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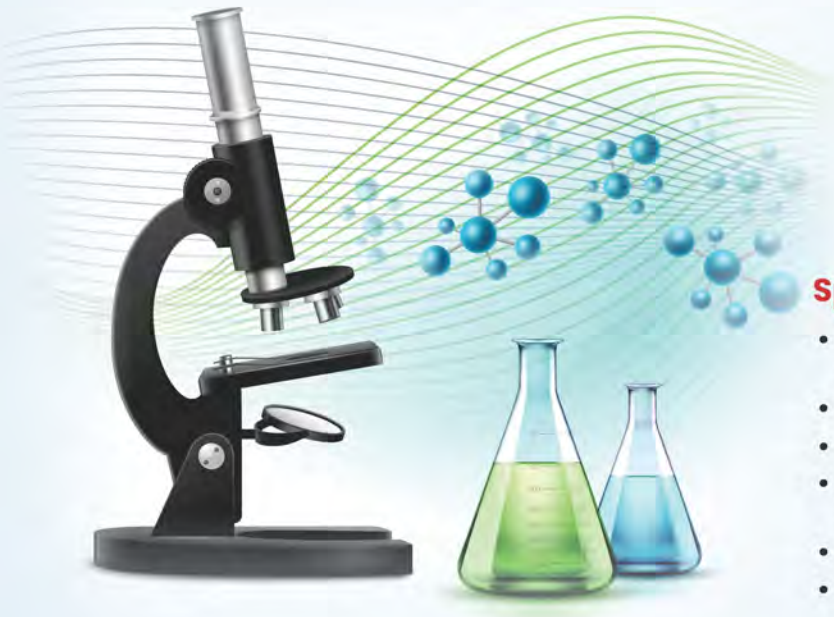
for Physiotherapy Students

As per Physiotherapy Curriculum of All Universities of India and Ministry of Health & Family Welfare



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Harbans Lal

CBS Physio Brid Series

Textbook of

Biochemistry

for Physiotherapy Students

As per Physiotherapy Curriculum of All Universities of India and Ministry of Health & Family Welfare

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About the Author

Harbans Lal *PhD, FIAO, FACBI, FSOBSI,* joined as a Lecturer in the Department of Biochemistry at Medical College (presently Postgraduate Institute of Medical Sciences, Pt BD Sharma University of Health Sciences), Rohtak, Haryana, and after nearly 34 years of illustrious service, retired in 2009 from the same institution as Professor. Thereafter, he joined as a Senior Professor and Head, Department of Biochemistry at Maharaja Agrasen Medical College, Agroha, Hisar (Haryana), from where he retired in July 2017. During this period, he supervised a large number of PhD and MD students, wrote 12 textbooks and published more than 150 research papers in various National and International Journals. He is also a peer reviewer of several National and International Research Journals.

The author has also been a visiting faculty at Louisiana State University Medical Center, New Orleans, USA; Department of Biosciences, MD University, Rohtak; and Swami Dayanand Postgraduate Institute of Pharmaceutical Sciences, Pt BD Sharma University of Health Sciences, Rohtak. He is a life member of several Scientific Bodies, including Nutrition Society of India, Association of Clinical Biochemists of India, International Federation of Clinical Chemistry, Society of Biological Chemists of India, Society of Biological Scientists of India, and Laboratory Animal Scientists Association. He is also a recipient of several National and International awards, including Nutrition Society of India's Young Scientists Award, World Health Organization Fellowship Award, Fellowship of the Association of Clinical Biochemists of India, Fellowship of the Society of Biological Scientists of India, Seth GS Medical College & KEM Hospital Oration Award, and Best Teacher Award for Excellence in Teaching from Postgraduate Institute of Medical Sciences, Rohtak.

PREFACE

It gives me pleasure to present the book entitled **Textbook of Biochemistry for Physiotherapy Students**. Many of the teachers taking classes of the physiotherapy students must be thinking of that when the market is full of the Textbooks on Biochemistry, why one more book? So, to clarify the point which is haunting their mind, it is asserted that Biochemistry is a subject which has its importance in every field, however, the complete list of topics may not be essentially required everywhere. Also, the students of different courses need not read and remember each and every topic. This is also the reason, the experts of various Councils from different specialities, namely, National Medical Council, Dental Council of India, Indian Nursing Council and All India Council of Technical Education, etc., have framed and prescribed a definite syllabus for medical, dental, nursing and other paramedical courses, including physiotherapy.

Keeping this in mind, it was planned to prepare this book for Physiotherapy students. Contents of the various chapters have been accordingly framed after compiling Physiotherapy curriculum prescribed by the Ministry of Health & Family Welfare, and the syllabi designed and adopted by several Indian Universities.

I am highly thankful to the faculty of Biochemistry teaching Physiotherapy students of some of the colleges for their helpful suggestions. I also express my sincere thanks to **Mr Satish Kumar Jain** (Chairman) and **Mr Varun Jain** (Managing Director), M/s CBS Publishers and Distributors Pvt Ltd for their wholehearted support in publication of this book. I have no words to describe the role, efforts, inputs and initiatives undertaken by **Mr Bhupesh Aarora** [Sr. Vice President – Publishing & Marketing (Health Sciences Division)] for helping and motivating me. I would like to thank Ms Nitasha Arora, Dr Anju Dhir, Mr Shivendu Bhushan Pandey and Mr Ashutosh Pathak from CBS Publishers & Distributors Pvt Ltd, New Delhi.

Helpful suggestions for improvement of the book are welcome and will be highly appreciated.

HARBANS LAL

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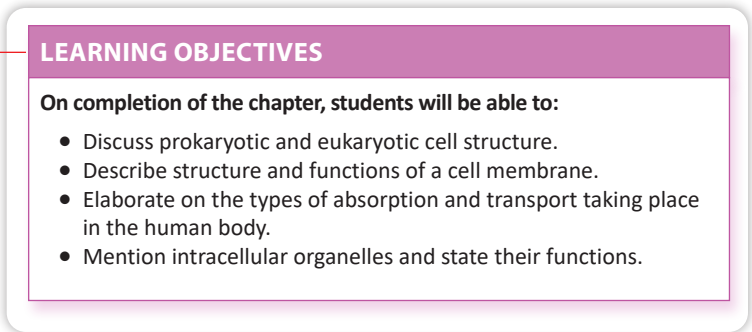
Special Features of the Book

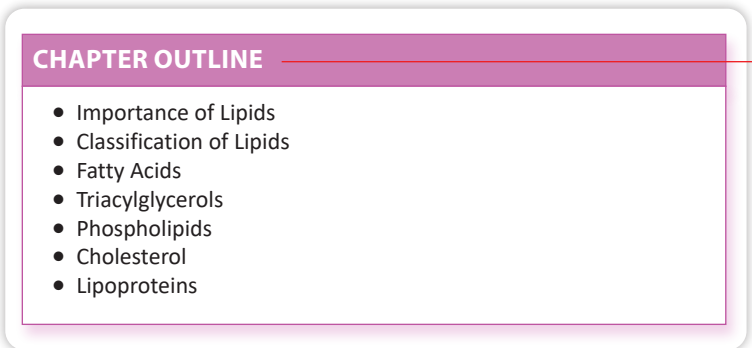
Learning Objectives in the beginning of every Chapter help readers understand the purpose of the chapter.



LEARNING OBJECTIVES

On completion of the chapter, students will be able to:

- Discuss prokaryotic and eukaryotic cell structure.
- Describe structure and functions of a cell membrane.
- Elaborate on the types of absorption and transport taking place in the human body.
- Mention intracellular organelles and state their functions.

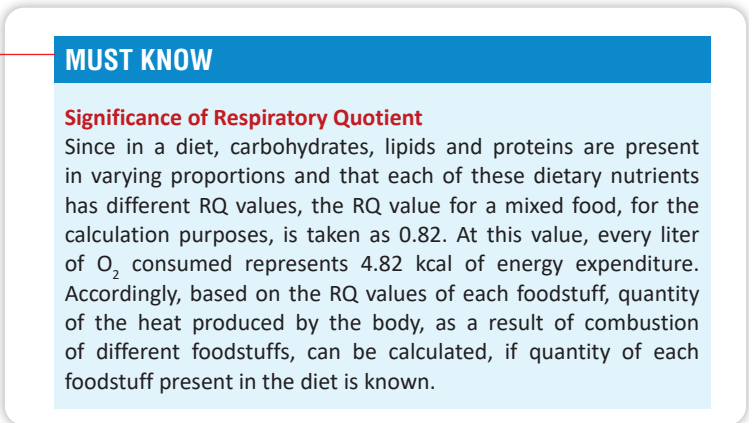


CHAPTER OUTLINE

- Importance of Lipids
- Classification of Lipids
- Fatty Acids
- Triacylglycerols
- Phospholipids
- Cholesterol
- Lipoproteins

Chapter Outline gives a glimpse of the content covered in the chapter.

Must Know boxes give an overview of important facts and terms of the concerned topic.



MUST KNOW

Significance of Respiratory Quotient

Since in a diet, carbohydrates, lipids and proteins are present in varying proportions and that each of these dietary nutrients has different RQ values, the RQ value for a mixed food, for the calculation purposes, is taken as 0.82. At this value, every liter of O_2 consumed represents 4.82 kcal of energy expenditure. Accordingly, based on the RQ values of each foodstuff, quantity of the heat produced by the body, as a result of combustion of different foodstuffs, can be calculated, if quantity of each foodstuff present in the diet is known.

TABLE 3.1: Classification of monosaccharides

Monosaccharides	Number of C-atoms	Aldoses	Ketoses
Trioses	3	Glyceraldehyde	Dihydroxyacetone
Tetroses	4	Erythrose	Erythrulose
Pentoses	5	Ribose	Ribulose
Hexoses	6	Glucose	Fructose

Numerous **Tables** have been used in the chapters to facilitate learning in a quick way.

The book is well illustrated with relevant colorful **Figures**, etc.

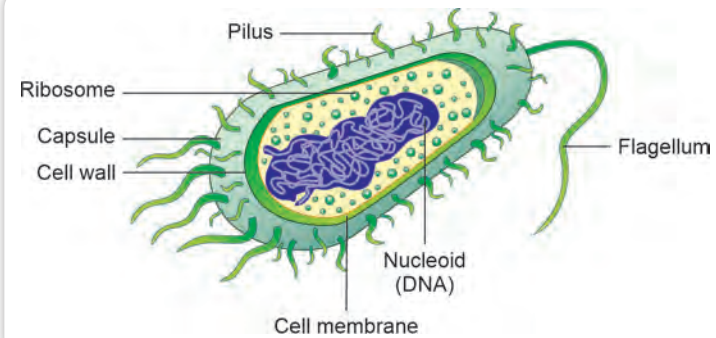


Fig. 1.1: A prokaryotic cell

CONCEPT TO CLINIC

Lysosomal Storage Disorders

Absence of the specific lysosomal enzyme is seen in a number of genetic disorders. This in turn results in accumulation of various cellular components which cannot be digested (hydrolyzed) due to inherited deficiency of the lysosomal enzyme. Lysosomes of the affected individuals become enlarged with the undigested material and thus interfere in normal cellular processes.

Evolving conceptual details for application in clinical situations are depicted in **Concept to Clinic** boxes.

Physio CORNER

Importance of BMR in Physiotherapy

One of the most important factors that increases metabolic rate is the amount of muscle you have. Muscle burns more calories than fat tissue; therefore, it is advantageous to have more muscle than fat. This is most effectively done through weight training. Exercise in general is a great way to improve the metabolism.

Physiotherapy correlation of the topics under study is mentioned as **Physio Corner**.

RECENT UPDATE

Recent experimental evidences, however, have suggested that instead of 3 ATP (for each NADH consumed) and 2 ATP (for $FADH_2$ consumed), the values are actually **2.5 ATP** and **1.5 ATP,** respectively. Also, it has been suggested that the new values should be followed in all energy-based calculations involving the electron transport chain, e.g., the energy yield during glycolysis, Krebs cycle, β-oxidation of fatty acids, etc.

Any advancements that have taken place in recent times relevant to study and practice are enlisted as **Recent Update**.

CASE STUDY

A 58-year-old male came complaining about generalized pain in the right foot sole, and complained of lateral pain in ankle and dorsum. The pain was worse at night. There was no fever.

His vitals were normal, with erythema over lateral aspect of the foot. The patient was diagnosed with gout based on the signs and symptoms, biochemical tests and radiographic findings.

Goals of Physiotherapy Management:

- Focus on reinforcement of management program, splinting, orthotics, or other assistive devices to protect the affected joint(s).
- Use of cryotherapy to alleviate the pain associated with acute bouts of gout.
- Assist with maintenance and improvement of ROM, strength, and function.
- Prescription of a suitable exercise routine and keeping the patient's weight under control.

Case Study demonstrates example(s) of specific clinical scenarios that are often encountered by Physiotherapists.

