Drugs used in Diabetes

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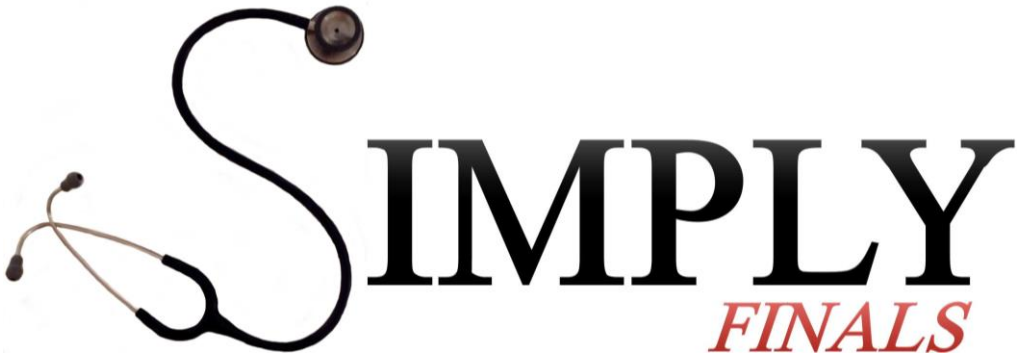
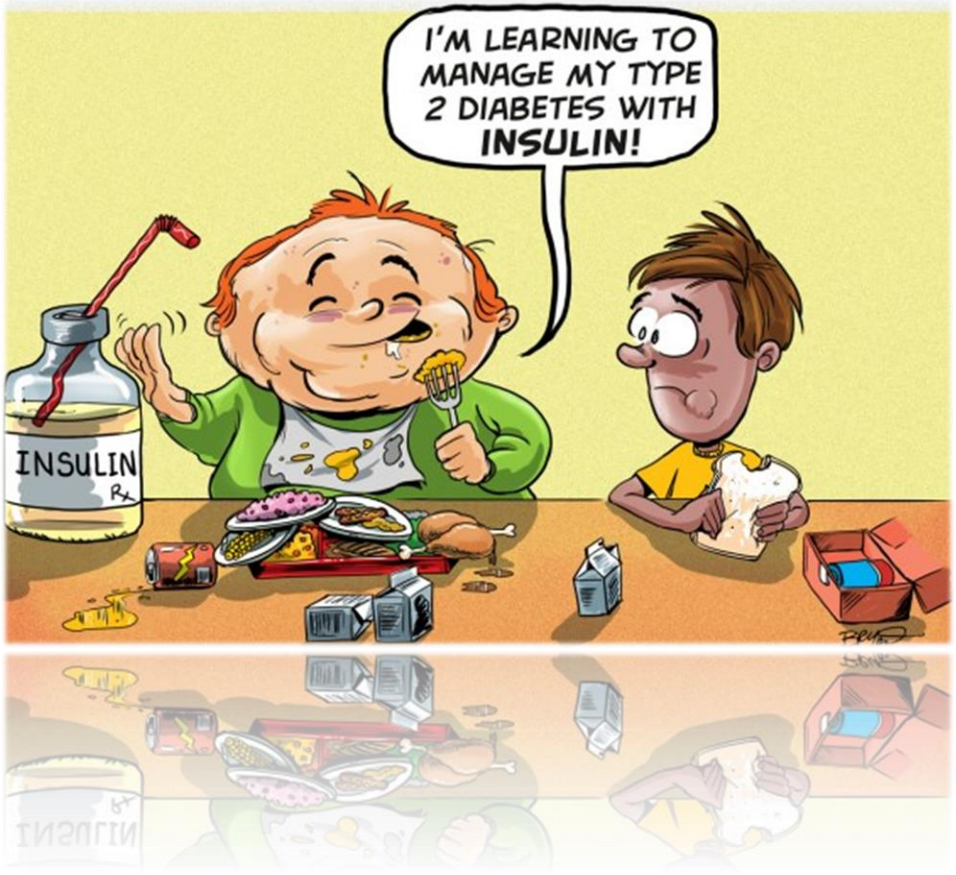


Plan

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



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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 → 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!

