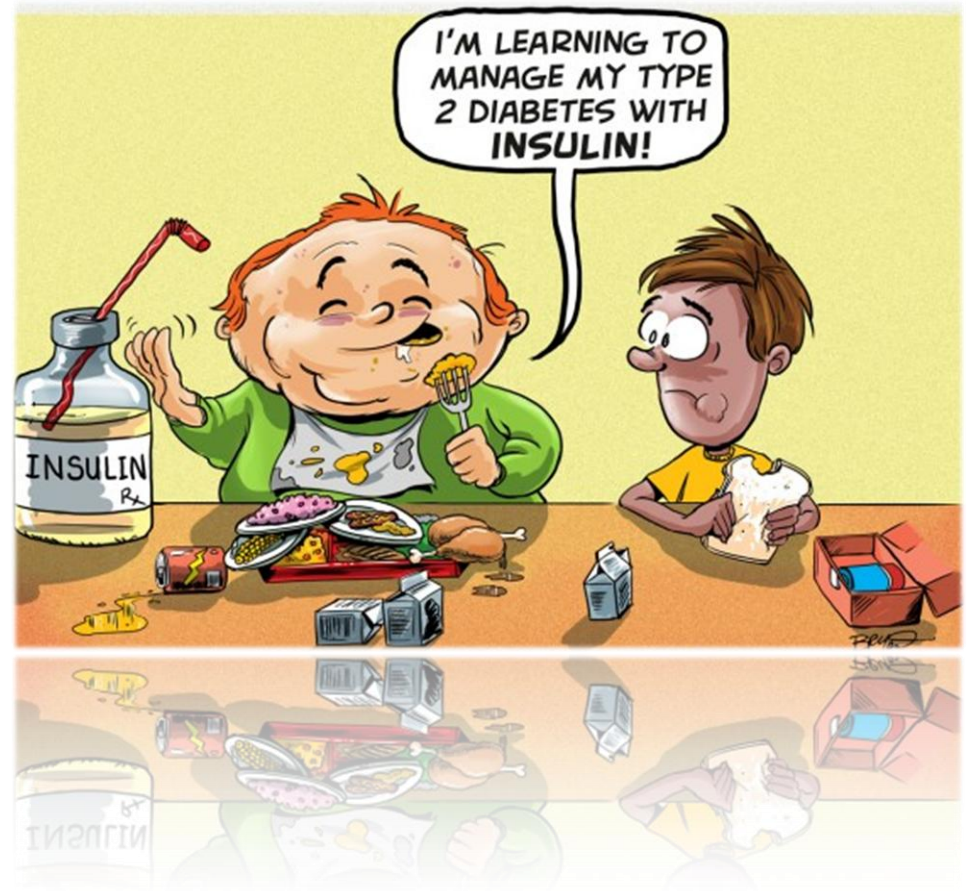
Drugs used in Diabetes

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Plan

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- Insulin Sensitising Drugs:
 - *Metformin*
 - *Glitazones*
- Insulin Secretagogues:
 - *Sulphonylureas*
 - *Meglitinides*
- Others:
 - *Acarbose*
 - *Incretins*
 - *Amylin Analogues*
 - *Damaglifozin*
- Drug Choice
- Insulin – Types and Regimes
- Summary



