Drug Therapy of Diabetes

Michael Veltman

MBBS FANZCA FASE

Director of Anaesthesia
Joondalup Health Campus

Overview

- Definition and Incidence
- Physiology
- Aetiology and Pathophysiology
- Treatment Aims
- Pharmacology
  - Insulin
  - Oral agents
- Non-pharmacological Treatments

Definition and Incidence

Diabetes Mellitus

- History
  - Mellitus versus Insipidus
  - Insulin treatments
- Definition
  - Plasma glucose > 7 mM, Fasting
  - Plasma glucose > 11.1 mM, 2 hours post GTT

Incidence

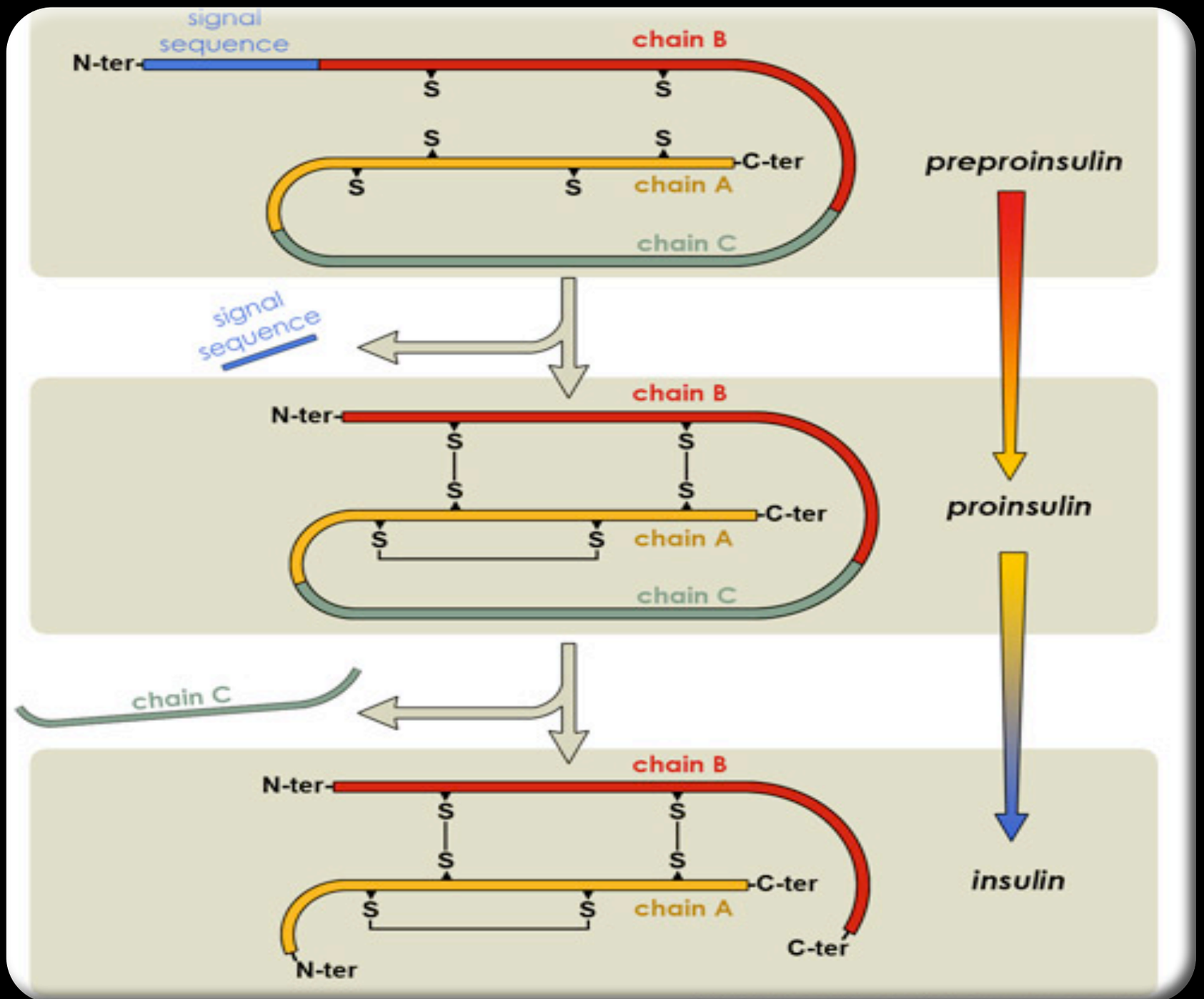
- Common Disease in the western world
  - 6% of the world's adult population (285 million)
  - Rising rapidly - was only 30 million people in 1985

