METABOLISM

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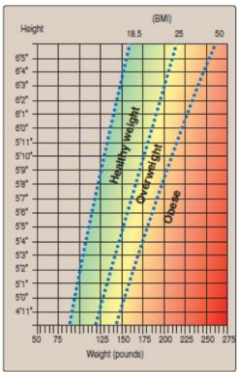
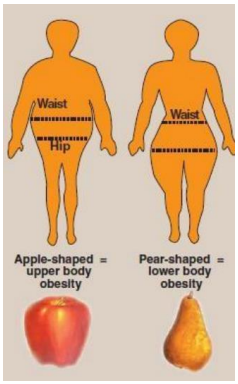
ARKAN ACADEMY

Integration of Metabolism

- The amount of body fat is difficult to measure directly, usually indirectly determined from the body mass index (***BMI***) which correlates (reflets) the *amount* (not distribution) of body fat in most individuals
  - *BMI= (weight in Kg)/(height in meters)*^{2}, which ranges:
    - ✓ **18.5 – 24.9**: healthy
    - ✓ **25 – 29.9**: Overweight
    - ✓ **> 30**: obese
    - ✓ **> 40**: extremely obese
      - These cutoffs are based on studies that examined the relationship of BMI to premature death, and are similar in men and women

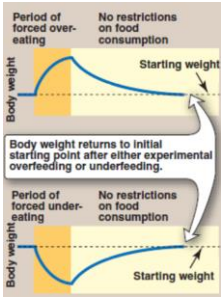


- Anatomic distribution of body fat has a major influence on associated health risks
  - ***Apple-shaped:*** A waist to hip ratio of ***more than 0.8*** for *women* and ***more than 1.0*** for *men* and can be called *android* or *upper body obesity* (associated with more fat deposition in the <u>trunk</u> and <u>more risks</u> for diseases)
  - ***Pear-shaped:*** A waist to hip ratio of ***less*** than 0.8 for women and ***less*** than 1.0 for men, also called *gynoid* or *lower body obesity* (reflects more fat distributed in the <u>hips and thighs</u>)
    - ✓ Pear shape is more commonly found in women, presents a much <u>lower risk</u> of metabolic disease, and some studies indicate it may actually be **<u>protective</u>**



- ~ 80–90% of the fat stored in the human body is in ***subcutaneous depots*** (just under the skin) in the abdominal (upper body) and the gluteal-femoral (lower body) regions
- 10–20% of body fat is stored in ***visceral depots*** (omental and mesenteric), which are located within the abdominal cavity in close association with the digestive tract
  - *Excess fat in visceral* stores and abdominal subcutaneous fat increases obesity-associated health *risks*
- Adipose tissue plays an active role in body weight regulation by secretion of hormones, such as:
  - ***Leptin:*** *Regulates appetite* and metabolism
  - ***Adiponectin:*** An adipocyte-derived cytokine, reduces levels of blood *free fatty acids* and improves *lipid profiles* and *glycemic control*, and *reduces inflammation* in diabetic patients
- Adipocytes can expand to 2-3 times their normal volume (limited-expansion), with age of 10 years
- With prolonged over-nutrition, pre-adipocytes in adipose tissue proliferate and differentiate into mature fat cells, increasing the number of adipocytes, so most obesity is due to a combination of increased fat ***cell size*** (*hypertrophy*) and ***number*** (*hyperplasia*)
  - Obese individuals can have up to five times the normal number of fat cells
  - If excess calories cannot be accommodated within adipose tissue, the excess fatty acids ‘spillover’ into other tissues, such as muscle and liver (ectopic fat) which is associated with ***insulin resistance***
  - With weight loss, ***size*** of the fat cells is reduced, but the ***number*** of fat cells is not usually affected where small fat cells are very efficient at reaccumulating fat, which drive appetite and wight regain

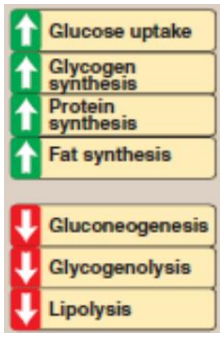
- Body weight seems to drift around a settling point reflecting a balance between:
  - Environmental factors (food intake and energy expenditure, and biologic factors)
  - Genetic contributions to obesity
  - Behavioral and Environmental contributions



