B.PHARM SEMESTER II | BP202T

BIOCHEMISTRY (THEORY)

UNIT II

Biomolecules, Bioenergetics, Carbohydrate Metabolism and Biological Oxidation

Short Notes for Quick Revision

What is covered in this unit

UNIT II TOPICS

Part A – Biomolecules: introduction to carbohydrates, lipids, nucleic acids, amino acids and proteins.

Part B – Bioenergetics: free energy, enthalpy and entropy; redox potential; energy-rich compounds (ATP, GTP) and their significance.

Part C – Carbohydrate metabolism and diabetes mellitus: glycolysis, TCA cycle, gluconeogenesis, HMP shunt, glycogen metabolism, regulation of blood glucose, fed state, fasting and starvation, and metabolic derangements in diabetes.

Part D – Biological oxidation: electron transport chain, oxidative phosphorylation and ATP synthesis, mitochondrial dysfunction and oxidative stress.

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PART A: BIOMOLECULES

1. Introduction to Biomolecules

Biomolecules are the organic molecules made and used by living organisms. They build the cell, supply energy, store genetic information and run every chemical reaction of life. Four elements, **carbon, hydrogen, oxygen and nitrogen**, make up about 96% of the body weight; phosphorus and sulphur are present in smaller amounts. Carbon is the central element because it forms four stable covalent bonds and can make long chains and rings.

Water forms 60–70% of the adult body and is the medium in which all biomolecules work. The four major classes of biomolecules are **carbohydrates, lipids, proteins and nucleic acids**. Vitamins, minerals and hormones are present in small amounts but are equally important.

Biomolecule	Building unit	Linkage	Major functions	Examples
Carbohydrates	Monosaccharides	Glycosidic bond	Quick energy, energy storage, structure, cell recognition	Glucose, starch, glycogen, cellulose
Lipids	Fatty acids, glycerol, cholesterol (not true polymers)	Ester bond	Energy storage, membranes, hormones, insulation	Triacylglycerol, phospholipids, cholesterol
Proteins	Amino acids	Peptide bond	Enzymes, transport, structure, defence, hormones	Albumin, haemoglobin, collagen, insulin
Nucleic acids	Nucleotides	Phosphodiester bond	Storage and transfer of genetic information, protein synthesis	DNA, RNA

2. Carbohydrates

Carbohydrates are polyhydroxy aldehydes or polyhydroxy ketones, or compounds that give these on hydrolysis. Many have the general formula **$Cn(H_2O)n$**, which is why they were called 'hydrates of carbon'. Exceptions exist, for example deoxyribose ($C_5H_{10}O_4$) and rhamnose ($C_6H_{12}O_5$).

Classification

Class	Units on hydrolysis	Examples
Monosaccharides	None (simplest sugars). Classified by carbon number (triose to heptose) and by group: aldose or ketose	Glyceraldehyde (aldotriose), ribose (aldopentose), glucose and galactose (aldohexoses), fructose (ketohexose)
Disaccharides	2 monosaccharides	Sucrose (glucose + fructose), lactose (galactose + glucose), maltose (glucose + glucose)
Oligosaccharides	3 to 10 monosaccharides	Raffinose (trisaccharide), stachyose
Polysaccharides	More than 10 monosaccharides. Homopolysaccharides have one type of sugar; heteropolysaccharides have different types	Starch, glycogen, cellulose, inulin (homo); hyaluronic acid, heparin, chondroitin sulphate (hetero)

Stereochemistry of monosaccharides

- **Asymmetric (chiral) carbon:** a carbon attached to four different groups. Glucose has 4 chiral carbons, so it has $2^4 = 16$ stereoisomers.
- **D and L forms:** decided by the –OH on the chiral carbon farthest from the carbonyl group. In D-sugars it is on the right. Almost all sugars in the body are **D-sugars**.
- **Optical activity:** a sugar that rotates plane-polarised light to the right is dextrorotatory (+), to the left is laevorotatory (–). Fructose is laevorotatory (–92°), so it is also called laevulose.
- **Epimers:** sugars that differ in configuration at only **one** carbon. Glucose and galactose are C-4 epimers; glucose and mannose are C-2 epimers.
- **Anomers:** the α and β forms of a cyclic sugar, which differ at the new asymmetric carbon (C-1, the anomeric carbon) formed on ring closure. In α-D-glucose the C-1 –OH is below the ring, in β-D-glucose it is above.
- **Mutarotation:** the gradual change in optical rotation of a freshly dissolved sugar until a constant value is reached. α-D-glucose (+112°) and β-D-glucose (+19°) interconvert to an equilibrium of +52.7°.

- **Ring structures:** glucose forms a six-membered **pyranose** ring; fructose usually forms a five-membered **furanose** ring (Haworth projection).

Important monosaccharides and derivatives

Sugar / derivative	Source and importance
Glucose (dextrose)	Blood sugar; the main fuel of the brain and red blood cells; building block of starch, glycogen and cellulose
Fructose (fruit sugar)	Fruits, honey, sucrose; sweetest sugar; metabolised mainly in the liver; found in seminal fluid
Galactose	Part of lactose; needed for glycolipids and glycoproteins; accumulates in galactosemia
Ribose, deoxyribose	Pentoses in RNA and DNA, ATP, NAD and FAD
Sugar alcohols	Sorbitol (from glucose, accumulates in the diabetic lens), mannitol (osmotic diuretic), glycerol, inositol
Amino sugars	Glucosamine and galactosamine in glycosaminoglycans; sialic acid (N-acetylneuraminic acid) in glycoproteins
Uronic acids	Glucuronic acid conjugates bilirubin, steroids and drugs, making them water-soluble for excretion

Important disaccharides

Disaccharide	Composition and bond	Reducing?	Remarks
Sucrose	α-D-glucose (1→2) β-D-fructose	No (both anomeric carbons are in the bond)	Table sugar; hydrolysed by sucrase to invert sugar
Lactose	β-D-galactose (1→4) D-glucose	Yes	Milk sugar; digested by lactase; lactase deficiency causes lactose intolerance
Maltose	α-D-glucose (1→4) D-glucose	Yes	Product of starch digestion by amylase

3. Lipids

Lipids are a heterogeneous group of organic compounds that are insoluble in water but soluble in organic solvents such as ether, chloroform and benzene. They are actually or potentially esters of fatty acids. Lipids yield the highest energy among the food groups: **9 kcal per gram**.

Classification

Class	Description	Examples
Simple lipids	Esters of fatty acids with alcohols	Fats and oils (triacylglycerols, esters with glycerol); waxes (esters with long-chain alcohols)
Compound lipids	Esters of fatty acids with alcohol plus an additional group	Phospholipids (phosphate), glycolipids (carbohydrate), lipoproteins (protein), sulpholipids
Derived lipids	Products of hydrolysis of the above groups	Fatty acids, glycerol, steroids (cholesterol), ketone bodies, fat-soluble vitamins A, D, E and K

Fatty acids

Fatty acids are long hydrocarbon chains with a terminal carboxyl group (R–COOH). They may be saturated (no double bond) or unsaturated (one or more double bonds, usually *cis*). The **omega (ω) number** shows the position of the first double bond from the methyl end.

Fatty acid	Carbons : double bonds	Type / remark
Palmitic acid	16 : 0	Saturated; main product of fatty acid synthesis
Stearic acid	18 : 0	Saturated
Oleic acid	18 : 1 (ω-9)	Monounsaturated; olive oil
Linoleic acid	18 : 2 (ω-6)	**Essential** fatty acid; precursor of arachidonic acid
α-Linolenic acid	18 : 3 (ω-3)	**Essential** fatty acid; precursor of EPA and DHA

Fatty acid	Carbons : double bonds	Type / remark
Arachidonic acid	20 : 4 (ω-6)	Precursor of prostaglandins, thromboxanes and leukotrienes

ESSENTIAL FATTY ACIDS

Humans cannot make linoleic and α-linolenic acids because we lack the enzymes that insert double bonds beyond carbon 9. They must come from the diet. Deficiency causes **scaly dermatitis, poor wound healing and growth retardation**. *Trans* fats raise LDL and lower HDL cholesterol and increase the risk of heart disease.

Triacylglycerols (fats and oils)

A triacylglycerol (TAG) is glycerol esterified with three fatty acids. It is the main **storage form of energy** in adipose tissue and also gives thermal insulation and organ protection. Fats are solid at room temperature because they are rich in saturated fatty acids; oils are liquid because they contain more unsaturated fatty acids.