SUMMARY

- A prokaryotic cell is small in size (1–10 nm), relatively simple in structure and has only a single membrane, called cell membrane, which is, usually, surrounded by a rigid cell wall of characteristic structure.
- Animals, plants, fungi and protozoa are called eukaryotes, which may be unicellular or multicellular.
- A cell membrane is composed of lipids, proteins and carbohydrates.
- Channels are pore-forming membrane proteins.
- An ionophore is a lipid-soluble molecule, usually, synthesized by the microorganisms to transport ions across the lipid bilayer of the cell membrane.
- Primary active transport a process that requires energy, which is provided by the direct hydrolysis of ATP.
- Drugs such as cardiac glycosides, e.g., digoxin and ouabain, inhibit Na^+/K^+-pump and are of clinical importance in the management of cardiac failure.

Important takeaway points of respective chapters have been highlighted under **Summary Boxes**.

ASSESS YOURSELF

Long/Short Answer Questions

1. **Define pH, acid, base and buffer.**
2. **Write notes on:**
   a. Acids
   b. Bases
   c. Buffers
   d. Amphoteric substances
   e. Henderson-Hasselbalch equation
   f. Effect of diet on acid base equilibrium
   g. Osmotic pressure

Multiple Choice Questions

1. **Which of the following is a correct representation of pH?**
   a. $\log_{10}[H^+]$
   b. $\log_{10}[1/H^+]$
   c. $\log_e[H^+]$
   d. $\log_e[1/H^+]$

At the end of chapters, **Assess Yourself** section is given which contains frequently asked questions in exams and multiple choice questions to help you attain mastery over the subject.

SYLLABUS

Time: 60 Hours

BIOCHEMISTRY

Nutrition

- Introduction, importance of nutrition, calorific values, respiratory quotient—definition, and its significance, RDA, SDA, energy requirement of a person—basal metabolic rate with reference to age, sex: Definition, normal values, factor affecting BMR, special dynamic action of food, thermogenesis.
- Physical activities—energy expenditure for various activities, calculation of energy requirement of a person, metabolism in exercise and injury.
- Balanced diet
  - Recommended dietary allowances.
  - Role of carbohydrates in diet: Digestible carbohydrates and dietary fibers.
  - Role of lipids in diet.
  - Role of proteins in diet: Quality of proteins—biological value, net protein utilization, nutritional aspects of proteins–essential and non-essential amino acids, nitrogen balance.
  - Diet for chronically ill and terminally ill patients.
- Nutritional disorders (protein energy malnutrition—kwashiorkor and marasmus).

Biophysics

Concepts of pH and buffers, acid base equilibrium osmotic pressure and its physiological applications.

Carbohydrate Chemistry

- Definition, general classification with examples, glycosidic bond.
- Structures, composition, sources, properties and functions of monosaccharides, disaccharides, oligosaccharides and polysaccharides.
- Glycosaminoglycan (mucopolysaccharides).

Carbohydrate Metabolism

- Introduction, glycolysis—aerobic, anaerobic, citric acid cycle, substrate level phosphorylation.
- Glycogen metabolism—glycogenesis, glycogenolysis, metabolic disorders glycogen, gluconeogenesis, Cori cycle.
- Hormonal regulation of glucose, glycosuria, diabetes mellitus.
- Metabolic disorders of glycogen metabolism, lactose intolerance.
- Biological oxidation.

Bioenergetics

Concept of free energy change, exogenic and endogenic reactions, concepts regarding energy rich compounds, respiratory chain and biological oxidation (electron transport chain, substrate level and oxidative phosphorylation).

Lipid Chemistry

- Definition, general classification.
- Definition, classification, properties and functions of fatty acids, triacylglycerol, phospholipids, cholesterol.
- Biochemical aspects of digestion and absorption of lipids.
- Beta oxidation of fatty acids—energetics, ketogenesis, ketolysis, ketosis.
- Essential fatty acids and their importance.
- Cholesterol and its importance (no synthesis).
- Lipoproteins: Definition, classification, properties, sources and function ketone bodies.
- Fate of acetyl CoA and glycerol.

Amino Acid Chemistry

- Amino acid chemistry: Definition, classification, peptide bonds.
- Peptides: Definition, biologically important peptides.
- Protein chemistry: Definition, classification, functions of proteins.
- Denaturation, coagulation, isoelectric pH and its significance.
- Fate of amino acids in the body (deamination, transamination, transmethylation), fates of ammonia and urea cycle.
- Biochemical aspects of digestion and absorption of proteins.

Enzymes

- Definition, active site, cofactor (coenzyme, activator), proenzyme. classification with examples.
- Factors effecting enzyme activity, enzyme inhibition and significance, Isoenzymes.
- Diagnostic enzymology (clinical significance of enzymes).

Nucleotide and Nucleic Acid Chemistry

- Nucleotide chemistry: Nucleotide composition, functions of free nucleotides in body.
- Nucleic acid (DNA and RNA) chemistry: Difference between DNA and RNA, structure of DNA (Watson and Crick model), functions of DNA, structure and functions of tRNA, rRNA, mRNA.
- Catabolism of purines and their related disorders.

Digestion and Absorption

General characteristics of digestion and absorption, Digestion and absorption of carbohydrates, proteins and lipids. Disorders of digestion and absorption—lactose intolerance.

Lipid Metabolism

- Introduction to lipid metabolism, lipolysis, oxidation of fatty acids.

- Lipogenesis—denovo synthesis of fatty acids, chain elongation, desaturation, triacylglycerol synthesis, fat metabolism in adipose tissues.
- Ketone body metabolism: Ketone body formation (ketogenesis), utilization (ketolysis), ketosis, Rothera's test.
- Cholesterol metabolism: Synthesis, degradation, cholesterol transport.
- Hypercholesterolemia and its effects (atherosclerosis and coronary heart diseases), hypocholesterolemic agents, common hyperlipoproteinemia, fatty liver.

Amino Acid and Protein Metabolism

- Catabolism of amino acids—Introduction, transamination, deamination, fate of ammonia, transport of ammonia.
- Plasma proteins and functions. Metabolism: General reactions of amino acids. Formation and fate of ammonia—urea cycle.
- Specialized products formed from amino acids—from glycine, arginine, methionine, phenylalanine and tyrosine.

Vitamins

- Definition, classification according to solubility.
- Individual vitamins—Sources, active forms and metabolic role, coenzyme forms of vitamin B complex group, functions, RDA of fat- and water-soluble vitamins, digestion, absorption and transport, daily requirement, deficiency disorders.
- Toxicity/hypervitaminosis.

Mineral Metabolism

Definition, sources, RDA, digestion, absorption, transport, excretion, functions, disorder of individual minerals—calcium, phosphate, iron, magnesium, magnesium, zinc, chloride, fluoride, iodine, selenium, molybdenum, copper, phosphate, calcium and iron in detail.

Cell Biology

Introduction, cell structure and kinetics, cell membrane structure and function, various types of absorption. Intracellular organelles and their functions, briefly on cytoskeleton.

Neuromuscular Biochemistry

- Contractile elements in muscle.
- Composition function and chemical mediators of nerve activity in muscle tissue.
- General Biochemistry of muscle contraction and relaxation.
- Energy metabolism in skeletal a n d cardiac muscle contraction.

Biochemistry of Connective Tissue

- Introduction, various connective tissue proteins: Collagen, elastin—structure and associated disorders. glycoproteins, proteoglycans.
- Chemistry of connective tissue, bone and teeth.

Hormone Action

Definition, classification, mechanism of hormone action, receptors, signal transduction, second messengers and cell function.

Acid-Base Balance

Acids, bases and buffers, pH, buffer systems of the body, bicarbonate buffer system, role of lungs and kidneys in acid-base balance, acid-base imbalance.

Water and Electrolyte Balance

- General outline of fluid compartments of the body with their water and electrolyte content.
- Water distribution in the body, body water, water turnover, regulation of water balance: role of ADH and thirst center.
- Osmolarity, distribution of electrolytes—sodium, potassium and their importance in body.
- Electrolyte balance: Role of aldosterone, rennin angiotensin system and ANF.
- Ideal daily intake and output, dehydration.

Study of Hemoglobin and Immunoglobulins with Functions.

Clinical Biochemistry

- Normal levels of blood and urine constituents, relevance of blood and urine levels of glucose, urea, uric acid, creatinine, calcium, phosphates, pH and bicarbonate. Liver function tests, renal function tests.
- Enzymes—Amylase, CPK, LDH and its isoenzymes.
- Lipid profile—triglyceride, cholesterol (HDL, LDL and VLDL)
- Proteinuria and glycosuria.
- **Normal levels of blood and urine constituents**
  (**Note:** This is for info, there is no practical examination)
  - Introduction to clinical biochemistry laboratory, blood collection and anticoagulants.
  - Demonstrate the estimation of blood glucose, its relevance.
  - Demonstrate the estimation of blood urea.
  - Demonstrate the estimation of serum creatinine and creatinine clearance.
  - Demonstrate estimation of serum proteins, albumin and A:G ratio.
  - Demonstrate estimation of calcium and phosphorous.
  - Demonstrate the estimation of serum bilirubin.
  - Demonstrate the estimation of SGOT and SGPT.
  - Demonstrate the estimation of alkaline phosphatase.
  - Demonstrate the estimation of uric acid.
  - Normal and abnormal constituents of urine.
  - Demonstrate the estimation of ABG analysis.
  - Water balance and imbalance and interpretation of serum electrolytes.

CONTENTS

10
CHAPTER

Carbohydrate Metabolism

LEARNING OBJECTIVES

On completion of the chapter, students will be able to:

- Define and outline glycolysis. Explain aerobic and anaerobic glycolysis.
- Understand the rationale behind hexose monophosphate shunt (HMP shunt).
- Describe Krebs cycle. Also, enlist the steps and energy production in this cycle.
- Discuss glucogenesis, glycogenesis, glycogenolysis, and gluconeogenesis.
- Elaborate on Cori cycle and outline the hormonal regulation of glucose.
- Mention a few disorders of carbohydrate metabolism.

CHAPTER OUTLINE

- Glycolysis
- Hexose Monophosphate Shunt
- Citric Acid Cycle
- Glycogen Metabolism
- Gluconeogenesis
- Cori Cycle
- Disorders of Carbohydrate Metabolism

INTRODUCTION

All the **dietary carbohydrates are** digested and **absorbed as glucose**, which enters the liver (as discussed earlier in Chapter 9).

In the liver, **glucose is utilized in various metabolic pathways** which include **glycolysis** (oxidized to produce energy), **glycogenesis** (stored as glycogen in the liver and muscle) and **pentose phosphate pathway** (to produce pentoses and NADPH). **During starvation**, when blood glucose is low, glucose is released from glycogen **(glycogenolysis)** or produced via **gluconeogenesis** (Fig. 10.1).

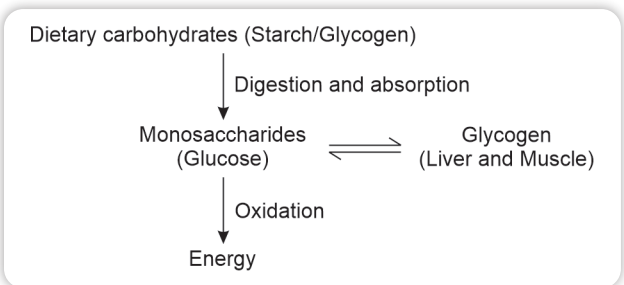


Fig. 10.1: Metabolic fates of glucose

GLYCOLYSIS

Glycolysis, also called **Embden-Meyerhof** (or **Embden-Meyerhof-Parnas) pathway**, is a process of utilization (catabolism) of glucose, mainly, in the liver **(aerobic glycolysis)** and skeletal muscle **(anaerobic glycolysis)**.

Glycolytic enzymes are present in the extramitochondrial compartment of the cell to produce energy. Various reactions of the glycolytic pathway are outlined in Figure 10.2.