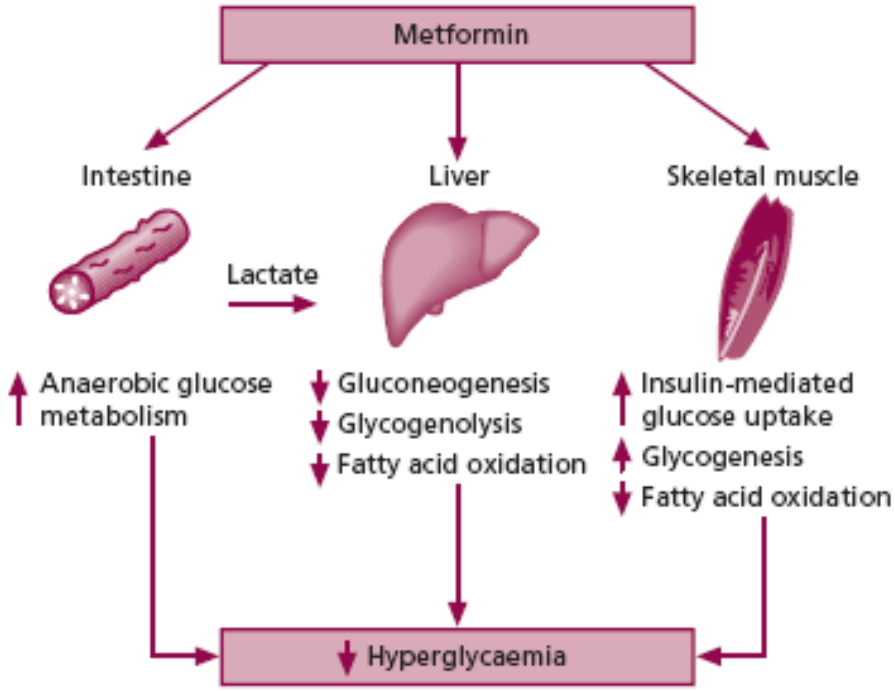
- There are a myriad of short and long term sequelae of diabetes which means good control is crucial.

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.



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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

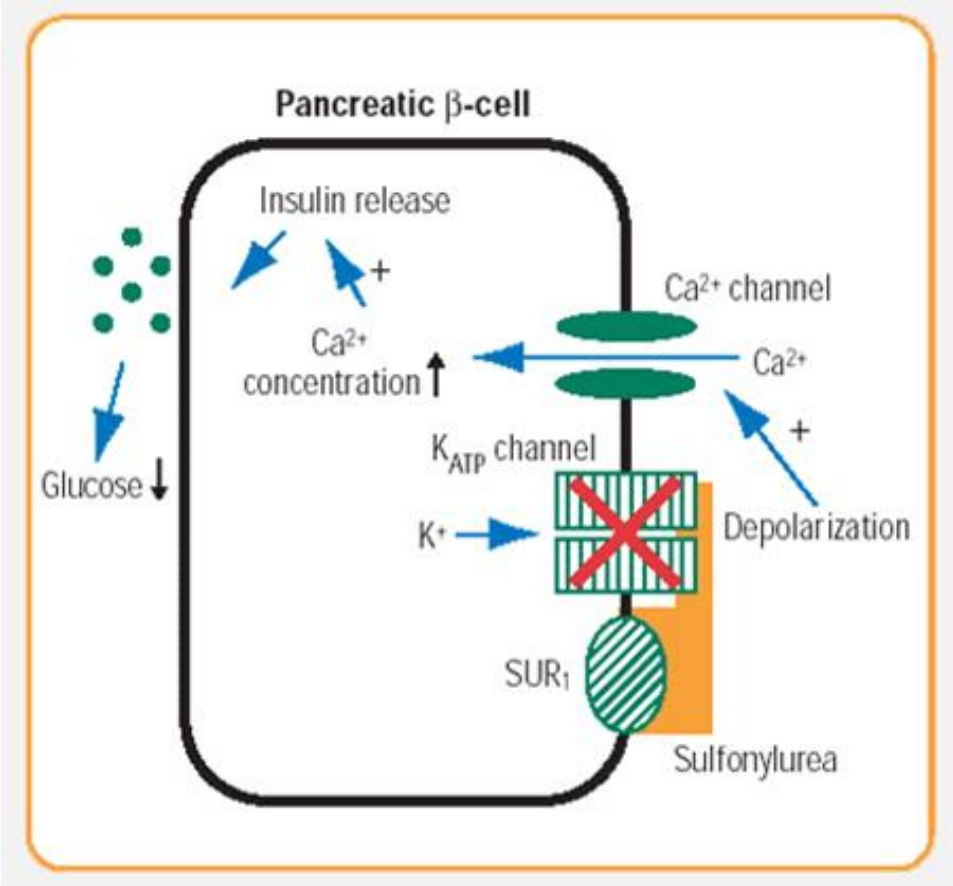
- It should be avoided in pregnancy and breastfeeding.
- Liver function should be monitored.
- Has been shown to increase rate of heart failure and bladder cancer.