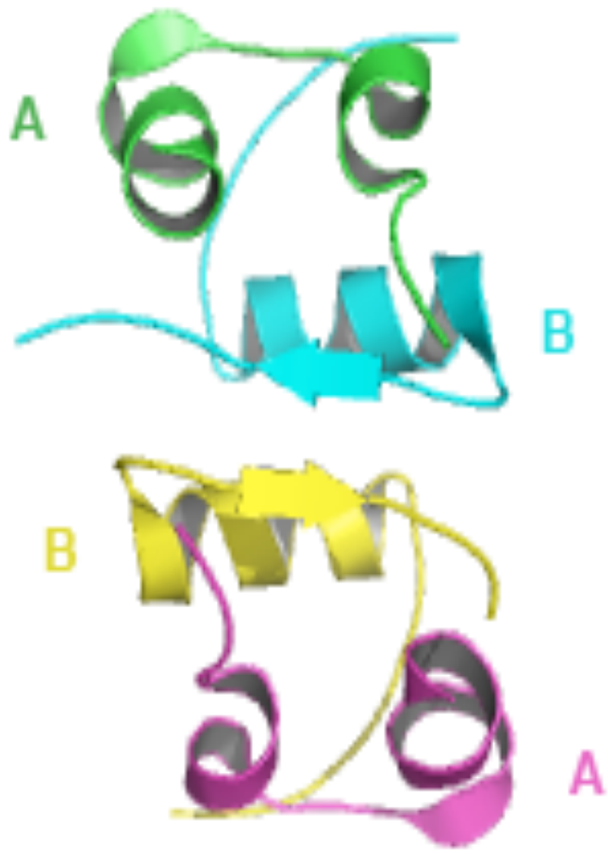
Classification

- Type I (5%)
  - Autoimmune
  - Other (rare) - Pancreatitis, toxins
- Type II (90-95%)
  - Insulin Resistance
- Gestational