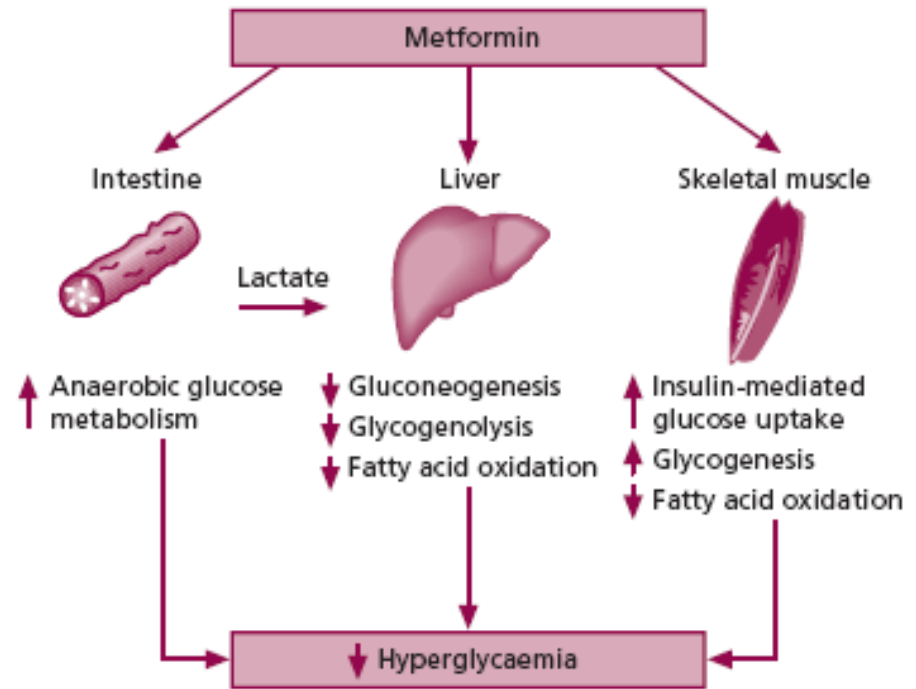
Diabetes

- It is estimated that around 4.5% of the UK population has diabetes.
- The two major types are:
 - Type 1 Diabetes (10%)
 - Pancreatic β -cell destruction \rightarrow insulin deficiency
 - Type 2 Diabetes (90%)
 - Relative insulin deficiency and peripheral insulin resistance
 - Other types include gestational diabetes and pancreatic disease (e.g. Cystic fibrosis)
- The type is important as it will influence treatment options; i.e. There's no point giving an insulin sensitising or secreting agent if there is no residual insulin!
- There are a myriad of short and long term sequelae of diabetes which means good control is crucial.



Insulin Sensitising Drugs - Metformin

- The only licensed biguanide
- It inhibits hepatic gluconeogenesis.
- Increases peripheral glucose uptake by sensitising the insulin receptors.
- Alters the intestinal absorption of glucose.
- Usual dose: Titrate up from 500mg od to maximum of 1g bd.
- Is safe in pregnancy and breastfeeding.



Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004

Insulin Sensitising Drugs - Metformin

Side-effects:

- Most side-effects are gastrointestinal e.g. diarrhoea, nausea, vomiting, taste-disturbance, flatulence.
- It does not increase insulin secretion so does not cause hypoglycaemia by itself.
- It predisposes to lactic acidosis (rare) due to its inhibition of gluconeogenesis (which utilises lactate).
 - Most vulnerable patients have pre-existing renal and/or liver failure.
 - Metformin should be stopped for 48 hours when iodinated contrast media is used.