Chemical constant	Meaning
Saponification number	mg of KOH needed to saponify 1 g of fat; indicates the average chain length of fatty acids (higher number, shorter chains)
Iodine number	g of iodine absorbed by 100 g of fat; measures the degree of unsaturation
Acid number	mg of KOH needed to neutralise the free fatty acids in 1 g of fat; shows rancidity
Reichert–Meissl number	Volatile water-soluble fatty acids; high in butter

Rancidity is the spoilage of fats, giving an unpleasant smell and taste. *Hydrolytic rancidity* is due to lipases and moisture; *oxidative rancidity* is due to oxidation of unsaturated fatty acids. It is prevented by antioxidants such as vitamin E, BHA and BHT.

Phospholipids and glycolipids

Lipid	Structure and important members	Function
Glycerophospholipids	Glycerol + 2 fatty acids + phosphate + alcohol: phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, cardiolipin	Membrane structure. Dipalmitoyl lecithin is the lung surfactant (deficiency causes respiratory distress syndrome of newborn). Phosphatidylinositol gives the second messengers IP_3 and DAG
Sphingophospholipids	Sphingosine + fatty acid + phosphocholine = sphingomyelin	Myelin sheath of nerves; Niemann–Pick disease is due to its accumulation
Glycolipids	Ceramide + sugar: cerebrosides, gangliosides	Cell recognition and nerve tissue; storage diseases such as Gaucher disease and Tay–Sachs disease

Cholesterol and lipoproteins

Cholesterol is a 27-carbon steroid with the cyclopentanoperhydrophenanthrene ring system and an –OH group at C-3. It is found only in animal tissues. It is made in the liver from acetyl-CoA, and the rate-limiting enzyme is **HMG-CoA reductase** (the target of statins). Cholesterol is a component of cell membranes and the precursor of **bile acids, steroid hormones and vitamin D**. Desirable total serum cholesterol is below 200 mg/dL.

Lipoprotein	Origin	Main lipid carried	Function
Chylomicron	Intestine	Dietary triacylglycerol	Carries dietary fat to tissues
VLDL	Liver	Endogenous triacylglycerol	Carries liver-made TAG to tissues
LDL	From VLDL in blood	Cholesterol (about 50%)	Delivers cholesterol to tissues; 'bad' cholesterol
HDL	Liver and intestine	Phospholipid and cholesterol	Reverse cholesterol transport to the liver; 'good' cholesterol

4. Amino Acids

Amino acids are the building blocks of proteins. Every standard amino acid has a central **α-carbon** attached to an **amino group (–NH_2)**, a **carboxyl group (–COOH)**, a **hydrogen atom** and a variable **side chain (R group)**. The R group decides the properties of each amino acid. Twenty amino acids are used in protein synthesis and all of them (except glycine) are optically active and occur as **L-α-amino acids**.

Classification based on the R group

Group	Amino acids	Remark
Non-polar, aliphatic	Glycine (Gly), alanine (Ala), valine (Val), leucine (Leu), isoleucine (Ile), proline (Pro), methionine (Met)	Hydrophobic; found inside proteins. Proline is an imino acid and breaks α-helices
Aromatic	Phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp)	Absorb UV light at 280 nm
Polar, uncharged	Serine (Ser), threonine (Thr), cysteine (Cys), asparagine (Asn), glutamine (Gln)	Form hydrogen bonds; cysteine forms disulphide bonds
Acidic (negative)	Aspartic acid (Asp), glutamic acid (Glu)	Extra –COOH group
Basic (positive)	Lysine (Lys), arginine (Arg), histidine (His)	Extra amino or imidazole group

5. Proteins

Proteins are high molecular weight polymers of L-α-amino acids joined by peptide bonds. They contain about **16% nitrogen**, which is the basis of the Kjeldahl method for protein estimation. Proteins are the most abundant organic molecules in the cell and carry out most of its work.

Classification

Basis	Types and examples
Composition	**Simple proteins** give only amino acids on hydrolysis: albumin, globulin, histones, glutelins. **Conjugated proteins** have a non-protein prosthetic group: glycoproteins (sugar), lipoproteins (lipid), nucleoproteins (nucleic acid), chromoproteins (haemoglobin), phosphoproteins (casein), metalloproteins (ferritin). **Derived proteins** are products of hydrolysis: proteoses, peptones, peptides.
Shape	**Globular** (compact, soluble): enzymes, albumin, haemoglobin. **Fibrous** (elongated, insoluble, structural): collagen, keratin, elastin.
Function	Enzymes (amylase), transport (haemoglobin, transferrin), structural (collagen), contractile (actin, myosin), defence (immunoglobulins), hormones (insulin), storage (ferritin), receptors.

Levels of protein structure

Level	Description	Stabilising forces
Primary	The linear sequence of amino acids joined by peptide bonds. Sanger first sequenced insulin (51 amino acids). The sequence decides all higher structure	Peptide (covalent) bonds
Secondary	Local folding of the chain: **α-helix** (right-handed, 3.6 residues per turn, 5.4 Å pitch) and **β-pleated sheet** (parallel or antiparallel strands); β-turns	Hydrogen bonds between C=O and N–H of the backbone
Tertiary	Complete 3-D folding of one polypeptide chain, forming domains and the active site	Hydrophobic interactions, ionic bonds, hydrogen bonds, disulphide bonds, van der Waals forces
Quaternary	Arrangement of two or more polypeptide subunits. Haemoglobin is $\alpha_2\beta_2$	Same non-covalent forces between subunits

6. Nucleic Acids

Nucleic acids (DNA and RNA) store and transfer genetic information. They are polymers of **nucleotides**. Each nucleotide has three parts: a **nitrogenous base**, a **pentose sugar** (ribose in RNA, deoxyribose in DNA) and a **phosphate group**.

Components

- **Purines:** adenine (A) and guanine (G), with a double-ring structure.
- **Pyrimidines:** cytosine (C), thymine (T, only in DNA) and uracil (U, only in RNA), with a single ring.
- **Nucleoside** = base + sugar (N-glycosidic bond). **Nucleotide** = nucleoside + phosphate (ester bond at C-5′).
- Nucleotides are joined by **3′→5′ phosphodiester bonds** to make the polynucleotide chain.

Base	Nucleoside	Nucleotide (monophosphate)
Adenine	Adenosine / deoxyadenosine	AMP / dAMP
Guanine	Guanosine / deoxyguanosine	GMP / dGMP
Cytosine	Cytidine / deoxycytidine	CMP / dCMP
Thymine	Thymidine (only in DNA)	dTMP
Uracil	Uridine (only in RNA)	UMP

Structure of DNA (Watson and Crick, 1953)

- Two polynucleotide chains coil round a common axis to form a **right-handed double helix**. The chains are **antiparallel** (one runs 5′→3′, the other 3′→5′).
- The sugar–phosphate backbone is on the outside and the bases are inside, paired by hydrogen bonds: **A = T (2 bonds)** and **G ≡ C (3 bonds)**.
- **Chargaff's rules:** A = T and G = C, so purines = pyrimidines.
- B-DNA (the usual form): 10 base pairs per turn, 3.4 nm pitch, 0.34 nm between base pairs and 2 nm diameter, with a major and a minor groove. A-DNA and Z-DNA (left-handed) are other forms.
- DNA is found in the nucleus (and in mitochondria); it carries the genetic code.

Types of RNA

RNA	Share of cell RNA	Function
Messenger RNA (mRNA)	About 5%	Carries the genetic code from DNA to the ribosome; eukaryotic mRNA has a 5′ cap and a 3′ poly-A tail
Transfer RNA (tRNA)	About 15%	Cloverleaf shape; carries amino acids to the ribosome; the anticodon pairs with the codon; the 3′ end (CCA) holds the amino acid
Ribosomal RNA (rRNA)	About 80%	Structural and catalytic part of ribosomes (28S, 18S, 5.8S and 5S in eukaryotes)
Other RNAs	Small	snRNA (splicing), miRNA and siRNA (gene silencing), ribozymes (catalytic RNA)

DNA versus RNA

Feature	DNA	RNA
Sugar	Deoxyribose	Ribose
Bases	A, G, C, T	A, G, C, U
Strands	Double stranded	Usually single stranded
Location	Nucleus, mitochondria	Nucleus, cytoplasm, ribosomes
Stability	Stable (no 2′-OH)	Less stable; easily hydrolysed by alkali
Function	Stores genetic information	Protein synthesis and gene regulation

PART B: BIOENERGETICS

7. Concept of Free Energy

Bioenergetics is the study of energy changes in living systems. It tells us whether a reaction can occur on its own and how much useful work it can give. It is based on the laws of thermodynamics. The **first law** says energy can be changed from one form to another but is neither created nor destroyed. The **second law** says that in any spontaneous process the total entropy (disorder) of the system and its surroundings increases.