Physiology

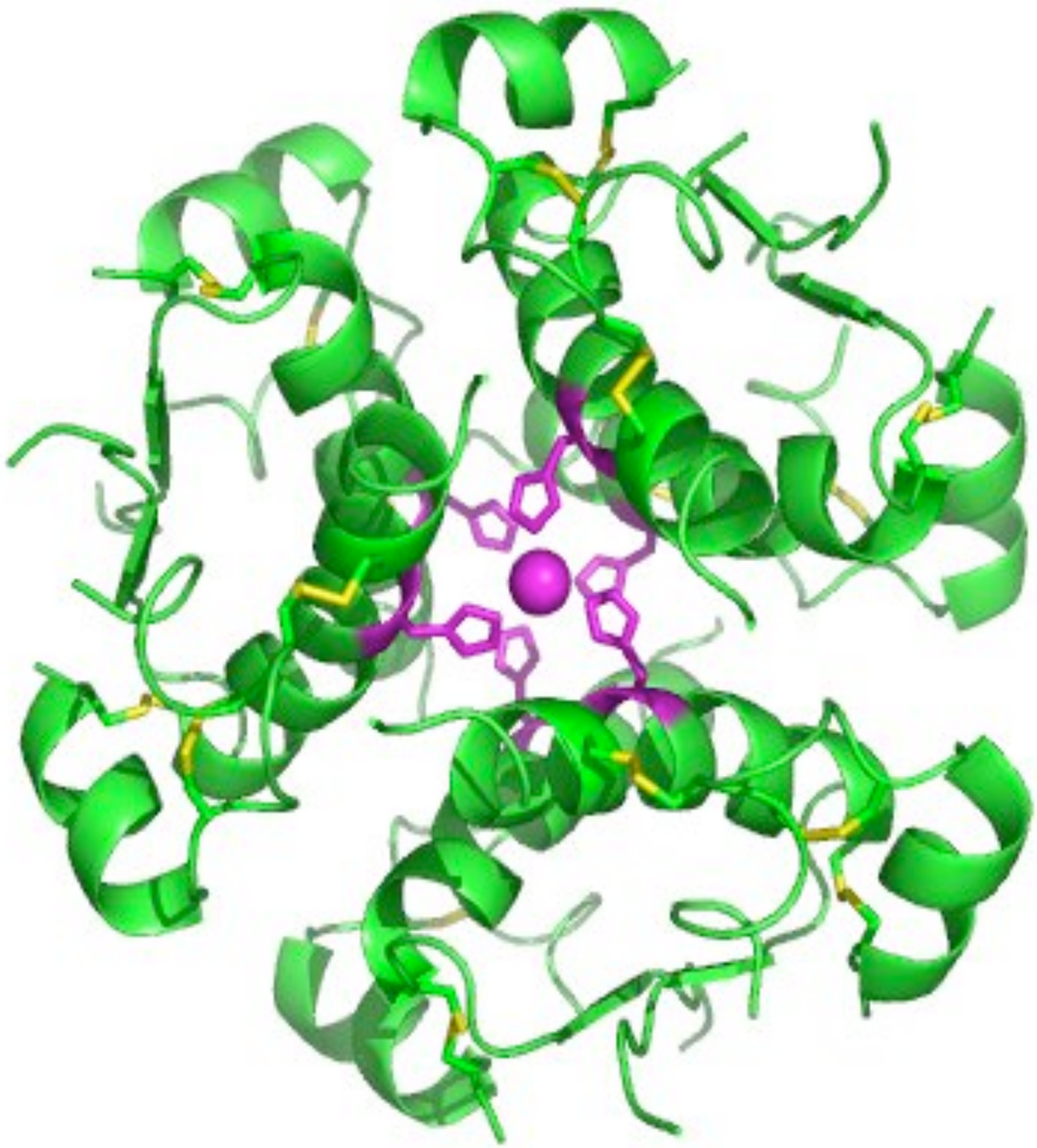
Insulin





- Produced in β islet cells in pancreas

Insulin



- Hormone produced by pancreas.
- Regulates metabolism:
  - Carbohydrate
  - Fat
- Insulin is needed for uptake of glucose

Insulin Effects

Cellular physiology

- Binds to the insulin receptor α subunit
  - Also binds to IGF-I
- Causes activation of
  - Tyrosine Kinase
  - Phosphorylation of of cytoplasmic protiens

Insulin - Rapid Effects

- Rapid increases in transport of
  - Glucose
  - Amino Acids
  - Potassium

Insulin - Intermediate Effects

- Increased protein synthesis
- Decreased protein degredation
- Glycolysis
- Inhibition of gluconeogenesis

Insulin - Delayed Effects

- Increased lipogenesis
  - Mediated through increased production of enzymes

Glucose Transport

	Location	Affinity	Capacity
GLUT-1	RBC, Endothelium, Fetal cells	1-2	Low *
GLUT-2	Pancreatic β cells, liver, renal tubules	12-20	High
GLUT-3	Neurons, Placenta	<1	Medium
GLUT-4	Fat, Muscle	5	Varies
GLUT-5	Fructose transport	1-2	

Aetiology

Aetiology -Type I

- Due to a loss of insulin secreting cells
  - β Islet cell produce insulin
- Multifactorial
  - Genetic (30-50%)
  - Autoimmune