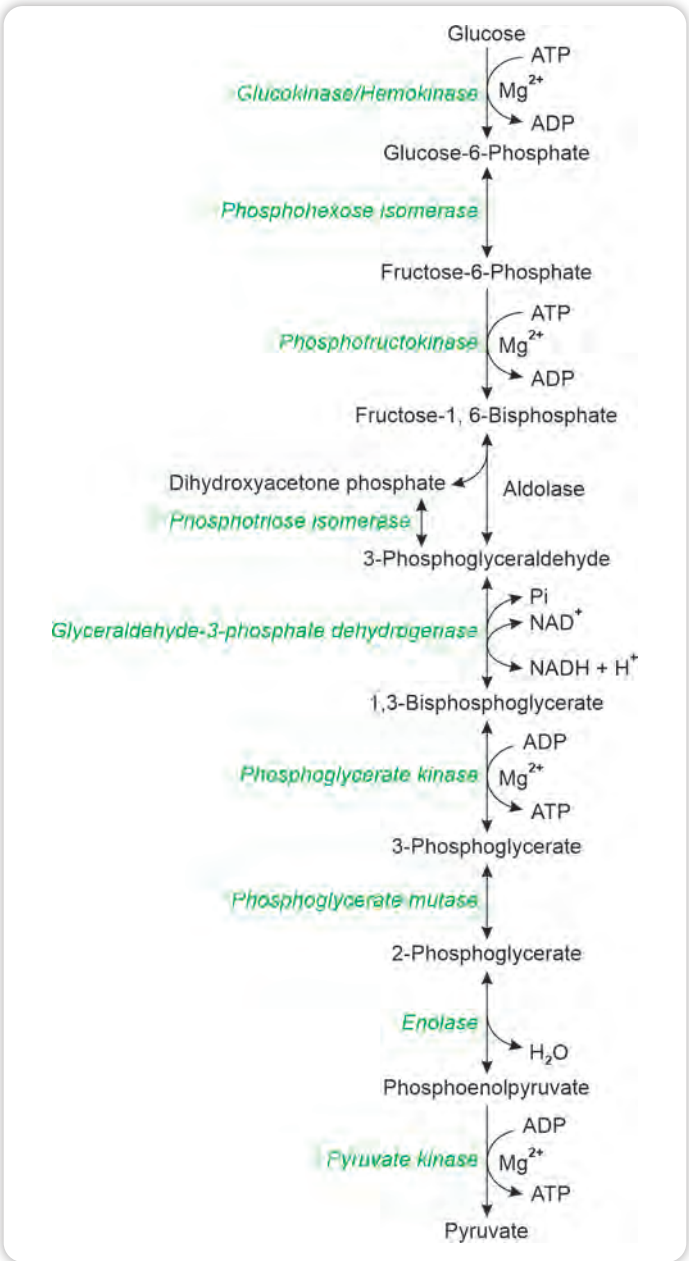


Fig. 10.2: Outline of glycolysis

1. **Glucose is** first **converted to glucose-6-phosphate**. This reaction is catalyzed by the enzyme hexokinase, which requires ATP and Mg. Hexokinase is present in all the tissues.
   In the fed state, this reaction is **catalyzed by** another enzyme, called **glucokinase**. This enzyme is found in the liver, where it is induced by high glucose concentration, found after meals. It has low affinity (high KM or Michaelis constant, an inverse measure for enzyme's affinity) for glucose and its function is to remove excess of glucose from blood, in the fed state.
2. In the next reaction, **glucose-6-phosphate is isomerized**, in a freely reversible reaction, **to fructose-6-phosphate**, by the enzyme phosphohexose isomerase.
3. **Fructose-6-phosphate is** then **phosphorylated** by an allosteric enzyme phosphofructokinase **to** form **fructose-1,6-bisphosphate**.
   This is an irreversible reaction and requires ATP. ATP acts as a co-substrate as well as allosteric inhibitor of the enzyme.
4. Thereafter, **fructose-1,6-bisphosphate** (a hexose) **is cleaved** by aldolase **to 3-phosphoglyceraldehyde** (**glyceraldehyde-3-phosphate**) and **dihydroxy-acetone phosphate**, two trioses.
5. Subsequently, since only 3-phosphoglyceraldehyde enters the pathway, hence, **dihydroxyacetone phosphate** also gets **converted to 3-phosphoglyceraldehyde**. This reaction is catalyzed by the enzyme phosphotriose isomerase.
   Glycerol can also enter glycolytic pathway at this point.
6. In the next step, in presence of NAD^+ and inorganic phosphate (Pi), glyceraldehyde-3-phosphate dehydrogenase oxidizes **3-phosphoglyceraldehyde to 1,3-bisphosphoglycerate**.
7. In the next step, **1,3-bisphosphoglycerate is converted to 3-phosphoglycerate**. This reaction is catalyzed by the enzyme phosphoglycerate kinase.
   In this reaction, there is a generation of ATP. It is called substrate level production of ATP (i.e., **substrate level phosphorylation**).
   In RBCs, this conversion occurs via formation of 2,3-BPG, where no formation of ATP occurs in this step.
   Arsenate inhibits phosphorylation at this step and, thus, ATP production.
8. Thereafter, **3-phosphoglycerate is converted to 2-phosphoglycerate** by the enzyme phosphoglycerate mutase.
9. In the next step, enolase converts **2-phosphoglycerate** to a high-energy compound, called **phosphoenolpyruvate**.
   Enolase requires Mg^{2+} for its activity, but **is inhibited by fluoride**.
   Since fluoride inhibits this reaction, therefore, **fluoride is added to the blood**, **as a preservative**, **in glucose estimation.**
10. Subsequently, **phosphoenolpyruvate is converted to pyruvate**, irreversibly. This reaction is catalyzed by the enzyme pyruvate kinase, which, in turn, phosphorylates ADP to ATP.
    Deficiency of pyruvate kinase leads to hemolytic anemia.

CONCEPT TO CLINIC

Pyruvate Kinase Deficiency

It results in reduced glycolytic activity, reduced ATP synthesis in RBC, failure to maintain membrane integrity and functions, leading to hemolysis. There is an accumulation of 2,3-BPG which partially compensates for the anemia, however, it also inhibits hexokinase and phosphofructokinase thereby further reducing the rate of glycolysis.

11. **Pyruvic acid is reduced to lactic acid** under anaerobic conditions or is oxidized to **acetyl CoA** under aerobic conditions:
    - **Under anaerobic conditions**, pyruvate is reduced to lactate. This reaction is catalyzed by the enzyme lactate dehydrogenase, which requires NADH.
      Tissues such as skeletal muscle, when function under hypoxic conditions, produce large amount of lactic acid (Fig. 10.3).

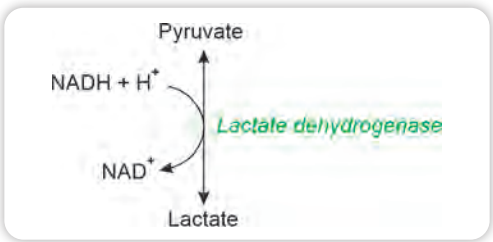


Fig. 10.3: Fate of pyruvate under anaerobic glycolysis

    - **Under aerobic conditions**, pyruvate is transported into mitochondria, where it is oxidatively decarboxylated to acetyl CoA by the enzyme pyruvate dehydrogenase complex (Fig. 10.4).

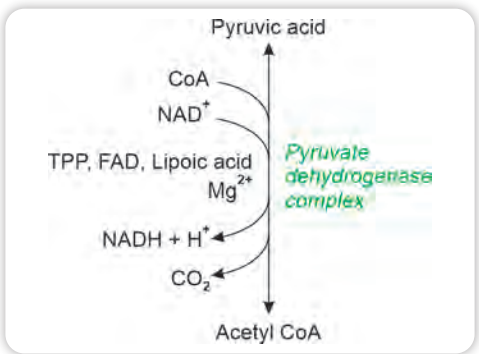


Fig. 10.4: Conversion of pyruvic acid to acetyl CoA

Pyruvate dehydrogenase complex requires five coenzymes, i.e., TPP, CoA, NAD, FAD and lipoic acid. Insulin stimulates its activity, whereas acetyl CoA, NADH and increased ATP/ADP ratio inhibit it.

CONCEPT TO CLINIC

Lactic Acidosis

Elevated concentration of lactate in the blood is termed lactic acidosis or lactacidosis. It occurs when there is reduced supply of oxygen to the tissues (hypoxia) such as in myocardial infarction, pulmonary embolism and hypovolemic shock. Hypoxia results in inadequate oxidative phosphorylation and decreased ATP synthesis, because oxygen is the terminal electron acceptor in the mitochondrial electron transport chain. To survive, cells rely on anaerobic glycolysis for generating ATP and thus produce lactic acid as the end product. The excess oxygen required to recover from a period of hypoxia is termed '**oxygen debt**'. It is related to the patient's morbidity or mortality. To assess the presence and severity of shock, measuring the blood levels of lactic acid helps in the rapid and early detection of oxygen debt.

Energy Production in Glycolysis

Number of ATP produced during glycolysis vary, depending upon the condition.

- **Under anaerobic conditions**, conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate and phosphoenolpyruvate to pyruvate, each produces one ATP, thus, a total of 2 ATP are produced per molecule of a triose, or **4 molecules of ATP per molecule of glucose** (Fig. 10.5).

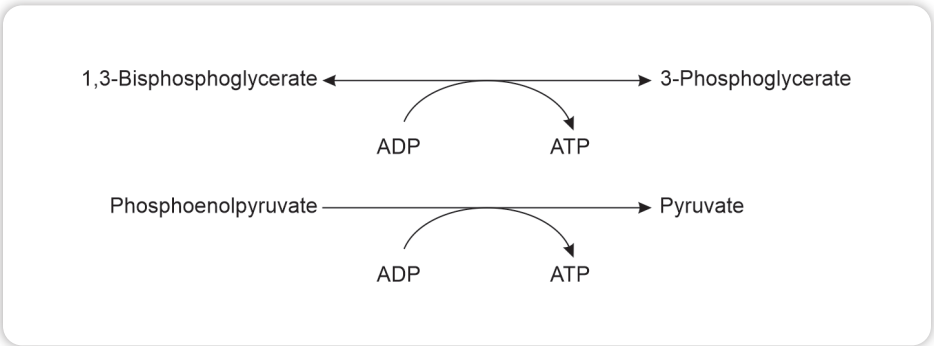


Fig. 10.5: ATP producing steps in anaerobic glycolysis

As 2 ATP are used in the initial two reactions of the process, i.e., in the conversion of glucose to glucose-6-phosphate and fructose-6-phosphate to fructose-1,6-bisphosphate, the **net energy yield per molecule of glucose is only 2 ATP**.

- **Under aerobic conditions**, NADH, which is produced during the conversion of 3-phosphoglycerate to 1,3-bisphosphoglycerate, enters the electron transport chain and releases 3 ATP, thus, additionally, 6 more ATP are produced per molecule of glucose. Therefore, a total yield under aerobic conditions is 10 ATP while the **net yield is 8 ATP**.

Physio CORNER

The reason why we stress on doing the large muscle group exercises slowly, and therefore, aerobically is that, on doing exercises too rapidly, one may end up feeling tired, with a buildup of anaerobic products, and less energy. One easy way to keep a check- if you can continue to talk or count aloud without getting breathless, then the exercise still is aerobic.

Regulation of Glycolysis

There are three irreversible steps which are catalyzed by hexokinase, phosphofructokinase and pyruvate kinase. These are also the sites of the regulation of glycolysis.

Insulin stimulates these enzymes and increases **utilization of glucose by glycolysis**. On the other hand, **glucagon inhibits** this process.

HEXOSE MONOPHOSPHATE SHUNT

Hexose monophosphate shunt (HMP shunt) or pentose phosphate pathway (PPP) is the second major pathway for the metabolism of glucose. Enzymes for this pathway are localized in the cytosol and the reducing equivalents are accepted by $NADP^+$ instead of NAD^+. This pathway is operative in many tissues, such as liver, erythrocytes, lactating mammary glands, testes and the adipose tissue. The rate of HMP shunt reactions is increased by insulin.

The Overall Process of HMP Shunt

Six molecules of hexoses (glucose) are utilized to give six molecules of CO_2 and six molecules of pentoses. These pentoses are rearranged to give four molecules of fructose-6-phosphate which also forms a molecule of glyceraldehyde-3-phosphate which also forms a molecule of hexose by the reversal of glycolysis, thus regenerating five molecules of hexoses (Fig. 10.6).

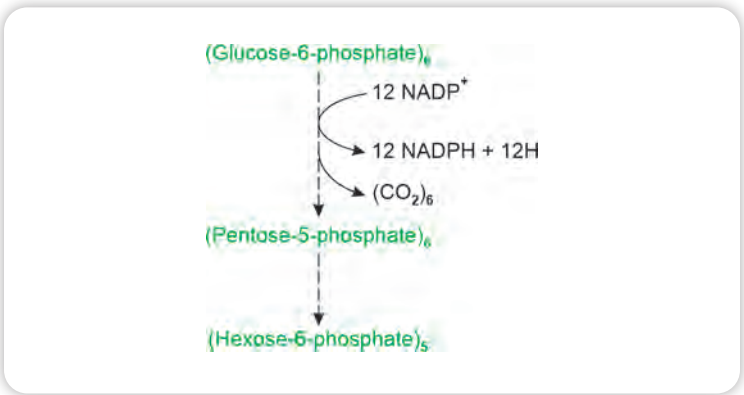


Fig. 10.6: HMP shunt— an overview

CITRIC ACID CYCLE

Citric acid cycle, also called **tricarboxylic acid cycle (TCA cycle)** or **Krebs cycle**, is a **process of the oxidation of acetyl CoA** (active acetate, produced under aerobic glycolysis) **to CO_2 and H_2O**.

During the course of the oxidation of acetyl CoA, reducing equivalents are produced, which enter respiratory chain and generate large amount of ATP.

Reactions of the TCA cycle are outlined in Figure 10.7.