Insulin Sensitising Drugs - Pioglitazone

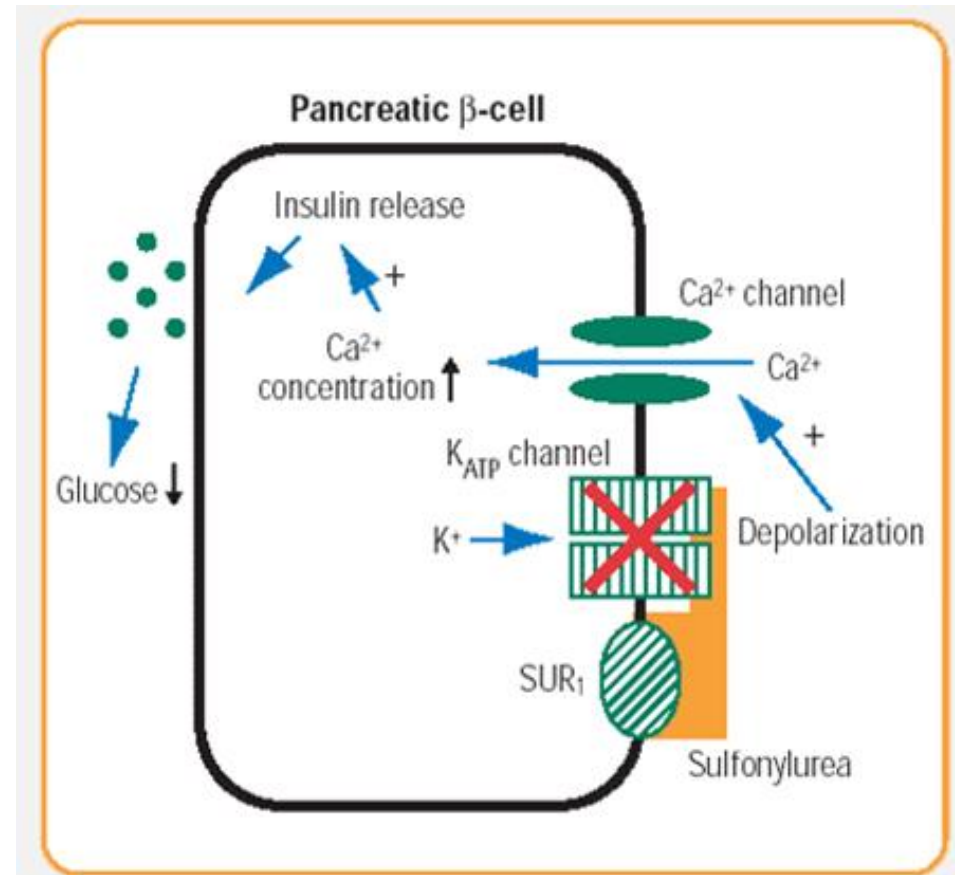
- Is a thiazolidinedione drugs (use of rosiglitazone has been suspended).
- Increases peripheral glucose uptake by altering gene transcription.
- Dose: 15-30mg od, up to max of 45mg od
- It should be avoided in pregnancy and breastfeeding.
- Liver function should be monitored.
- Has been shown to increase rate of heart failure and bladder cancer.

Insulin Secretagogues - Sulphonylureas

- Stimulate insulin release from the Pancreatic β -cells by binding to ATP-dependent K channels.
- Reduce both fasting and post-prandial glucose

Examples include:

- Gliclazide (initially 40-80mg at breakfast up to a max of 320mg in split doses)
- Tolbutamide (0.5-1.5mg divided doses after meals)
- Glibenclamide (longer acting - 5mg with breakfast up to max of 15mg)



Insulin Secretagogues - Sulphonylureas

Side effects:

- Weight gain (due to anabolic effects of insulin).
- Gastrointestinal e.g. Nausea, vomiting, diarrhoea, constipation.
- They can cause hypoglycaemia (increased risk in hepatic and renal failure).
- Blood disorders are rare but can occur.
- Should be avoided in pregnancy and breastfeeding.

Insulin Secretagogues - Meglitinides

- Similar mechanism of action as sulphonylureas but shorter half life – should be given before meals.

Examples:

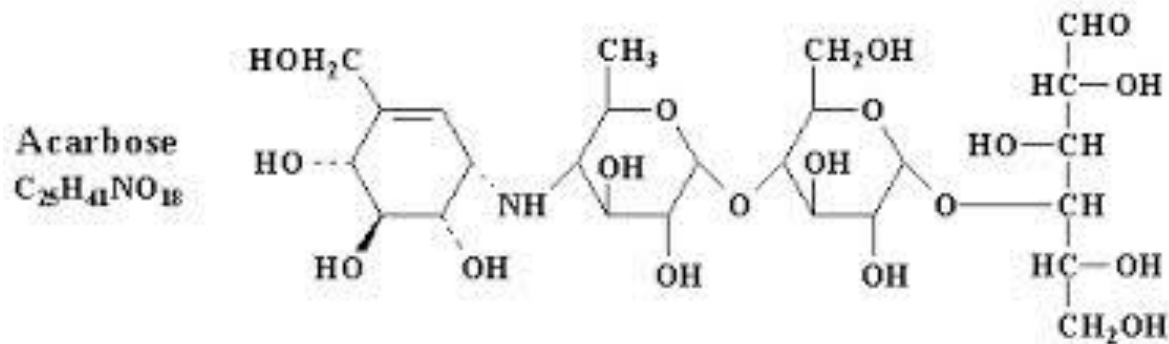
- Repaglinide (500µg up to 16mg in split doses)
- Nateglinide (60mg tds up to 180mg tds)

