# MIND MAPS IN CLINICAL CHEMISTRY

## PART I

Simmi Kharb

Bentham Books

# Mind Maps in Clinical Chemistry

***(Part I)***

Authored by

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# Mind Maps in Clinical Chemistry (Part I)

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# PREFACE

This book treats clinical chemistry as an interdisciplinary subject to teach the importance of lab both for students in basic science as well as clinical medicine.

The approach to clinical chemistry in real clinical situations requires knowledge, experience and an integrated and clinically relevant model. I have attempted to bring this integrated model together in the book.

The book has been written in a lucid manner and is packed with practical approach of lab tests targeting undergraduate and also 1st postgraduate students of various streams of medicine. The reader should gain the knowledge and understanding of the value, limitations and interpretation of lab tests in modern medicine.

**ACKNOWLEDGMENT & CONFLICT OF INTEREST**

No potential conflict of interest is declared by the author. It is also declared the complete work is an individual effort by the author and there was no financial/ administrative/academic support availed from any individual/institution/ organization.

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# Section I
# Introduction

CHAPTER 1

# Collection and Processing of Specimens

**Learning objectives:**

1. Describe the method of sample collection.
2. Differentiate the factors affecting lab results of the patient.
3. Explain about sample processing.
4. Recognize and analyse the causes of errors in the lab.
5. Define POCT (Point of Care Testing) and its applications.

## Collection of Sample

While blood, serum, plasma, urine, feces, saliva, sweat, amniotic, cerebrospinal, pericardial, peritoneal, pleural and synovial fluids are the biological specimens, they are analyzed in clinical chemistry laboratories.

Steps -
1. Preanalytical testing – Request
   – Preparation of patient
   – Preparation for collecting sample
2. Sample collection

### Lab Test Request

The process of clinical laboratory investigation starts with a clinician making a request.

Test request form includes patient's demographics:
- patient's name, age, sex
- date of admission
- date on which request for lab test is made
- ward/clinic/address
- clinical diagnosis
- tests requested
- physician's identity.

Test request information is conveyed through written or computer order entry.

## Patient

- Correct interpretation of lab results can only be performed after careful consideration of individual patient factors (Table 1.1).

**Table 1.1:** Patient factors affecting interpretation of lab results

| |
|---|
| Age |
| Sex |
| Stress |
| Body temperature |
| Previous intake of food or liquid |
| Drug therapy |
| Race, individual variables |

In general, patients scheduled for sampling should refrain from strenuous physical activity, alcohol, drugs, dietary change and should have usual time and amount of sleep (Table 1.2).

**Table 1.2:** Patient factors affecting lab reports

| *Factor* | *Examples* | *Reasoning* |
|---|---|---|
| *1. Between individual differences* | | |
| Age | urea, alkaline phosphatase | Rise with age |
| Sex | uric acid | Higher in males |
| | gonadal steroids | Different between sexes |
| | HDL-C | Higher in premenopausal women |
| Race | Creatine kinase | Higher in Africans than Caucasians |
| 2. *Within individual variations* | | |
| Circadian rhythm* | Cortisol | Highest between 7-9 am |
| | | Lowest between 11 pm to 4 a m |
| | | Rise in stress |
| | | Lost in Cushing's syndrome |
| | | Higher in morning |
| | | Reversed in night workers |
| Iron | | Monthly variation in female |
| | | Low concentration just before or during menses |
| Diurnal rhythm | | |
| * Travel across several time zones affects normal circadian rhythm. Also, during prolonged flight, fluid and sodium retention occurs. | | |
| 3. *Others* | | |
| Pregnancy | Thyroxine | Thyroxine binding globulin elevate from supine to upright position |
| Posture | Proteins | |
| Exercise | Creatine kinase | elevated |
| *Nutritional status*: | | |
| High meat or protein: Urea, urate, | | Rises |

*Contd...*

*Contd...*

| | | |
|---|---|---|
| *serotonin-rich diet*: bananas, pine apple, tomato | | raised serotonin |
| *recent food intake:* FF, glucose, lipid | | increased |
| *fasting* | Glucose | Fall |
| time | Bilirubin | Rise after 48 hrs of fasting |
| | Cortisol | Circadian rhythm |
| | Uric acid | Elevated |
| Alcohol | Lactic acid | Elevated |
| | Triglyceride | Elevated |
| | GGT | Elevated |
| | Carboxyhemoglobin | High levels |
| Smoking | Cortisol | High levels |
| | Catecholamine | High levels |
| | Protein, AST | Decrease |
| | | Excretion increased |
| Immobilization | | Falsely increased |
| Tourniquet | Ca, Na, K, $PO_4$, $SO_4$ Lactate, calcium, proteins triglycerides | |
| Stress | Hormone, Lactate, FFA | Hormone secretion affected Elevated |

## Few Important Points

### How Often a Test should be Ordered?

i. Over investigation may be harmful, causing unnecessary discomfort or inconvenience to patient.
ii. Frequency of sampling should be carefully decided, e.g. plasma protein concentration are unlikely to change significantly in less than a week, plasma urea will not change significantly during first 12 hours of oliguria.
iii. Numerically significant changes sometimes do not alter treatment or course of disease, e.g. plasma transaminases.
iv. Plasma potassium concentration may alter after diuretics and indicate need to investigate or change treatment.

## Urgency

An urgent lab request is indicated when that investigation will alter the clinical management of patient.

## Are the Differences Significant?

Biochemical results obtained on specimens taken sequentially from a single individual are frequently numerically different; consider the possible sources of variation:

i. Pre-analytical variation

**CHAPTER 2**

# Lab Hazards: Biological Hazards

**Learning objectives:**

1. Recognise the different lab hazards.
2. Illustrate Labelling identification system.

To operate a clinical laboratory safely, it is essential to prevent the exposure of laboratory workers to infectious agents (Hepatitis B virus, HIV) by:

i. accidental puncture with needles
ii. spraying of these materials by syringe or spilling on benchtop or floor
iii. centrifuge accidents
iv. cuts or scratches from contaminated vessels (Fig 2.1)

It is essential that specimens should be handled using universal precautions such as:

1. Handle all specimens with care by using barriers protection (glove, gown, lab coats, face shield, eye protection)
2. Never mouth pipette or blow out pipettes that contain potentially infectious materials.
3. Dispose all sharps appropriately.
4. Hepatitis B vaccination should be offered to all employees at risk of potential exposure (technician, phlebotomist, etc.) (Fig. 2.1).


**Fig. 2.1:** Lab hazards

Nine classes of hazardous materials (UN classification)

1. Explosives
2. Compressed gases
3. Flammable liquids
4. Flammable solids
5. Oxidizer materials
6. Toxic materials
7. Radioactive materials
8. Corrosive materials
9. Miscellaneous materials.

## Hazard symbols and Labelling

Hazard symbols are recognizable symbols to warn about hazardous materials or locations. They may appear with different colors, backgrounds, border and supplemental information in order to signify the hazard (Fig 2.2, Fig 2.3)

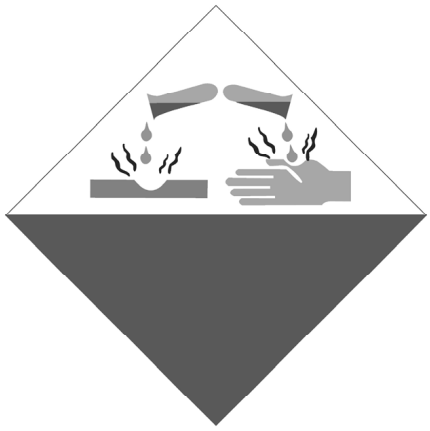

**Fig. 2.2:** Label for corrosive

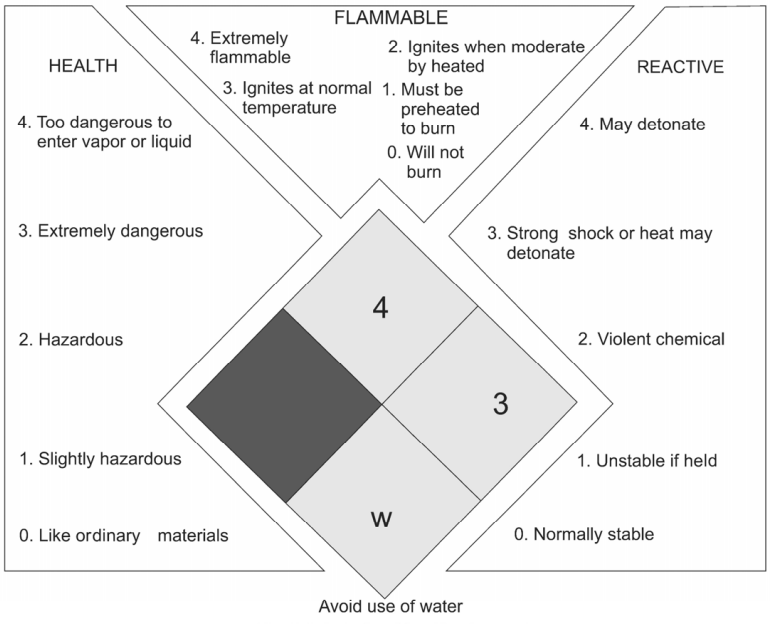


Fig. 2.2: Labeling identification system

**Fig. 2.3:** Labeling identification system

## Safety in the Laboratory

One must always be aware that chemicals used in the laboratory are potentially toxic, irritating or inflammable. Such chemicals are a hazard, however, only when they are mishandled or improperly disposed off.

Proper disposal of all waste chemicals, sharp objects, and infectious agents is essentially not only to maintain safe laboratory working condition, but also to protect the general public and local environment.

**Questions:**

1. What are biological lab hazards?
2. Classify hazardous materials?
3. What are hazard symbols and labelling?
4. Elaborate the various safety measures taken in laboratory?
5. Explain Labeling identification system.

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**CHAPTER 3**

# Safety in the Laboratory

**Learning objectives:**

1. Evaluate the aspects of safe operations of a Clinical Chemistry lab.
2. Explain the guidelines for Lab safety.

A clinical chemistry laboratory should have formal safety program.

Aspects of Safe Operations of a Clinical Chemistry Lab:

• Formal safety program

• Mandated plans: Chemical hygiene plans

Blood-borne pathogen plans

• Identification of lab hazards:

biological

chemical

electrical

fire

• OSHA, CDC approved hazard

• Communication standards

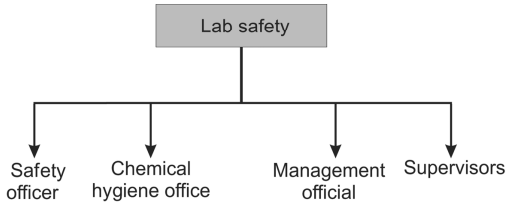


**Fig. 3.1**: Lab safety network material

## Guidelines for Lab Safety

1. Each new employee should get general lab safety material, undergo orientation program.
2. Each employee should have knowledge of location of available evacuation routes, firefighting equipments and their operation.
3. Employee should undergo continuing education programs on lab safety.

4. Supervision of lab safety measures in terms of:
– proper labeling, handling and disposal of chemicals in terms of hazards
– fire extinguisher
– hoods
– earthing of electrical equipment
– proper handling and disposal of patient specimens.
5. Inspection: Periodic and scheduled safety inspections should be the routine.
6. Accreditation of lab with Health Care Organization.
7. Safe and scientific waste disposal and management.

**Questions:**

1. What are the aspects of Safe Operations of a Clinical Chemistry Lab?
2. Write the guidelines for lab safety.

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**CHAPTER 4**

# Biochemical Tests in Clinical Medicine

**Learning objectives:**

1. Discuss the purpose of biochemical tests.
2. Illustrate the outline of Lab workflow.

The purpose and function of laboratorians are to provide biochemical information to assist clinicians (Fig. 4.1) in:

1. diagnosis
2. management
3. prognosis
4. detection and screening
5. monitoring follow-up of disease
6. teaching, research and development.

For results to be useful for any of these purposes, they must be free of error.

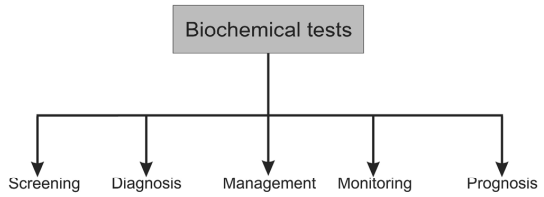


**Fig. 4.1:** Purpose of lab tests

## Lab Test Request

Most clinicians use lab tests primarily on the basis of their own clinical expertise and interpret results intuitively, and their results are used on the basis of outcome measure. In selecting a test, it is essential to consider what type of information is required and whether the test would provide it or not.

A clinical chemistry laboratory performs a large number of biochemical analytes on body fluids which can give answers to specific clinical questions about an individual patient. Such analyses are requested by clinicians in blood and urine samples or treatment.

The entire process from a request for analysis to receipt of a result involves several steps and can take many hours. Also, quality assurance for analyte is performed to ensure that results thus produced are analytically and clinically valid. Also timeliness, promptness or turnaround time of a test report is equally important in patient care.

The usual procedure by which a clinician obtains a medically useful result is an extremely complex chain of events (Fig. 1.1). This chain involves: clinicians, nurses, porter, technical staff, clinical biochemists or lab physician. Errors can occur at every link in the chain.

Samples to be analyzed must be collected under appropriate conditions and the analytical methods selected must be reliable. Also, the possible contribution of any analytical or biological variation should be considered.

## Outline of Lab Workflow

Steps involved in generation of lab results (Fig. 1.4) towards a test result must be considered.
The laboratory personnel must ensure that data are accurate and precise and the clinician should appreciate how useful the test is, the context in which it is used. Also, clinical staff should avail the opportunity to consult their lab colleagues about applications of lab tests in management of their patients.