Gibbs free energy (G)

Free energy (G) is the part of the total energy of a system that is available to do useful work at constant temperature and pressure. Only the **change** in free energy (ΔG) can be measured.

KEY EQUATION

$\Delta G = \Delta H - T\Delta S$ (ΔG = change in free energy, ΔH = change in enthalpy, T = absolute temperature in kelvin, ΔS = change in entropy)

Term	Meaning	Interpretation
Free energy change (ΔG)	Energy available for work	ΔG negative: reaction is spontaneous (**exergonic**). ΔG positive: needs energy input (**endergonic**). ΔG = 0: equilibrium
Enthalpy change (ΔH)	Change in total heat content of the system	ΔH negative: heat released (exothermic). ΔH positive: heat absorbed (endothermic)
Entropy change (ΔS)	Change in randomness or disorder	ΔS positive: disorder increases (favourable). ΔS negative: more order

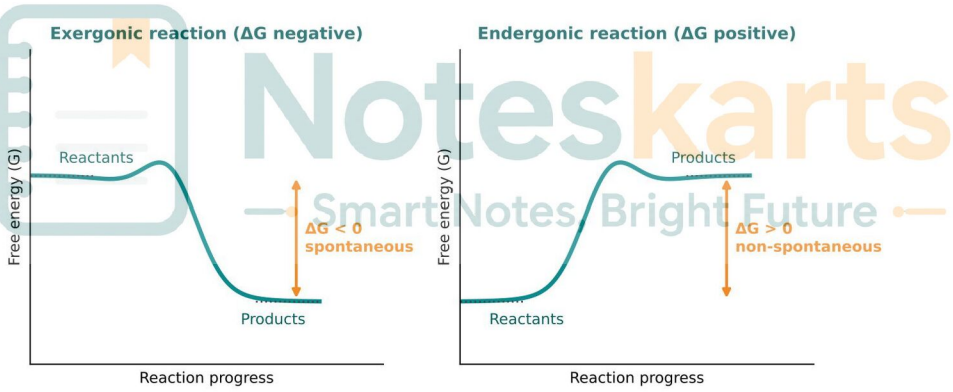

Figure 1: Free energy changes in exergonic and endergonic reactions

How ΔH and ΔS decide whether a reaction occurs

ΔH	ΔS	Result for ΔG
Negative	Positive	Always negative: spontaneous at all temperatures
Positive	Negative	Always positive: never spontaneous
Negative	Negative	Spontaneous only at low temperature
Positive	Positive	Spontaneous only at high temperature

8. Redox Potential

Oxidation is loss of electrons (or removal of hydrogen, or gain of oxygen). **Reduction** is gain of electrons. The two always occur together as **redox reactions**. A substance that gives electrons is a **reducing agent** (electron donor) and one that accepts electrons is an **oxidising agent** (electron acceptor). An oxidised and reduced pair, such as NAD^+/NADH, is called a **redox couple**.

- The **standard reduction potential (E°′)** measures the tendency of a couple to accept electrons. It is measured in volts at pH 7 against the hydrogen electrode (the H^+/H_2 couple is –0.42 V at pH 7).
- A **more negative** E°′ means a stronger reducing agent (good electron donor). A **more positive** E°′ means a stronger oxidising agent (good electron acceptor).

- Electrons flow spontaneously from the couple with the **lower (more negative) E°′** to the couple with the **higher (more positive) E°′**.
- **Link with free energy:** $\Delta G^{\circ\prime} = -n\ F\ \Delta E^{\circ\prime}$, where n is the number of electrons, F is Faraday's constant (96.5 kJ/V·mol) and $\Delta E^{\circ\prime} = E^{\circ\prime}$ (acceptor) – $E^{\circ\prime}$(donor).
- **Nernst equation:** $E = E^{\circ\prime} + (RT/nF) \ln([\text{oxidised}]/[\text{reduced}])$. It gives the potential at actual concentrations.

Redox couple	E°′ (volts)	Role
NAD^+ / NADH	–0.32	Starting point of the respiratory chain
FAD / $FADH_2$ (free)	about –0.22	Complex II electron carrier
Pyruvate / lactate	–0.19	Lactate dehydrogenase
Coenzyme Q (ox / red)	+0.04	Mobile carrier in the membrane
Cytochrome c (Fe^{3+} / Fe^{2+})	+0.25	Mobile carrier in the intermembrane space
½ O_2 / H_2O	+0.82	Final electron acceptor

WORKED EXAMPLE

NADH → O_2: $\Delta E^{\circ\prime}$ = (+0.82) – (–0.32) = **1.14 V**. $\Delta G^{\circ\prime} = -2 \times 96.5 \times 1.14$ = **about –220 kJ/mol**. This large amount of energy is released in small steps along the electron transport chain and part of it is trapped as ATP.

NADH is mostly used in catabolism (to make ATP), while **NADPH** is used in biosynthesis and antioxidant defence. The cell keeps the NAD^+/NADH ratio high and the $NADP^+$/NADPH ratio low.

9. Energy-Rich Compounds

Energy-rich (high-energy) compounds release a large amount of free energy on hydrolysis, usually more than **–25 kJ/mol** (about –7 kcal/mol). The bond that releases this energy is sometimes marked with a wavy line (~). The energy is released because the products are more stable than the reactant: they have less electrostatic repulsion, better resonance stabilisation and better solvation.

Class	Compound	ΔG°′ of hydrolysis (kJ/mol)	Role
Enol phosphate	Phosphoenolpyruvate (PEP)	–61.9	Makes ATP in glycolysis (pyruvate kinase)
Acyl phosphate	1,3-Bisphosphoglycerate	–49.4	Makes ATP in glycolysis (phosphoglycerate kinase)
Acyl phosphate	Carbamoyl phosphate	–51.4	Urea cycle, pyrimidine synthesis
Phosphagen	Creatine phosphate	–43.1	Rapid ATP store in muscle and brain
Phosphoanhydride	ATP → AMP + PPi	–45.6	Activation of fatty acids and amino acids
Thioester	Acetyl-CoA, succinyl-CoA	–31.4, –33.5	Acetyl and acyl group donors; TCA cycle
Phosphoanhydride	ATP → ADP + Pi	–30.5	Universal energy currency
Phosphoanhydride	Pyrophosphate (PPi)	–19.2	Hydrolysis drives biosynthetic reactions
Low-energy ester	Glucose-6-phosphate	–13.8	Energy acceptor, not a donor

The compounds above ATP can phosphorylate ADP to make ATP, and ATP can phosphorylate the compounds below it. This places ATP at the **middle of the energy scale**, so it can accept and also give phosphate groups easily.

Adenosine triphosphate (ATP)

ATP consists of **adenine, ribose and three phosphate groups** (α, β and γ). It exists in the cell as a complex with **Mg^{2+}**. The two terminal phosphoanhydride bonds (β and γ) are energy-rich. An adult has only about 50 g of ATP at any time, but turns over roughly his or her own body weight in ATP every day, so it must be made constantly.

Ways of making ATP

- **Substrate-level phosphorylation:** direct transfer of phosphate from an energy-rich compound to ADP (glycolysis, TCA cycle).
- **Oxidative phosphorylation:** ATP made using energy of the electron transport chain; the major source (about 90%).
- **Creatine phosphate** reserve: creatine phosphate + ADP → creatine + ATP (creatine kinase).
- **Adenylate kinase:** 2 ADP ⇌ ATP + AMP, which helps to keep ATP level constant.

Biological significance of ATP

- **Mechanical work:** muscle contraction and movement of cilia and flagella.
- **Active transport:** Na^+–K^+ ATPase and Ca^{2+} ATPase pumps.
- **Biosynthesis:** making proteins, nucleic acids, lipids and glycogen.
- **Activation of molecules:** glucose to glucose-6-phosphate, amino acids to aminoacyl-tRNA, fatty acids to acyl-CoA.
- **Signalling:** protein phosphorylation by kinases; ATP is the substrate for cAMP.