Side effects

- Weight gain and hypoglycaemia.
- Should be avoided in liver disease, breast-feeding and pregnancy.

Other Anti-Diabetic Agents - Acarbose

- An α -glucosidase inhibitor (50mg od up to 200mg)
- Decreases intestinal absorption of carbohydrates by inhibiting their digestion – must be taken with food.
- **Side effects:** bloating and diarrhoea.
- Avoid in hepatic and renal failure, previous intestinal disease/surgery, pregnancy and breastfeeding.



Other Anti-Diabetic Agents - Incretins

Glucagon-like peptide 1 (GLP-1) analogues

- Increase insulin secretion, suppress glucagon secretion and slows gastric emptying.
- Examples are Exenatide (sub-cut 5 μ g bd up to 10 μ g bd) and Liraglutide (0.6mg od, up to 1.8mg)
- They do increase weight-loss.
- **Side-effects:** persistent nausea, pancreatitis.
- Caution in renal and hepatic disease. Avoid in pregnancy and breast-feeding.



Other Anti-Diabetic Agents - Incretins

Dipeptidyl peptidase (DPP)-4 Inhibitors

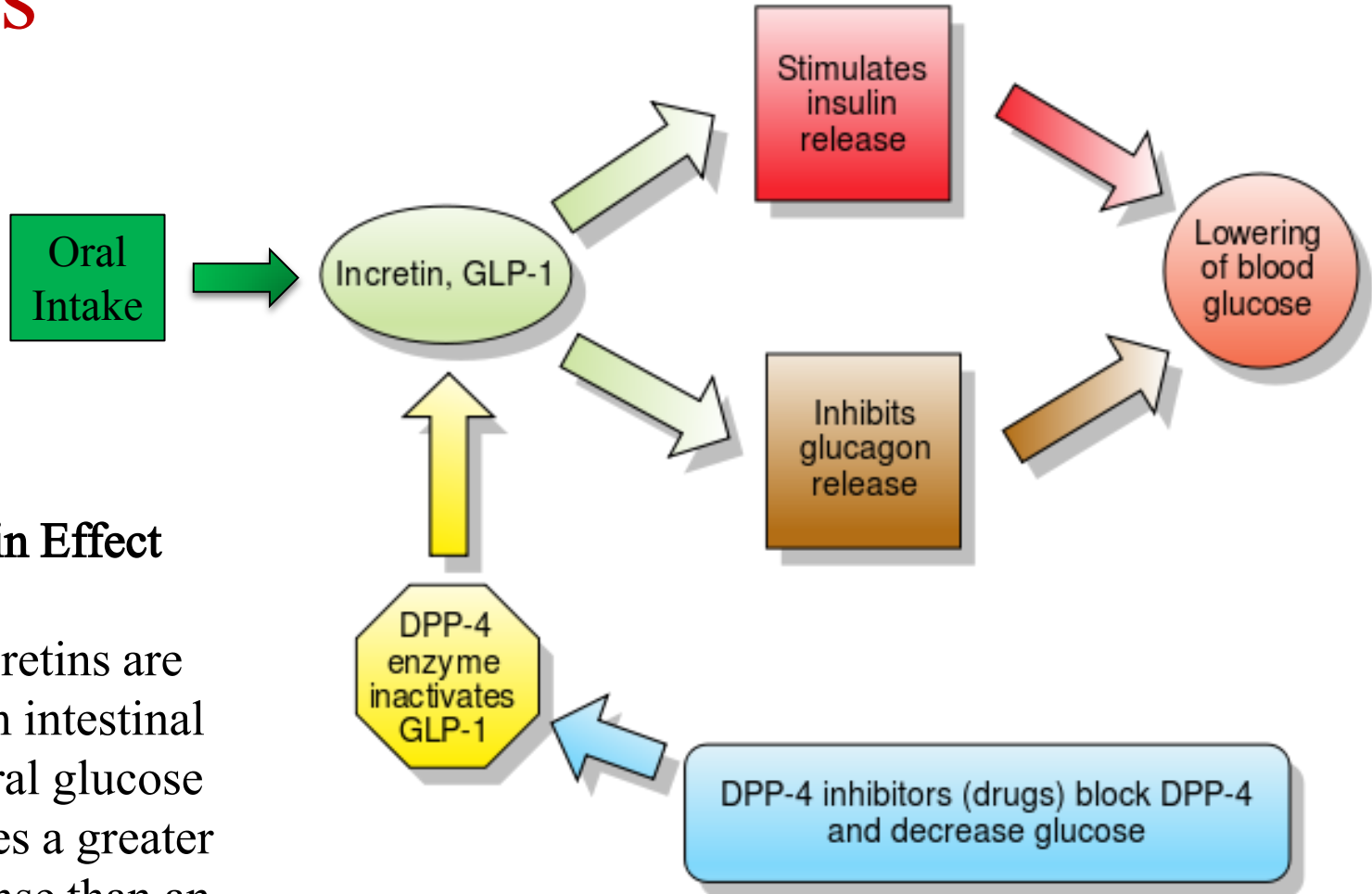
- DPP-4 inhibits GLP-1 and GIP, therefore, by inhibiting it, these drugs increase insulin secretion and lower glucagon
- Examples include Saxagliptin (5mg od) and Sitagliptin (100mg od)