**Questions:**

1. What is the purpose and functions of lab tests?
2. Discuss Lab Test Request.

**Bibliography:**

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# Section II
# Metabolic Disorders

**CHAPTER 5**

# Bone Metabolism: Calcium, Phosphate and Magnesium

**Learning objectives:**

1. Discuss the normal metabolism of Calcium, Phosphorus and Magnesium in body.
2. Describe the metabolic disorders associated with Calcium, Phosphorus and Magnesium.
3. Demonstrate the markers of Bone Turnover.
4. Compare different disorders of mineralization of bone.

## Normal Calcium Homeostasis

Calcium is the most abundant mineral in the human body. Bones and teeth contain 99 percent of calcium. An average human body contains 1 kg (24.95 mol) of calcium (Fig 5.1). Calcium is present in three main compartments:

- Skeleton 99 percent
- Soft tissue
- Extracellular fluid (ecf ) 1 percent

Calcium is physiologically classified as either intracellular or extracellular. The skeleton is major reservoir for providing both extracellular and intracellular pools.

| | |
|---|---|
| Intracellular calcium | Physiology of calcium |
| | Muscle contraction |
| | Hormonal secretion |
| | Glycogen metabolism |
| | Cell division |
| Extracellular calcium | Source for maintenance of intracellular calcium |
| | for bone mineralization |
| | Coagulation cascade |
| | Maintaining plasma membrane potential |

| *Functions of calcium* | |
|---|---|
| Structural | Bone |
| | Teeth |
| | Controls membrane potential |
| Neuromuscular | Neuromuscular excitability |
| | Neurotransmitter release |
| Enzymatic Signaling | Coagulation cascade (as coenzyme) |
| | Intracellular second messenger |

Total calcium in extracellular fluid is only 22.5 mmol (10 mg/dl) of which 9 mmol (4.1 mg/dL) is in plasma.

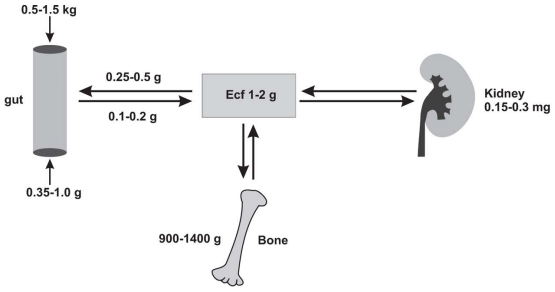


Fig 5.1: Calcium homeostasis

## Calcium in Plasma

Calcium exists in three physiochemical states in plasma:

| | |
|---|---|
| 50 percent | free or ionized |
| 40 percent | bound to plasma proteins: 80 percent with albumin, 20 percent with globulin |
| 10 percent | complexed with small anions. |

## Calcium Concentration

In normal adults, range of plasma concentration is 2.2 to 2.6 mmol/L (8.8 to 10.4 mg/dL). The concentration of free calcium ions, mean value being 1.2 mmol/L (4 to 8 mg/dL), is subject to tight hormonal control (Fig. 5.2). A decrease in serum free calcium concentration causes increased neuromuscular excitability and tetany.

## Calcium Intake and Absorption

### Calcium Intake

Average dietary calcium intake should be 0.6 to 0.8 g/d in adults.
Less than half of it is absorbed. (Fig. 5.2)

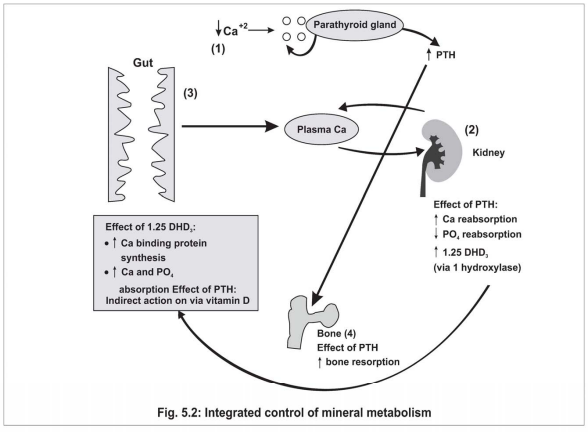


Fig. 5.2: Integrated control of mineral metabolism

### Calcium Absorption

Increased during period of rapid growth in
- children
- pregnancy
- lactation

Decreased with advancing age

## Site

Most calcium absorbed in proximal small intestine by active transport in upper part and by simple diffusion in lower part.

**Table 5.1:** Factors affecting absorption

| | *Favor* | *Decrease* |
|---|---|---|
| *pH* | Acidic pH | Alkaline pH |
| *Dietary factors:* | | |
| | High protein-diet (esp. lysine, arginine) | Oxalate, phytate |
| | sugar and organic acid | fibers |
| | citric acid | Excess $PO_4$ and Mg |
| | | Fe |

## Calcium Homeostasis

### Key Target Organs of Control

Intestine
Parathyroid glands
Kidneys

**CHAPTER 6**

# Carbohydrates

**Learning objectives:**

1. Describe the role of different enzymes and hormones involved in carbohydrate metabolism.
2. Analyse the mechanism of blood glucose homeostasis.
3. Discuss Inborn errors of metabolism.
4. Describe disorders of Carbohydrates metabolism in detail.
5. Differentiate between Type I and Type II Diabetes Mellitus.
6. Explain the metabolic complications of Diabetes.

Carbohydrates are widely distributed in plants and animals performing multiple functions (Table6.1).

**Table 6.1:** Functions of carbohydrates

| |
|---|
| 1. Structural |
| 2. Source of energy |
| 3. Storage |
| 4. Constituent of: |
| DNA and RNA (deoxyribose, ribose sugars) |
| Proteoglycan |
| Glycosaminoglycan |
| Glycoproteins |
| Cell membranes |
| 5. Stored as glycogen |

Glucose is a major fuel of tissues and cells. The body depends on glucose for energy. Body closely regulates blood glucose to maintain an adequate supply of glucose for cells. Diseases associated with carbohydrates include diabetes mellitus, galactosemia, glycogen storage diseases, and lactose intolerance. This chapter discusses carbohydrate metabolism and its abnormalities.

## Metabolism: Carbohydrates

Through the process of digestion and absorption, carbohydrates in diets following metabolism provide glucose — primary source of energy. (Figs 6.1 to 6.3 and Table 6.1).

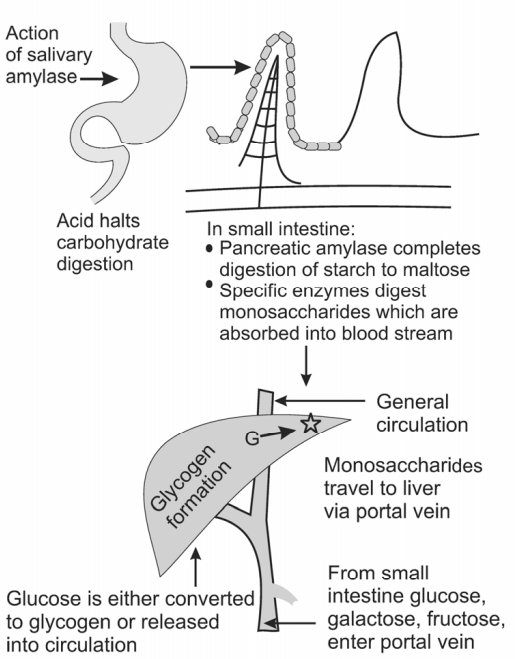


Fig. 6.1: Digestion and absorption of carbohydrates

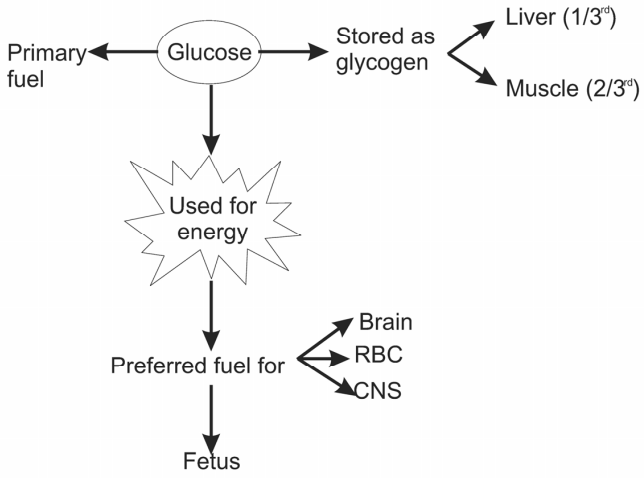


Fig. 6.2: Glucose in action

## REGULATION OF BLOOD GLUCOSE

Main hormones regulating blood glucose:

Insulin
Glucagon

(Fig 6.3, Fig 6.4, Table 6.2)

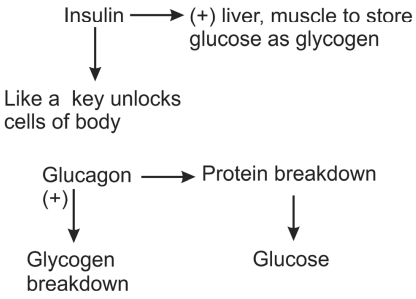


**Fig. 6.3:** Actions of insulin and glucagon

**Table 6.2:** Hormones affecting carbohydrate, lipid metabolism and protein metabolism

| *Enzymes* | *Fed state* | *Fasting* | *Insulin* | *Glucagon* | *Other activators/ inhibitions* |
|---|---|---|---|---|---|
| I | | | | | |
| 1. glycogen synthase | + | – | (+) | (–) | G-6-P |
| II. GLYCOLYSIS | | | | | |
| 1. Hexokinase | | | (+) | (–) | AMP, F-6-P, F2,6-BIS P/ CITRATE, ATP |
| 2. Glucokinase | + | - | (+) | (–) | |
| 3. PFK-1 | + | - | (+) | (–) | F1,6 BIS P/ ATP, ALANINE |
| 4. Pyruvate kinase | + | - | (+) | (–) | ADD:ADP,NAD,PYRUVAT, |
| 5. PDH | + | - | (+) | (+) | CoA/ATP, NADH, ACETYL CoA |
| GLUCONEOGENESIS | | | | | |
| III | | | | | |
| 1. Pyruvate carboxylose | - | + | - | + | Acetyl CoA/ADP |
| 2. PEP carboxykinase | - | + | - | + | (-) |
| 3. F-1-6, bisphosphatase | - | + | - | + | –/F 1, 6 bis $PO_4$, AMP, F 2, |
| 4. G-6-Pase | - | + | - | + | 6 bis $PO_4$ |
| PPP | | | | | |
| IV 1. G-6-PD | | | + | | |
| 2. 6- DeH | + | | + | | |
| | | - | + | | |
| V LIPID METABOLISM | | | | | – |
| LIPOGENESIS | | | | | |
| 1. Acetyl CoA carboxylase | + | - | + | | |
| 2. FA synthase | + | - | + | | |
| VI LIPOLYSIS | | | | | |
| Synthesis | | | (-) | | |
| VII PROTEIN | | | | | |
| Breakdown | | | (-) | | |

Net effect:
Insulin: Plasma glucose and NEFA fall
Glucagon: Plasma glucose rise

CHAPTER 7

# Lipids and Lipoproteins

**Learning objectives:**

1. Define the role of Fatty Acids in lipid formation and their classification.
2. Illustrate different groups of Lipoproteins.
3. Discuss about disorders of Lipid metabolism.

Lipids play an important role in almost all aspects of biological life (Table 7.1).

**Table 7.1:** Functions of lipid

| |
|---|
| Structural component in cell |
| Structural and functional component in biomembranes |
| Provides insulation |
| Serves as hormone or hormone precursors |
| Aids in digestion |
| Involved in metabolic and hormonal pathway |
| Source of energy |

Knowledge of lipid disorders is important since they are common in clinical practice and have a role in atherosclerosis.

**NEFA (Non-esterified FA)**

They are liberated from adipose tissue by action of lipase, transported to liver and muscle, bound to albumin, NEFA are important source of energy in body.

## Essential Fatty Acid

Such FA which can not be synthesized in the body and must be supplied in diet.

e.g. Linoleic acid (C18 : Δ9,12) ( Table 7.2).

**Table 7.2:** Major FA in plasma

| *Carbon* | *Saturated* | *Unsaturated* | *Source* |
|---|---|---|---|
| C16 | Palmitic acid | Palmitoleic Acid | Plant |
| | (C16 : 0) | (C16 $\Delta^{9}$) | |
| C18 | Stearic acid | Linoleic Acid (C18 : $\Delta^{9,12}$) | Animal/Plant oil |
| | (C18 : 0) | Linoleic Acid (C18 : $\Delta^{9,12,15}$) | Plant |
| | | Arachidonic Acid (C20 : $\Delta^{5,8,16,14}$) | – |
| | | Eicosapentamoic Acid (C20) | Fish oil |

**Simmi Kharb**

# Lipids: Classification

## Based on Chemical Structure

### Fatty Acids

| | |
|---|---|
| Short chain FA | ($C_{2-4}$) |
| Medium FA | ($C_{6-10}$) |
| Long chain FA | ($C_{12-26}$) |
| Eicosanoids | ($C_{20}$) |

### Glycerols

TA G
DAG
MAG
Phosphoglycerides

### Sphingosine Derivatives

Sphingomyelin
Glycosphingolipids

### Sterol Derivatives

Cholesterol
Vitamin D
Steroid hormones

### Isoprenes

Vitamin A
Vitamin E
Vitamin K

## PPAR: Peroxisome Proliferator- Activator (Table 7.3)

**Table 7.3:** PPAR: Peroxisome proliferator - activator receptors

| |
|---|
| Family of nuclear receptors |
| Activated by FA |
| Implicated in insulin resistance, dyslipidemia |
| Types : α PPAR |
| γ PPAR |
| Drugs targets for different PPAR |
| α (+) by fibrates |
| γ (+) by thiazolidenedione |
| e.g. Pioglitazone |
| Rosiglitazone |

### TAG (Triacylglycerol): Also called as triglycerides (TG)

Storage form of fat
Transported from intestine to liver and adipose tissue as lipoproteins
Contain both saturated and unsaturated FA.