1. In the first step, **acetyl CoA** (formed from pyruvate under aerobic condition) **combines with oxaloacetate** and **forms citric acid** (a tricarboxylic acid).
   This reaction is catalyzed by the enzyme citrate synthase, also called the condensing enzyme.
2. **Citrate is** then rearranged to cis-aconitate, which is subsequently **changed to isocitrate**. Both of these steps are catalyzed by aconitase.
   Conversion of citrate to isocitrate by **aconitase is inhibited by fluoroacetate**.
3. In the next step, in the presence of isocitrate dehydrogenase, **isocitrate is converted to oxalosuccinate**, which is subsequently **decarboxylated to α-ketoglutarate**.
4. Thereafter, **α-ketoglutarate** undergoes oxidative decarboxylation and gets **converted to succinyl CoA** by the enzyme α-ketoglutarate dehydrogenase complex. α-Ketoglutarate dehydrogenase complex requires five coenzymes, i.e., TPP, NAD^+, FAD, coenzyme A and lipoic acid.
   This reaction is **similar to the conversion of pyruvate to acetyl CoA** by pyruvate dehydrogenase complex, which also requires TPP, NAD^+, FAD, coenzyme A and lipoic acid.
5. In the next step, **succinyl CoA is converted to succinate**, by the enzyme succinate thiokinase.
   During this reaction, **a molecule of GTP is formed**.
   This is known as **substrate level phosphorylation**, as a high-energy molecule is formed at the substrate level.

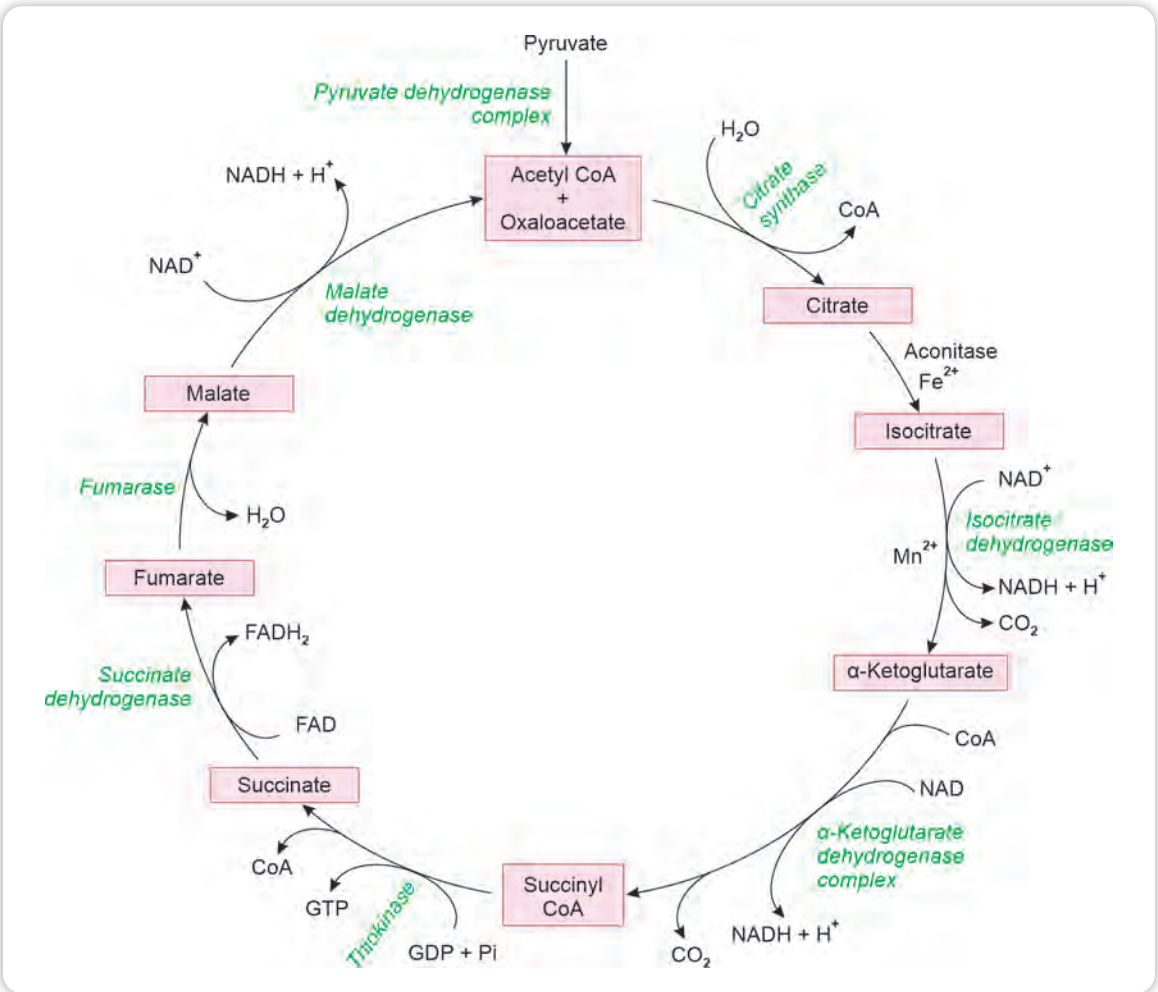


Fig. 10.7: Outline of citric acid cycle

6. Thereafter, **succinate is converted to fumarate**, by the enzyme succinate dehydrogenase.
   Due to structural similarities between malonate and succinate, **malonate inhibits succinate dehydrogenase, competitively**.
7. In the next step, with the addition of a molecule of water, by the enzyme fumarase (fumarate hydratase), **fumarate is converted to L-malate**.
8. Finally, **malate dehydrogenase**, in the presence of NAD^+, **converts malate to oxaloacetate**.

CONCEPT TO CLINIC

Arsenic Poisoning

Both pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex require lipoic acid as a coenzyme. Arsenite forms a stable complex with the enzyme-bound lipoic acid and brings respiration to a halt. In arsenic poisoning, arsenic content in the hair is greatly increased which is an important observation in forensic science.

Energy Production in Citric Acid Cycle

As a result of the oxidation of one molecule of acetyl CoA in the Krebs cycle, three molecules of NAD^+ and one molecule of FAD are reduced.

As discussed in Chapter 7, reducing equivalents (from NADH + H^+) enter respiratory chain and result in the production of three molecules of ATP. Similarly, $FADH_2$ yields 2 ATP. Besides, there is also a substrate level production of GTP.

Thus, total ATP yield, per molecule of acetyl CoA, is 12 ATP (Table 10.1).

TABLE 10.1: Energy producing steps in citric acid cycle

Reaction	Reducing equivalents produced as	Number of ATP produced
Isocitrate → α-Ketoglutarate	NADH + H^+	3
α-Ketoglutarate → Succinyl CoA	NADH + H^+	3
Succinyl CoA → Succinate	—	1
Succinate → Fumarate	$FADH_2$	2
Malate → Oxaloacetate	NADH + H^+	3
	Total	**12**

As mentioned above, conversion of pyruvate to acetyl CoA also generates NADH+ H^+ and gives 3 ATP. Thus, total number of ATP produced from the oxidation of pyruvate is 15. Since 2 molecules of pyruvate are formed from one molecule of glucose, therefore, in addition to energy yield during aerobic glycolysis, (8 ATP) a molecule of glucose also produces 30 ATP via the Krebs cycle.

Regulation of Citric Acid Cycle

Citric acid cycle is regulated by the availability of acetyl CoA, oxaloacetate and NADH. Citrate synthase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase are the rate limiting enzymes of the cycle.

MUST KNOW

A total of 38 molecules of ATP are obtained when a molecule of glucose is completely oxidized to CO_2 and H_2O under aerobic conditions, i.e., via glycolysis and Krebs cycle.

Significance of the Citric Acid Cycle

Citric acid cycle has a dual role, i.e., it is important in oxidation as well as synthetic processes. It is, thus, amphibolic in nature.

- It is **catabolic for the oxidation of carbohydrates, lipids and proteins**, as they are completely oxidized to CO_2 and H_2O, and release energy.
- It is also important in the **anabolic reactions**, as various intermediates of the cycle can be used for the **biosynthesis of the nonessential amino acids**.
- Various intermediates of the cycle are also potentially glucogenic and, thus, can give rise to glucose in liver and kidney.

GLYCOGEN METABOLISM

Glycogen is the major form of carbohydrate present in the body. It corresponds to starch in plants, but is comparatively more branched. It is stored in the body mainly in the liver and the muscle. The process of

glycogen synthesis is called **glucogenesis**, while the process of **glycogen breakdown** is referred to as **glycogenolysis**.

Glycogenesis

Glycogenesis (**glycogen synthesis**) is the process of the **conversion of glucose to glycogen**. Although, it is operative in several tissues, liver and muscle are the main organs for the synthesis of glycogen. It is stimulated by insulin.

Various reactions of glycogenesis are outlined in Figure 10.8.

1. **Glucose is** first activated (phosphorylated) and **converted to glucose-6-phosphate**.
   In the liver, glucokinase converts most of the **glucose into glucose-6-phosphate**, **in the fed state**. This is an inducible enzyme and has greater specificity for its substrate.
   In the muscle and other tissues, this reaction is **catalyzed by hexokinase**.

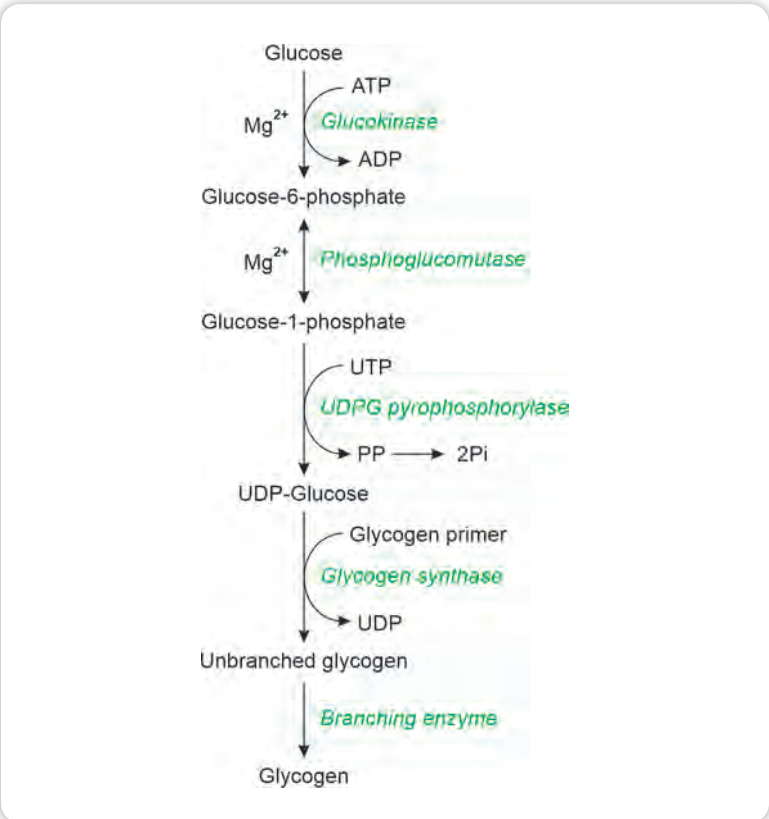


Fig. 10.8: Outline of glycogenesis

2. **Glucose-6-phosphate is isomerized to glucose-1-phosphate**, by the enzyme phosphoglucomutase.
3. **Glucose-1-phosphate** reacts with UTP and gets **converted to uridinediphosphate glucose** (**UDP-Glu** or **UDPG**). This reaction is catalyzed by UDPG pyrophosphorylase (glucose-1-phosphate uridyltransferase). **Pyrophosphate**, so released during this process, is immediately **hydrolyzed to two molecules of inorganic phosphate**, by pyrophosphatase.

4. From UDP-Glu, **glucose is transferred to the glycogen primer** (i.e., the preformed oligosaccharide), by the enzyme glycogen synthase.
   The incoming glucose is linked to the primer at the non-reducing end by 1,4-α-glycosidic linkage and results in elongation of the pre-existing branch. This results in the **formation of an unbranched glycogen**.
   Both, glycogen primer and UDP-Glu are the substrates for glycogen synthase, which is a key enzyme of glycogenesis.
5. Once the straight chain containing nearly 11-glucose residues is formed, the branching enzyme removes a block of 7-8 glycosyl-residues from the growing chain, and transfers it to the neighboring chain (Fig. 10.9).
   This branch point again grows with the addition of more glucose molecules at the 1→4 linkage. This, in turn, results in the formation of a highly branched glycogen structure.