- Metabolic changes in obesity (primarily in the liver, muscle and adipose tissue)
  - ***Dyslipidemias:*** Abnormal ***high LDL and TAG***, with ***low HDL*** levels
  - ***Glucose intolerance:*** ***Hyperglycemia*** below that classified as diabetes
  - ***Insulin resistance:*** ***Decreased sensitivity*** to insulin (larger amount of insulin for the same effect)
  - ***Metabolic syndrome:*** A cluster of metabolic abnormalities associated with abdominal obesity
    - ✓ Includes glucose intolerance, insulin resistance, hyperinsulinemia, dyslipidemia
    - ✓ Hypertension: Due to the increased accumulation of lipids in the blood vessels (narrowing them)
    - ✓ Chronic systemic inflammation that contributes to insulin resistance and ***atherosclerosis***
  - In obesity, low levels of adiponectin (dampens inflammation and sensitizes tissues especially liver) may contribute to the metabolic syndrome and risk of ***type 2 diabetes*** and ***heart disease***

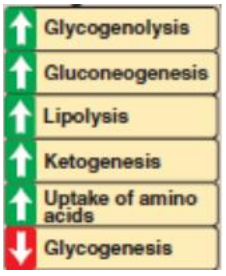
- Insulin effects on carbohydrate metabolism:
  - ↑ *glycogen synthesis* in the liver and muscle
  - ↑ *glucose uptake* by increasing transporters in muscle and adipose tissue
  - ↓ *glycogenolysis and gluconeogenesis* in the liver

Glucose storage mostly in three tissues: liver, muscle, and adipose tissue



- Insulin effects on protein synthesis: ↑ *entry of amino acids* into cells, *protein synthesis*
- Insulin effects on lipids metabolism: ↓ *release of fatty acids from adipose tissue*
  - ↓ *TAG degradation* by inhibiting hormone-sensitive lipase (HSL) that degrades TAGs in adipose
  - ↑ *TAG synthesis* by increasing the transport and metabolism of glucose into adipocytes, providing glycerol 3-phosphate for TAG synthesis
    - ✓ ↑ *lipoprotein lipase* activity of adipose tissue, thus providing fatty acids for esterification
    - ✓ In liver, insulin promotes the conversion of glucose to triacylglycerols

- **Glucagon** is a polypeptide (29 aa) hormone secreted by ***α cells of the pancreatic islets of Langerhans***
  - *Glucagon*, *epinephrine*, *cortisol*, *growth hormone* (**counter-regulatory** hormones) opposes insulin
  - Glucagon receptors are found in hepatocytes but not on skeletal muscle and acts to maintain blood glucose levels by *activation of hepatic glycogenolysis and gluconeogenesis*
  - It secretion is increased by low blood glucose, amino acids, epinephrine or norepinephrine
  - Glucagon secretion is inhibited by elevated blood glucose and by insulin



- Glucagon effects on carbohydrate metabolism:
  - ↑ *breakdown of glycogen* (liver not muscles) and an ↑ *gluconeogenesis*

- Glucagon effects on protein metabolism: ↑ *uptake of amino acids* by the liver, resulting in increased availability of carbon skeletons for **gluconeogenesis**, thus, plasma levels of amino acids are decreased

- Glucagon effects on lipid metabolism: ↑ *lipolysis* in adipose (activate *HSL*, breaking TAGs)
  - The free fatty acids released are taken up by liver and oxidized to acetyl coenzyme A, which is used in *ketone body synthesis*

Diabetes and Metabolism

- ***Type I Diabetes Mellitus (DM)*** caused by ***insulin deficiency*** (mainly affects liver, muscle, adipose)
  - A juvenile disease, affects mainly ***children*** caused by ***autoimmune destruction*** of *pancreatic β cells*
  - It doesn't affect absorption and digestion but affects the uptake of glucose by **GLUT4**
  - No glucose uptake causing the release of glucagon, glycogen degradation and gluconeogenesis
  - It can cause the release of ketone bodies causing *diabetic ketoacidosis*
  - Elevated levels of blood glucose (**Hyperglycemia**) and **ketones** are the hallmarks of untreated type 1
  - Dyslipidemia and Hyper-triacylglycerolemia
    - ✓ Excess fatty acids are converted to TAG, which is packaged and secreted in **VLDL**
    - ✓ ↑ **Chylomicrons** synthesis because lipoprotein degradation catalyzed by lipoprotein lipase in the capillary beds of muscle and adipose tissue is low in diabetics