*Cholesterol: Salient Features*

Present in all cells and body fluids
Precursor of steroid hormones and bile acids
Absorbed from intestine and also synthesized endogenously by liver mainly
Rate-limiting step of its synthesis : *HMGCoA reductase* is controlled by :
- feedback inhibition by cholesterol
- therapeutic agents - statins

2/3rd cholesterol in plasma exists as cholesterol ester
Excreted in bile as such or after metabolism to bile acids
If excess amount of cholesterol is excreted in bile, it results in gallstone formation.

## Phospholipids

Complex lipids
Similar to TG containing a phosphate group and N-base in place of one FA residue.

## Lipoproteins

Lipoproteins are transport form of lipid and contain lipid in association with proteins. Lipoprotein particle consists of non-polar core of TG and CE surrounded by polar groups of phospholipids, proteins and free cholesterol (Table 7.4, 7.5).

**Table 7.4:** Main groups of lipoproteins

| *Particle* | *Property* | *Electrophoretic mobility* | *Source* |
|---|---|---|---|
| Chylomicron (CM) | Largest<br>Least dense | Origin | Intestine |
| VLDL | Formed from TG | Pre -β | Liver |
| IDL | Intermediate form | broad β | Catabolism of VLDL |
| LDL | Principal carrier of cholesterol | β | Catabolism of VLDL via IDL |
| HDL | Nascent HDL is disc-shaped which is converted to $HDL_2$ and $HDL_3$ | α | Liver, intestine |

# CHAPTER 8

# Plasma Proteins

**Learning objectives:**

1. Define different categories of plasma proteins.
2. Discuss functions of all plasma proteins.
3. Explain albumin in detail.
4. Describe proteinuria and its causes.

More than hundred different proteins are present in blood known as *Plasma Proteins*. Examination of proteins in plasma can provide information reflecting disease states in many different organ systems.

Different categories of plasma proteins can be:

Acute phase reaction proteins
Carrier proteins
Fibrinogen
Coagulation factor
Complement
Immunoglobulins
Enzymes
Enzyme inhibitors
Transport proteins.

| *Functions of proteins* | |
|---|---|
| | ***Example*** |
| Acute phase reaction | Alpha-1 AT<br>Haptoglobin<br>Ceruloplasmin<br>CRP |
| Buffering | All proteins |
| Oncofetal | AFP |
| Complement | C4, C3 |
| Enzymes | Albumin<br>Renin<br>Coagulation factors |
| Immunity | Complement<br>Immunoglobulin |
| Coagulation | Clotting factors<br>Fibrinogen |

*Contd...*

*Contd...*

| | |
|---|---|
| Enyme inhibitors | Alpha-1 AT<br>Antiplasmin<br>Antithrombin III |
| Transport proteins | Albumin<br>Thyroxine binding protein<br>Apoproteins<br>Transferrin |
| Hormones* | Erythropoietin |

* Other protein hormones circulating in blood are not designated as plasma proteins. Even ferritin is not a plasma protein.

**Table 8.1**: Proteins in other body fluids

| *Fluid* | *Condition* |
|---|---|
| CSF | ↑ in infection<br>Tumor<br>Hemorrhage<br>Demyelinating diseases |
| Amniotic fluid | AFP<br>Acetylcholinesterase<br>Fetal Hb |
| Saliva | Secretory IgA |
| Feces | $\alpha_1$ AT |
| Pleural fluid and ascitic fluid | ↑ in infection<br>Malignancy |

# Plasma Proteins

Plasma contains water, electrolyte, metabolites, nutrients, proteins and hormones.

Salient Features of Plasma Proteins

1. Proteins in plasma can be simple, conjugated (glycoprotein, lipoproteins).
2. Concentration of protein in plasma determine distribution of fluid between blood and tissues.
3. Plasma proteins exert osmotic pressure.
4. Most plasma proteins are synthesized in liver.
5. Most plasma proteins are glycoproteins, and removal of terminal sialic acid residues from them shorten their half-life (Table 8.2, 8.3).

**Table 8.2**: Total plasma protein concentration

| *Increase* | *Decrease* |
|---|---|
| ↑ Synthesis:<br>Hypergammaglobinemia<br>Paraproteinemia | ↓ Synthesis:<br>Malnutrition<br>Malabsorption<br>Chronic liver disease<br>Immunodeficiency |
| ↓ Blood volume:<br>Hemoconcentration<br>Dehydration | ↑ Blood volume:<br>Overhydration |
| | Increased permeability:<br>Septicemia<br>Hypoxia |
| ↑ Loss/catabolism:<br>Catabolic state<br>Protein losing states:<br>Enteropathy<br>Nephrotic syndrome<br>Exfoliative disorder of skin, e.g. pemphigus<br>Extensive burns<br>Hemorrhage | |

**Table 8.3**: Principal plasma proteins

| | |
|---|---|
| Prealbumin | |
| albumin | |
| $\alpha_1$-globulin | $\alpha_1$-antitrypsin |
| $\alpha_2$-globulin | Haptoglobin |
| | $\alpha_2$-macroglobulin |
| | Ceruloplasmin |
| β-globulin | Transferrin |
| | LDL |
| | C3 |
| γ-globulin | IgG, IgA, IgM, IgD, IgE |

**Table 8.4**: Other plasma proteins

| *Plasma proteins* | *Functions* | ↑ | ↓ |
|---|---|---|---|
| α1 acid glycoprotein | Glycoprotein group of protein:<br>control bioavailability of drugs<br>downregulation of immune response | Acute phase response by glucocorticoides (GC) | by estrogen<br>nephrotic syndrome |
| α1 AT | Serpin (serine protease inhibitor)<br>inhibit leukocyte elastase<br>prevent elastic recoil in bronchial tree | Acute phase response<br>estrogens | Genetic deficiency:<br>emphysema<br>Hepatic damage |
| Ceruloplasmin | α2 globulin, contains 95% of total serum copper<br>regulates ionic state of iron (Fe2+ → Fe3+) | Acute phase<br>estrogen | Wilson's disease |
| CRP | Activator of classical complement system | Acute phase response | — |
| Haptoglobin | Binds Hb irreversibly | Acute phase response<br>protein-losing syndrome<br>GC, androgens | genetic deficiency<br>estrogen<br>hemolytic disease<br>hepatocellular disease |
| $\alpha_2$ macroglobulin | Plasma proteinase inhibitor<br>inhibits kinin, complement, coagulation, fibronolytic pathways | Estrogen<br>nephrotic syndrome | genetic deficiency<br>pancreatitis<br>prostate CA |
| $\beta_2$ microglobulin | It is light or β-chain of HLA on cell surface | Renal failure<br>neoplasm<br>inflammation | — |
| Retinol binding protein | Binds all trans-retinol<br>prevents retinol from being filtered by glomeruli | Chronic renal disease<br>Diabetic nephropathy | Liver disease<br>protein - malnutrition<br>acquired immunodeficiency |

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**CHAPTER 9**

# Nucleic Acid

**Learning objectives:**

1. Explain metabolism of purines and its clinical importance.
2. Describe metabolic disorders of Purine Catabolism.
3. Discuss Diagnostic application of Nucleic Acid.

***Purine and urate metabolism***

Abnormalities of purine metabolism commonly found in clinical practice, include gout, hyperuricemia, Lesch Nyhan's syndrome, adenosine deaminase deficiency.

## Purine Metabolism

*Humans catabolize purines to uric acid.*

Uric acid is end-product of purine degradation in humans. Since humans lack uricase (that converts uric acid to water-soluble allantoin), their uric acids are higher.

Purine synthesis and breakdown occurs in all tissues, urate is produced only in tissues containing xanthine oxidase, i.e. liver and small intestine (Table 9.1).

**Table 9.1:** Factors affecting urate production

| |
|---|
| Dietary intake of purine |
| Rate of purine biosynthesis, degradation and salvage |
| Renal function |
| Age, sex |
| Alcohol intake |

Four steps of renal handling of urate (Fig. 9.1)

1. Glomerular filtration
2. Reabsorption in PCT (proximal convoluted tubule)
3. Secretion into distal portion of PCT
4. Reabsorption in DCT (distal convoluted tubule)
5. 75 percent of uric acid is excreted in urine and rest is eliminated through intestine.

## Properties of Uric Acid (UA)

- Weak acid, pKa of 5.75 and 10.3
- Exists predominantly as ionized form: urate

- 98 percent exists as monosodium urate at pH 7.4
- UA is poorly soluble in plasma and urate is ionized
- Ionization of UA decreases as pH falls and becomes less soluble.

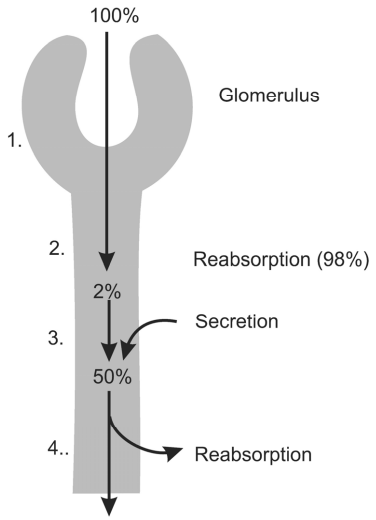


**Fig. 9.1:** Renal handling of urate

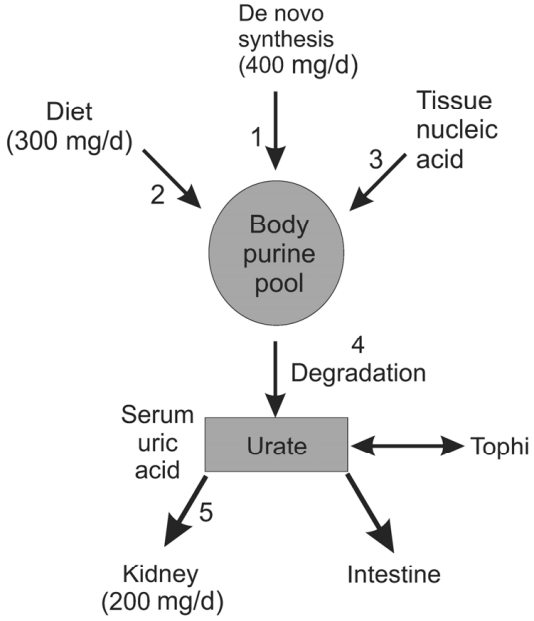


**Fig. 9.2:** Total body urate pool and causes of hyperuricemia

## Hyperuricemia

Defined as a plasma/serum urate concentration greater than 7 mg/dL.

## Causes of Hyperuricemia

*Causes:* According to underlying physiology:
1. Increased synthesis of purines
2. Increased intake of purines
3. Increased breakdown (turnover)
4. Increased rate of urate formation
5. Decreased rate of excretion (Table 9.2, Fig. 9.2).

**Table 9.2:** Causes of hyperuricemia

| *Cause* | *Reason* |
|---|---|
| I. Increased formation of UA | |
| a. Primary Increase | |
| i. Purine synthesis | *de Novo*:↑ PRPPS*<br>Salvage:↓ HGFRT* |
| ii. Inherited metabolic disease (IMD) GSDI | Insulin/glucagon<br>↑ ATP degradation<br>Lactic acidemia block uric acid excretion<br>Metabolism of G-6-P through PPP,↑R-5-P Purine synthesis<br>More G-6-P available diverted to HMP shunt: ↑ R-5-P Purine |
| F1P Aldolase deficiency | aldolase deficiency (both mechanisms) |
| b. Secondary increase | |
| i. Increased dietary intake of purines | Purines oxidized to urate |
| ii. increased nucleic acid turnover *Cause* trauma surgery Malignancy, starvation, Psoriasis cytotoxic drugs | Purines oxidized to urate |
| iii. Altered ATP metabolism *causes:* | |
| Alcohol, tissue hypoxia | Hypoxia and ↓ATP synthesis, causing lacticacidosis which blocks UA excretion, alcohol ↓ excretion of UA |

* HGPRT deficiency: ↓activity of salvage pathway causing decreased purine utilization and ↑uric acid synthesis (Fig 9.3)
** PRPPS: ↑PRPPS result in increased purine synthesis and increased uric acid synthesis

*Contd...*

CHAPTER 10

# Inherited Metabolic Diseases

**Learning objectives:**

1. Enlist and describe all Inherited Metabolic Disorders with Clinical Laboratory Assessment.
2. Discuss Autosomal Recessive Inherited Metabolic Disorders.
3. Explain Metabolic Disorders caused as a result of mutation.

## Inherited Metabolic Disorders IMD

Inborn metabolic disorders are caused by genetically determined abnormalities that lead to a block in one of many interrelated biochemical pathways.

The block frequently leads to accumulation of substrate and secondary metabolites or to deficiencies of downstream products (Table10.1).

## Features

1. IMD are categorized by type of metabolic pathways that are impaired, such as disorders of carbohydrates, fats or amino acids.
2. These disorders may involve pathways of specific cellular organelles, including lysosomes, mitochondria, peroxisomes.

## When to Suspect an IMD?

When there are unusual, unexplained clinical features or abnormal lab findings in infancy or childhood, the possibility of an IMD should be considered. Also, history of consanguineous marriage or more than one infant in family affected by same abnormality.