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PART C: CARBOHYDRATE METABOLISM AND DIABETES MELLITUS

10. Overview of Carbohydrate Metabolism

Dietary starch, sucrose and lactose are digested by salivary and pancreatic **amylase** and the intestinal disaccharidases (maltase, sucrase, lactase) into **glucose, fructose and galactose**. These are absorbed in the small intestine and reach the liver through the portal vein. Glucose enters cells through **glucose transporters** and then follows one of several pathways, depending on the needs of the cell and the hormonal state.

Pathway	Site	Main purpose	Key regulated enzyme
Glycolysis	Cytosol of all cells	Oxidises glucose to pyruvate; makes ATP	Phosphofructokinase-1
Citric acid cycle	Mitochondrial matrix	Completely oxidises acetyl-CoA; makes NADH and $FADH_2$	Isocitrate dehydrogenase
Gluconeogenesis	Liver, kidney cortex	Makes glucose from non-carbohydrate sources in fasting	Fructose-1,6-bisphosphatase, PEPCK
HMP shunt	Cytosol (liver, adipose, RBC, adrenal cortex)	Makes NADPH and ribose-5-phosphate	Glucose-6-phosphate dehydrogenase
Glycogenesis	Liver, muscle	Stores glucose as glycogen	Glycogen synthase
Glycogenolysis	Liver, muscle	Releases glucose from glycogen	Glycogen phosphorylase

11. Glycolysis

Glycolysis (Embden–Meyerhof–Parnas pathway) is the series of ten reactions in the **cytosol** that convert one molecule of **glucose (6C) into two molecules of pyruvate (3C)**. It is the only pathway that works with or without oxygen, and it is the sole source of energy for **red blood cells** (they have no mitochondria). The pathway has two phases: an **energy investment phase** (2 ATP used) and an **energy pay-off phase** (4 ATP and 2 NADH made).

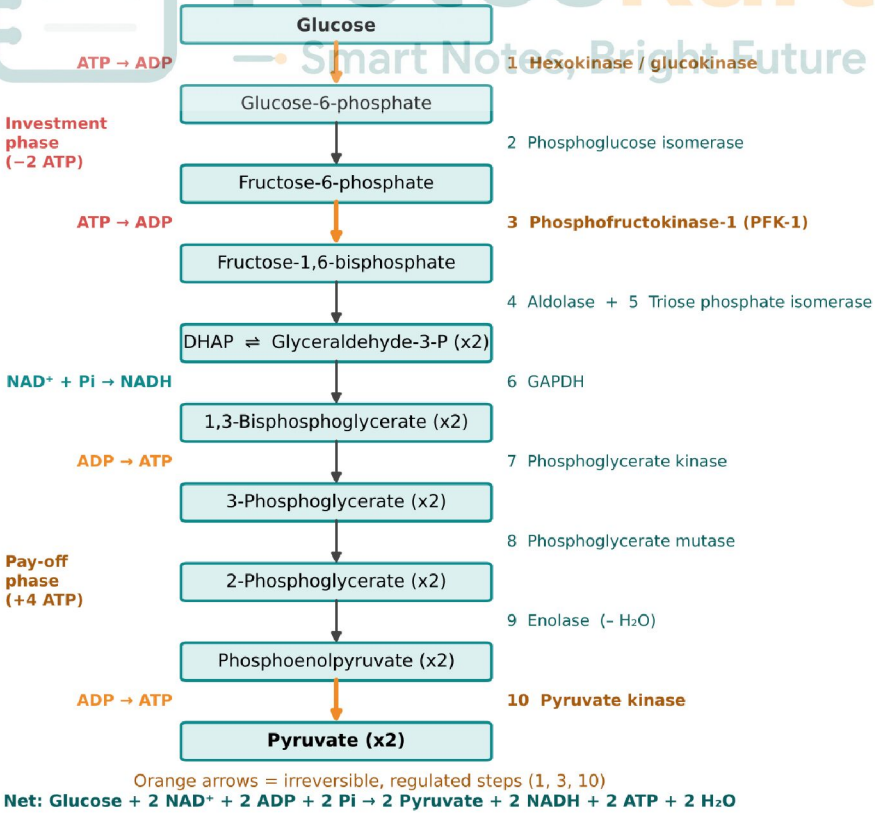

Figure 2: Reactions of glycolysis with key enzymes and ATP changes

Step	Enzyme	Reaction type	Remarks
1	Hexokinase (glucokinase in liver)	Phosphorylation	**Irreversible**; uses 1 ATP; traps glucose in the cell
2	Phosphoglucose isomerase	Isomerisation	Aldose to ketose
3	Phosphofructokinase-1 (PFK-1)	Phosphorylation	**Irreversible; rate-limiting** and committed step; uses 1 ATP
4	Aldolase	Cleavage	Fructose-1,6-bisphosphate to DHAP + glyceraldehyde-3-phosphate
5	Triose phosphate isomerase	Isomerisation	DHAP to glyceraldehyde-3-phosphate; one glucose gives 2 GAP
6	Glyceraldehyde-3-phosphate dehydrogenase	Oxidation + phosphorylation	Makes **NADH**; inhibited by iodoacetate
7	Phosphoglycerate kinase	Substrate-level phosphorylation	Makes **ATP** (2 per glucose)
8	Phosphoglycerate mutase	Isomerisation	3-PG to 2-PG
9	Enolase	Dehydration	Makes PEP; inhibited by **fluoride**
10	Pyruvate kinase	Substrate-level phosphorylation	**Irreversible**; makes **ATP** (2 per glucose)

Energetics

Condition	Net product per glucose	Net ATP
Anaerobic glycolysis	2 lactate (NADH is used to reduce pyruvate to lactate by lactate dehydrogenase, regenerating NAD^+)	**2 ATP**
Aerobic glycolysis	2 pyruvate + 2 NADH (NADH enters the mitochondria through shuttles and gives 3–5 ATP)	2 ATP (+ 3 to 5 ATP from NADH)

Pasteur effect: the presence of oxygen reduces glucose consumption and lactate production because aerobic oxidation gives far more ATP. Cancer cells show the opposite (**Warburg effect**): they use glycolysis heavily even when oxygen is present.

Regulation of glycolysis

Key enzyme	Activators	Inhibitors
Hexokinase	—	Glucose-6-phosphate (product inhibition). Glucokinase is induced by insulin and has a high Km (about 10 mM), so the liver takes up glucose only when blood glucose is high
PFK-1 (most important)	AMP, **fructose-2,6-bisphosphate**, insulin (induces enzyme)	ATP, citrate, low pH, glucagon (lowers F-2,6-BP)
Pyruvate kinase	Fructose-1,6-bisphosphate (feed-forward), insulin (dephosphorylation)	ATP, alanine, glucagon via cAMP-dependent phosphorylation (liver)

Fate of pyruvate

- **Aerobic:** enters mitochondria and forms acetyl-CoA (pyruvate dehydrogenase complex) for the TCA cycle.
- **Anaerobic:** reduced to lactate in red cells and exercising muscle.
- Transaminated to **alanine**; carboxylated to **oxaloacetate** (pyruvate carboxylase); in yeast forms ethanol.

CLINICAL CORRELATION

Pyruvate kinase deficiency causes chronic haemolytic anaemia because red cells cannot make enough ATP. **Lactic acidosis** occurs when pyruvate cannot enter the TCA cycle: hypoxia, shock, thiamine deficiency, pyruvate dehydrogenase deficiency or metformin toxicity.

12. Citric Acid Cycle (TCA Cycle)

The **citric acid cycle** (Krebs cycle, tricarboxylic acid cycle) is the final common pathway for the oxidation of carbohydrates, fats and proteins. It was described by **Hans Krebs in 1937**. It takes place in the **mitochondrial matrix** (except succinate dehydrogenase,

which is in the inner membrane) and needs oxygen indirectly because it depends on the electron transport chain to reoxidise NADH and $FADH_2$.