- T***ype II Diabetes Mellitus (DM):*** Most common (90%), develops **gradually** without obvious symptoms
  - A combination of *insulin resistance* and *dysfunctional β cells*
  - Pathogenesis does **not** involve viruses or autoimmune antibodies
  - ***Polyuria*** and ***polydipsia*** and ***polyphagia***
  - The metabolic alterations are ***milder*** than those for type 1, because insulin secretion in type 2, restrain ketogenesis and blunts (prevents) the development of diabetic ketoacidosis (DKA)
  - Hyperglycemia (increased hepatic production of glucose, diminished peripheral use)
  - Ketosis is usually minimal or absent because the presence of insulin, diminishes hepatic ketogenesis
  - Dyslipidemia (**↑ Chylomicrons, ↑ VLDL)**, and **Low HDL**
  - Patients usually improves on **Metformin**

- ***Insulin-resistance (IR):*** *Decreased ability* of target tissues *to respond properly* to normal (or elevated) circulating concentrations of insulin characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue
  - **Obesity** is the most common cause of IR
  - IR alone will not lead to type 2 diabetes it also requires impaired β-cell function

Fasting and Metabolism

- Fasting begins if no food is taken ***after the absorptive period***
  - Result from an inability to obtain food, the desire to lose weight rapidly, clinical situations in which an individual cannot eat, for example, because of trauma, surgery, cancer, or burns
- In the absence of food, plasma levels of ***glucose, amino acids and TAG fall***, *reducing insulin* secretion, *increasing glucagon* (nutrient deprivation activates catabolic degradation of TAG, glycogen, protein)
- Priorities:
  - Maintain adequate plasma ***levels of glucose*** to supply **brain**, **RBCs**, other glucose-requiring tissues
  - ***Mobilize fatty acids*** from adipose tissue, and the synthesis and ***release of ketone bodies*** from the liver, to supply energy to all other tissues
  - Although ***protein*** is an energy source, each protein also has another function, therefore, only ~1/3 of the body's protein can be used for energy production without fatally compromising vital functions

- The flow of intermediates through the pathways of energy metabolism is controlled by four mechanisms availability of substrates, allosteric regulation of enzymes, covalent modification of enzymes and induction-repression of enzyme synthesis

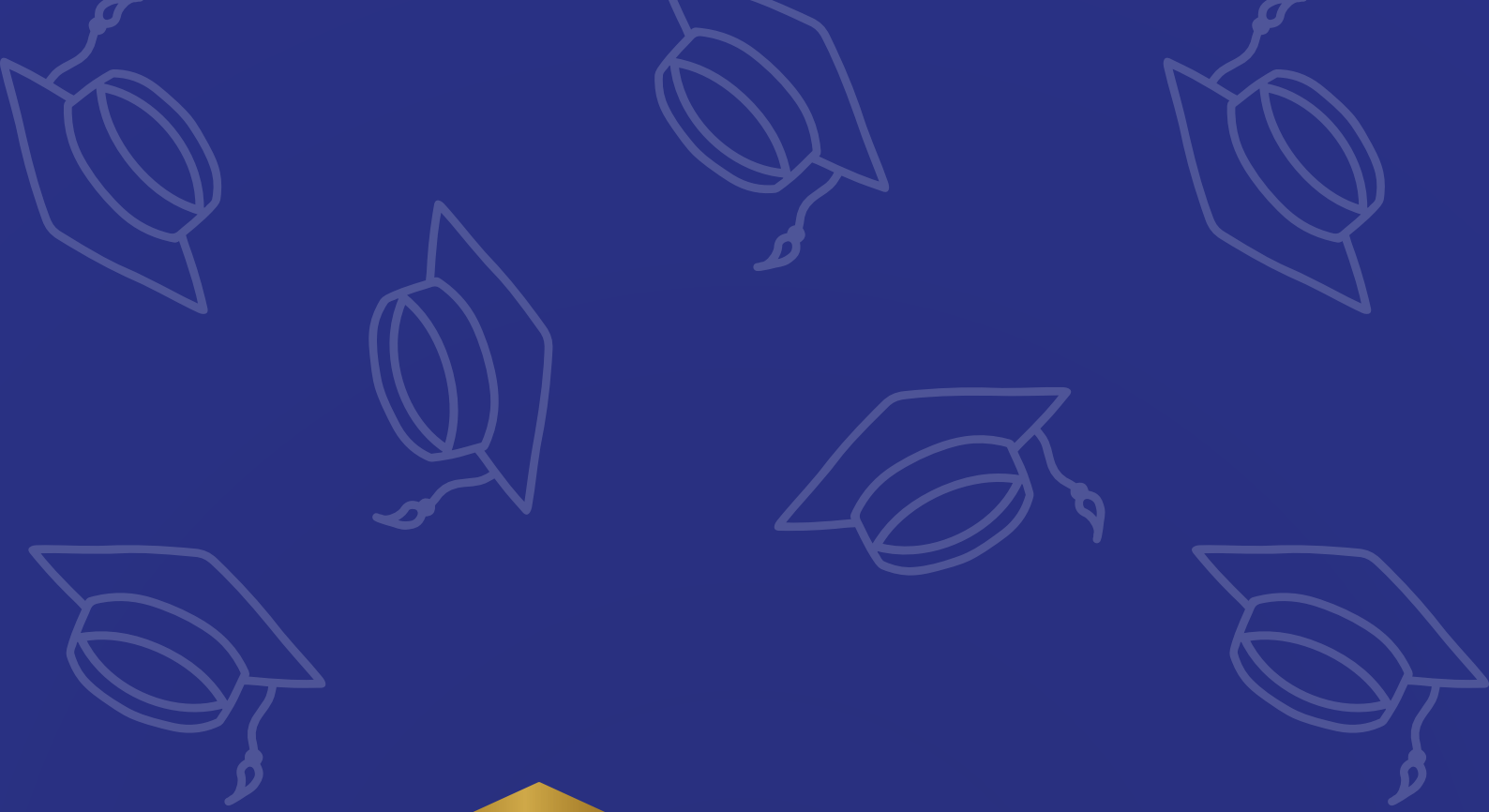
- In fasting, substrates are not provided by the diet but are available from the ***breakdown of stores***
- The primary role of the liver during fasting is to maintain blood glucose (synthesis fuel molecules)
  - The liver first uses *glycogen degradation* and then *gluconeogenesis* fasting (postabsorptive) state
  - Increased *fatty acid oxidation* as a **major source** of energy for liver
  - Increased synthesis of *ketone bodies* especially 3- hydroxybutyrate