Side-effects

- Gastrointestinal disturbances, peripheral oedema, Upper Respiratory infections, dyslipodaemia, hypersensitivity reactions
- Use with caution in hepatic and renal disease. Avoid in pregnancy and breast-feeding



Incretins



The Incretin Effect

Because incretins are released from intestinal L-cells, an oral glucose load stimulates a greater insulin response than an IV glucose load.

Other Anti-Diabetic Agents

- **Amylin Analogues**, e.g. Pramlintide (sub-cut 15 μ g up to 60 μ g), decreases gastric emptying, suppresses glucagon secretion and decreases appetite. Amylin is normally secreted along with insulin.
- **Damaglifozin** (10mg od) reversibly inhibits sodium-glucose cotransporter-2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.



Choice of Drug

- Metformin is the first line agent – especially in the overweight.
- If not overweight or metformin not tolerated, a sulphonylurea is used.
- If monotherapy does not reach adequate control, metformin and a sulphonylurea together are used.
- Other agents can then be added in if various NICE criteria are met.
- If these treatments fail, use of Insulin must be considered.



Insulin

- Only treatment choice in Type 1 diabetes. Used in Type 2 once failure of oral hypoglycaemics occurs.
- Is mostly human insulin (rather than animal) and divided into 3 broad categories:
 - Rapid/Short acting
 - Intermediate acting
 - Long acting
- Recombinant Insulin analogues are also available.
*Denoted by an * in the following slides.*



Short Acting Insulins

Rapid/Short Acting:

- *Insulin Aspart (NovoRapid)*
onset 5-15 minutes, peak 45-75 minutes duration 2-4 hours
- Soluble Insulin (Actrapid)
onset 30-60 minutes, peak 2-4 hours, duration 8 hours
- Can be given subcutaneously, intramuscularly and intravascularly
- They are typically used to control meal-time surges and in continuous insulin infusions.
- The insulin analogues have a more rapid onset and short half-life.
- Biphasic insulins are a mixture of a rapid/short acting insulin with an intermediate insulin, so they can be given together.