*Cause of presentation* can be due to (i) direct or enzyme abnormality and (ii) can be demonstrated indirectly.

## Disorders of Intermediary Metabolism

It occurs as a result of three basic mechanisms:

1. *Enzyme deficiency* with defective substrate conversion (Table10.2).
2. *Membrane transport defect* resulting in failure of absorption or excessive excretion of a compound (Table10.3).
3. *Defects in receptors* involved in mediating metabolism.

**Simmi Kharb**

## Biochemical Basis of Resulting Disease (Fig. 10.1)

1. Accumulation of a substrate to toxic levels (↑A)
2. Deficiency (due to lack of production) or excessive loss of desired compound (↓B)
3. Conversion of accumulated compound to altered/toxic metabolite (↑C)

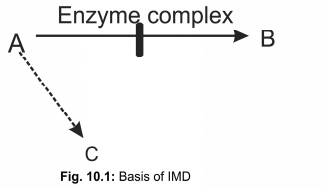


**Fig. 10.1:** Basis of IMD

Inherited metabolic diseases are the result of gene mutations causing production of an abnormal protein or preventing synthesis of a protein (Table 10.1-10.5).

**Table 10.1:** Inherited metabolic diseases

| |
|---|
| α, antitrypsin deficiency |
| Cystic fibrosis |
| Classic galactosemia |
| Familial hypercholesterolemia |
| Glycogen storage disease |
| Hereditary fructose intolerance |
| Lesch-Nyhan syndrome |
| Liver: (disorders of conjugation and excretion of bile:) Gilbert, Crigler-Najjar, Dubin Johnson, Rotor syndrome |
| Hemochromatosis: |
| Lysosomal storage disease |
| Maple syrup urine disease |
| Phenylketonuria |
| Porphyrias |
| Renal glycosuria |
| Steroid 21-hydroxylase deficiency |
| Tyrosinemia type 1 |
| Vitamin D-dependent and resistant rickets |
| Wilson's disease |

**Table 10.2:** IMD

| | *Diseases* | *Inheritance* | *Defect* | *Clinical Features* | *Diagnostic approach/ detection* |
|---|---|---|---|---|---|
| 1. | $\alpha_1$-antitrypsin | Homozygosity for Z allele | Single amino acid | Liver or lung disease | Phenotyping screening of |

*Contd...*

*Contd...*

| | *Diseases* | *Inheritance* | *Defect* | *Clinical Features* | *Diagnostic approach/ detection* |
|---|---|---|---|---|---|
| | | (PiZZ) | Substitution | Emphysema and risk increased In smokers Liver: Neonatal Hepatitis Cirrhosis Lung disease | affected individual's members antenatal screening using fetal DNA from Chorionic Villous α1 AT levels high sweat sodium high plasma immunoreacti-ve trypsin molecular genetic analysis of CFTR gene |
| | | Heterozygotes (PiMZ) | | | |
| 2. | Cystic fibrosis | Familial | Impaired $Cl^-$ Transport Due to CFTR Gene defect (cystic fibrosis transmembrane Conductance receptor) involved in chloride trans-port, deletion of single codon: common: Δ F 508 | affected children develop recurrent respiratory infections irreversible lung disease pancreatic insufficiency leading to malabsorption Intestinal obstruction in neonates infants: failure to thrive vomiting hepatospleno-megaly | |
| 3. | Classical Galactosemia | Autosomal recessive | Galactose-1-phosphate Uridyl trans-ference absent (GALT) | | plasma galactose ↑ urine galactose positive GALT deficien-cy in RBCs & chorionic villi |
| | | Adults | cataract | Jaundice cataract, Impaired renal function | |
| 4. | Familial Hypercholes-terolemia | Autosomal dominant | defect in uptake and catabolism of LDL | cholesterol deposition in skin, tendon, arteries | high serum HDL, total cholesterol |
| 5. | Glycogen Storge Disease Type I | | Glucose-6-phosphatase deficiency | fasting hypoglycemia accumulation of glycogen in liver and hepato-megaly | liver biopsy for G-6-Pase enzyme deficiency lact-acidosis common hyperlipidemia hyperuricemia |

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**CHAPTER 11**

# Oral Manifestations of Inherited Disorders

**Learning objectives:**

1. Describe oral manifestation of all Metabolic Disorders.

## ···Hypophosphatemic Vitamin D Resistant Rickets

X-linked AD.

### Clinical Features

- Hypophosphatemia
- Rickets or osteomalacia
- Resistant to usual doses of vitamin D.

### Causes of Hypophosphatemia

- Defective reabsorption and increased excretion of phosphate by renal tubules
- Rickets secondary to biochemical abnormality.

### Oral Manifestations

Gingival and periapical abscess without concurrent evidence of caries or tooth fracture.

### Systemic Manifestation

- Rickets
- Osteomalacia.

### Laboratory Investigations

- Serum Calcium n
- ALP n/↑
- Serum Phosphate. ↓

## Pseudohypoparathyroidism (PHP) and Pseudopseudo-hypoparathyroidism (PPHP)

PHP Hypocalcemia
PPHP Normocalcemia
X-linked AD

*Causes:* Lack of end-organ receptor for PTH.

### Oral Manifestation

- Enamel covered with pits
- Pulp stones near pulp horns
- Retarded root development with large root canals.

### Systemic Manifestation

*PHP*

- Short stature
- Obesity
- Mental retardation.

*PPHP*

- Tall
- Less obese.

### Common Features

- Short metacarpals
- Calcification in subcutaneous tissues of scalp and extremities.

### Laboratory Investigations

- S. Ca low
- S. $PO_4$ high.

## Fabry Syndrome

X-linked AR
α-galactosidase deficiency.

### Oral Manifestations

Angiokeratoma of lips (lower lip).

### Systemic Manifestations

- Angiokeratoma of skin
- Pain in hand and feet.

### Clinical Features

- Pain in extremities
- High blood pressure
- Cardiomegaly
- Albuminuria.

### Laboratory Findings

- Proteinuria
- Anemia
- Uremia
- Urine-birefringent lipid inclusion.

## Lesch-Nyhan Syndrome

- X-linked AR
- HGPRTase deficiency
- Hyperuricemia
- Choreoathetosis
- Mental retardation
- Self-mutilation.

*Facies*

- Distorted due to chewing of lips
- Multiple scars on ears, face, head due to self-inflicted trauma.

*Oral Manifestation*

Self-chewing of lips.

*Systemic Manifestations*

- Mental retardation
- Amputation due to chewing of distal phalanges.
- Choreoathetosis
- Quadriparesis.

*Laboratory Investigations*

Urine: Uric acid raised.

## MPS VIII

AR

- β-glucuronidase absent
- Accumulation of acid mucopolysaccharides.

**CHAPTER 12**

# Heme, Iron and Porphyria

**Learning objectives:**

1. Explain the synthesis of Porphyrin and describe Porphyria.
2. Discuss Iron in detail.
3. Enumerate all abnormal derivatives of Heme.

## Porphyrin

A cyclic compound with four pyrrole rings connected by methenyl bridges. The arrangement of four nitrogen atoms in the center of porphyrin ring enables porphyrins to chelate various metal ions, e.g.:

Iron chelate : Iron porphyrin—heme
Magnesium : Magnesium porphyrin—chlorophyll

Metal-free porphyrins have no biological function in humans and protoporphyrin that contains iron is HEME.

## Hemoproteins

*Proteins that contain heme are hemoproteins* (Table 12.1).

Examples:

- Hemoglobin (Hb)
- Myoglobin (Mb)
- Cytochrome C (Cyto C)
- Cyt $P_{450}$
- Catalase
- Tryptophan pyrrolase.

**Table 12.1:** Hemoproteins

| *Proteins* | *Function* |
|---|---|
| Hb | Transport of oxygen in blood |
| Mb | Storage of oxygen in muscle |
| Cytochromes: | |
| Cyt C | Electron transport chain |
| Cyt $P_{450}$ | detoxification of xenobiotics (hydroxylation) |

*Contd...*

*Contd...*

| | |
|---|---|
| Enzymes: | |
| Catalase | Uses $H_2O_2$ as electron donor and acceptor to form water and oxygen (degrades $H_2O_2$) |
| Tryptophan pyrrolase (oxygenase) | Cleaves indole ring with incorporation of oxygen to form N-formylkynurenine (Tryptophan catabolism) |

## Heme

Heme is synthesized from porphyrin and iron and is type III porphyrin belonging to series IX. (Fig. 12.1, Table 12.2)

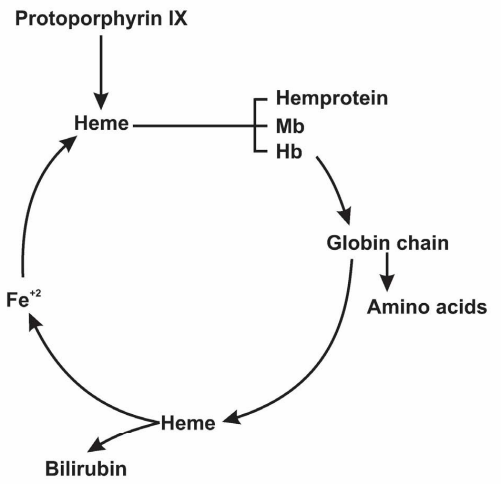


**Fig. 12.1:** Heme formation and breakdown

**Table 12.2:** Fact-file—heme

| |
|---|
| 1. ***Synthesis*** |
| 85% heme synthesized in erythroid cells → Heme for |
| ***Rest:*** Heme produced in liver → cyt $P_{450}$ enzyme |
| 2. ***Breakdown*** |
| Under physiological condition, 1-2 × $10^8$ RBCs destroyed/hour |
| 70 kg adult turns ~ 6 g Hb/day |
| IgHb yields 35 mg bilirubin. |

Heme synthesis begins with succinyl CoA and glycine and ends with insertion of $Fe^{2+}$ into molecule of protophyrin using eight enzymes (four mitochondrial and four cytosolic). Each step produces a progressively less water-soluble molecule until, with protophyrin and heme which are insoluble in water.

Thus, excess intermediates early in the pathway tend to appear in urine, while intermediates late in the pathway (particularly protoporphyrin) are found in blood, bile and feces and not in urine.

Porphyria are rare group of disorders of heme synthesis resulting from deficiency of one of the enzymes of this pathway (Fig.12.2).

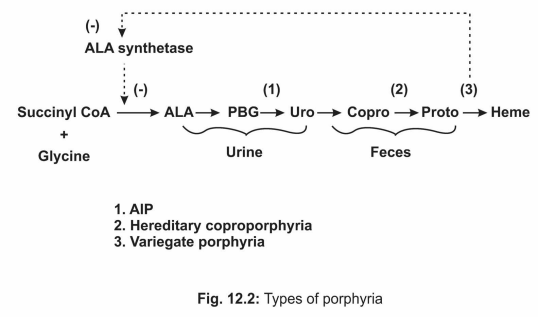


**Fig. 12.2:** Types of porphyria

## Porphyrin Synthesis (Fig. 12.3)

- ❖ Types of Porphyria
  - Inherited
  - Acquired.
- ❖ Classification of Porphyria
  - Hepatic
  - Erythropoietic
- ❖ Types of Porphyria
  - Acute
    - Acute intermittent porphyrias (AIP)
    - (HCP) Hereditary coproporphyria } hepatic
    - (VP) Variegate hepatic porphyria
  - Chronic
    - Cutaneous hepatic porphyria (CHP)
    - Congenital erythropoietic porphyrias (EP) } erythropoietic
    - Erythropoietic protoporphyria (EPP)

**CHAPTER 13**

# Nutrition

**Learning objectives:**

1. Discuss the causes, classification and signs of Malnutrition.
2. Illustrate Nutraceuticals.
3. Describe Nutritional Anemias.
4. Explain Vitamins, functions and deficiency symptoms.

For normal growth and development and maintenance of health, adequate intake of nutrients is essential (Table 13.1)

**Table 13.1:** Essential nutrients

| | |
|---|---|
| Water | |
| Carbohydrates | |
| Proteins (amino acids) | |
| Fats | Fat soluble : A, D, E, K |
| Vitamins: | Water soluble : B, C |
| Minerals: | Na, K, Ca, M g, P, Cl |
| Trace elements: | Cu, Fe, Zn, Cr, Mn, Se, I, F, Mo |

Malnutrition is suboptimal nutrition arising from inadequate or unbalanced intake, bioavailability of nutrients which leads to biochemical and metabolic consequences (Table 13.2).

In malnutrition, deficiency of energy, protein, vitamin and minerals can occur.

Two forms of protein energy malnutrition are marasmus and kwashiorkor (Table 13.3).

| | *Marasmus* | *Kwashiorkor* |
|---|---|---|
| Cause | Inadequate intake of protein and calories | Inadequate intake of proteins after trauma or infection |
| Muscle fat | Loss of sub-cutaneous tissue | Muscle and subcutaneous tissue preserved |
| Weight | Loss of weight | Weight loss, edema |
| S. albumin | S.albumin normal | S. albumin low (a state of PEM, where adaptation has failed). |

In malnutrition, patient shows features of deficiency of energy, protein, vitamins and mineral.