Aetiology - Type II

- Due to insulin resistance.
  - Compensatory hypersecretion
  - Ultimately leading to islet cell failure

Pathophysiology

Diabetic Complications Acute

- Hyperglycaemia
  - Polyuria. (+ loss of electrolytes)
  - Impaired immune function
  - Impaired injury response
    - Myocytes
    - Neurons
  - Diabetic ketoacidosis

Diabetic Ketoacidosis

- Medical Emergency
  - Acidosis is the key feature
- Excess production of
  - Aceto-acetate, β Hydroxy butyrate.
  - Fall in pH
  - Acidic Urine
  - Loss of Na^+ and some K^+ in urine

Chronic Diabetes

- More a disease of fat metabolism
  - Elevated free fatty acids
  - Altered metabolism of Acetyl-CoA
  - Ketone formation (source of energy)

Diabetic Complications Chronic

- Accelerated Vascular Disease
  - Peripherally
  - Coronary
  - Cerebral
- Retinopathy
- Neuropathy
- Nephropathy

Aims of therapy

Critical Care Setting

- Aiming to prevent high (>8.0 mMol) levels of glucose
  - Intravenous insulin is the drug of choice
- Benefits:
  - Critically unwell
  - Myocardial injury
  - Neurological injury (?)

Diabetic Ketoacidosis

- Aim to restore deficits in:
  - Insulin
  - Potassium and Sodium
  - Water
- Life threatening condition
  - 5% mortality

Critical Care Setting

- Insulin can be used to lower potassium
  - Usually given with glucose
  - Doesn't shift potassium out of the body

Aim in the community

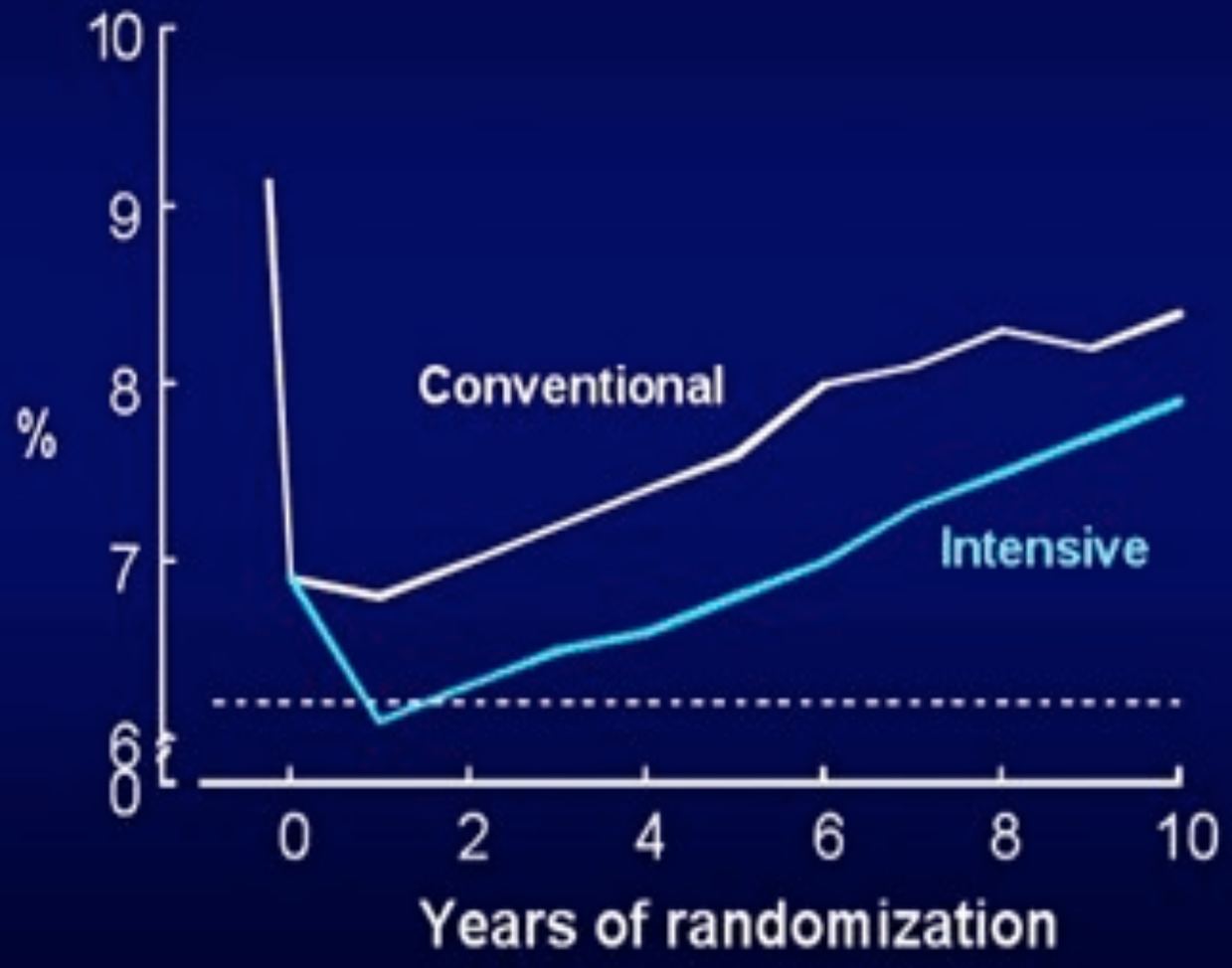
- Minimise the longer term impact of elevated glucose
  - Day to day fluctuation is not that important
  - Glycosylated Haemaglobin is very good measure
- Avoid hypoglycaemic events