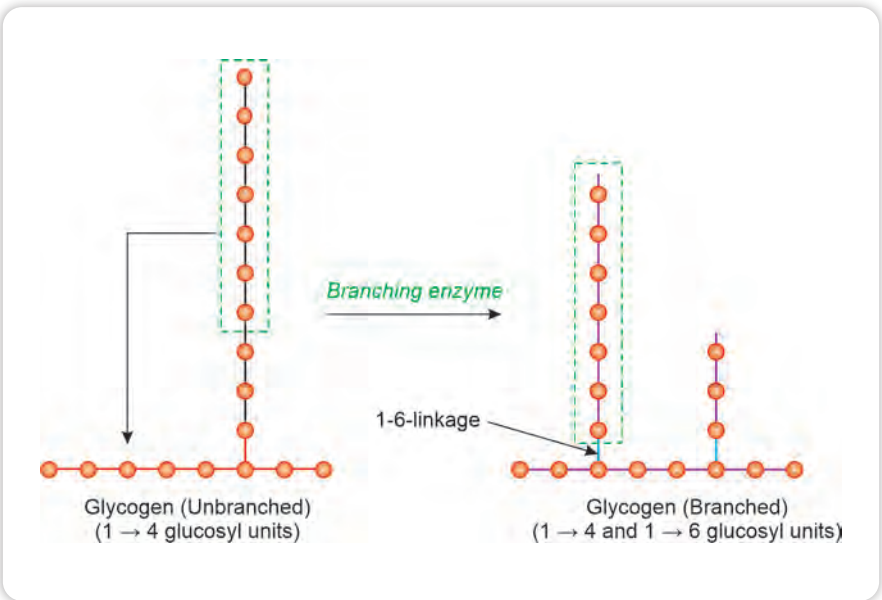


Fig. 10.9: Formation of a branch point by the branching enzyme during glycogenesis

Glycogenolysis

Glycogenolysis (**glycogen breakdown**) is the process of the **conversion of glycogen to either glucose-6-phosphate in muscle or free glucose in the liver** and the kidney (Fig. 10.10).

1. In the first step, **glucose molecules are** sequentially **removed, from** the **glycogen, as glucose-1-phosphate**.
   This reaction is catalyzed by the enzyme phosphorylase.
   It is the rate limiting step of this pathway.
   Phosphorylase hydrolyzes the α-1,4-glycosidic bond and **removes glucose** units **as glucose-1- phosphate**, until nearly four glucose residues are left.
   After the action of phosphorylase, **glycogen is partially hydrolyzed, leaving limit dextrin**.

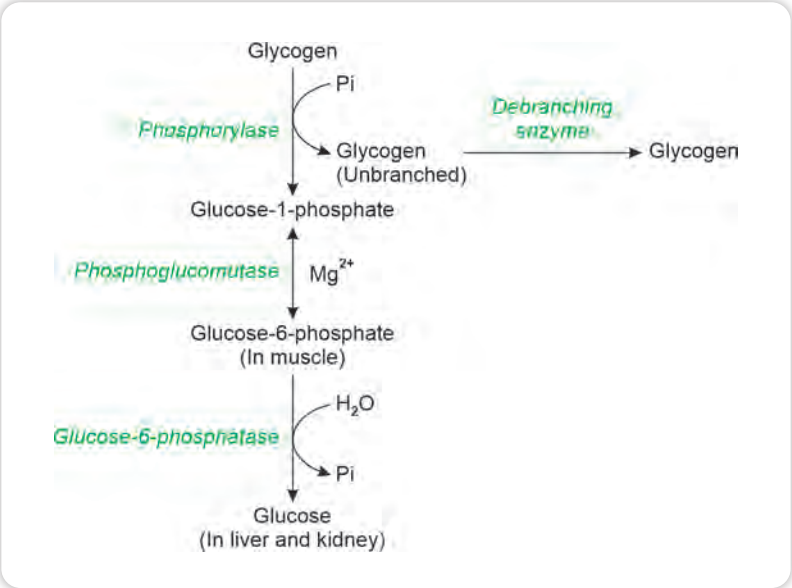


Fig. 10.10: Outline of glycogenolysis

2. **Limit dextrin is further hydrolyzed** by the debranching enzyme **to glucose-1-phosphate** and **free glucose**.
   Debranching enzyme is a **bifunctional enzyme**. Its first unit has **glycosyltransferase** activity, which **removes a strand of three glucosyl residues** from the four glucosyl-residues of the branch and **attaches the same to the nonreducing end of another branch**. This reaction forms a new α(1→4) linkage and, thus, three more glucose units become available for the phosphorylase reaction (Fig. 10.11).

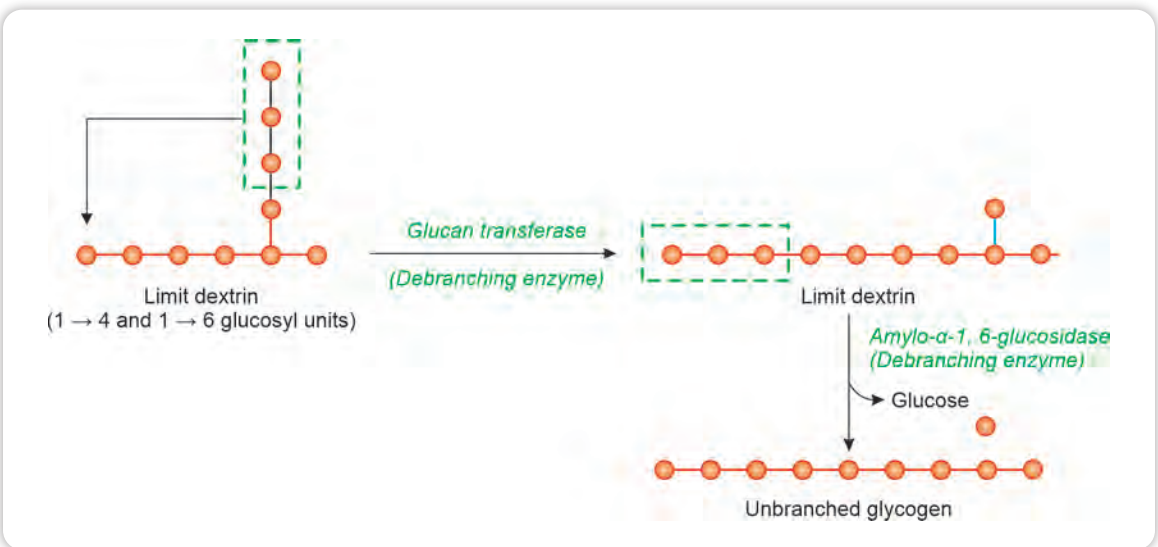


Fig. 10.11: Removal of a branch point by the debranching enzyme during glycogenolysis

The **α(1→6) bond**, which is linking **the remaining glucosyl residue on the branch point** to the main chain, **is hydrolyzed by** the second unit of the debranching enzyme that is referred to as **amylo-α-1,6-glucosidase**. This glucosyl residue is **released as free glucose**, rather than as glucose-1-phosphate, leaving the unbranched glycogen molecule.

Cooperative and repetitive actions of phosphorylase and debranching enzyme result in complete hydrolysis of glycogen.

3. **Glucose-1-phosphate**, produced as a result of the action of phosphorylase, **is converted to glucose-6-phosphate** by the enzyme phosphoglucomutase.

   Glucose-6-phosphate is the **end product** of glycogen breakdown **in the muscle**, where it is used in the glycolytic pathway to liberate energy, that is required during exercise. Thus, glycogenolysis is followed by glycolysis, due to the absence of the enzyme glucose-6-phosphatase in the muscle.
4. **In the liver and kidney**, **glucose-6-phosphate is** further **hydrolyzed to glucose**. This reaction is catalyzed by glucose-6-phosphatase.

MUST KNOW

Significance of Glycogen Metabolism

Glycogen which is stored in the liver, is converted to free glucose and is used to maintain blood glucose level in a hypoglycemic state. On the other hand, in the muscle, glycogen is used for providing energy during exercise.

Regulation of Glycogen Metabolism

Glycogen metabolism in the liver is controlled by glucagon while in the muscle and other tissues, it is controlled by insulin and norepinephrine/epinephrine.

Glycogenesis is regulated by glycogen synthase, whereas **glycogenolysis is regulated by glycogen phosphorylase**. Both the enzymes are under allosteric control and are regulated by the availability of ATP and glucose-6-phosphate, reversibly.

Metabolic Disorders of Glycogen Metabolism

This is a group of inherited disorders that are associated with glycogen metabolism, where an abnormal type or quantity of the glycogen is deposited in different tissues. According to the deficiency of the enzyme involved, there are several types of glycogen storage diseases (Table 10.2).

GLUCONEOGENESIS

Gluconeogenesis **(neoglucogenesis)** is the process of the **formation of glucose from various non-carbohydrate sources**, such as the glucogenic amino acids, lactate, glycerol, or propionate.

- Gluconeogenesis takes place **in the fasting state** or on a **low carbohydrate diet**, particularly, in the liver and some other tissues, which are solely dependent on glucose for their energy demand. It does not take place in muscle.
- Gluconeogenesis, thus, enables **maintenance of blood glucose** when all the dietary glucose has been absorbed and oxidized. This process is essential since blood glucose level has to be maintained, to support metabolism of the tissues that use glucose as the primary substrate such as the brain, red blood cells and lens.
- Gluconeogenesis is said to be the reversal of glycolysis but, truly, it is not a reversal of glycolysis, since there are **three irreversible reactions** in the glycolytic pathway (Fig. 10.12).

TABLE 10.2: Glycogen storage diseases

Type	Glycogen storage disease	Deficient enzyme	Features
I	von Gierke disease	Glucose-6-phosphatase	Liver, renal and intestinal epithelial cells are loaded with glycogen. There also occurs hypoglycemia, lactic acidosis, ketosis, hyperlipemia, and hyperuricemia
II	Pompe's disease	Lysosomal acid maltase	Accumulation of glycogen in the lysosomes. It is fatal and may result in heart failure
III	Limit dextrinosis/Forbes disease or Cori disease	Debranching enzyme	Accumulation of the branched polysaccharide in liver, muscle, heart and leukocytes.
IV	Amylopectinosis or Andersen disease	Branching enzyme	Accumulation of the polysaccharide having few branch points. Death may occur due to liver or cardiac failure within first year of life.
V	McArdle's syndrome	Muscle phosphorylase	Muscle has abnormally high glycogen content. There is diminished exercise tolerance with little or no lactate in blood after exercise
VI	Her's disease	Liver phosphorylase	High glycogen content in liver. There is also a tendency toward hypoglycemia
VII	Tarui disease	Phosphofructokinase	As in type V, but there is also a possibility of hemolytic anemia
VIII	—	Liver phosphorylase kinase	As in type VI

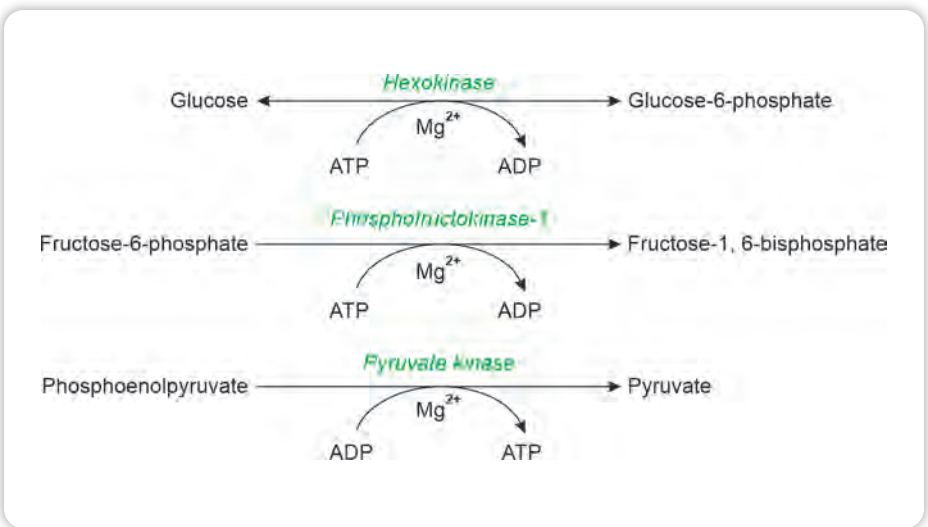


Fig. 10.12: Irreversible steps in glycolysis

Outline of Gluconeogenesis

A. Reversal of the Irreversible Reactions in Glycolysis

It includes the following set of reactions:

- **Conversion of pyruvate to phosphoenolpyruvate:**
  - In the reversal of the pyruvate to phosphoenol-pyruvate, **pyruvate is** first **converted to oxaloacetate** by the enzyme pyruvate carboxylase, in the mitochondria (Fig. 10.13).
  - Thereafter, malate dehydrogenase converts **oxaloacetate to malate**, which is freely transported across the mitochondrial membrane. Malate, thus, comes out from the mitochondria to the cytosol, where it is reconverted back to oxaloacetate by the same enzyme. This also reduces NAD^+ to NADH + H^+. This enzyme, thus, not only transports oxaloacetate (via malate) but also reduces equivalents from mitochondria into cytosol.
    Reactions of gluconeogenesis, thus, occur both in the cytosol as well as mitochondria.
  - In the next step, **oxaloacetate is converted to phosphoenolpyruvate**, by the enzyme phosphoenolpyruvate carboxykinase (PEP-carboxykinase; Fig. 10.14).