**Malnutrition: Causes**

| | *Causes* | *Lab investigations* |
|---|---|---|
| 1. | Fat malabsorption | Fecal fat<br>Breath Test ($^{14}$C glycocholate)<br>$B_{12}$ absorption test<br>Pancreatic enzymes in stool :<br>trypsin, chymotrypsin, elastase<br>microscopic examination for fat droplets |
| 2. | Protein malabsorption | Serum protein<br>α – 1 anti-trypsin in feces<br>α -anti-trypsin clearance by intestine |
| 3. | Celiac disease | Visualization technique<br>antigliadin (AGA) Ab assay in serum<br>anti-*endomysium* (AEA) Ab in serum<br>antireticulin (ARA) Ab in serum |
| 4. | Carbohydrate malabsorption | D-Xylose absorption test<br>Breath $H_2$ after lactose administration |
| 5. | Vitamin malabsorption | $B_{12}$ malabsorption, correction by pancreatic enzyme administration<br>Lab investigation of megaloblastic anemia<br>Vitamin A and D absorption test |
| 5. | Mineral malabsorption | 59Fe absorption |

**Table 13.2:** Classification: Malnutrition

| | | |
|---|---|---|
| ***I. On the basis of lesion*** | | |
| 1. Gastric: | | Deficiency of intrinsic factor causing defective absorption by vitamin $B_{12}$. |
| 2. Small intestine: | | Luminal |
| a. | Liver | Cirrhosis of liver<br>Extrahepatic biliary obstruction causing defective bile secretion |
| b. | Pancreas | Pancreatitis<br>CA pancreas<br>Zollinger-Ellison Syndrome |
| c. | Brushborder defect | |
| i. | Lesion of mucosa: | Celiac disease<br>Gluten-induced enteropathy<br>Tropical sprue<br>Infiltration by tumor<br>Sarcoidosis<br>Radiation<br>Drug-induced<br>Infection<br>Parasite |

*Contd...*

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ii. Inborn errors:
- Amino acid transport defect
- Glucose transport defect
- Abetalipoproteinemia

***II. On the basis of nutrient***

1. Fat malabsorption
   - Steatorrhea
   - Hepatobiliary disease
   - Pancreatic disorder
   - Brushborder lesion
2. Carbohydrate malabsorption
   - Brushborder lesions
   - Enzymatic defect:
     - Disaccharidase deficiency (maltase, sucrase, lactase)
3. Protein malabsorption
   *Protein losing enteropathy*:
   - Tropical sprue
   - Colitis
   - Crohn's disease
   - Infantile allergy
   - Amino acid transporter defect
4. Malabsorption of vitamin
   Water-soluble vitamin: B (pernicious anemia: IF deficiency)
   Fat-soluble vitamin: In fat malabsorption
5. Malabsorption of minerals

   Iron:
   - Parasite infestation
   - Phytates, oxalates

**Table 13.3:** Signs associated with malnutrition

| *Organ* | *Signs* | *Deficiency* |
|---|---|---|
| Face | Diffuse depigmentation | Riboflavin |
| Skin | Purpura | Vitamin K |
| | Hyperpigmentation | Cobalamin, folic acid |
| | Hyperkeratosis | Retinol, EFA |
| | | Ascorbic acid, niacin |
| | Petechial hemorrhage | |
| Eyes | Poor dark adaptation, Bitot's spots | |
| Lips | Angular stomatitis, cheilosis | |
| | Raw tongue | Retinol |
| Tongue | Scarlet tongue | Riboflavin or niacin |
| | Glossitis | Riboflavin |
| | | Riboflavin |
| | Atrophic filiform papillae | Niacin, riboflavin, folic acid, cobalamin, iron |
| | | Niacin, folate, |
| Teeth | Mottled enamel, caries | riboflavin, iron, cobalamin |
| Gums | Pale | Fluoride |
| Nails | Koilonychia, pallor | Ascorbic acid |
| CVS | Cardiomegaly, wet beri-beri | Niacin |
| Nervous system | Neuropathy, sensory and motor loss, | Thiamin |
| | dry beri-beri | Thiamin |

**CHAPTER 14**

# Malignancy

**Learning objectives:**

1. Describe Endocrine Syndromes.
2. Illustrate Biochemical Changes in Cancer.
3. Discuss MEN and differentiate between MEN I and MEN IIa.

## Malignancy

Term *paraneoplastic syndrome* includes all the systemic manifestations of cancer not directly related to presence of primary tumor, whether or not they are due to a hormone termed as *Ectopic hormone* (Table 14.1).

Most of these endocrine syndromes occur with tumors of non-endocrine tissue which have embryonic origin from neural crest cells. However, non-APUD tumors do occur.

**Table 14.1:** Endocrine syndromes

| | *Syndrome* | *Tumor* | *Hormone* |
|---|---|---|---|
| 1. | Cushing's syndrome | Small cell CA bronchus<br>Carcinoid tumors | ACTH |
| 2. | Hypercalcemia of malignancy* | Non small cell CA lung<br>Renal adeno CA | PTHRP |
| 3. | Hyponatremia (SIADH) | Small cell CA lung | Vasopressin |
| 4. | Hypoglycemia | Mesenchymal tumors (non β cell tumors)<br>Small cell cancer<br>Lung testicular cancer<br>Hepatic tumor<br>Carcinoid | Insulin-like growth factors (IGFs) |
| 5. | Gynecomastia | | hCG |
| 6. | Ectopic acromegaly | Small cell lung CA | GHRH<br>GH |
| 7. | Polycythemia | Pancreatic islet tumors<br>Uterine fibromyomata<br>Cerebellar hemangioblastoma | IGF - I<br>Erythropoietin |

* Hypercalcemia is common in hematological malignancies, particularly myeloma due to release of osteoclast-activating cytokines (IL-1, TNPβ) by tumors.

## Metabolic Effects of Tumors

Neoplastic cells differentiated tissues sometimes synthesize compounds that are not normally produced from that tissue. These substances may alter the metabolism and may produce clinical effects and hormone syndromes. Also, these substances may be biologically inactive and serve as *tumor markers.*

Also, neoplasias are associated with rare syndromes with endocrine or neurotransmitter properties showing common tumors, cytological characteristics, e.g. in *APUDomas* staining technique show ability for *Amine Precursor Uptake and Decarboxylation* (Table 14.2, 14.3).

Certain tumors secrete physiologically active amines, while others secrete peptide hormones (e.g. pituitary, parathyroid and C-cells of thyroid).

## Biochemical Changes in Cancer

Metabolic changes in cancer are not always due to aberrant hormone secretion, but may be due to some other effect of tumor or as a consequence of treatment.

1. *Serum:* *High*: Calcium, uric acid, lactate, globulin, potassium, phosphate
   *Low*: Fasting glucose, albumin, magnesium
2. *Anemia:* Common, could be due to hemorrhage, hemolysis, malnutrition or bone marrow infiltration by tumor cells.
3. *Hypercoagulable* state resulting in thromboembolism.
4. *Cancer cachexia*: A syndrome of weakness and generalized wasting. Causes can be deficient food intake, intestinal obstruction or anorexia of malignancy, malabsorption, increased demands and consumption of nutrients by tumor, release of cachectin (TNFα). The condition is rarely reversible unless the underlying tumor can be treated successfully.

**Table 14.2:** Carcinoid tumor

| | | |
|---|---|---|
| Site | : | Enterochromaffin cells of gut: cells of APUD series<br>90% in appendix and ileocecal region<br>Others: Gut, gallbladder, pancreatic duct, bronchi |
| Property | : | Low grade malignancy<br>Locally invasive<br>Rarely metastasize |
| Clinical features | : | GIT: nausea, vomiting, diarrhea, colic<br>Cardiovascular: flushing, hypotension<br>Respiratory: bronchospasm<br>Pellagra |
| Others | : | Manifestation of secretion of other hormones<br>Vasoactive amines: serotonin mainly<br>Histamine |
| Mediators | : | Kinin Hormones<br>ACTH<br>5 HIAA in urine |
| Lab. diagnosis | : | Plasma 5 HTP, histamine, peptide hormone |

**Table 14.3:** Origin of APUD tumors

| *Origin* | *Tumor* |
|---|---|
| GIT | Carcinoid |
| Pancreas | Islet cell CA |
| CNS | Ganglioneuroblastoma<br>Neuroblastoma |
| Thyroid | Medullary thyroidal CA |
| Skin | Melanoma |
| Adrenal medulla | Pheochromocytoma |
| Lung | Small cell CA<br>Carcinoid tumor |

**Argentaffin cells:**

Round and stain with silver salts
Derived from embryonic gut
Present in ileum, appendix in abundance
so, present in pancreas, stomach, rectum

## Multiple Endocrine Neoplasia (MEN)

MEN are familial disorders with autosomal dominant inheritance, where tumor hyperplasia occurs in two or more endocrine glands (Table 14.4).

| *MEN I* | *MEN IIa* |
|---|---|
| *Parathyroid* | *Thyroid (medullary cell CA)* |
| Pancreas | Adrenal medulla (pheochromocytoma) |
| Pituitary (anterior) | Parathyroid CA |
| Thyroid (follicular cell) | **MEN II b** |
| Adrenal cortex | Thyroid (medullary cell CA)<br>Adrenal medulla (pheochromocytoma)<br>Mucosal neuroma<br>may be associated with Marfanoid, Hirschsprung disease |

**Table 14.4:** Pancreatic tumors

| *Pancreatic islet tumors* | *Hormone produced* |
|---|---|
| Zollinger-Ellison syndrome<br>Peptic ulcer gastrinoma | <br>Gastrin |
| Insulinoma - Hypoglycemia | Insulin |
| Glucagonoma - Hyperglycemia | Glucagon |
| VIPoma - Watery diarrhea, hypokalemia | VIP |
| Somatostatinoma - diarrhea, steatorrhea, gallstones | Somatostatin |
| DM | Serotonin, PG |
| Carcinoid syndrome - diarrhea, hepatomegaly | Serotonin<br>Histamine<br>Kinin<br>ACTH |

**Questions:**

1) What are the metabolic effects of tumors?
2) Discuss the biochemical changes in cancer?
3) What is Carcinoid tumor?
4) Explain Mutiple Endocrine Neoplasia (MEN) in detail.
5) Name some endocrine syndromes and hormones associated with it.

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**CHAPTER 15**

# Toxicology

**Learning objectives:**

1. Enlist Toxic agents and discuss its features.
2. Describe Forensic Toxicology
3. Illustrate common methods for analysis of different drugs.
4. Explain Toxicology disciplines.

Toxicology includes analysis of drugs, heavy metals and other chemical agents in body fluids and tissues for three main purposes:

1. Diagnosis and management in drug-overdose (Table 15.1, 15.6)
2. Therapeutic monitoring of drug (TDM) (Table 15.2-15.4)
3. Screening for the presence of drugs of abuse

**Table 15.1:** Reasons for high serum drug concentrations

| |
|---|
| Patient noncompliance |
| Improper dosage |
| Poor bioavailability of preparation |
| Malabsorption |
| Drug interaction |
| Liver disease |
| Kidney disease |
| Altered protein binding |
| Genetic factors affecting metabolism |

**Table 15.2:** Need for monitoring of drug therapy

| |
|---|
| 1. Patient taking more than one drug has increased probability of drug interaction and toxicity |
| 2. To follow patient compliance |
| 3. Indicated in drug groups which show individual variation or are toxic above therapeutic range like: |
| Antiepileptics |
| Theophylline |
| Tricyclic antidepressants |
| Lithium carbonate |
| Aminoglycosides |

**Table 15.3:** Drugs requiring TDM

| | *Drug* | *Therapeutic range (toxic level)* |
|---|---|---|
| 1. | Carbomazapine | 4–12 µg/ml (>15.0 µg/ml) |
| 2. | Digoxin | 0.5–2 ng/ml (> 2.5 mg/ml) |
| 3. | Cyclosporine | 12 hrs after dose 100–400 ng/ml (renal transplant)<br>24 hrs after dose 100–200 ng/ml (> 400 ng/ml) |
| 4. | Phenytoin | 10–20 µg/ml ( > 20 µg/ml) |
| 5. | Phenobarbitone | 15–40 µg/ml (> 35 µg/ml) |
| 6. | Theophylline | 8–20 µg/ml (>20 µg/ml) |

**Table 15.4:** Features of toxic agents

| *Agent* | | *Properties* | *Clinical features* | *Analysis/Measurement* |
|---|---|---|---|---|
| 1. | ***Alcohol*** | | | |
| a. | Ethyl alcohol | Principal pharmacologic action :<br>CNS depression<br><br>*Legal intoxication :*<br>80–100 mg/dl<br>>400 mg/dl : death | disorientation or mild euphoria<br>stupor<br>coma | blood alcohol<br>breath alcohol<br>saliva alcohol<br>urine alcohol* |
| | * Can detect alcohol ingestion within previous 8 hours | | | |
| b. | Methyl alcohol | Used as solvent in a number of commercial product<br><br>consumed as illicit liquor | severe metabolic acidosis<br>peripheral circulatory failure<br>blindness<br>causes optic neuropathy and blindness<br>death | serum formate |
| c. | Isopropanol | Used as rubbing alcohol<br>has twice the CNS depressant action as ethanol<br>not as toxic as methanol | similar to ethanol | Urine isopropanol levels<br>Urine acetone |
| 2. | ***Analgesics*** | used in treatment of | | |
| a. | Acetaminophen (paracetamol) | mild pain or fever | nausea, vomiting, abdominal discomfort<br>*over dosage* causes hepatic, nephrotoxicity<br>liver toxicity (which can be predicted after 4 hrs post ingestion | *Reference internal :*<br>Serum 10–30 µg/ml<br>*Toxic level* :<br>>200 µg/ml<br><br>Immunoassay (EMIT) for acetaminophen |
| b. | Acetyl salicylic Acid (Aspirin) | Analgesic<br>Antipyretic | *Therapeutic* <100 µg/ml<br>*Toxic*>100<br>GI intolerance | S.salicylate<br>U.salicylate |

*Contd...*

*Contd...*

| | | | | |
|---|---|---|---|---|
| | | Anti-inflammatory | impaired hemostasis, deafness, headache, vertigo, tinnitus, nausea, vomiting, hyperventilation | (photometric GC HPLC) |
| 3. | ***Barbiturates*** | | | |
| | | Low therapeutic index | Coma hypothermia | S.barbiturate level |
| | | High abuse potential Suppress CNS and neuronal activity sedative and hypnotic | hypotension cardiorespiratory arrest | (immunoassay) |
| 4. | ***Benzodiazepines*** | CNS depressants anxiolytic sedative hypnotic muscle relaxant anticonvulsant *"date-rape" pill* | drowsiness slurred speech ataxia coma | S. benzodiazepine U. benzodiazepine (HPLC immunoassay) |
| 5. | ***Cannabinoids: Principal cannabinoid is $\Delta^9$-*** | illegal drug *psychoactive effects* : euphoria Inhaled in smoke t½ THC - day in casual user and 3-5 d. in chronic users | drug of abuse in infrequent users : Impairment of intell-ectual performance | THC +ve in urine for 2-5 d after use immunoassay cut off value of 20 ng/ml THC |
| 6. | ***Cocaine*** | CNS stimulant Euphoria | mydriasis tachycardia hypertension hyperthermia agitation seizure coma | Urinary benzoylecgonine and ecgonine methyl ester (Immunoassay GC, HPLC) |
| 7. | ***Lysergic acid diethylamide (LSD)*** | Hallucinogenic | mydriasis tachycardia salivation lacrimation vomiting panic attack | Urine LSD immunoassay |
| 8. | ***Amphetamines*** | Used to treat obesity CNS stimulant | *Overdose :* dizziness tremor hypertension cardiac arrhythmia convulsion coma | Urine Immunoassay GC/MS |
| 9. | ***Opioids/Opiates*** | analgesic sedative | sedation euphoria | Immunoassay Urine opiate |

*Contd...*

# Section III
# Endocrines

**CHAPTER 16**

# Endocrine Hypothalamus

**Learning objectives:**

1. Examine the role of Hypothalamus in body

The brain is also one of the most important endocrinal glands.