Link reaction: pyruvate dehydrogenase complex

Pyruvate is converted to acetyl-CoA in the mitochondria: **Pyruvate + NAD^+ + CoA → Acetyl-CoA + CO_2 + NADH**. This is irreversible, so acetyl-CoA cannot be converted back to glucose. The pyruvate dehydrogenase (PDH) complex has three enzymes (E1 pyruvate dehydrogenase, E2 dihydrolipoyl transacetylase, E3 dihydrolipoyl dehydrogenase) and needs **five coenzymes: TPP (vitamin B_1), lipoic acid, CoA (pantothenic acid, B_5), FAD (riboflavin, B_2) and NAD^+ (niacin, B_3)**. PDH is inhibited by acetyl-CoA, NADH and ATP, and activated by pyruvate, ADP and insulin (through PDH phosphatase).

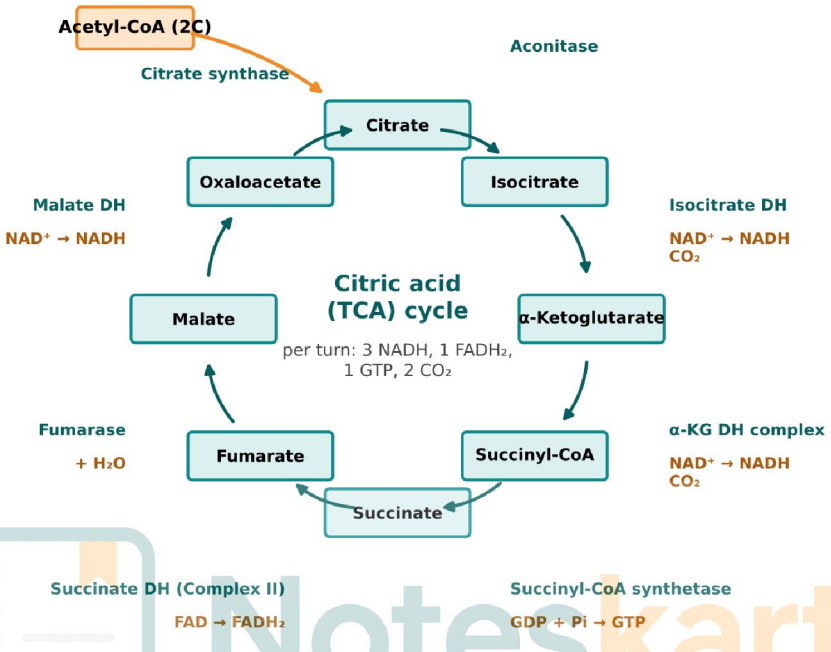

Figure 3: Reactions of the citric acid cycle

Step	Enzyme	Reaction	Products and remarks
1	Citrate synthase	Acetyl-CoA (2C) + oxaloacetate (4C) → citrate (6C)	Rate-limiting; inhibited by ATP, NADH, succinyl-CoA
2	Aconitase	Citrate → isocitrate	Inhibited by **fluorocitrate**
3	Isocitrate dehydrogenase	Isocitrate → α-ketoglutarate	**NADH + CO_2**; main regulatory step; activated by ADP and Ca^{2+}
4	α-Ketoglutarate dehydrogenase	α-KG → succinyl-CoA	**NADH + CO_2**; needs the same 5 coenzymes as PDH; inhibited by arsenite
5	Succinyl-CoA synthetase	Succinyl-CoA → succinate	**GTP** (substrate-level phosphorylation)
6	Succinate dehydrogenase	Succinate → fumarate	**$FADH_2$**; Complex II; inhibited by **malonate**
7	Fumarase	Fumarate + H_2O → malate	Hydration
8	Malate dehydrogenase	Malate → oxaloacetate	**NADH**; regenerates oxaloacetate

SUMMARY OF ONE TURN OF THE CYCLE

Acetyl-CoA + 3 NAD^+ + FAD + GDP + Pi + 2 H_2O → 2 CO_2 + 3 NADH + $FADH_2$ + GTP + CoA. This gives **10 ATP per acetyl-CoA** (3 × 2.5 + 1.5 + 1) and about **20 ATP per glucose** from the two acetyl-CoA formed.

13. Gluconeogenesis

Gluconeogenesis is the synthesis of glucose from non-carbohydrate precursors. It maintains blood glucose during fasting, starvation and intense exercise, and supplies glucose to the brain and red cells. It occurs mainly in the **liver (about 90%)** and the **kidney cortex** (more in prolonged starvation), using enzymes of the cytosol, mitochondria and endoplasmic reticulum.

The three bypass reactions

Gluconeogenesis uses the reversible reactions of glycolysis but must bypass the **three irreversible steps** with different enzymes.

Glycolysis step (irreversible)	Gluconeogenic bypass	Location
Pyruvate → PEP (pyruvate kinase)	Pyruvate → oxaloacetate by **pyruvate carboxylase** (biotin, ATP; activated by acetyl-CoA), then oxaloacetate → PEP by **PEP carboxykinase (PEPCK)** (GTP)	Mitochondria then cytosol
Fructose-6-P → F-1,6-BP (PFK-1)	**Fructose-1,6-bisphosphatase**	Cytosol
Glucose → Glucose-6-P (hexokinase)	**Glucose-6-phosphatase**	Endoplasmic reticulum (liver, kidney; not in muscle or brain)

Energy cost: making one glucose from two pyruvate uses **6 high-energy phosphate bonds** (2 ATP by pyruvate carboxylase, 2 GTP by PEPCK, 2 ATP by phosphoglycerate kinase) and 2 NADH.

Cori cycle and glucose–alanine cycle

- **Cori cycle:** muscle and red cell lactate → blood → liver → glucose → blood → muscle. It costs the liver 6 ATP but gains only 2 ATP in muscle, and it shifts the load of the lactic acid from muscle to liver.
- **Glucose–alanine cycle:** muscle pyruvate is transaminated to alanine → liver → pyruvate for gluconeogenesis; the amino group is removed as urea.

Regulation

- **Glucagon and cortisol** increase gluconeogenesis (induce PEPCK, fall in fructose-2,6-bisphosphate). **Insulin** inhibits it.
- **Acetyl-CoA** (from fatty acid oxidation) activates pyruvate carboxylase. **Fructose-2,6-bisphosphate and AMP** inhibit fructose-1,6-bisphosphatase; ATP and citrate activate it.
- Glycolysis and gluconeogenesis are **reciprocally regulated** so that both are never fully active together, preventing a futile cycle.

CLINICAL CORRELATION

Alcohol causes hypoglycemia in fasting people. Ethanol oxidation raises the NADH/NAD^+ ratio, which diverts pyruvate to lactate and oxaloacetate to malate, so gluconeogenesis stops. **Metformin** works partly by reducing hepatic gluconeogenesis. **Von Gierke disease** is due to glucose-6-phosphatase deficiency.

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14. Hexose Monophosphate (HMP) Shunt

The **HMP shunt** (pentose phosphate pathway or phosphogluconate pathway) is an alternative pathway for glucose oxidation. **No ATP is made or used.** It takes place in the **cytosol** of liver, adipose tissue, adrenal cortex, lactating mammary gland, testis and **red blood cells**, tissues that need NADPH. It is minimal in resting skeletal muscle.

Phases

Phase	Reactions	Products
Oxidative (irreversible)	Glucose-6-P → 6-phosphogluconolactone (**glucose-6-phosphate dehydrogenase, G6PD**) → 6-phosphogluconate (lactonase) → ribulose-5-phosphate (6-phosphogluconate dehydrogenase)	**2 NADPH** + CO_2 + ribulose-5-phosphate per glucose-6-P
Non-oxidative (reversible)	Ribulose-5-P is converted to ribose-5-P and xylulose-5-P (isomerase, epimerase). **Transketolase** (TPP; transfers 2 carbons) and **transaldolase** (transfers 3 carbons) rearrange sugars	Ribose-5-P, fructose-6-P and glyceraldehyde-3-P, which return to glycolysis

Overall: 3 glucose-6-phosphate + 6 $NADP^+$ → 3 CO_2 + 6 NADPH + 2 fructose-6-phosphate + 1 glyceraldehyde-3-phosphate.

Significance

Product	Uses
NADPH	Fatty acid, cholesterol and steroid hormone synthesis; keeps **glutathione** reduced (protects red cells from oxidative damage); **NADPH oxidase** respiratory burst in phagocytes; cytochrome P450 drug metabolism; nitric oxide synthesis
Ribose-5-phosphate	Synthesis of nucleotides, DNA and RNA, ATP, NAD, FAD, CoA

Product	Uses
Link with glycolysis	Excess pentoses return to glycolysis, so the shunt can also convert 5-carbon sugars to 6-carbon sugars

Regulation: G6PD is the controlling enzyme. It is strongly inhibited by a high NADPH/$NADP^+$ ratio and induced by insulin.