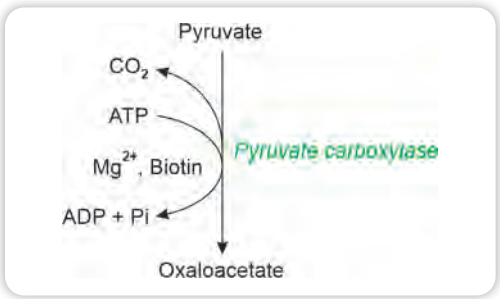


Fig. 10.13: Conversion of pyruvate to oxaloacetate

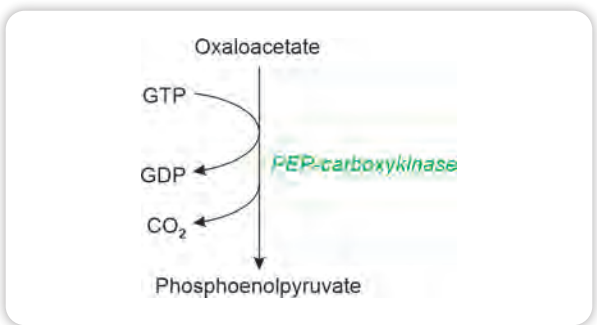


Fig. 10.14: Conversion of oxaloacetate to phosphoenolpyruvate

- **Conversion of fructose-1,6-bisphosphate to fructose-6-phosphate: Fructose-1,6-bisphosphate is converted to fructose-6-phosphate** by the enzyme fructose-1,6-bisphosphatase (Fig. 10.15).

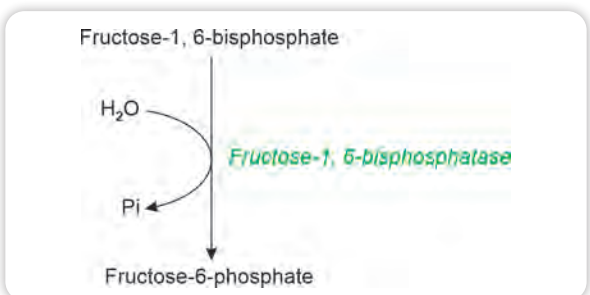


Fig. 10.15: Conversion of fructose-1,6-bis-phosphate to fructose-6-phosphate

- **Conversion of glucose-6-phosphate to glucose: Glucose-6-phosphate is converted to glucose** by the enzyme glucose-6-phosphatase. This **enzyme is not found in the muscle and adipose tissue** (Fig. 10.16).

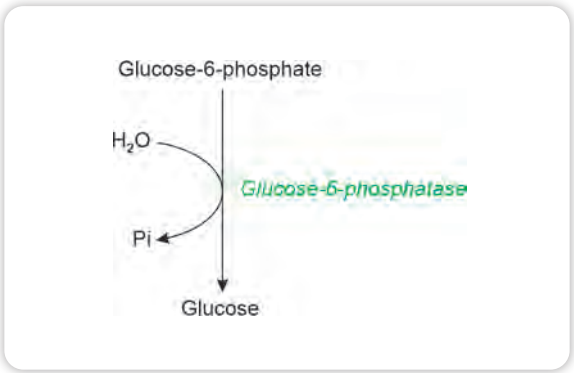


Fig. 10.16: Conversion of glucose-6-phosphate to glucose

B. Conversion of Lactate to Glucose

Lactate is produced during the process of anaerobic glycolysis. For its conversion to glucose, firstly, **lactate is oxidized to pyruvate**. This reaction is catalyzed by the enzyme lactate dehydrogenase, which requires NAD^+ (Fig. 10.17).

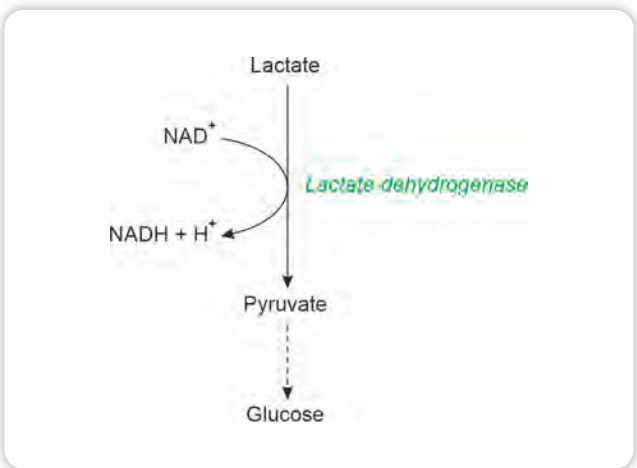


Fig. 10.17: Conversion of lactate to glucose

Subsequently, **pyruvate is converted to glucose by the reversal of the glycolytic reactions**, as discussed above.

C. Conversion of Glucogenic Amino Acids to Glucose

Various glucogenic amino acids transfer their α-amino group by transamination and release carbon skeletons, which form intermediates of the citric acid cycle (Table 10.3).

TABLE 10.3: Formation of some of the citric acid cycle intermediates from various glucogenic amino acids

Amino acid	Citric acid cycle intermediate formed
Gly, Ala, Ser, Thr, Cys, Trp and HO-Pro	Pyruvate
Arg, His, Glu, Gln and Pro	α-Ketoglutarate
Phe and Tyr	Fumarate
Val, Ile and Met	Succinyl CoA

These citric acid cycle intermediates, in turn, form glucose by the reversal of the glycolytic reactions, via pyruvate.

D. Conversion of Glycerol to Glucose

Glycerol is produced as a result of lipolysis in the adipose tissue. Glycerol kinase converts it to α-glycerol-phosphate in the liver, which is later reduced by a dehydrogenase to dihydroxyacetone phosphate and enters glycolysis at this point (Fig. 10.18).

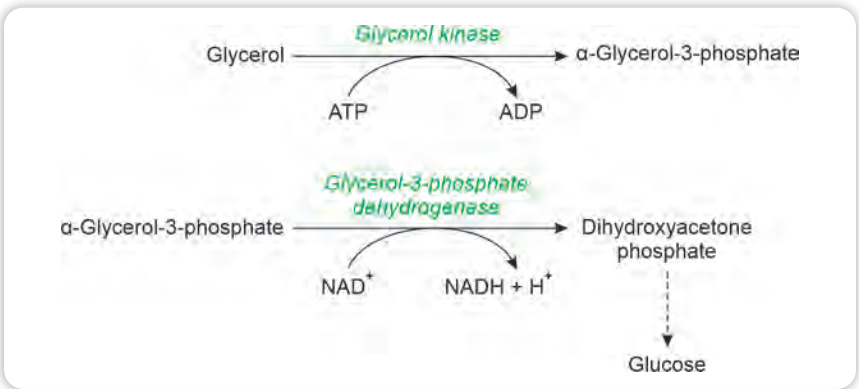


Fig. 10.18: Conversion of glycerol to glucose

E. Conversion of Propionyl CoA to Glucose

Oxidation of fatty acids containing odd number of carbon atoms, in addition to acetyl CoA, also produces a molecule of propionyl CoA, particularly, in ruminants. **In human beings, propionyl CoA is obtained from branched chain amino acids** (Ile, Val and Thr).

- Firstly, **propionyl CoA is converted to D-methylmalonyl CoA** by propionyl CoA carboxylase.
- **D-Methylmalonyl CoA is then converted to L-methylmalonyl CoA** and, **finally**, by an isomerase **to succinyl CoA**, which is an intermediate of the citric acid cycle.
- Succinyl CoA, in turn, is converted to glucose via pyruvate (Fig. 10.19).

MUST KNOW

Significance of Gluconeogenesis

Gluconeogenesis occurs in the fasting state, or on a low carbohydrate diet, in the liver and other tissues, which are solely dependent on glucose for their energy demand. Thus, it enables the maintenance of blood glucose, when it is in short supply.

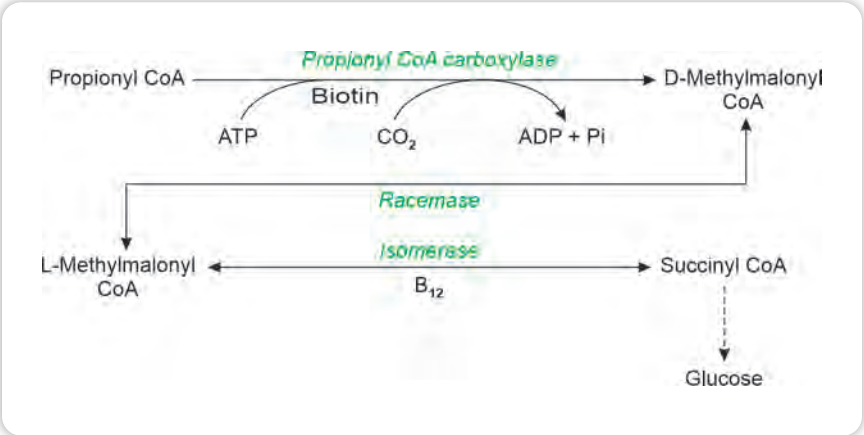


Fig. 10.19: Conversion of propionyl CoA to glucose

Regulation of Gluconeogenesis

Gluconeogenesis is regulated by pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase, which catalyze reversal of the irreversible steps of glycolysis.

CORI CYCLE

The end product of glycogen breakdown in the muscle is glucose-6-phosphate, and not free glucose, due to the absence of glucose-6-phosphatase. Glucose-6-phosphate so produced is used for energy production, particularly, during exercise (anaerobic glycolysis) and results in the production of lactic acid. Lactic acid is transported to the liver and reforms glucose by the process of gluconeogenesis. Glucose via circulation again becomes available for its oxidation in the muscle and other tissues. This is called lactic acid cycle or Cori cycle. It results in the net exchange of glycogen (via glucose-6-phosphate) and lactic acid in the two tissues, i.e., muscle and the liver (Fig. 10.20).

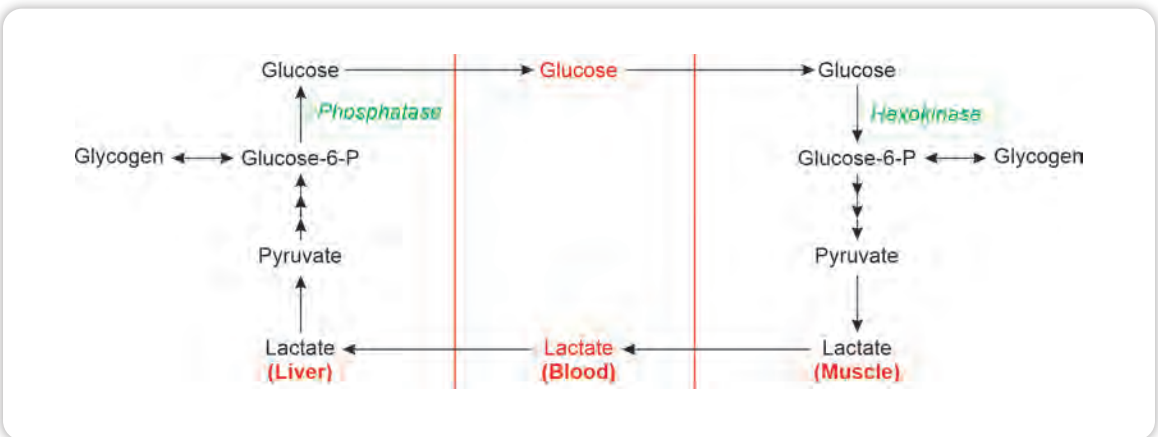


Fig. 10.20: Glucose-lactate cycle (Cori cycle)

Hormonal Regulation of Blood Glucose

Blood glucose level is maintained within the normal physiological range of 60–90 mg/100 mL in the fasting (post-absorptive) state by various hormones, e.g., insulin lowers blood glucose while various other hormones increase blood glucose level (Fig. 10.21).

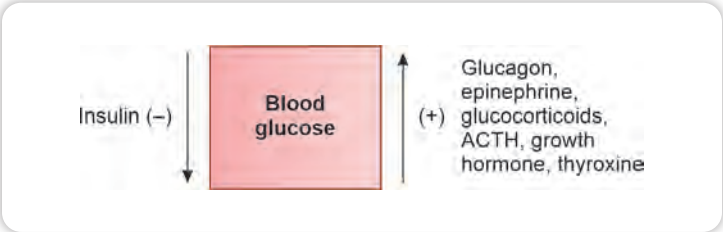


Fig. 10.21: Regulation of blood glucose by hormones

By Insulin

Insulin is the only hormone which **has hypoglycemic action**. It is released into the blood stream under the direct influence of hyperglycemia. It is a polypeptide containing 2 chains and is produced by the β-cells of the islets of Langerhans of the pancreas.