Intermediate and Long-Acting Insulins

Intermediate Acting:

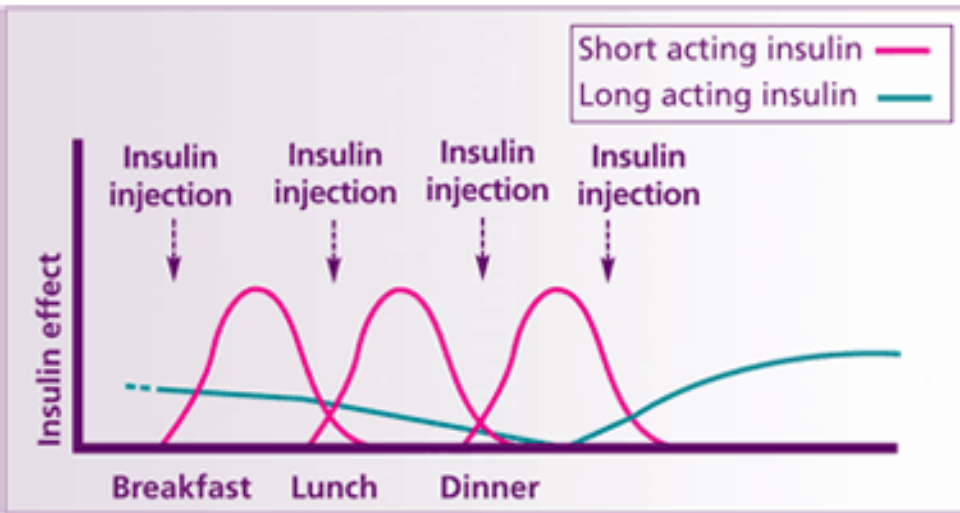
- Isophane (Humulin I) – *onset 1-2h, peak 2-8h, duration 18-20h*

Long Acting:

- Insulin Zinc – *onset 2-4h, peak 6-16h, duration 20-24h*
- *Insulin Detemir (Levemir)* – *onset 2h, no peak, duration 6-20h*
- *Insulin Glargine (Lantus)* – *onset 2-4h, no peak, duration 20h*
- Absorption is prolonged by binding to other molecules such as zinc.
- Only given by SC.
- Used to provide steady background insulin levels – durations vary slightly (see above).
- The insulin analogues have a smoother action profile.

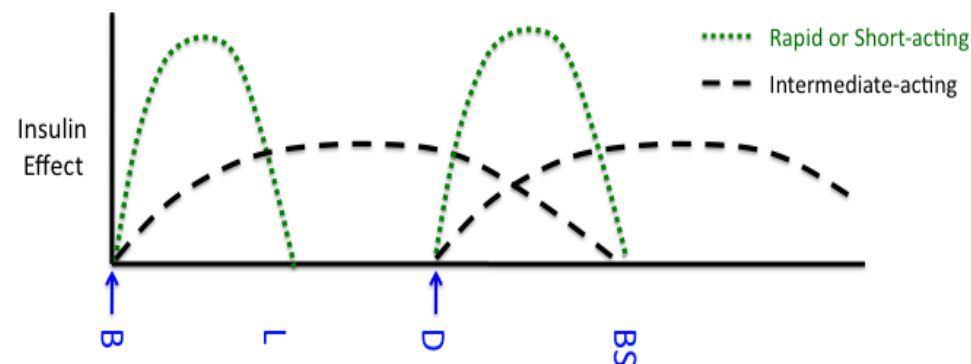


Typical Insulin Regimes



Basal-Bolus

- 3 x rapid/short acting insulins given before mealtimes with a long acting given at night.
- Allows more flexibility of timing and quantity of food.
- Does involve 4 injections daily.