CLINICAL CORRELATION: G6PD DEFICIENCY

G6PD deficiency is the **commonest enzyme deficiency** of humans (X-linked recessive; high frequency in Mediterranean, African and Asian populations). Red cells cannot make enough NADPH to keep glutathione reduced, so H_2O_2 and oxidants damage haemoglobin and the membrane. The result is **acute haemolytic anaemia** with **Heinz bodies** and 'bite cells', jaundice and dark urine. Triggers: **primaquine, sulphonamides, dapsone, nitrofurantoin, rasburicase**, fava beans (favism) and infections. The deficiency gives some protection against malaria.

Transketolase needs thiamine; red cell transketolase activity is used to assess thiamine status. **Chronic granulomatous disease** is due to defective NADPH oxidase.

15. Glycogen Metabolism

Glycogen is the storage polysaccharide of animals: a branched polymer of α-D-glucose with α-1,4 links in chains and α-1,6 links at branches (every 8–12 residues). The branching gives many non-reducing ends so glucose can be added and removed quickly. **Liver glycogen** (about 100 g, 6–8% of liver weight) maintains blood glucose. **Muscle glycogen** (about 250–400 g in total, 1–2% of muscle weight) is used only inside the muscle, because muscle lacks glucose-6-phosphatase.

Glycogenesis (synthesis)

- Glucose → glucose-6-phosphate (hexokinase or glucokinase) → **glucose-1-phosphate** (phosphoglucomutase).
- Glucose-1-phosphate + UTP → **UDP-glucose** + PPi (UDP-glucose pyrophosphorylase). The PPi is hydrolysed, which drives the reaction forward.
- **Glycogen synthase** (rate-limiting) adds glucose from UDP-glucose to the non-reducing end by α-1,4 links. It needs a primer, the protein **glycogenin**.
- **Branching enzyme** (amylo-(1,4→1,6)-transglycosylase) moves a block of about 7 residues to make an α-1,6 branch.
- **Energy cost:** 1 ATP and 1 UTP (equal to 2 ATP) for each glucose added.

Glycogenolysis (breakdown)

- **Glycogen phosphorylase** (rate-limiting; cofactor pyridoxal phosphate, vitamin B_6) cleaves α-1,4 links by phosphorolysis to give **glucose-1-phosphate**. It stops 4 residues before a branch point.
- **Debranching enzyme** has two activities: a transferase moves 3 residues to another chain, and α-1,6-glucosidase releases the branch glucose as **free glucose** (about 10% of the products).
- Phosphoglucomutase converts glucose-1-P to glucose-6-P. In **liver and kidney**, glucose-6-phosphatase then releases free glucose into blood. Muscle lacks this enzyme, so muscle glucose-6-P enters glycolysis.

Regulation

Glycogen synthesis and breakdown are **reciprocally regulated** so they do not run together. Control is by covalent modification (phosphorylation) and allosteric effectors.

Signal	Effect on glycogen phosphorylase	Effect on glycogen synthase
Glucagon (liver) or adrenaline (liver and muscle): receptor → cAMP → protein kinase A → phosphorylase kinase	Phosphorylated to active **phosphorylase a**: glycogenolysis ↑	Phosphorylated to inactive form: glycogenesis ↓
Insulin: activates protein phosphatase-1	Dephosphorylated to inactive form	Dephosphorylated to active form: glycogenesis ↑
Ca^{2+} (muscle contraction)	Activates phosphorylase kinase via calmodulin	—
AMP (muscle) / glucose (liver)	AMP activates phosphorylase b; glucose inhibits liver phosphorylase a	G-6-P activates synthase

Glycogen storage diseases (GSD)

Type	Name	Enzyme deficiency	Main features
I	Von Gierke	Glucose-6-phosphatase	Severe fasting hypoglycemia, hepatomegaly, lactic acidosis, hyperuricemia, hyperlipidemia
II	Pompe	Lysosomal acid α-glucosidase	Cardiomegaly, muscle weakness, early death in infants
III	Cori / Forbes	Debranching enzyme	Hypoglycemia, hepatomegaly, abnormal glycogen with short branches
IV	Andersen	Branching enzyme	Cirrhosis; long unbranched glycogen
V	McArdle	Muscle phosphorylase	Exercise intolerance, cramps, no rise in lactate
VI	Hers	Liver phosphorylase	Mild hypoglycemia, hepatomegaly
VII	Tarui	Muscle PFK-1	Exercise intolerance

16. Regulation of Blood Glucose Level

The blood glucose level is kept within narrow limits because the brain and red cells depend on a constant supply of glucose. **Hypoglycemia** causes brain dysfunction and **hyperglycemia** damages blood vessels and nerves.

Parameter	Normal value
Fasting plasma glucose	70–100 mg/dL (3.9–5.6 mmol/L)
2-hour postprandial glucose	Below 140 mg/dL
Random glucose	Below 140 to 200 mg/dL (depends on the last meal)
Renal threshold for glucose	About 180 mg/dL (10 mmol/L); above this glucose appears in urine

- **Sources of blood glucose:** diet, glycogenolysis and gluconeogenesis.
- **Uses of glucose:** oxidation for energy, storage as glycogen, conversion to fat, HMP shunt, and loss in urine (diabetes).

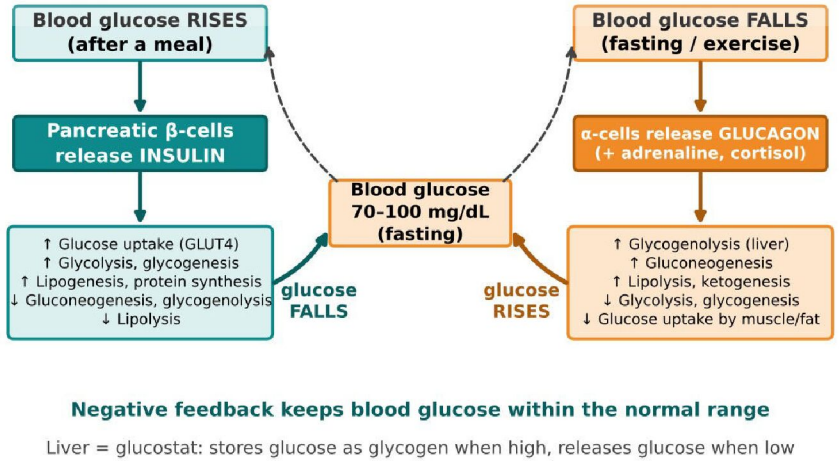

Figure 4: Hormonal regulation of blood glucose

Hormones that regulate blood glucose

Hormone	Source	Effect on blood glucose	Main actions
Insulin	Pancreatic β-cells	**Lowers**	↑ GLUT4 uptake in muscle and fat; ↑ glycolysis, glycogenesis, lipogenesis, protein synthesis; ↓ gluconeogenesis, glycogenolysis, lipolysis
Glucagon	Pancreatic α-cells	Raises	↑ Glycogenolysis, gluconeogenesis, ketogenesis in liver (acts through cAMP)
Adrenaline	Adrenal medulla	Raises	Glycogenolysis in liver and muscle; lipolysis

Hormone	Source	Effect on blood glucose	Main actions
Cortisol	Adrenal cortex	Raises	↑ Gluconeogenesis; ↓ glucose uptake in tissues
Growth hormone	Anterior pituitary	Raises	Anti-insulin effect; ↓ glucose uptake
Thyroxine	Thyroid	Raises	↑ Absorption and glycogenolysis
Somatostatin	Pancreatic δ-cells	Lowers hormone secretion	Inhibits insulin and glucagon release
GLP-1, GIP (incretins)	Gut	Lower	Increase glucose-dependent insulin secretion; decrease glucagon

17. Metabolic Adaptations: Fed State, Fasting and Starvation

The body switches between storing and releasing fuel depending on the food supply. The switch is controlled mainly by the **insulin to glucagon ratio**.