- Insulin lowers blood glucose concentration by increasing uptake of glucose by the extrahepatic tissues.
- It also promotes glycolysis and glycogenesis, both in the liver and the muscle.
- Insulin also suppresses glycogenolysis in the liver and the kidney.
- It also suppresses gluconeogenesis.
- Insulin also promotes transport of amino acids across the cell membrane and, thus, stimulates protein synthesis.
- It also inhibits ketogenesis and promotes lipogenesis.

By Hormones which have Hyperglycemic Action

Several hormones have hyperglycemic action. These are called **diabetogenic hormones** and include **glucagon, epinephrine, glucocorticoids, growth hormone** and **thyroxine**.

Note: This does hint at a potential link between stress, release of sympathetic and steroidal hormones, and diabetes. So that speaks for the link of diabetes with a stressful lifestyle.

- **Glucagon:** Glucagon is produced by the α-cells of the islets of Langerhans of the pancreas. Its synthesis is stimulated under the influence of hypoglycemia. It acts only in the liver and promotes glycogenolysis. It also promotes gluconeogenesis from amino acids and lactate.
- **Epinephrine:** Epinephrine, also called adrenaline, is secreted by the adrenal medulla. It is a hormone in the first line of defense against hypoglycemia. It is a derivative of tyrosine. Epinephrine promotes glycogenolysis, both in the liver and muscle. Epinephrine also promotes gluconeogenesis in the liver. It also inhibits release of insulin from the pancreas, and decreases transport and utilization of glucose in different tissues. At the same time, epinephrine also stimulates secretion of glucagon.
- **Glucocorticoids:** Glucocorticoids are steroids secreted by the adrenal cortex. They are antagonist to insulin. Cortisol is a major glucocorticoid present in the blood. It stimulates protein catabolism in the muscle and promotes gluconeogenesis in the liver. It also stimulates lipolysis and inhibits glucose oxidation

by the liver. Cortisol also facilitates the action of other hyperglycemic hormones (permissive effects), such as glucagon, epinephrine, and growth hormone, which further inhibit uptake and utilization of glucose by the peripheral tissues.

- **Growth hormone:** Anterior pituitary secretes growth hormone. Its secretion is stimulated under the influence of hypoglycemia. Prolonged administration of the growth hormone stimulates secretion of insulin. As a result of increased insulin secretion, β-cells are exhausted producing diabetes like situation. Growth hormone also decreases glucose uptake and utilization by the muscle. It also promotes lipolysis in the adipose tissue.
- **Thyroxine:** Thyroxine is secreted by the thyroid gland. It stimulates the intestinal absorption of glucose and promotes glycogenolysis as well as gluconeogenesis in the liver. Hyperthyroidism is, generally, associated with hyperglycemia and mild diabetes.

DISORDERS OF CARBOHYDRATE METABOLISM

Renal Glycosuria

Renal glycosuria, also referred to as renal diabetes, results from an inherited defect in the proximal tubular Na^+-glucose cotransport, due to mutated SGLT2 (the membrane protein responsible for majority of tubular glucose reabsorption). It is characterized by osmotic diuresis and glucosuria despite of normal blood glucose levels. It is a benign condition not warranting any treatment.

Diabetes Mellitus

Diabetes mellitus is a major disorder of carbohydrate metabolism. It is characterized by persistent hyperglycemia with or without glycosuria (glucosuria). This is the most common endocrine disease caused by the deficiency in secretion or action of insulin. Besides insulin, several diabetogenic hormones influence metabolism of glucose.

Diabetes mellitus is defined as a state of chronic hyperglycemia, which may be a result of genetic and/or environmental factors. It is a multifactorial disease. There are two major clinical classes of diabetes mellitus, which are referred to as insulin dependent diabetes mellitus (IDDM) and noninsulin dependent diabetes mellitus (NIDDM).

Insulin Dependent Diabetes Mellitus

Insulin dependent diabetes mellitus (IDDM) or **type I diabetes** is also called **juvenile-onset diabetes**, because it, usually, appears in the childhood or in younger age group (commonly less than 40 years of age). There is absolute deficiency of insulin, due to a gradual depletion of β-cells of the pancreas, which may get destroyed by an autoimmune process (Fig. 10.22).

- IDDM is characterized by **hyperglycemia, hyperlipoproteinemia** (raised chylomicron and VLDL) and **severe ketoacidosis**. This, in turn, suggests that besides defects in carbohydrate metabolism, there are abnormalities in fat and protein metabolism also in such patients.
- Hyperglycemia in IDDM is a result of **inability of the insulin-dependent tissues to take up glucose** as well as due to **accelerated hepatic gluconeogenesis** from amino acids (derived from muscle protein).
- **Increased lipolysis** (in the adipose tissue) and **accelerated fatty acid oxidation** (in the liver) result in ketoacidosis.

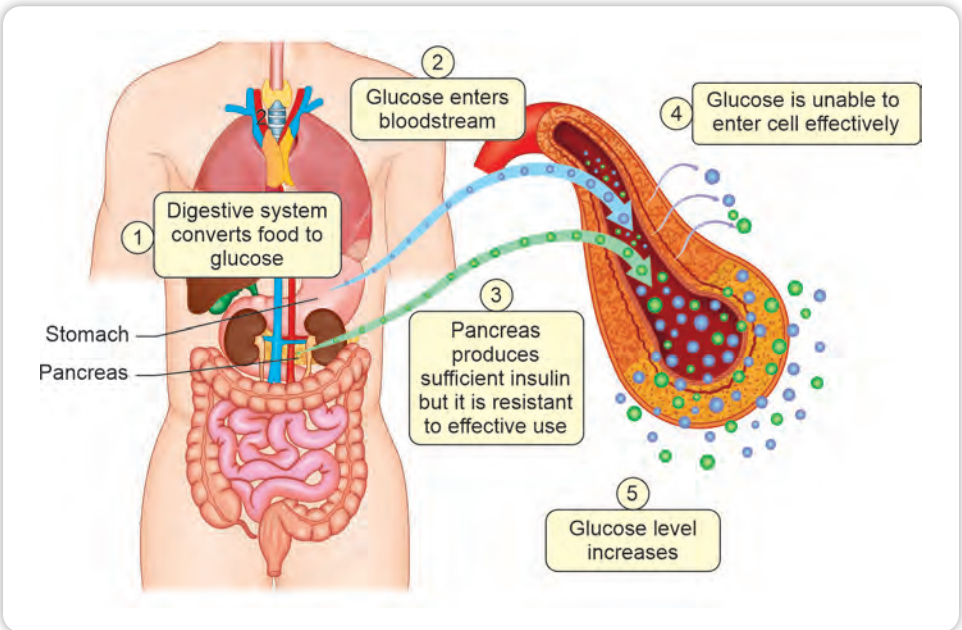


Fig. 10.22: Diabetes mellitus

- Insulin deficiency also **reduces lipoprotein lipase** activity, thereby resulting in hyperchylomicronemia.
- Patients with IDDM can, usually, be recognized by abrupt appearance of **polyuria** (frequent urination), **polydipsia** (excessive thirst) and **polyphagia** (excessive hunger), often triggered by the stress or some other illness. These symptoms are, usually, accompanied with **fatigue, weight loss and weakness**.
- Its diagnosis is confirmed by **high fasting blood glucose**, commonly accompanied with **ketoacidosis**. Insulin injection, though does not cure the disease but promotes glucose uptake by the tissues and inhibits gluconeogenesis, lipolysis and proteolysis.
- **Lifespan** of the patient **is reduced** as a result of the degenerative complications such as **kidney malfunction**, **nerve impairment** and **cardiovascular disease**.
- Hyperglycemia also leads to **blindness** through retinal degeneration and glycosylation of the lens proteins, which, in turn, causes cataract.
- The treatment of ketoacidosis is planned according to the specific pathophysiology of the diagnosis. Regardless of the specific etiology, it is important for a physical therapist to be aware of the condition.

CONCEPT TO CLINIC

Type 1 Diabetes Mellitus

Type 1 diabetes is one of the most intensively studied autoimmune disorders. Although most cases of type 1 diabetes are the consequence of an inappropriate autoimmune destruction of the pancreatic β-cells, an autoimmune-independent subtype of type 1 diabetes also occurs. Recommendations have been put forth to divide type 1 diabetes into **type 1A (immunemediated) and type 1B (other forms of diabetes with severe insulin deficiency)**. Type 1B appears to be a form of type 1 diabetes in which histological examination of pancreatic sections demonstrates inflammation (i.e. insulitis as in type 1A) but no anti-islet autoantibodies. Irrespective of the subtype, since the net result is the inability of the β-cells to secrete insulin, these patients must be treated with injections of insulin.

Noninsulin Dependent Diabetes Mellitus

Majority of the diabetic patients **(over 80%)** suffer from noninsulin dependent diabetes mellitus (NIDDM) or **type II diabetes**. It is also called **maturity-onset diabetes**, since it, usually, occurs in the middle age group (usually more than 40 years of age), in those who are, generally, **obese**. Occurrence of the disease is almost completely determined by the **genetic factors**. NIDDM develops gradually, without obvious symptoms. Metabolic alterations are milder than IDDM.

- NIDDM is characterized by **hyperglycemia**, often with **hypertriglyceridemia**. In spite of high level of insulin, glucose levels are poorly controlled because of the **lack of normal response to insulin**.
- **Insulin resistance** in these patients may be due to increased expression of the tumor necrosis factor-α in the adipocytes of obese individuals. Hyperglycemia is, mainly, a result of the poor peripheral utilization of glucose, especially in muscle.
- **Ketoacidosis does not develop** because adipocytes remain sensitive to the effect of insulin.
- Rapid de novo synthesis of fatty acids and VLDL leads to **hypertriglyceridemia** without **hyperchylomicronemia**.
- Blood glucose concentration is much higher than normal, particularly, after a meal.
- Weight reduction and dietary modifications often correct hyperglycemia of type II diabetes. Hypoglycemic agents, such as sulphonylureas, may be required to achieve a satisfactory fall in blood glucose level.

Salient features of diabetes mellitus are shown in Table 10.4.

TABLE 10.4: Salient features of the two types (IDDM and NIDDM) of diabetes mellitus

	IDDM	NIDDM
Type of diabetes	Juvenile onset (Type I)	Maturity-onset (Type II)
Prevalence	About 20%	About 80%
Age of onset	<40 years	>40 years
Body habitus	Normal to wasted (weight loss)	Obese
Plasma insulin	Low (due to β-cell destruction)	Normal to high (insulin resistance)
Plasma glucagon	High (suppressible)	High (resistant)
Acute complications	Ketoacidosis	Hyperosmolar coma (ketoacidosis is rare)
Insulin therapy	Responsive	Resistant
Oral hypoglycemic agents	Unresponsive	Responsive

CONCEPT TO CLINIC

Treatment options for Diabetes Mellitus: Artificial Sweeteners

Owing to the fact that diabetic patients and even those having impaired glucose tolerance are advised to avoid glucose or sucrose in their diet, 'artificial sweeteners' have become popular substitutes. The **non-nutritive sweeteners** do not yield energy, e.g., saccharin and sucralose. Their RDA is 5 mg/kg body weight. The **nutritive sweeteners**, e.g., aspartame, yield 4 kcal/g of energy that is insignificant owing to their RDA of 15 mg/kg body weight. However, aspartame also yields the amino acid phenylalanine, hence, it should be avoided in patients suffering from phenylketonuria.

Disorders of Fructose Metabolism

Fructokinase deficiency results in **essential fructosuria**, due to which fructose appears in the urine, after a high fructose or sucrose diet is ingested. On the other hand, individuals with **aldolase B deficiency** suffer from **hereditary fructose intolerance**.

Subsequently, glyceraldehyde is phosphorylated by ATP in the presence of triose kinase and is changed to 3-phosphoglyceraldehyde that, in turn, can get conjugated with dihydroxyacetone phosphate and form glucose-6-phosphate, by the reversal of the glycolytic reaction (Fig. 10.23).