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

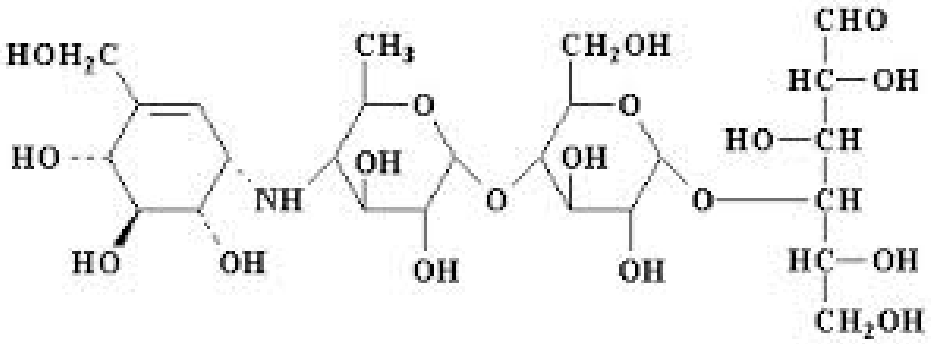
- Weight gain and hypoglycaemia.
- Should be avoided in liver disease, breast-feeding and pregnancy.

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.

Acarbose
$C_{25}H_{43}NO_{18}$



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 5µg bd up to 10µg 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