HbA1c

- Haemoglobin has a 120 day lifespan
  - Glycosylation happens spontaneously
  - Glycosylation is proportional to glucose level
- Normal level is 4.0-5.9 %
  - Level above 6.5% suggests diabetes
- Target in diabetes is < 7.0%

Disease Progression

UKPDS HbA_{1c} Values Over 10 Years



UKPDS 33. *Lancet*. 1998;352:837-853.

- Type II diabetes is a progressive disease

Insulin

Insulin Manufacture

- Done with recombinant DNA
  - USE bacteria or yeast.
- Species variation exists
  - Essentially all human insulin now.
  - Lower reaction rates to human insulins

Insulin Administration

- Subcutaneous
- Intravenous Insulin
- Other routes
  - Inhalational, transdermal, intranasal, oral

Insulin Pharmacology

- Types of insulin
- Mechanisms of action
- Dosage

Insulin

- Ultra fast acting
- Fast Acting
- Intermediate Acting
- Long Acting

Ultra Fast Acting

- Lispro (Lysine and proline swap on B chain)
- Aspart (Aspartic Acid for Proline on B chain)
  - Both have high soluability
  - Rapid uptake - Onset 15 minutes
  - Peak effect at 45-90 minutes
  - Duration 3-5 hours.

Fast Acting

- Insulin (“Actrapid”)
- Standard insulin
  - Onset 30 minutes
  - Peak 2-4 hours
  - Duration up to 6 hours

Intermediate Acting

- Mixtard (Insulin/protamine)
  - Onset 2 hours
  - Peak 4-6
  - Duration 12 hours

Long Acting

- Used to use Zinc (Ultralente insulin)
- Mostly now use modified insulins
  - Glargine
    - Adds arginine to C end of B chain
    - Low pKa leads to slow absorption
  - Detemir
    - Binds myristic acid to the Lysine at B29
    - High affinity for Albumin

Long Acting

- Onset slow - ? 4 hours
- Duration 24 hours
- No discernable peak.