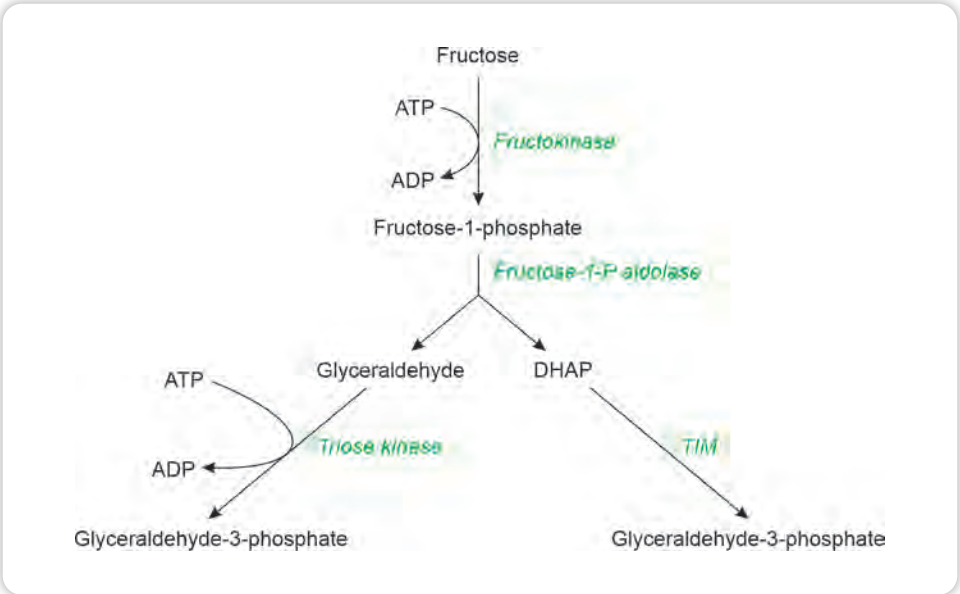


Fig. 10.23: Hereditary fructose intolerance

Galactosemia

It refers to increased galactose levels in blood, and is of several types:
Type 1 (classical): Deficiency of galactose-1-phosphate uridyltransferase.
Type 2: Deficiency of galactokinase.
Type 3: Deficiency of UDP-galactose-4-epimerase.

Features

- Galactosemia, i.e., increased levels of galactose in the blood results in galactosuria (excretion of galactose in the urine).
- Increased galactose concentration in the blood results in a higher galactose concentration in the lens of the eyes where this sugar is reduced to galactitol. This causes osmotic retention of water and damage to the lens protein (crystallin) with cataract formation.
- In classical galactosemia, accumulation of galactose-1-phosphate inhibits glycogenolysis resulting in hypoglycemia and seizures. It also depletes the hepatic stores of inorganic phosphate (Pi) leading to liver damage and jaundice.

- Deficiency of UDP-galactose impairs the synthesis of galactose-containing cerebral glycolipids, which, along with hypoglycemic episodes, hyperbilirubinemia and cerebral edema (due to accumulation of galactitol) may be responsible for mental retardation.

Treatment: Galactose and lactose-free diet.

SUMMARY

- All the dietary carbohydrates are digested and absorbed as glucose, which enters the liver.
- In the liver, glucose is utilized in various metabolic pathways which include glycolysis, glycogenesis and pentose phosphate pathway.
- During starvation, when blood glucose is low, glucose is released from glycogen (glycogenolysis) or produced via gluconeogenesis.
- Glycolytic enzymes are present in the extramitochondrial compartment of the cell to produce energy.
- Under anaerobic conditions, pyruvate is reduced to lactate.
- Tissues such as skeletal muscle, when function under hypoxic conditions, produce large amount of lactic acid.
- Under aerobic conditions, pyruvate is transported into mitochondria, where it is oxidatively decarboxylated to acetyl CoA by the enzyme pyruvate dehydrogenase complex.
- Under anaerobic conditions, conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate and phosphoenol-pyruvate to pyruvate, each produces one ATP, thus, a total of 2 ATP are produced per molecule of a triose, or 4 molecules of ATP per molecule of glucose.
- The net energy yield per molecule of glucose is only 2 ATP.
- A total yield under aerobic conditions is 10 ATP while the net yield is 8 ATP.
- Insulin stimulates these enzymes and increases utilization of glucose by glycolysis. On the other hand, glucagon inhibits this process.
- Citric acid cycle, also called tricarboxylic acid cycle (TCA cycle) or Krebs cycle, is a process of the oxidation of acetyl CoA (active acetate, produced under aerobic glycolysis) to CO_2 and H_2O.
- Total ATP yield, per molecule of acetyl CoA, is 12 ATP.
- Total number of ATP produced from the oxidation of pyruvate is 15.
- A total of 38 molecules of ATP are obtained when a molecule of glucose is completely oxidized to CO_2 and H_2O under aerobic conditions, i.e., via glycolysis and Krebs cycle.
- Citrate synthase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase are the rate limiting enzymes of the cycle.
- The process of glycogen synthesis is called glucogenesis, while the process of glycogen breakdown is referred to as glycogenolysis.
- Glycogenesis (glycogen synthesis) is the process of the conversion of glucose to glycogen.
- In the liver, glucokinase converts most of the glucose into glucose-6-phosphate, in the fed state.
- Glycogenolysis (glycogen breakdown) is the process of the conversion of glycogen to either glucose-6- phosphate in muscle or free glucose in the liver and the kidney.
- In the liver and kidney, glucose-6-phosphate is further hydrolyzed to glucose. This reaction is catalyzed by glucose-6-phosphatase.
- Glycogen which is stored in the liver, is converted to free glucose and is used to maintain blood glucose level in a hypoglycemic state.
- Glycogen metabolism in the liver is controlled by glucagon while in the muscle and other tissues, it is controlled by insulin and norepinephrine/epinephrine.
- Glycogenesis is regulated by glycogen synthase, whereas glycogenolysis is regulated by glycogen phosphorylase.
- Gluconeogenesis (neoglucogenesis) is the process of the formation of glucose from various noncarbohydrate sources.
- Gluconeogenesis is said to be the reversal of glycolysis but, truly, it is not a reversal of glycolysis, since there are three irreversible reactions in the glycolytic pathway.

Contd...

- Lactate is produced during the process of anaerobic glycolysis.
- Pyruvate is converted to glucose by the reversal of the glycolytic reactions.
- Various glucogenic amino acids transfer their α-amino group by transamination and release carbon skeletons, which form intermediates of the citric acid cycle.
- Glycerol kinase converts it to α-glycerolphosphate in the liver, which is later reduced by a dehydrogenase to dihydroxyacetone phosphate and enters glycolysis.
- In human beings, propionyl CoA is obtained from branched chain amino acids.
- Gluconeogenesis occurs in the fasting state, or on a low carbohydrate diet, in the liver and other tissues, which are solely dependent on glucose for their energy demand.
- Gluconeogenesis is regulated by pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase and glucose-6-phosphatase, which catalyze reversal of the irreversible steps of glycolysis.
- Cori cycle results in the net exchange of glycogen (via glucose-6-phosphate) and lactic acid in the two tissues, i.e., muscle and the liver.
- Insulin lowers blood glucose while various other hormones increase blood glucose level.
- Insulin also suppresses glycogenolysis in the liver and the kidney.
- Epinephrine, also called adrenaline, is secreted by the adrenal medulla. It is a hormone in the first line of defense against hypoglycemia.
- Cortisol is a major glucocorticoid present in the blood. It stimulates protein catabolism in the muscle and promotes gluconeogenesis in the liver.
- Anterior pituitary secretes growth hormone.
- Thyroxine is secreted by the thyroid gland. It stimulates the intestinal absorption of glucose and promotes glycogenolysis as well as gluconeogenesis in the liver.

ASSESS YOURSELF

Long/Short Answer Questions

1. **Outline the reactions of citric acid cycle. Give energetics of the cycle and explain the amphibolic role of this cycle.**
2. **Give outline of glycolytic reactions. What are the regulatory steps? What is the energy yield of this pathway?**
3. **Define glycogenolysis. Outline reactions of this pathway. How is it regulated?**
4. **What is glycogenesis? Give reactions of glycogenesis. How is it regulated?**
5. **Explain:**
   a. Why does aerobic glycolysis release more energy than anaerobic glycolysis?
   b. How can glycolysis be reversed?
   c. Anaplerotic reactions of TCA cycle and its energetics.
6. **Discuss briefly:**
   a. Regulation of blood glucose
   b. Glycogenolysis
7. **Write notes on:**
   a. Diabetes mellitus
   b. Glycogenesis
   c. Energetics of TCA cycle
   d. Gluconeogenesis
   e. Glycogen storage diseases

Multiple Choice Questions

1. **Fluoroacetate inhibits:**
   a. Hexokinase
   b. Pyruvate dehydrogenase
   c. Aconitase
   d. Lactate dehydrogenase

2. Anderson's disease is due to deficiency of:

a. Lysosomal acid maltase
b. Debranching enzyme
c. Branching enzyme
d. Muscle phosphorylase

3. Which of the following is true for type 2 diabetes mellitus?

a. Also called maturity onset diabetes
b. Responds to oral hypoglycemic agents
c. Lack of normal response to insulin
d. All of these

4. Renal glycosuria:

a. Results from an inherited defect in the proximal tubular Na^+-glucose cotransport
b. Osmotic diuresis
c. Normal blood glucose
d. All of these

5. Which of the following hormone is hyperglycemic?

a. Glucagon
b. ACTH
c. Cortisol
d. All of these

Glossary

A

Acidosis: Diminished capacity of the body to buffer protons in various respiratory/metabolic conditions.
Active site: The restricted part of a protein (enzyme) to which a substrate binds.
Active transport: Energy-driven, uphill transport of a solute across a membrane.
Adenosine diphosphate (ADP): A nucleotide serving as phosphate group acceptor in cellular respiration.
Adenosine triphosphate (ATP): A nucleotide serving as a phosphate group donor in metabolic reactions.
Aldose: A monosaccharide where terminal carbonyl carbon is an aldehyde.
Alkalosis: Diminished capacity of the body to buffer hydroxyl ions in various respiratory/metabolic conditions.
Allosteric enzyme: A regulatory enzyme whose catalytic activity is modulated by the noncovalent association with a specific metabolite at a site (other than the active site) known as the allosteric site.
Amino acid: α-Amino substituted carboxylic acid, the monomeric unit of protein.
Aminotransferases: Transaminases catalyzing the transfer of amino group from α-amino acid to α-keto acid.
Anomers: Stereoisomers of a sugar differing in configuration about the carbonyl (anomeric) carbon atom.
Apoenzyme: The protein portion of an enzyme.
Apolipoprotein (Apoprotein): The protein portion of a lipoprotein.
Avidin: The raw egg-white factor which can bind to biotin.

B

Basal Metabolic Rate (BMR): The rate of oxygen consumption by an animal's body at complete physical and mental rest, 12–14 hours following the last meal.
Bile salts: Amphipathic steroid derivatives with detergent properties, helping in lipid digestion and absorption.
Biotin: A water soluble vitamin involved in carboxylation reactions.
Buffer: A system consisting of a conjugate acid-base pair that tends to resist change in pH.

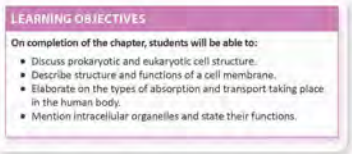
C

Carotenoids: Lipid-soluble pigments made up of isoprene units.
Catabolism: Phase of metabolism concerned with the energy-yielding breakdown of larger molecules.

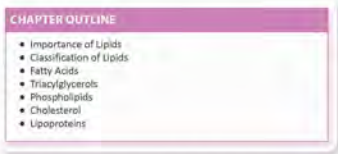
Textbook of

Biochemistry for Physiotherapy Students

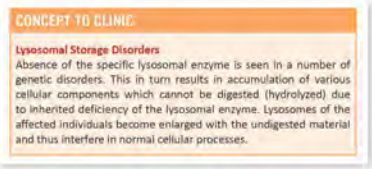
Learning Objectives in the beginning of every chapter help readers understand the purpose of the chapter.



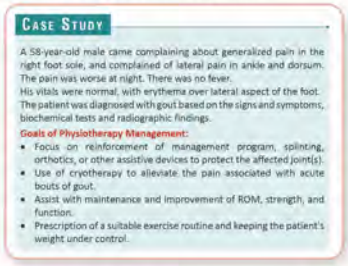
Chapter Outline provides a glimpse of the content covered in the chapter.



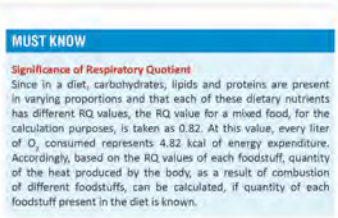
Concept to Clinic boxes depict evolving conceptual details for application in clinical situations.



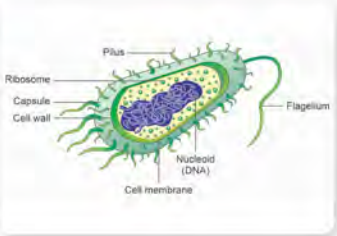
Case Study demonstrates example(s) of specific clinical scenarios that are often encountered by Physiotherapists.



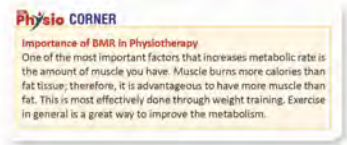
Must Know boxes provided the overview of important facts and terms of the concerned topic.

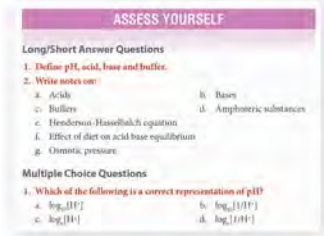


Colorful Figures are well illustrated in the book.



Physio Corner mentions physiotherapy correlation of the topics under study.





Assess Yourself section contains frequently asked questions in exams and multiple choice questions to help students attain mastery over the subject.

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