Endocrine cells of the Islets of Langerhans

β cells - produce Insulin
α cells - produce Glucagon

Insulin & Glucagon have antagonistic effects on blood glucose levels.

Amylin - produced by β cells inhibits α cells from releasing glucagon.

Insulin & Amylin are secreted in response to a rise in blood glucose levels above ~100 mg/dL
Glucagon is secreted when blood glucose levels fall below 100 mg/dL. Target of glucagon is the liver.

- Stimulates enzymes involved in glycogenolysis (glycogen -> glucose)
- Stimulates enzymes involved in gluconeogenesis (conversion of non-carbohydrate precursor into glucose, e.g., amino acid -> glucose)
- Stimulates enzymes involved in Ketogenesis (fatty acids -> ketones)
The glucose + ketones are released from the liver into the blood and can be used as a source of energy. Neurons use glucose as their primary energy source, but can use ketones if necessary.

Normally, the way these hormones work is:

As blood glucose rises above 100 mg/dL

↓

stimulate β cells to secrete insulin + amylin

stimulates uptake + use of glucose by cells

↓

Inhibit release of glucagon from α cells
As blood glucose levels fall below 100mg/dL

↓

Decreases release of Insulin and Amylin from β-cells

↓

removes inhibition of α-cells

↓

α-cells secrete glucagon

↓

Glucagon will act on the liver to bring blood glucose levels back up.

When insulin levels fall, most of the cells will shift their metabolism to breakdown stored biomolecules for energy.
Ex. Adipose cells will breakdown fat stores and release fatty acids into the blood for use by the liver in ketogenesis. Skeletal muscle fibers will breakdown stored glycogen + proteins → pyruvate + amino acids which will be released into the blood and used by the liver in gluconeogenesis.

In Diabetes Mellitus (DM) these hormones are disrupted. Group of disorder that involve:
- deficient secretion of Insulin + Amylin, and
- Increased secretion of glucagon.
  - Impairment of insulin effects on its target tissues so that they are not as responsive to insulin
  - Or a combination of both.

Characteristics of DM
- Hyperglycemia - chronically elevated blood glucose levels
  \[ \geq 126 \text{ mg/dL in a fasted person} \]
  or
  \[ \geq 200 \text{ mg/dL during a glucose tolerance test} \]
- Acidity of the blood due to ketones (Ketoacidosis)
- Polyuria - excessive urination
- Polydipsia - excessive fluid intake
- Polyphagia - excessive hunger

Two primary types of DM:
Type I DM a.k.a. Insulin dependent diabetes mellitus
~10% of all diabetics

Type II DM a.k.a. Non-insulin dependent diabetes mellitus
~90% of all diabetics

Gestational diabetes - occurs during pregnancy
cause is uncertain, but thought to be caused by combination of increased fat deposits & placental hormones.

Type I DM is an autoimmune disease in which antibodies are produced against the β cells.

Damages & kills the β cells

↓ results in insufficient Insulin & Amylin secretion

↓ without insulin the cells of the body can't uptake & use glucose for generating ATP

causes polyphagia
Cells turn to alternate sources for energy and start breaking down proteins and fat stores.

Excess amino acids and fatty acids are released into the blood and taken up by the liver.

Liver can't take up glucose in the absence of insulin. In the absence of amylin, glucagon levels are increasing.

Glucagon stimulates glycogenolysis and gluconeogenesis.

Liver is also taking up fatty acids released from the adipose cells and converting it into ketones. Ketones are released into the blood, making it acidic.
The blood more (Ectoacidosis) acidic

Some of the glucose remaining in the bloodstream is overproduced by the kidneys, excessive glucosuria. Glucose reabsorption in the kidneys is overwhelmed by the amount of glucose excreted in the urine.

Liver glycolysis (ACh and glycogen) results in release of glucose into the blood from the liver.

Together with glucose from the food eaten, glucose from the liver elevates blood glucose levels.
Some of the glucose passes into the urine (primary clinical sign of DM) raising its osmolarity preventing reabsorption of water from the filtrate which results in polyuria.

Filtrate:
- ↑ volume of the urine
- ↓ results in polyuria
- ↓ results in dehydration

Dehydration stimulates the thirst centers in the hypothalamus causing excessive thirst + ↑ fluid intake (polydipsia)
If the decreased insulin levels are not corrected, the decreased blood pH, dehydrating + breakdown of proteins + fits in the body leads to systemic collapse and death.

To avoid this, type I diabetics require daily injections of insulin and regulation of dietary intake of glucose to control blood glucose levels.
Type II DM has a variety of causes.

- Insensitivity of β cells to rising blood glucose levels so that they fail to secrete enough insulin.

Most common cause of Type II DM:

- Insensitivity of peripheral tissues to insulin.

Obesity is strongly correlated with Type II DM.

Relationship is thought to be due to the combination of excessive nutrients and increased release of cytokines from adipose cells.
causing a decrease in the sensitivity of the insulin receptors on cells.

Weight loss can reverse this and primary treatment for Type II DM is weight loss and regulation of dietary intake of glucose.

Acute complications of DM

- Hypoglycemia - a drop in blood glucose levels below 45-60mg/dL
  can result from administration of too much insulin.
  Can cause a diabetic coma.
Diabetic ketoacidosis — increased fat metabolism causing a dramatic drop in blood pH.

If blood pH drops below 7.0, the person can go into acidotic coma.

Chronic complications of DM due primarily to prolonged hyperglycemia:

- Non-enzymatic glycosylation of proteins, lipids, and nucleic acids.

