

ENDOCRINE DISORDERS

ANTIDIABETIC AGENTS

- The normal pancreas secretes a number of hormones:
 - Insulin (β cells)
 - Amylin (β cells)
 - Amylin suppresses release of insulin
 - Glucagon (α cells)
 - Somatostatin
 - Reduces secretions of both insulin and glucagon
- Normally, whenever there is a glucose load, the secretion of insulin is increased
 - Diabetes is when there is chronic hyperglycemia due to:
 - Lack of insulin (IDDM)
 - Resistance to insulin (NIDDM)

Actions of insulin

1. Increases glucose uptake into muscle and fat
2. Increases glycogenesis
3. Decreases glycogenolysis
4. Decreases gluconeogenesis
5. Stimulates growth (anabolic)
6. Decreases lipolysis
7. Decreases protein breakdown

- These actions are opposed by glucagon, catecholamines and glucocorticoids (diabetogenic hormones)

Types of diabetes

- Type I
 - IDDM
 - Hyperglycemia
 - Weight loss
 - Due to protein breakdown because glucose cannot be utilised
 - Ketoacidosis
 - An autoimmune disease
 - The condition is linked to certain HLA subtypes
 - See destruction of β cells and see mononuclear cell infiltrate
- Type II
 - NIDDM
 - Much more common than IDDM
 - Occurs in older people (> 40 years)
 - It is a polygenic, multifactorial disease (often associated with obesity and a sedentary lifestyle)
 - Strong hereditary link
- Management of diabetes is very important to prevent the development of long term complications:
 - Macrovascular changes:
 - Coronary artery disease
 - Atherosclerosis
 - Microvascular changes
 - Peripheral neuropathy
 - Angiopathy
 - Retinopathy
 - Retinal detachment
 - Exudates
 - Microinfarcts
 - Nephropathy
 - Immunosuppression
 - Cataracts

All these complications are related to the duration of the disease and how adequately the blood glucose is controlled during the disease

- Aims of therapy:
 1. Restore metabolism
 2. Restore glucose homeostasis
 3. Reduce the risk of developing complications

Treatment of IDDM

- Give insulin
- Insulin binds to a surface receptor on cells which activates a tyrosine kinase
- This leads to the formation of IP_3 which activates protein kinase C
- Protein kinase C phosphorylates enzymes required in the production of the glucose transporter (e.g. GLUT4)
- This leads to the increased uptake of glucose into the cell
- Kinetics of insulin:
 - Insulin, being a polypeptide, cannot be given orally (it will be digested)
 - Human recombinant insulin is now used
 - Multiple injections of insulin needed to be given throughout the day due to a short half life (metabolised in the liver and kidney)
 - Recent advancement:
 - Insulin with different durations of action to suit the person
 - Short, intermediate and long acting insulin
 - Uses:
 - Short + intermediate twice daily or,
 - Short before meals, intermediate overnight
- Adverse effects:
 - Hypoglycemia if inject too much (required IM injection of glucagon)
 - Can also get hypoglycemia if insulin is injected and nothing is eaten
 - Local reaction
 - Fat hypertrophy at the site of injection

Treatment of NIDDM

- Progressive, insidious disorder
- Presents with polyuria and polydipsia but no ketoacidosis
- Over time, insulin therapy may be required
- Treatment involves:
 - Changing diet
 - Complex carbohydrates should be eaten rather than refined sugars
 - This is because when complex CHO are eaten, the glucose contained in them is absorbed slowly, so that the rise in blood glucose is not that great. If refined sugars are eaten, there will be a very high rise in blood glucose
 - Changing lifestyle:
 - Stop smoking
 - Exercise
 - Hypoglycemic agents may be useful:

Hypoglycemic agents

1. Biguanides

- **Metformin**
 - Mechanism of action:
 - Increases glucose uptake into skeletal muscle
 - May decrease the absorption of glucose
 - Kinetics:
 - Has a short half life, excreted by the kidney
 - Side effects:
 - Hypoglycemia
 - Nausea, vomiting, Diarrhoea
 - **Lactic acidosis**
 - Benefits:
 - No weight gain

2. Sulphonylureas

- **Tolbutamide, Glibenclamide**

- Mechanism of action:
 - Requires a pancreas which is able to produce insulin
 - These drugs stimulate the secretion of insulin from β cells via an ATP sensitive K^+ channel.
 - Often used in combination with metformin
- Kinetics:
 - Orally available
 - Bound to plasma proteins
 - Metabolised by the liver, excreted by the kidney
 - Can cross the placenta (hence not used in pregnancy)
 - Taken before a meal
- Side effects:
 - Hypoglycemia
 - GIT effects
 - Rash
 - Increased weight
 - Interaction with NSAIDs and sulphonamides (making hypoglycemia more likely)
 - If used with alcohol - will cause a severe hypoglycemia

THYROID DISORDERS

Hyperthyroidism

- Normally the disorder lies at the level of the thyroid
 - Multinodular goitre
 - Graves disease
- May also be due to a pituitary adenoma or brain tumor
- Treatment:
 - Surgery
 - Radioactive iodine
 - Since the thyroid gland is the only organ in the body which takes up iodine, giving radioactive iodine will selectively cause radiation damage to the thyroid gland
 - Damage to the thyroid can be partial, and thus make the person euthyroid (have normal thyroid functioning). If the damage is more severe, the person will be hypothyroid and so thyroid supplements would be required
 - Antithyroid drugs
 - **Carbimazole, Propylthiouracil (PTU)**
 - Mechanism of action:
 - Decreases the iodination of tyrosyl residues in thyroglobulin (by inhibiting the peroxidase which is required to convert iodide to iodine)
 - PTU also has another action of preventing the conversion of T4 to the more active T3.
 - Kinetics:
 - Carbimazole has a long half life because it is metabolised to an active metabolite (methimazole)
 - PTU is rapidly absorbed, has a short half life
 - Both drugs are stored in the gland
 - Both cross the placenta and are concentrated in the foetal thyroid
 - Side effects:
 - Rash
 - Headache
 - Jaundice
 - Agranulocytosis (rare)

- Other therapies:
 - High dose Iodine
 - This causes the inhibition of TH secretion (useful for short term)
 - β blockers
 - To reduce the effects of excess TH (palpitations, tremors)
 - Guanethidine used in eye drops

Treatment of hypothyroidism

- Hypothyroidism is due to:
 - Congenital dysfunction
 - Autoimmune thyroiditis
 - Treatment of hyperthyroidism
- Therapy involves thyroxine replacement therapy (T4)
 - T4 has a longer half life
 - It is less cardiotoxic
 - People can use this drug to decrease weight