Biphasic

- 2 injections a a of a premixed rapid/short and intermediate insulin.
- Less flexibility and quality of glucose control, but more convenient.

Other Insulin Regimens

- **Single dose long acting** – most commonly combined with oral hypoglycaemics or in the conversion of Type 2 diabetics onto a full insulin regimen.
- **Continuous SC infusion** – A portable device which provides a continual basal dose of insulin. Boluses can be given by pressing a button. Requires frequent glucose monitoring.
- **Insulin Sliding Scale** – Variable IV infusion used in hospitals during critical illness or periods of fasting



Parents who got insulin pump tattoos so their diabetic child wouldn't feel different

Side effects of Insulin

- Hypoglycaemia (patients can lose the warning signs of hypoglycaemia and β -blockers exacerbate this).
- Weight-gain.
- Lipodystrophy (lipohypertrophy/lipoatrophy) at injection sites.
- Transient peripheral oedema.
- Hypersensitivity reactions are rare.



Lipohypertrophy



Lipoatrophy

Other considerations in Diabetes

Diet and Exercise

- Encourage a healthy, low fat diet. Modest weight loss can have profound impact on glucose control.
- The Glycaemic index is a measure of how quickly blood glucose levels rise after eating (GI of Glucose = 100).
- Low glycaemic index foods are encouraged.
- Exercise increases insulin sensitivity

Low Glycemic Foods List 0 - 55	Medium Glycemic Foods List 56 - 70	High Glycemic Foods List 70+
Most non starchy vegetable <15 Peanuts <15 Low-fat yogurt, no sugar<15 Tomatoes 15 Cherries 22 Peas 22 Plum 24 Grapefruit 25 Pearled barley 25 Peach 28 Can peaches, natural juice 30 Soy milk 30 Baby lima beans 32 Fat-free milk 32 Low-fat yogurt, with sugar 33 Apple 36 Pear 36 Whole wheat spaghetti 37 Tomato soup 38 Carrots, cooked 39 Apple juice 41 All-Bran 42	Canned kidney beans 52 Kiwifruit 52 Orange juice 52 Banana 53 Potato chips 54 Special K 54 Sweet potato 54 Brown Rice 54 Linguine 55 Oatmeal cookies 55 Popcorn 55 Sweet corn 55 Muesli 5 White rice 56 Pita bread 57 Blueberry muffin 59 Bran muffin 60 Hamburger bun 61 Ice cream 61 Canned apricots, light syrup 64 Macaroni and cheese 64 Raisins 64	Bagel 72 Corn chips 72 Watermelon 72 Honey 73 Mashed potatoes 73 Cheerios 74 Puffed wheat 74 Doughnuts 75 French fries 76 Vanilla wafers 77 White bread 79 Jelly beans 80 Pretzels 81 Rice cakes 82 Mashed potatoes, instant 83 Cornflakes 84 Baked potato 85 Rice, instant 91 French bread 95 Parsnips 97 Dates 100

Risk Factor Control

- Aspirin in those with high cardiovascular risk, consider statins and good blood pressure control.
- Smoking Cessation.



Other considerations in Diabetes

Driving

- Patients with diabetes may need to inform the DVLA. Requirements are stronger if on insulin and/or drive HGVs/Public Service vehicles



Pregnancy

- Metformin can be used but further control should be with insulin.
- There are risk of congenital malformation with poor control



Summary

- Diabetes is a common condition which needs to be well controlled. Education is an important part of its management.
- Medications for insulin can be divided into the following categories:
 - Insulin Sensitising Drugs:
 - *Metformin*
 - *Glitazones*
 - Insulin Secretagogues:
 - *Sulphonylureas*
 - *Meglitinides*
 - Others:
 - *Acarbose*
 - *Incretins*
 - *Amylin Analogues*
 - *Damaglifozin*
 - Insulin – Short/Intermediate/Long
- The choice of which medications and regimes are multi-factorial – involve the patient.



Any Questions?

Bibliography

The British National Formulary

K+C's Medical Therapeutics