## Hypothalamus

Hypothalamus lies at the base of the brain and contains specialized nerve cells (nuclei) that synthesize hormones to regulate hormone secretion from the pituitary. These hormones are transported along the axon of the nerve terminal to be finally released into portal blood system.

Hypothalamus is composed of three regions:

- Rostral or supraoptic hypothalamus
- Middle or tuberal hypothalamus
- Caudal or mammary hypothalamus

## Biorhythm

In most endocrine systems, rhythmic secretion of hormones occurs which may vary over minutes to hours, days, weeks, or even longer periods.

### Circadian or Diurnal Rhythm

When rhythm occurs with a time interval of approximately 24 hrs, they are termed as *circadian* or *diurnal*. They are usually regulated by one or more internal "clocks" synchronized by factors such as dark/light cycle and sleep.

### Ultradian Rhythm

They are the biorhythms that occur more frequently than once a day.

## ❖ Infradian Rhythm

They occur over time periods longer than 24 hours, e.g. menstrual cycle.
Endocrine rhythms involve pulsatile and circadian release of pituitary hormones, e.g. LH (every 90 min) ACTH (peak at 8 am).

**Questions:**

1. Write the functions of Hypothalamus.
2. What is Biorhythm? Write its types.

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**CHAPTER 17**

# Pituitary Gland

**Learning objectives:**

1. Describe Hypothalamic Pituitary axis.
2. Enlist and explain all Pituitary hormones.
3. Discuss all disorders related to Pituitary gland.

## ❖ Pituitary Gland

Pituitary consists of three lobes—anterior lobe, or adenohypophysis (primary glandular tissue), posterior lobe, or neurohypophysis and intermediate lobe. Anterior pituitary grows from primary oral cavity (Rathke's pouch) and consists of glandular tissue; posterior pituitary is neural in origin (Table 17.1).

**Table 17.1**: Pituitary hormones

| | |
|---|---|
| *Adenohypophysis :* | GH |
| | Prolactin (PRL) |
| | Thyroid stimulating hormone (TSH) |
| | Follicle stimulating hormone (FSH) |
| | Luteinizing hormone (LH) |
| | Adrenocorticotropic hormone (ACTH) and β-Lipotropin (LPH) |
| *Neurohypophysis hormones:* | |
| | ADH (Antidiuretic Hormone) |
| | Oxytocin |

| *Flow sheet of trophic hormones and target gland hormones* | | | | | | |
|---|---|---|---|---|---|---|
| Hypothalamic hormone | GnRH | TRH | SS (GHRH) | GHRH | CRH | AVP ADH |
| Pituitary hormone | FSH, LH | TSH | - | GH | ACTH | - |
| Target gland hormone | Estrogen Progesterone Testosterone | T3, T4 | - | - | Corticosteroids | |

## ❖ Combined Test (Triple Bolus Test) of Anterior Pituitary Function

### Procedure

In a overnight fasting patient, take basal blood sample.
Analyze for glucose, cortisol (or ACTH), FSH, LH, TSH, fT4, GH.
Give 200 μg TRH, 100 μg GnRH, 1.5 U/kg body weight soluble insulin.
Take blood samples at various interval and Table 17.2 describes assessment of pituitary function.

| | Analysis | | | | |
|---|---|---|---|---|---|
| *Time (min)* | *Glucose* | *Cortisol* | *TSH* | *GH* | *FSH, LH* |
| 0 | √ | √ | √ | √ | √ |
| 15 | √ | - | - | - | - |
| 20 | - | - | √ | - | √ |
| 30 | √ | √ | - | √ | - |
| 45 | √ | - | - | - | - |
| 60 | √ | √ | √ | √ | √ |
| 90 | √ | √ | - | √ | - |
| 120 | √ | √ | - | √ | - |
| Response | <2.2 | > 200 *mmol/L* | > 5 mU/L | >20 *nmol/L* | > 1.5 times, *>5 times* |

**Table 17.2:** Assessment of pituitary function

***Indications***

1. Detection of hormonal deficiency
   a. before and after treatment of pituitary tumors
   b. as a result of pituitary surgery or irradiation.
2. Recognition of hormone producing tumors

***Methods***

| *Gland/Organ* | *Test* |
|---|---|
| *a. Before surgery* | Serum cortisol |
| Adrenal | Cosyntropin stimulation test<br>Estradiol in females |
| Gonads | Testosterone in males |
| Thyroid | TSH |
| b. *After surgery* | |
| Adrenal | Cosyntropin stimulation test |
| Gonads | Sex hormones |
| Thyroid | TSH |

# Hypothalmic Pituitary Axis

Hypothalamus synthesize hormones to regulate hormone secretion from the pituitary (Table 17.3-17.6)

**Table 17.3:** Test for hypothalamic target gland/organ axis

***Hypothalamic-Pituitary-Adrenal axis***
Normal morning cortisol
Cosyntropin stimulation test

***Hypothalamic-Pituitary-Thyroid axis***
Serum free thyroxine
TSH

***Hypothalamic-Pituitary-Gonadal axis***
Serum gonadotropin (LH, FSH)
Sex steroids (estradiol/testosterone)

**Table 17.4:** Problems in evaluation of hypothalamic pituitary axis

| *Condition* | *Reason* |
|---|---|
| Obesity | GH dynamics impaired<br>insulin induced hypoglycemia<br>GHRH, arginine, levodopa test fail to provoke GH secretion |
| DM (Diabeters Mellitus) | Diabetics have normal or elevated GH levels which do not further rise in response to hypoglycemia, arginine |
| CRF<br>(Chronic Renal Failure) | Due to prolongation of their half-life, GH, PRL, LH, FSH, TSH and free cortisol levels are elevated<br>Dexamethasone suppression of cortisol impaired |
| Starvation | With fasting and malnutrition, GH secretion increases |
| Depression | PRL and TSH dynamics are normal<br>Dexamethasone suppression altered |

**Table 17.5:** Endocrine tests of hypothalamic pituitary function

| |
|---|
| Cosyntropin test<br>(ACTH stimulation) |
| Insulin hypoglycemia test (IHT) |
| Metyrapone test |
| GHRH - arginine infusion test |
| Glucose GH suppression test |
| TRH test |
| GnRH test |
| Clomiphene test |
| CRH test |

**Table 17.6:** Causes of hypothalamic and pituitary dysfunction

| | |
|---|---|
| Invasion | Craniopharyngioma<br>Primary central nervous system tumor<br>Epidermoid and dermoid tumors<br>Pituitary adenoma |
| Infarction | Postpartum hemorrhage<br>Spontaneous hemorrhage |
| Infiltration | Sarcoidosis<br>Hemochromatosis<br>Histiocytosis X |
| Injury | Head trauma |

*Contd...*

# CHAPTER 18

# Adrenals

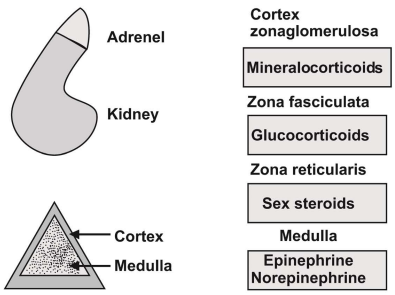



Fig. 18.1: Adrenal cortex and medulla

**Learning objectives:**

1. Explain Pituitary – Adrenal axis.
2. Describe all hormones secreting from Adrenals.
3. Illustrate Cushing's Syndrome.
4. Discuss all endocrinal disorders associated with Adrenal gland.

Adrenals lie just above kidneys and can be divided into cortex and medulla on the basis of anatomical and functional grounds.
Cortex secretes glucocorticoids (GC) mineralocorticoids (MC) and sex steroid hormones which are synthesized from cholesterol obtained from both HDL and LDL in plasma.
Medulla secretes, catecholamines, mainly epinephrine.

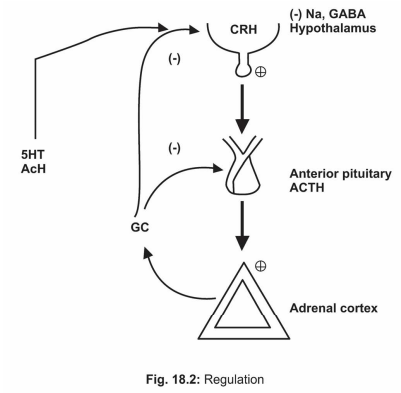



Fig. 18.2: Regulation

Corticosterol binding globulin or transcortin CBG

90% CBG bound
10% free
CBG ↑ pregnancy
estrogen treatment
↓ hypoproteinemia
(Nephrotic syndrome)

**Simmi Kharb**

## Adrenal Cortex Hormones (Fig 18.1, 18.2)

Glucocorticoids
Mineralocorticoids
Sex hormones

## Adrenal Medulla Hormones

Epinephrine
Norepinephrine

## Cortisol: Characteristics

Show diurnal variation
Circadian rhythm with peak secretion in early morning and declining with lowest level at midnight.

*Sampling* at 8 to 9 am and 11 pm to detect loss of diurnal variation.

Stresses such as fever, trauma, exercise, anxiety cause increased secretion of CRH (Table 18.3-18.6).

*Caution:* Synthetic glucocorticoid prednisolone cross-reacts with cortisol in immunoassay.

*Diurnal Rhythm of GC = Biological Clock.*
Biological clock resides in suprachiasmatic area of bran synchronized by exogenous influences of light.
Related to sleeping waking cycle.
Levels are highest at start of working day and 8 am sample cortisol is normal but, 10 pm cortisol falling to lowest with onset of sleep.

**Table 18.1:** Diagnostic test for causes of Cushing's syndrome

| | *Pituitary macroadenoma* | *Pituitary microadenoma* | *Ectopic ACTH or CRH* | *Adrenal tumor* |
|---|---|---|---|---|
| ACTH | ↑ ↑↑ | n - ↑ | ↑/↑↑↑ | ↓ |
| Response to high dose dexamethasone | < 10 | 95 | <10 | <10 |
| Response CRH to | > 90 | > 90 | < 10 | < 10 |

**Table 18.2:** Tests of pituitary-adrenal axis

| |
|---|
| ACTH stimulation test |
| IHT |
| CRH test |
| Metyrapone test |

**Table 18.3**: Adrenal hypofunction

| | |
|---|---|
| **Causes** | |
| Glucocorticoid treatment | |
| Autoimmune | |
| Infection (TB, viral) | |
| **Tests** | |
| Plasma cortisol : | Low |
| Synacthen test : | Response absent or blunt |

**Table 18.4**: Adrenal hyperfunction

| | |
|---|---|
| **Causes:** | Cushing's Syndrome<br>Corticosteroid or ACTH treatment<br>Pituitary hypersecretion of ACTH (Cushing's disease)<br>Adrenal adenoma<br>Adrenal carcinoma<br>Ectopic ACTH secreting tumors carcinoid, carcinoma bronchus |
| **Tests:** | 24 hrs U. Cortisol excretion increased<br>Dexamethasone suppression test: failure to suppress ACTH release<br>IHT: glucose intolerance<br>Loss of diurnal variation of cortisol secretion |

ACTH

# Cushing's syndrome (Fig 18.4-18.6)

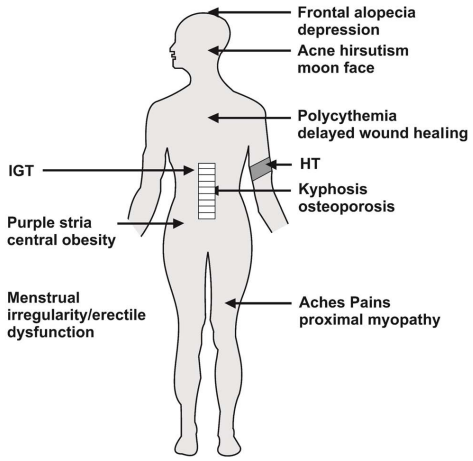



**Fig. 18.4:** Cushing's Syndrome

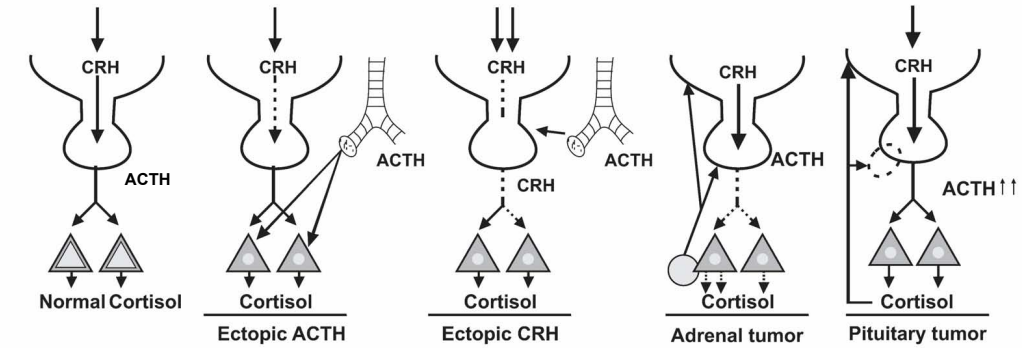



**Fig. 18.5:** Causes of Cushing's syndrome

**CHAPTER 19**

# Thyroid

**Learning objectives:**

1. Explain about synthesis of Thyroid hormones.
2. Discuss utility of measuring free T4 and T3.

| Hormones secreted | Cells |
|---|---|
| Thyroxine (T4) | Follicular cell |
| Tri-iodothyronine (T3) | Follicular cell |
| Calcitonin | C-cells |

While T4 is 10 times more in concentration, than T3, T3 is 3-4 times more potent than T4.