Exogenous Versus Endogenous

- Insulin has different effects depending on route of administration
  - Ideal route is into the portal vein
  - Next best is in peritoneal dialysis bag
  - Intravenous is better in the acute setting
  - Subcutaneous is the easiest for most.

Oral Agents

Types of oral agents

- Sensitisers
  - Biguanides (Metformin, Phenyformin)
  - Thiazolidinedines (Rosiglitazone, Pioglitazone)
- Secretagogues
  - Sulphonylureas (glipizide, glyburide, gliclazide)
  - Meglitinides (repaglinide, nateglinide)
- α glucosidase inhibitors
- Peptide analogs

Sulphonylureas

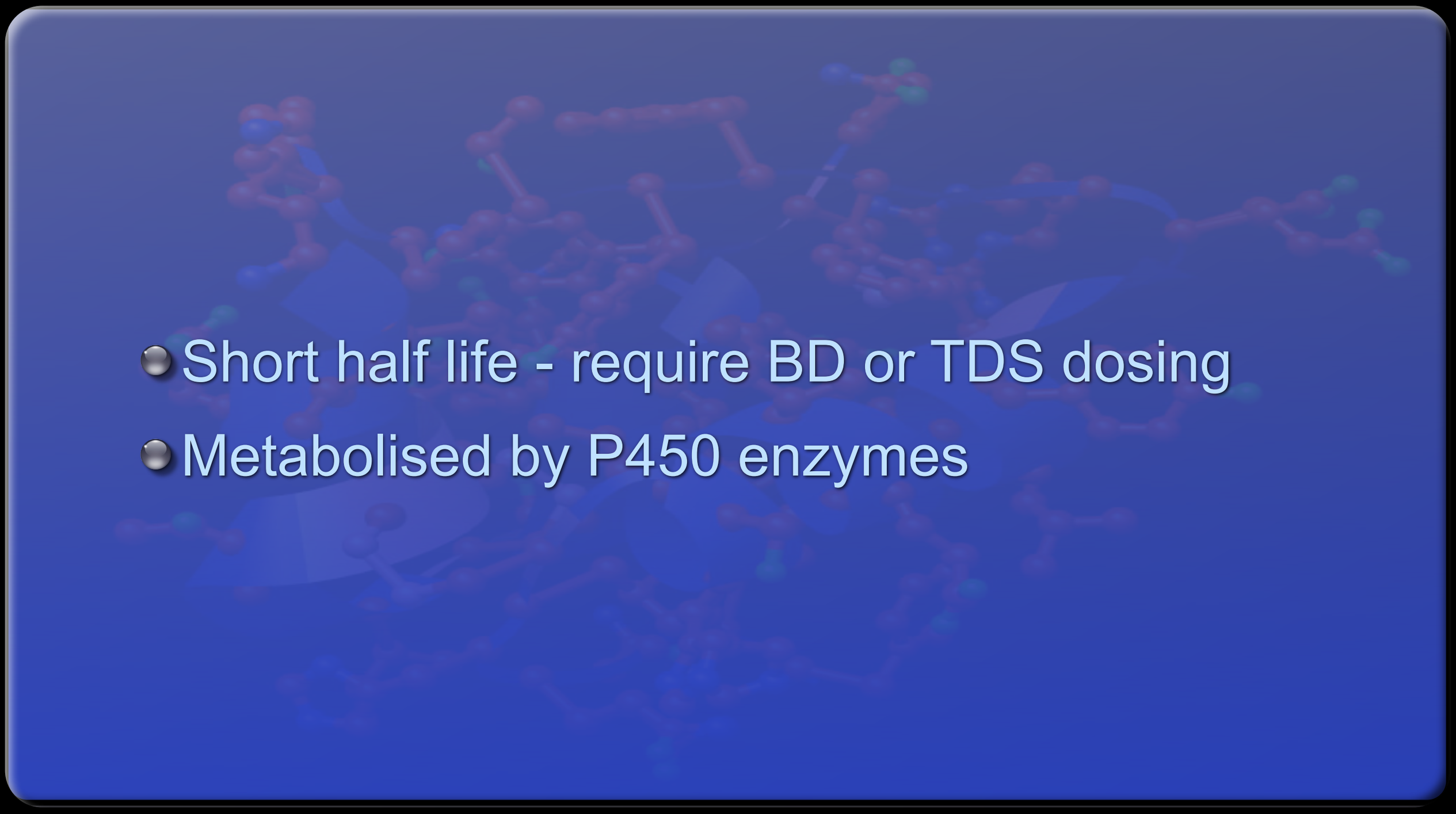
Sulphonylureas

- Glicizide, glipizide, glibenclamide
  - Inhibit potassium channel
  - Increase the amount of insulin secreted.
- Effective, inexpensive
- Hypoglycaemia & Weight Gain

Mechanism of action

- Bind to ATP-dependent K^+ channel
  - Hyperpolarises the β cell membrane
  - Opens voltage gated Ca^{++} channels
  - Fusion of insulin granulae with membrane

Sulphonylureas



- Short half life - require BD or TDS dosing
- Metabolised by P450 enzymes

Interactions

- Increased risk of hypoglycaemia
  - Aspirin, allopurinol, sulphonylamides, fibrates
- Worsening glucose tolerance
  - Steroids, isoniazide, OCP, sympathomimetics, thyroid hormones

Complications

- Hypoglycaemia
- Weight Gain
- Overstimulation of β cells
  - Possible risk of disease acceleration.
- Teratogenic
- Little to no survival benefit seen

Biguanides (Metformin)

Uses

- Type II diabetes
- Prediabetes (less benefit than lifestyle Δ)
- Polycystic ovarian disease
- Gestational diabetes (? foetal safety)
- Reduced pancreatic cancer risk
- Reduced weight gain from other agents.

Mechanism of Action

- Inhibits gluconeogenesis to 1/3 baseline
  - Most Type II diabetics have 3x increase