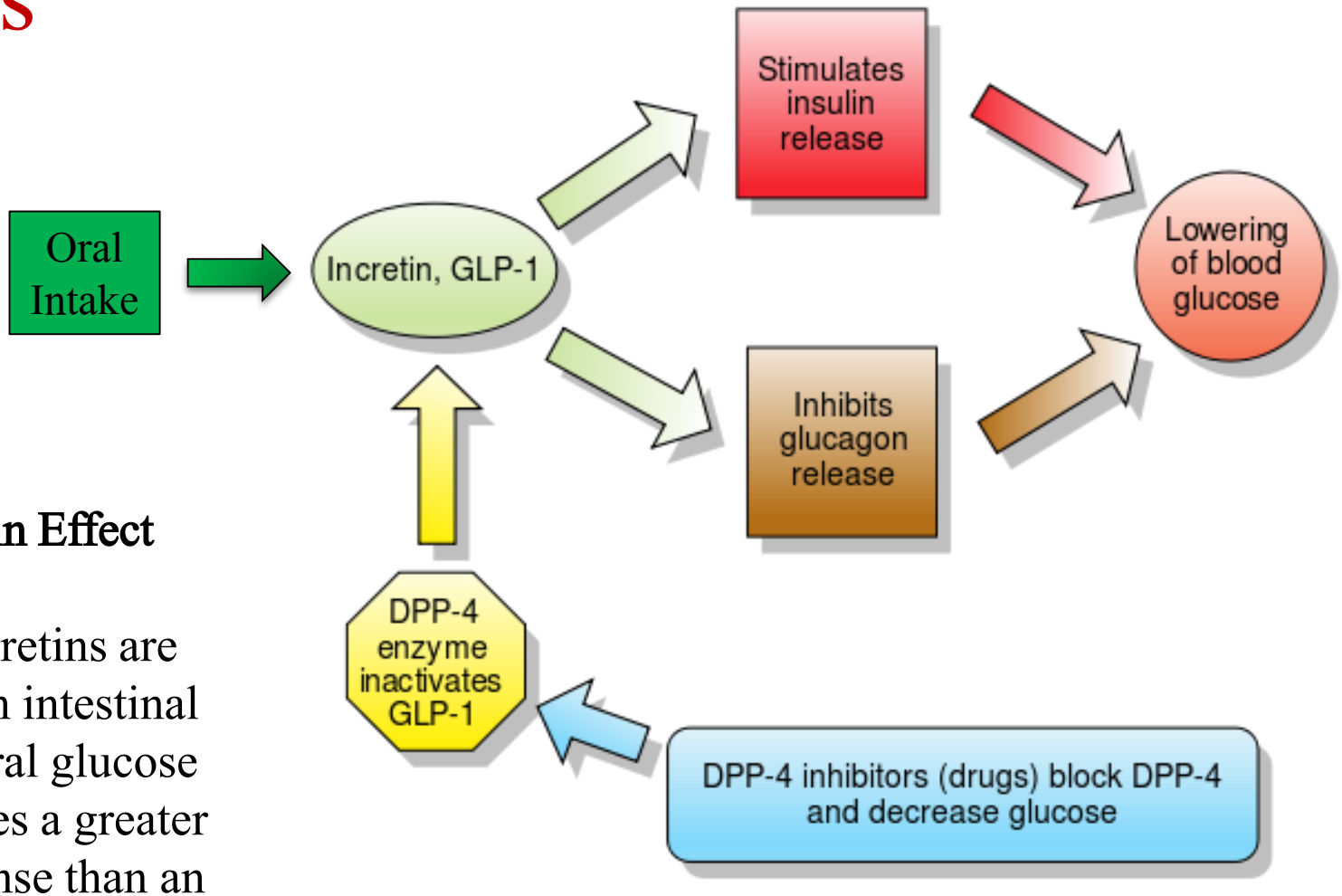
Dipeptidyl peptidase (DPP)-4 Inhibitors

- 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 15µg up to 60µg), decreases gastric empting, suppresses glucagon secretion and decreases appetite. Amylin is normally secreted along with insulin.

- **Damaglifozin** (10mg od) reversibly inhibits sodium-glucose contransporter-2 in the renal proximal convuluted 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.*

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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.

Recombinant Insulin Analogue

Intermediate and Long-Acting Insulins

Intermediate Acting:

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

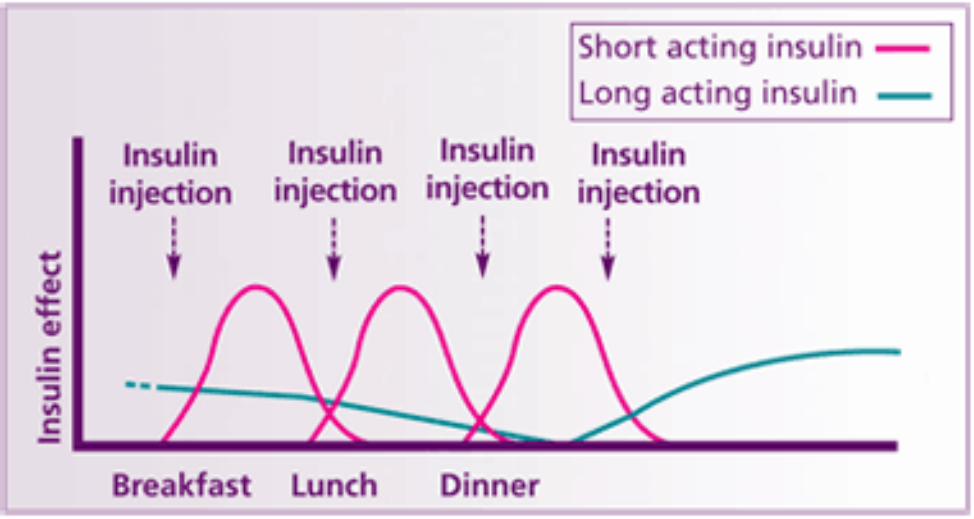
Long Acting:

- 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.

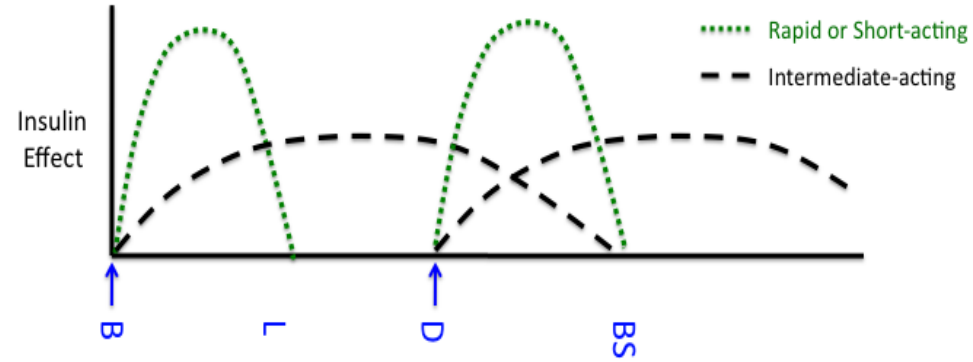
Recombinant Insulin Analogue

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.

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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

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

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

DVLA®
Driver and Vehicle Licensing Agency

Pregnancy

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

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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.

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Any Questions?

Bibliography

The British National Formulary

K+C's Medical Therapeutics

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