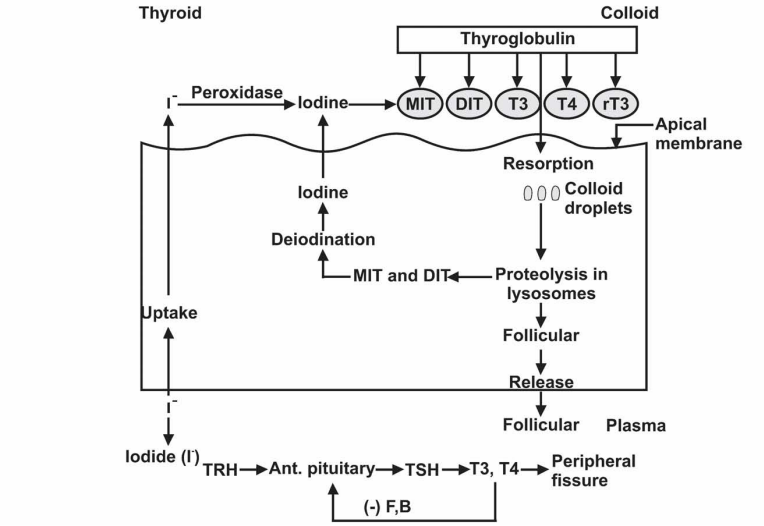



**Fig. 19.1:** Synthesis of thyroid hormones

- **Biologically active hormone T3,**
- 85% T3 in plasma formed by deiodination of T4
- rT3 arise from monodeiodination of T4 and is biologically inactive

70% of plasma T4 bound to TBG
80% of plasma T3 bound to TBG
Rest bound to transthyretin and albumin
Only 0.05% T4 are free
0.2% T3 are free

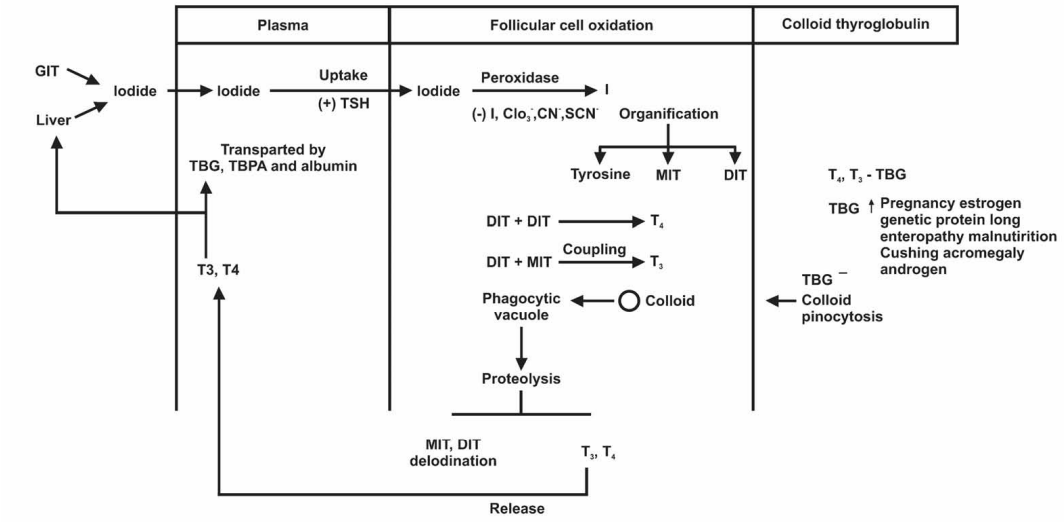
**Simmi Kharb**

*Lab investigations*
p TSH
p T3, T4
Thyroid antibody
Serum thyroglobulin
Thyroid enzyme
USE OF THYROID TESTS
• TT3 is reliable measure of hyperthyroidism, but is no value in hypothyroidism.
• Normal TSH rules out primary thyroid dysfunction

**Utility of measuring free T4 & T3 (fT4, fT3):**
Free T3, T4 concentration are independent of changes in concentration and affinity of thyroid hormones finding proteins and provide reliable measure to diagnose thyroid disorders.

| *Condition* | *Reason* |
|---|---|
| Assay interference | Endogenous heterophilic Ab<br>Observed in thyrotoxicosis |
| Pregnancy | Ist trimester – weak thyrotroplic effect of placental hCG (present in high concentrations) |
| (TBG) | ↑[TBG] during pregnancy results in ↑plasma (TT4) and (TT3)<br>Transient postpartum thyroid dysfunction. |
| Secondary thyroid disorders: | |
| Central hypothyroidism | [TSH] normal [FT3], [FT4] low TSH bioactivity reduced |
| Thyroid tumor | ↑ [FT3], [FT4] |
| (TSH secreting tumor) | hyperthyroidism ↑ [TSH] |
| Endorgan resistance | ↑ P $T_3$, $T_4$ |
| Non-thyroidal illness (NTI) | n or ↑ [TSH]<br>Sick-Euthyroid syndrome low [$T_3$]<br>• Alteration in hypothalamus – pituitary thyroid axis (-)<br>(–) TSH release by ↑ dopamine, cytokine, cortisol, somatostatin<br>• Change in TBG and affinity characteristics.<br>• Impaired uptake of thyroid hormone in peripheral tissues<br>↓ Production of T3 in peripheral tissues. |
| In NIT, TSH < 0-1 m U/L and increase due to recovery | Change in T3 ® |
| Drug intake | |
| G.C. dopamine | |
| Li, amiodarone, iodide | ↓ TSH<br>↓ Thyroid hormone secretion |
| Estrogen, tamoxifen, raloxifene clofibrate | Induce hyperthyroidism |
| Androgen, GC, anabolic steroids | ↓ TBG |
| Phenytoin carbamazepine barbiturates | ↑ hepatic metabolism |

## ❖ Synthesis




| *Disorder* | *Causes* | *Tests* |
|---|---|---|
| 1. Hyperthyroidism | • Grave's disease<br>• Toxic multinodular goiter<br>• Exogenous iodine and iodine containing drugs<br>• Ectopic thyroid tissue | High $fT_3$ and $fT_4$<br>low TSH |
| 2. Hypothyroidism | • Atrophic hypothyroidism (Hashimoto's) autoimmune<br>• Postsurgery<br>• Congenital<br>• Iodine deficiency<br>Secondary<br>(pituitary hypothalamic) | high TSH, $fT_4$ low |

# Screening Tests for Thyroid Disease

Congenital hypothyroidism

- TSH in capillary blood
- T4

**Questions:**

1. Write the mechanism of synthesis of thyroid hormones.
2. Describe hyper and hypothyroidism.
3. What are screening tests for thyroid disease?

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# Section IV

# Pathophysiology

**CHAPTER 20**

# Cardiac Function

**Learning objectives:**

1. Discuss Cardiac biomarkers.
2. Explain markers in Cardiac failure.
3. Enumerate Cardiovascular risk factors.

Cardiac Marker is a clinical laboratory test useful in detection of acute myocardial infarction (AMI) or minor myocardial injury.

## Cardiac Biomarkers (Table 20.1, 20.2)

Creatine kinase (CK)
Lactate dehydrogenase (LDH)
Myoglobin
Troponin

**Table 20.1:** Cardiac biomarkers

| | *CK* | *CK-2* | *LDH-1* | *Myoglobin* | *Troponin* |
|---|---|---|---|---|---|
| 1. Hours until marker increases above upper reference limit | 3–8 | 3–8 | 8–12 | 1–3 | 3–8 |
| 2. Hours until peak concentration | 10–24 | 10–24 | 72–144 | 6–9 | 24–48(1st peak)<br>72–100 (2nd peak) |
| 3. Days until return to within reference interval | 3–4 | 2–3 | 8–14 | 1 | 4–10 |

**Table 20.2:** Prediction of reperfusion status

| *Test* | *Utility* |
|---|---|
| CK-2 | Rate of appearance of CK-2 in association with reperfusion occurs 90 minutes after thrombolysis |
| Troponin<br>Myoglobin | Useful in detecting reinfarction in postinfarct angina |

*Contd...*

*Contd...*

| |
|---|
| Myoglobin to total CK ratio > 5 implies reperfusion<br>(specificity of > 96%)<br>(sensitivity of 75%)<br>best indicator for prediction |

### Ischemia-Modified Albumin (IMA)

It is an early and sensitive marker of cardiac ischemia. N-terminal of albumin gets altered in myocardial infarction and it no longer can bind to metals such as Cu, Co, Ni. This is termed as *ischemia-modified albumin (IMA)* and can be detected by reduction in albumin's ability to bind cobalt. IMA is promising marker for early detection and has greater sensitivity than ECG and troponin. However, its precise role in patient management remains to be established.

Details of apolipoproteins and lipid profile can be referred in concerned section.

*Marker of deep vein thrombosis: D-dimers*

*D-dimers* are released during conversion of fibrinogen to fibrin (during thrombus formation). Presence of raised values of D-dimer in plasma is diagnostic of presence of a thrombus.

## Cardiovascular risk factors (Table 20.3)

**Table 20.3:** Cardiovascular risk factors

| |
|---|
| Classic risk factors:<br>i. Abnormal levels of lipids:<br>ii. Cholesterol<br>Triglyceride<br>HDL-C (low)<br>Others:<br>Hypertension<br>Smoking<br>Diabetes mellitus<br>Obesity<br>Family history<br>Recent Biochemical risk factors:<br>Homocysteine<br>C-reactive protein (hs-CRP)<br>Lipoprotein (a)<br>Fibrinogen<br>IMA |

## Markers of Cardiac Failure

*Cardiac failure* is a clinical condition associated with signs and symptoms of left or right ventricular dysfunction.

## Natriuretic Peptides (Table 20.4)

Three natriuretic peptides are:
1. Atrial natriuretic peptide (ANP)
2. Brain natriuretic peptide (BNP)
3. C-type natriuretic peptide (CNP)

**Table 20.4:** Natriuretic peptides

| | *ANP* | *BNP* | *CNP* |
|---|---|---|---|
| Site of production | atria | brain<br>cardiac<br>ventricles | brain<br>kidney<br>endothelial cells |
| Binding to receptors | A-type<br>C-type | A-type<br>C-type | B-type<br>C-type |
| Function | natriuresis<br>reduce ecf volume | natriuresis<br>reduce ecf volume | vasodilator<br>local tissue action |
| Utility | diagnostic marker<br>of cardiac failure | prognostic marker<br>in cardiac failure<br>marker of both<br>right and left<br>ventricular<br>dysfunctions | no proven value<br>as a cardiac hormone |

| *Analyte* | *Assay* | *Reference range* |
|---|---|---|
| CRP | Immunoassay | 6.8-820 µg/dl |
| Homocysteine | GC-MS, HPLC | 4–12 µmol/L |
| Fibrinogen | Colorimetric | 200–400 mg/dL |

## Tests useful in diagnosis and management of hypertension (Table 20.5)

**Table 20.5:** Clinical biochemistry tests useful in diagnosis and management of hypertension

| *Analyte* | *To rule out* |
|---|---|
| Glucose | Diabetes mellitus |
| Urea | Kidney disease |
| Creatinine | Kidney disease |
| Urine protein | Kidney disease |
| Potassium | Primary hyperaldosteronism monitoring treatment |
| Aldosterone:renin ratio | Primary hyperaldosteronism monitoring treatment |
| Calcium | Primary hyperparathyroidism |
| Phosphate | Primary hyperparathyroidism |
| PTH | Primary hyperparathyroidism |
| IGF-1 | GH excess: acromegaly |
| OGT | GH excess: acromegaly |
| Catecholamine metabolites (HMMA) | Pheochromocytoma |
| Urine cortisol | Cushing's syndrome |

**Questions:**

1. What are cardiac biomarkers?
2. Define Ischemia Modified Albumin (IMA).
3. Discuss Natriuretic Peptides.
4. Write the name of tests useful in diagnosis and management of hypertension.