Glucose binds to these biomolecules results in the formation of Advanced Glycosylation End Products (AGEs) that disrupt normal cell functions.
AGES also damage blood vessels resulting in microvascular and macrovascular diseases, which contribute to:

- coronary artery disease
- neuropathies (pain, numbness, tingling) due disruption of blood flow to nerves
- Diabetic nephropathy (kidney damage)
- Diabetic retinopathy (retinal damage) may lead to blindness
- Peripheral vascular disease resulting in decreased blood flow to the distal extremities. Damage to hands or feet can quickly progress to gangrene requiring amputation.
Hyperglycemia can also activate the polyol pathway in cells that don't require insulin to take up glucose. Ex. Neurons

Activation of the polyol pathway results in conversion of glucose into fructose + sorbitol.

The accumulation of fructose + sorbitol in the neurons causes swelling due to increased osmolarity + water, resulting in neural damage. Contributes to development of neuropathies, as well as, motor disturbances and autonomic disturbances.
The adrenal glands secrete a variety of hormones:
  - Cortisol
  - Aldosterone
  - Estrogens + Androgens
  - Epinephrine - secreted by adrenal medulla

All hormones secreted by the adrenal cortex are steroid hormones.

Secretion of these cortical hormones is regulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates synthesis & secretion of the cortical hormones.
Synthesis + secretion of aldosterone is also regulated by Na+ levels in the blood.

Hypercortisolism — hypersecretion of cortisol hormones may be independent of stimulation by ACTH (Cushing's Syndrome), usually due to a tumor in adrenal gland or ectopic secretion of cortical hormones.

Hypercortisolism that results from hypersecretion of ACTH is called Cushing's Disease, and usually results from a pituitary adenoma.
In either case, hypercortisolism results in increased weight due to accumulation of fat, particularly in the face, neck, and trunk. Results from increased secretion of cortisol. The increased cortisol levels promote the breakdown of proteins, and release of glucose from the liver. Excess glucose and amino acids are taken up by the adipose cells and converted to fat.

Hypertension—caused by increased sensitivity of vascular smooth muscle to vasoactive
agents (which is caused by ↑ cortisol levels), resulting in vasoconstriction of blood vessels → ↑ BP

Virilization in females, feminization in males. Caused by hypersecretion of estrogens + androgens.

Treatment strategy depends on the cause of the hypercortisolism.

If due to hypersecretion of ACTH from a pituitary adenoma, then surgical removal of the adenoma is done.

If due to ectopic tissue, the ectopic tissue is removed.
If it is due to tumor in adrenal gland, then the tumor or gland is removed followed by hormone replacement therapy for the cortical hormones.

**Hypocortisolism**—can be due to

- **inadequate secretion of ACTH**
  ("secondary hypocortisolism")

- **inadequate secretion of cortical hormones from the adrenal gland**
  ("primary hypocortisolism" or **Addison's disease**)

**Autoimmune disease** in which antibodies are produced against the cells of the adrenal gland.
characterized by:

- Increased secretion of ACTH due to lack of negative feedback of cortical hormones on the anterior pituitary.

- Hyperpigmentation of the skin due to increased ACTH levels.

- Decreased level of the cortical hormones.

- Easy fatigability caused by decreased protein metabolism and hypoglycemia that results from low cortisol levels.

- Hypotension from decreased blood volume due to decreased aldosterone levels.


Ciclosterone levels result in ↓ reabsorption of Na+ from the filtrate, preventing water reabsorption from the filtrate.

↓ cortisol levels also result in decreased sensitivity of vascular smooth muscle to vasoactive agents → vasoconstriction of blood vessels

↓ BP

Treatment for Addison's disease

- Cortical hormone replacement therapy to bring cortical hormone levels up to normal

- ↑ Na+ dietary intake to replace Na+ lost in the urine.
Alterations in Hematologic Functions

Dysfunctions of RBCs

Anemias — result from a decrease in the number and/or volume of RBCs

Polycythemia — result from an increase in the # or volume of RBCs and WBCs

Anemias

Clinical signs:
- Pale or of the nail beds, gums, and conjunctiva of the eyes
- Fatigue
- Pounding heart
- Shortness of breath (dyspnea)
- dizziness.

The anemias are classified based on the size, shape, and hemoglobin content of the RBCs.

3 general classes:

- Macrocytic - Normochromic Anemias
  - RBCs are larger than normal
  - Have normal hemoglobin content

- Microcytic - Hypochromic Anemias
  - RBCs are smaller than normal
  - Have decreased hemoglobin content
Normocytic-Normochromic Anemias
- RBCs are normal in size and hemoglobin content
- but are reduced in #

Macrocytic-Normochromic Anemias

Caused by vitamin deficiency that disrupts normal DNA synthesis in the RBC stem cells.

Delays cell division, but not protein synthesis.

Results in larger RBCs, with normal hemoglobin content for an RBC of that size.

Because RBC production is slowed, there are fewer RBCs in circulation.
Ex.
- Pernicious anemia
- Folate deficiency anemia

Pernicious anemia results from a deficiency of Vitamin B12 due to decreased absorption of B12 in the digestive tract.

Absorption of B12 requires that it be complexed with a protein called intrinsic factor produced by the epithelial cells in the lining of the stomach.

Abnormal intrinsic factor production:
- congenital defect
- chronic gastritis
- damage to stomach lining from...
alcohol abuse

Vitamin B₁₂ is required for normal DNA synthesis and nuclear maturation.

Absence of B₁₂ delays cell division.

Affects both RBCs and WBCs.

B₁₂ is also important in myelination of axons. So as well as having signs of anemia, people with pernicious anemia also have neurologic deficits (paresthesias, and motor deficits.)

Treatment

Daily injections of B₁₂ until the anemia is resolved and underlying