- Glucose transport by insulin-sensitive GLUT-4 into the adipocyte is depressed due to low insulin levels
- Decreased *fatty acid and TAG synthesis* and Increased degradation of TAG by HSL
- Increased release of *hydrolyzed fatty acids* from stored TAG into the blood as albumin bound FA to be transported to a variety of tissues for use as fuel
  - The ***glycerol*** produced from TAG degradation is used as a ***gluconeogenic precursor*** by the liver
  - Decreased uptake of FAs since lipoprotein lipase activity of adipose tissue is low during fasting
  - Rapid breakdown of muscle protein during the first few days of fasting to provide amino acids (such as Ala, Gln) for gluconeogenesis in the liver

- During the **first days** of fasting, the brain continues to use glucose exclusively as a fuel
  - Glucose passes to the brain by GLUT 1 and GLUT 3
  - Blood **glucose** is maintained by hepatic gluconeogenesis from glucogenic precursors, such as amino acids from proteolysis and glycerol from lipolysis
  - In **prolonged fasting** (greater than 2–3 weeks), plasma **ketone bodies** reach significantly elevated levels, and replace glucose as the primary fuel for the brain reducing the need for protein catabolism for gluconeogenesis and sparing glucose

- **Resting muscle** uses ***fatty acids*** as its major fuel source
- **Exercising muscle** initially uses its ***glycogen*** stores as a source of energy but during intense exercise, glucose 6-phosphate derived from glycogen is converted to lactate by anaerobic glycolysis
  - Glycogen reserves are depleted, ***FFAs*** from TAG become the dominant energy source
- During the **first 2 weeks** of fasting, muscle uses ***fatty acids*** (adipose) and ***ketone bodies*** (liver) as fuels
- After about **3 weeks of fasting**, muscle decreases use of ketone bodies, **fatty acids** used exclusively

- **Kidney** expresses the enzymes of ***gluconeogenesis***, including G-6- phosphatase, and in **late fasting** about 50% of gluconeogenesis occurs here
  - The Gln released from the muscle's metabolism of branched-chain amino acids is taken up by the kidney and acted upon by renal glutaminase and glutamate dehydrogenase, producing α-ketoglutarate that can be used as a substrate for gluconeogenesis
  - Kidney also provides ***compensation for the acidosis*** that accompanies the increased production of ketone bodies where **NH_3** produced from deamination picks up H^+ from ketone body dissociation, and is excreted in the urine as NH_4^+, decreasing the acid load in the body
  - In long-term fasting, nitrogen disposal occurs in the form of ***ammonia rather than urea***



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