Well-fed (absorptive) state

- Insulin is high and glucagon is low.
- **Liver:** takes up glucose (glucokinase), makes glycogen, oxidises glucose and converts excess to fatty acids and **VLDL**.
- **Adipose tissue:** takes up glucose (GLUT4) and stores fat from chylomicrons and VLDL (lipoprotein lipase).
- **Muscle:** takes up glucose, stores glycogen and makes protein from amino acids.
- **Brain:** uses glucose only.

Fasting and starvation

Feature	Fed state	Early fasting (4–24 h)	Prolonged starvation (days to weeks)
Insulin / glucagon	High / low	Falling / rising	Very low / high
Source of blood glucose	Diet	**Liver glycogenolysis**, then gluconeogenesis	**Gluconeogenesis** (liver and kidney); glycogen is exhausted after about 24 h
Liver	Glycogen and fat synthesis	Glycogenolysis, gluconeogenesis, ketone body synthesis starts	Gluconeogenesis and **ketogenesis** at a high rate
Adipose tissue	Fat storage	Lipolysis begins	Strong lipolysis; glycerol for gluconeogenesis; fatty acids as fuel
Muscle	Glucose and glycogen use	Glucose, then fatty acids	Fatty acids and ketone bodies; proteolysis supplies amino acids (falls later)
Brain fuel	Glucose	Glucose	**Ketone bodies** supply about two-thirds of the brain's energy after some weeks, which reduces glucose need and **spares muscle protein**
Blood ketones	Negligible	Starting to rise	Raised (several mmol/L); much higher in uncontrolled diabetes

Ketone bodies

- **Ketone bodies** are acetoacetate, **β-hydroxybutyrate** and acetone (a by-product, exhaled, fruity smell). They are made only in **liver mitochondria** from acetyl-CoA when fatty acid oxidation is high and oxaloacetate is scarce. The rate-limiting enzyme is **HMG-CoA synthase**.
- They are used by brain, heart and muscle, but **not by the liver** (it lacks thiophorase, succinyl-CoA–acetoacetate CoA transferase) or red cells (no mitochondria).
- **Ketosis** occurs in fasting and prolonged exercise (a mild, adaptive condition). **Ketoacidosis** in uncontrolled diabetes is dangerous because acetoacetate and β-hydroxybutyrate are acids.

18. Diabetes Mellitus and Related Disorders

Diabetes mellitus (DM) is a group of metabolic diseases marked by chronic **hyperglycemia** due to defective insulin secretion, insulin action, or both. It disturbs carbohydrate, fat and protein metabolism.

Classification

Type	Cause	Key features
Type 1 (5–10%)	Autoimmune destruction of pancreatic β-cells (HLA-DR3/DR4; antibodies to GAD65, islet cell, IA-2, insulin)	Absolute insulin deficiency; usually young onset; lean; abrupt onset; **ketosis-prone**; needs insulin
Type 2 (90–95%)	**Insulin resistance** plus relative insulin deficiency (β-cell failure); obesity, inactivity, age, genetic factors	Gradual onset; usually adults; often overweight; ketosis rare; hyperosmolar state possible; treated with lifestyle, oral drugs, then insulin
Gestational	Glucose intolerance first found in pregnancy (placental hormones antagonise insulin)	Increases the risk of type 2 DM later; risk of large baby
Other specific types	MODY (monogenic, e.g. glucokinase gene), pancreatic disease, Cushing syndrome, acromegaly, drugs such as glucocorticoids	Depends on the cause

Diagnosis (ADA criteria)

Test	Normal	Prediabetes	Diabetes
Fasting plasma glucose (mg/dL)	Below 100	100–125	126 or more
2-h OGTT (mg/dL)	Below 140	140–199	200 or more
HbA_1c	Below 5.7%	5.7–6.4%	6.5% or more
Random glucose with symptoms	—	—	200 mg/dL or more

Classic symptoms: polyuria, polydipsia, polyphagia, weight loss, fatigue and blurred vision. A result in the diabetic range must be confirmed on a second occasion unless there are clear symptoms.

Metabolic derangements in diabetes

Area	Changes	Result
Carbohydrate	↓ Glucose uptake (GLUT4); ↑ gluconeogenesis and glycogenolysis	**Hyperglycemia**; glycosuria and osmotic diuresis (polyuria, thirst)
Lipid	↑ Lipolysis (hormone-sensitive lipase unrestrained); ↓ lipoprotein lipase; ↑ acetyl-CoA	↑ Free fatty acids, **ketone bodies**; hypertriglyceridemia (↑ VLDL, ↑ chylomicrons)
Protein	↑ Proteolysis, ↓ protein synthesis; amino acids used for gluconeogenesis	Negative nitrogen balance; muscle wasting; weight loss
Water and electrolytes	Osmotic diuresis; loss of Na^+, K^+, Mg^{2+}	Dehydration; total body potassium deficit (serum K^+ may look normal or high because of acidosis)

Chronic complications and their biochemical basis

- **Polyol pathway:** in tissues that do not need insulin for glucose uptake (lens, nerves, retina, kidney), excess glucose is reduced to **sorbitol** by **aldose reductase**. Sorbitol cannot leave the cell, so it draws water in and causes osmotic damage: **cataract, neuropathy**. NADPH is also consumed.
- **Non-enzymatic glycation:** glucose binds proteins to form advanced glycation end products (AGEs), which cross-link collagen, thicken basement membranes and damage vessels. HbA_1c is an example.
- **Other mechanisms:** activation of protein kinase C, oxidative stress and the hexosamine pathway.

Complication	Description
Retinopathy	Microvascular damage to the retina; leading cause of blindness in adults
Nephropathy	Glomerular basement membrane thickening (Kimmelstiel–Wilson nodules); first sign is **microalbuminuria**; can lead to kidney failure
Neuropathy	Peripheral (glove and stocking numbness), autonomic and foot ulcers
Macrovascular disease	Accelerated atherosclerosis: myocardial infarction, stroke, peripheral vascular disease, diabetic foot

PART D: BIOLOGICAL OXIDATION

19. Biological Oxidation and the Mitochondrion

Biological oxidation is the oxidation of food substrates in cells to release energy that is trapped as ATP. Most of the energy is released when electrons from NADH and $FADH_2$ pass along the **electron transport chain** to oxygen. Together with **oxidative phosphorylation**, this process is called **cellular respiration**.

20. Electron Transport Chain (ETC)

The **electron transport chain** is a series of four protein complexes (I to IV) and two mobile carriers (coenzyme Q and cytochrome c) in the **inner mitochondrial membrane**. Electrons pass from NADH and $FADH_2$ down a gradient of increasing redox potential to **oxygen**, which is reduced to water. The energy released at Complexes I, III and IV is used to **pump protons (H^+)** from the matrix to the intermembrane space.

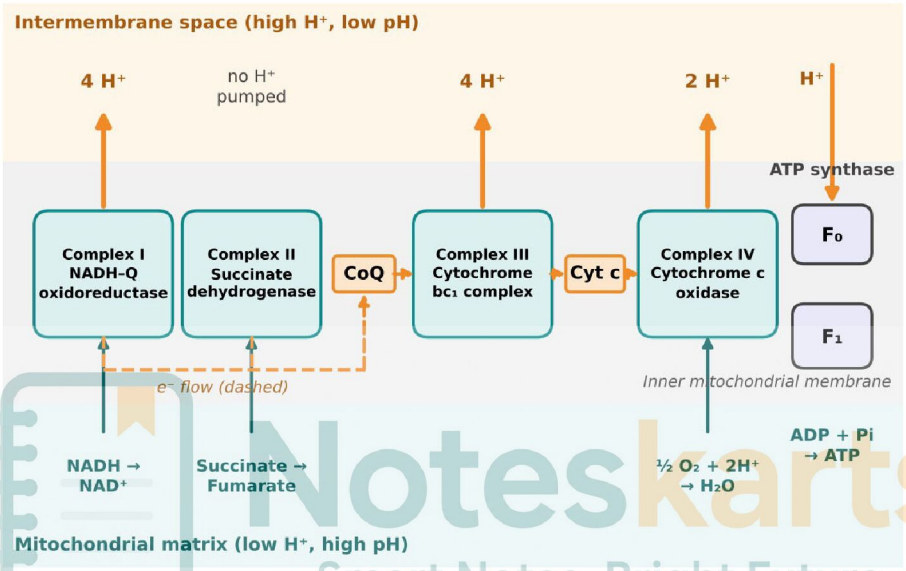

Figure 5: Electron transport chain and ATP synthase in the inner mitochondrial membrane