- Activates AMP-activated protein kinase
  - AMPK activation increases SHP
  - Inhibits gluconeogenesis genes

Kinetics

- Bioavailable 50-60%
- Peak 1-3 hours, 8 hours with SR
- Minimal plasma protein binding
- High volume of distribution (10 L/kg)
- Not metabolised
- Cleared by tubular secretion (T1/2 6.2 hrs)

Advantages

- Reduces diabetic complications
  - Mortality reduction of 30% c.f. insulin or sulphonylureas
  - Mortality reduction of 40% c.f. diet control
- Less weight gain
- Lower risk of hypoglycaemia

Contraindications

- Lactic acidosis risks
  - Renal, Lung, Liver, Heart disease
  - No actual evidence of harm however
  - Cease before iodine contrast
- Actual risk is 9/100 000 person years

Adverse Effects

- GIT
  - Diarrhoea, GI upset, Nausea, Vomiting
- Hypoglycaemia
  - Alcohol

Glitazones

Glitazones

- Insulin sensitiser (Binds PPAR receptor)
  - Makes cells more sensitive to insulin
- Third line drug
  - Usually in combination with metformin

Adverse effects

- Increased risk of
  - AMI(Rosiglitazone)
  - Heart failure (Pioglitazone)
  - Stroke (Rosiglitazone)
  - Bone fractures
  - Bladder Cancer (Pioglitazone)
  - Macular oedema (?) & Acute hepatitis (?)

Adverse Effects

- Most glitazones have been withdrawn from some market, somewhere for some safety concern.
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Advantages

- Low risk of hypoglycaemia
  - Caution with alcohol or other hypoglycaemic agents.
- May be a better alternative than going to insulin
- Pioglitazone may reduce rate of atheroma progression.
  - Raises HDL, lowers TG and hsCRP.

Non Pharmacological Treatments

Other treatments

- Diet
  - Avoid High GI carbohydrate
- Surgery
  - Bariatric surgery
  - Pancreatic transplantation
  - Implantable pumps
- Exercise

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