Complex	Name	Prosthetic groups	Electron path	H^+ pumped	Inhibitors
I	NADH–Q oxidoreductase (NADH dehydrogenase)	FMN, Fe–S	NADH → CoQ	4	Rotenone, amobarbital, piericidin A
II	Succinate–Q reductase (succinate dehydrogenase)	FAD, Fe–S	Succinate → CoQ	0	Malonate, carboxin
III	Q–cytochrome c oxidoreductase (cytochrome bc_1)	Haem b, c_1, Rieske Fe–S	$CoQH_2$ → cyt c	4 (Q cycle)	Antimycin A
IV	Cytochrome c oxidase	Haem a, a_3; Cu_A, Cu_B	Cyt c → O_2 → H_2O	2	Cyanide, carbon monoxide, azide, H_2S

Electron flow

- **NADH** gives electrons to Complex I → coenzyme Q (reduced to $CoQH_2$) → Complex III → cytochrome c → Complex IV → O_2.
- **$FADH_2$** (from succinate in the TCA cycle, and from fatty acid oxidation and glycerol-3-phosphate) feeds electrons into the chain at the level of coenzyme Q (Complex II), **bypassing Complex I**. So it pumps fewer protons.
- Complex IV transfers 4 electrons to one O_2 molecule to give 2 H_2O. Oxygen never leaves the enzyme until it is fully reduced.
- About **10 H^+** are pumped per NADH (4 + 4 + 2) and about **6 H^+** per $FADH_2$ (4 + 2).

Chemiosmotic theory

Proposed by **Peter Mitchell (1961, Nobel Prize 1978)**. The electron flow pumps protons across the inner membrane, making an **electrochemical proton gradient** (a pH difference plus a membrane potential, together called the **proton-motive force**) with the intermembrane space positive and acidic. The protons flow back through ATP synthase, and this flow drives ATP synthesis. The inner membrane must stay impermeable to H^+ for this to work.

ENERGY EFFICIENCY

Passing 2 electrons from NADH to O_2 releases about 220 kJ/mol. Making 2.5 ATP stores about 2.5 × 30.5 = 76 kJ, so roughly **35%** of the energy is trapped as ATP and the rest is released as heat, which helps to keep body temperature.

21. Oxidative Phosphorylation and Mechanism of ATP Synthesis

Oxidative phosphorylation is the formation of ATP from ADP and Pi using the energy of the proton gradient made by the electron transport chain. The two processes are coupled: ATP synthesis needs the gradient, and electron flow continues only if protons can return through ATP synthase.

ATP synthase (Complex V, F_0F_1-ATPase)

- **F_0** is embedded in the inner membrane. It contains a ring of **c-subunits** and the **a-subunit**, which together form the proton channel.
- **F_1** projects into the matrix and has the subunits **$\alpha_3\beta_3\gamma\delta\varepsilon$**. The three **β-subunits** carry the catalytic sites.
- **Binding-change mechanism (Paul Boyer; Nobel Prize 1997, shared with John Walker):** as protons pass through F_0, the c-ring and the **γ-subunit rotate**. This makes each β-subunit change in turn between the **open (O)** form that releases ATP, the **loose (L)** form that binds ADP and Pi, and the **tight (T)** form that makes ATP. One full rotation makes 3 ATP.
- About **4 H^+** are needed for each ATP made (3 for the rotation and 1 to bring Pi and ADP into the matrix). This gives the **P/O ratios**: **2.5 ATP per NADH** (10 H^+) and **1.5 ATP per $FADH_2$** (6 H^+). Older textbooks use 3 and 2.

ATP yield from one glucose (aerobic)

Stage	Product	ATP (2.5 / 1.5 per NADH / $FADH_2$)	ATP (older 3 / 2)
Glycolysis (substrate level)	2 ATP	2	2
Glycolysis NADH	2 NADH (cytosolic)	3 or 5	4 or 6
Pyruvate dehydrogenase	2 NADH	5	6
TCA cycle (2 turns)	6 NADH + 2 $FADH_2$ + 2 GTP	15 + 3 + 2 = 20	18 + 4 + 2 = 24
Total		**30 to 32 ATP**	**36 to 38 ATP**

Regulation: respiratory control

- The main control is the **availability of ADP** (acceptor control). When the cell uses ATP, ADP rises and oxygen consumption increases; when ATP is plentiful, ADP is low and the chain slows down.
- A raised **ATP/ADP ratio** and NADH/NAD^+ ratio slow the TCA cycle and PDH; **Ca^{2+}** in the matrix activates the dehydrogenases in active tissue.
- **Inhibitory factor IF_1** blocks ATP synthase from running in reverse (hydrolysing ATP) when the proton gradient collapses, as in ischemia.

Inhibitors and uncouplers

Type	Agent	Site / effect
ETC inhibitors	Rotenone, amobarbital; antimycin A; cyanide, CO, azide, H_2S	Block Complex I; Complex III; Complex IV. Electron flow, proton pumping and ATP synthesis all stop
ATP synthase inhibitor	**Oligomycin**	Blocks the F_0 proton channel. The gradient builds up and electron flow stops
Translocase inhibitors	Atractyloside, bongkrekic acid	Block ADP–ATP exchange
Uncouplers	**2,4-Dinitrophenol (DNP)**, FCCP, high-dose **salicylates**, **thermogenin (UCP1)**	Carry protons across the membrane, so the gradient is lost. **O_2 uptake rises, ATP synthesis falls and the energy is lost as heat**
Ionophores	Valinomycin (K^+), gramicidin	Make the membrane leaky to ions

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CLINICAL CORRELATION

Cyanide poisoning: cyanide binds Fe^{3+} in Complex IV; cells cannot use oxygen (histotoxic hypoxia) although blood oxygen is normal. Treatment: **amyl nitrite and sodium nitrite** (form methemoglobin, which binds cyanide), **sodium thiosulfate** (rhodanese converts cyanide to thiocyanate) or **hydroxocobalamin**.

Brown adipose tissue contains thermogenin (UCP1), a natural uncoupler, which makes heat in newborns. **DNP** was once used for weight loss, but caused fatal hyperthermia. **Aspirin overdose** can cause fever by uncoupling.

22. Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction

Mitochondrial dysfunction means that mitochondria cannot make enough ATP, or they release too many reactive oxygen species. Tissues with a high energy need (**brain, heart, skeletal muscle, kidney, eye and endocrine glands**) are affected first.

- **Mitochondrial DNA (mtDNA)** is a circular molecule of about 16.6 kb with **37 genes** (13 proteins of the respiratory chain, 22 tRNAs and 2 rRNAs). It is inherited **only from the mother** (maternal inheritance).
- mtDNA mutates more easily than nuclear DNA (no histones, limited repair, close to the source of free radicals). A cell can contain both normal and mutant mtDNA (**heteroplasmy**), and symptoms appear only above a threshold.

Disease	Defect	Features
LHON (Leber hereditary optic neuropathy)	Complex I (ND genes)	Sudden loss of central vision, mostly young males
MELAS	tRNA-Leu (A3243G)	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes
MERRF	tRNA-Lys	Myoclonic epilepsy, **ragged red fibres** in muscle biopsy
Leigh syndrome	Complex I, IV or PDH	Progressive brain damage in infants
Kearns–Sayre syndrome	mtDNA deletion	Ophthalmoplegia, retinitis, heart block

Clinical and laboratory clues: lactic acidosis with a high lactate/pyruvate ratio, muscle weakness, exercise intolerance, neurological problems, and ragged red fibres on muscle biopsy.

Acquired causes

- **Drugs:** zidovudine and other nucleoside analogues (inhibit mitochondrial DNA polymerase γ), **statins** (lower coenzyme Q_{10}), metformin (mild Complex I inhibition), valproate, aminoglycosides and linezolid (affect mitochondrial ribosomes), doxorubicin (cardiotoxicity).
- **Toxins:** cyanide, carbon monoxide, rotenone, MPTP (causes parkinsonism by blocking Complex I).
- **Conditions:** ageing, ischemia–reperfusion injury, neurodegenerative diseases (Parkinson's, Alzheimer's), diabetes and heart failure.
- **Apoptosis:** damaged mitochondria release **cytochrome c**, which activates caspase-9 and programmed cell death.

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NOTE FOR STUDENTS

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