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**CHAPTER 21**

# Liver Functions

**Learning objectives:**

1. Illustrate different functions of liver.
2. Discuss Bilirubin metabolism and laboratory tests of Bilirubin.
3. Describe Jaundice and Cirrhosis in detail.
4. Explain different tests done in liver disease.

## Liver

### Functions of Liver

Liver is the 'metabolic factory' of the body.
It has essential metabolic, synthetic and excretory functions (Table21.1-21.3).

**Table 21.1:** Normal liver function

| |
|---|
| **Metabolic** |
| Carbohydrate metabolism |
| Lipid and lipoprotein metabolism |
| Protein metabolism |
| **Synthetic** |
| Protein synthesis: |
| Most plasma proteins: (except Ig, RhF, complement) |
| Blood coagulation factors: II, V, VII, IX, XI |
| Primary bile acids |
| Lipoprotein |
| Urea |
| Bilirubin glucuronide |
| **Excretory** |
| Detoxification of: |
| Xenobiotics |
| Drugs |
| Toxic metabolic wastes (ammonia, bilirubin) |

**Table 21.2:** Half-life of plasma proteins

| *Plasma protein* | *t½* |
|---|---|
| Albumin | 20 d |
| Factor VII | 4–6 hrs |
| Transthyretin | 1–2 d |
| Transferrin | 6 d |

**Table 21.3:** Excretion and detoxification

| |
|---|
| a. Inactivation of steroids:<br>Cholesterol<br>Steroid hormones |
| b. Inactivation and metabolism of drugs, toxins |
| c. Urea synthesis |
| d. Excretion<br>Cholesterol<br>Bile acids<br>Conjugated steroid hormones (with glucuronate/sulfate)<br>Drugs<br>Toxins |

## Bilirubin metabolism (Fig 21.1)

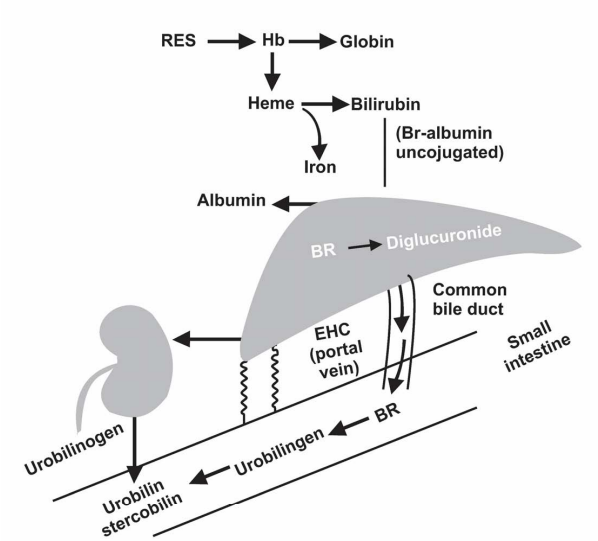


**Fig. 21.1:** Bilirubin metabolism

## Laboratory Tests of Bilirubin (Fig 21.4-21.7)

Total bilirubin
Direct bilirubin or conjugated
Indirect bilirubin or unconjugated (total minus direct).

**Table 21.4:** Location of hepatocellular enzymes

| *Site* | *Enzyme* |
|---|---|
| Cytoplasmic | LDH |
| | AST |
| | ALT |
| Mitochondrial | mt AST |
| | Glutamate dehydrogenase (GDH) |
| Canalicular surface of hepatocyte | ALP |
| | GGT* |

* also found in microsomes

**Table 21.5:** Localization of liver damage with the help of enzymes

| | |
|---|---|
| 1. Serial enzyme determination: | ALT |
| | LDH |
| 2. Isoenzyme determination: | CK |
| 3. Estimation of more than one enzyme: | ALT |
| | AST |

**Table 21.6:** Storage (depot) function of liver

| |
|---|
| *Site of storage of:* |
| Iron (700 mg iron) |
| Glycogen |
| Amino acids |
| Lipids (TAG) |
| Vitamins |
| *Investigating a liver disease:* |
| Bilirubin excretory function |
| Hepatocellular damage: |
| ALT/AST |
| GGT |
| Cholestasis: |
| ALP |
| Synthetic: |
| Albumin |
| Prothrombin time |

**Table 21.7:** Tests for assessment of cell damage

| | |
|---|---|
| Acute cell damage | Very high ALT |
| Cirrhosis | Slightly raised ALT |
| Severe liver disease (terminal) | Fall in enzyme activity |

Extent of cell damage and rate of release of enzyme from damaged cells and their clearance from plasma determine the plasma levels of enzymes.

**CHAPTER 22**

# Renal Functions

**Learning objectives:**

1. Explain Renal functions and Renal function tests.
2. Describe Renal failure.
3. Illustrate Urine osmolarity and its importance clinically.
4. Discuss Acid-base balance and disorders associated with it.

## Kidneys

Kidneys are paired organ system lying in lumbar region, each having about 1 million nephrons. (Table 22.1, 22.2)

**Table 22.1:** Major functions of kidney

| |
|---|
| *Excretion:* |
| excretion of end products of metabolism |
| *Regulation of ecf:* |
| regulation of extracellular fluid (ecf) volume and composition and acid-base status |
| *Endocrine function:* |
| synthesis of hormones namely, renin, erythropoietin, calcitriol |

## Glomerular Fluid (GF)

It is an ultrafiltrate of plasma and its composition is similar to plasma except that proteins are absent. (Table 22.3, 22.4)

## Glomerular Filtration Rate (GFR)

Normal GFR is 120 mL/min approximately and is equivalent to volume of 170 L/24 h.

*GFR depends on:*

- rate of blood flow
- balance between hydrostatic and oncotic forces in afferent arterioles and glomerular filter (tubular fluid).

**Table 22.2**: Functions of kidney

| |
|---|
| Formation of urine |
| Regulatory function: |
| acid-base balance |
| water-electrolyte balance |
| Excretion of end products of protein metabolism |
| Endocrine function: |
| Vitamin D metabolism |
| Renin release |
| Erythropoietin production |
| PG and TX production |
| Body protein homeostasis |

**Table 22.3**: Glomerular permeability: Salient features

| |
|---|
| Glomerulus is a size- , charge- and shape-dependent filter |
| Glomerular basement membrane has strong negative charge: |
| for negatively charged molecules, size cut off is 18 nm. |
| Proteins of molecular weight lower than albumin (66.3 kD) filterable. |
| Damage to negative charge results in leakage of albumin (molecular radii 3.6 nm) through basement membrane. |

**Table 22.4**: Renal function tests

| |
|---|
| 1. *Glomerular function*: |
| a. GFR: |
| Exogenous substance: |
| Inulin |
| Cr – EDTA |
| Endogenous substance: |
| Urea |
| Creatinine |
| β macroglobulin |
| Retinol-binding protein |
| α1 microglobulin |
| Cystatin C |
| b. *Glomerular permeability*: |
| Urine protein |
| 2. *Tubular function*: |
| Tubular proteinuria |
| Osmolality |
| Specific gravity |
| Concentration and dilution tests |
| Tubular secretory mass measurement by diodone/PAH |

*Clearance*

It is ml of plasma cleared off a particular substance by both the kidneys per minute. (Table 22.5-22.6)

*Properties of ideal substance for clearance:*

1. It should be neither secreted nor reabsorbed by the kidney.
2. It should not be affected by rate of urine flow.
3. Its levels in blood should remain constant.
4. Its clearance should be equivalent to GFR.

**Table 22.5**: Comparison of urea and creatinine clearance

| Urea clearance | Creatinine clearance |
|---|---|
| 1. Its value is 3/5th of GFR | 1. Values are nearly equal to GFR |
| 2. Plasma values of urea are not constant throughout the day | 2. Its plasma values remain constant over 24 hrs |
| 3. Urea is both secreted and reabsorbed by kidney | 3. Creatinine is neither secreted nor reabsorbed by kidney |
| 4. It is affected by rate of urine flow | 4. 4. It does not depend on rate of urine flow |

**Table 22.6**: Plasma urea/Creatinine ratio

| Increased | Decreased |
|---|---|
| High protein intake | Low protein intake in diet |
| Hypercatabolic state | Severe liver disease |
| Dehydration | Dialysis |
| GI bleeding | |

# Overflow Proteinuria

Abnormal amounts of low molecular weight proteins appearing in plasma and urine.

**Table 22.7**: Principal proteins that appear in urine

| Protein | Disease |
|---|---|
| Amylase | Acute pancreatitis |
| Bence Jones | Multiple myeloma |
| Hemoglobin | Hemolysis (intravascular) |
| Lysozyme | Myeloid Leukemia |
| Myoglobin | Crush injury to muscle |

# Microalbuminuria

More correctly termed as *minimal albuminuria*. It is mildly increased excretion (200 to 300 mg/L) of albumin in urine.

It appears to be a predictor of future development of clinical renal disease in patients with DM or hypertension.

Guidelines for investigating microalbuminuria

1. Measure albumin/creatinine, if > 30 mg/d, do albumin excretion rate (AER) in 24 hours collection.
2. AER between 30 to 300 mg/24h is microalbuminuria.
3. Further monitor AER, blood pressure, baseline GFR on every follow-up.

The incidence of microalbuminuria may be reduced by optimal control of glycemia, blood pressure.

# CHAPTER 23

# Pregnancy

**Learning objectives:**

1. Enumerate all substances that can pass and cannot pass through placenta.
2. Describe monitoring during pregnancy.
3. Explain characteristics and features of Amniotic fluid.

## Transport Across Placenta

1. Passive transport
   i. Limited passive transport:
      FFA
      Unconjugated steroids
      Steroid sulfates
   ii. Passive transport:
      $O_2$
      $CO_2$
      Na
      Cl
      Urea
      Ethanol
      Lipid soluble molecules up to 5000 Da
2. Active transport
   Glucose
   Calcium
   Many amino acids
3. *Receptor mediated endocytosis*
   Insulin
   LDL
   Maternal IgG

## Substances not Transported Across Placenta

Maternal IgM
Thyroid hormones
Most proteins
Maternal and fetal RBCs

**Simmi Kharb**

# MONITORING DURING PREGNANCY (Table 23.1-23.4)

**Table 23.1**: Lab evaluation during pregnancy

| 1st Trimester | 2nd Trimester |
|---|---|
| Hb | 15–21 weeks |
| ABO, Rh (D) | Maternal serum αAFP |
| Urine: | 24–24 weeks: |
| Protein | Hb |
| Culture | Diabetes detection/screening |
| Toxoplasma Ab (if indicated) | Urine protein |
| Syphilis Ab | |
| HIV Ab | |

**Table 23.2**: Metabolic changes during pregnancy

| Decreased | Increased |
|---|---|
| Urea | Cortisol |
| Albumin | Copper |
| Total protein | Thyroxine |
| Glucose tolerance | HDL - C |
| LDL – C | ALP |

**Table 23.3**: Hormonal changes during pregnancy

| | Hormone | Source |
|---|---|---|
| 1. | hCG | Corpus luteum |
| 2. | Estrogen | Corpus luteum |
| | | Placenta |
| | | Fetal Adrenal |
| 3. | Human placental lactogen | Placenta |
| 4. | Placental ALP | Placenta |

**Table 23.4**: Aminocentesis: Biochemistry

| Parameter | Diagnostic value |
|---|---|
| Lecithin/Sphingomyelin ratio (L/S) | Fetal lung maturity |
| Phosphatidylglycerol | Fetal lung maturity |
| Creatinine | > 2 mg/dl - Fetus is mature |
| Bilirubin | Reserved for monitoring blood group immunized cases |
| Blood acid-base and electrolyte level | Feto-placental well-being |
| Hormones: | Feto-placental well-being |
| Estriol | Feto-placental well-being |
| hCG | Feto-placental well-being |
| hPL | Feto-placental well-being |
| AFP | Diagnosis of neural tube defects, Down's syndrome |
| Chorionic villus sampling and analysis of fetal chromosome and DNA | Screening of inherited disorders |

## Amniotic Fluid: Characteristics

*Origin *:*

Placenta
Fetal kidney
Skin membrane
Lung
Intestine

* relative contribution of each source depends on stage of fetal development

*Biochemistry*

i. *before keratinization* of fetal skin: it can result as a *transudation* from fetal surface
ii. *after keratinization of fetal skin:* fetal urine makes a significant centribution.

## Amniotic Fluid: Features

Isotonic (early pregnancy) to hypotonic (term, 255 m Osm/kg of water)
*Nitrogenous products*:

Urea
Creatinine
Uric acid

*Proteins*:

Source : fetal (skin, urinary, GIT and respiratory tract)
: maternal (by transudation)

*Hormones:*

| *Peptide* | *Steroid* | *PG* |
|---|---|---|
| ACTH | Estradiol | $PGE_2$ |
| FSH | Estriol | $PGF_{2\alpha}$ |
| LH | Estrone | |
| hCG | | |
| HPL | | |
| PRL | | |
| Oxytocin | | |
| Relaxin | | |
| Thyrotropin | | |
| Thyroxine | | |

## Monitoring in Gestational Diabetes*

Maternal blood glucose
OGT
$HbA_{IC}$
Urine albumin
Serum creatinine

*for further details, see section on diabetes.

# Section V

## Oral Cavity

**CHAPTER 24**

# The Oral Cavity—A Diagnostic Window to the Body

**Learning objectives:**

1. Discuss saliva as a diagnostic tool.

Saliva is the protective fluid of the oral cavity with its vast supply of microbe killers, saliva combats invading pathogens such as HIV and a host of bacteria associated with oral and systemic diseases. Antibodies directed against pathogens such as polio and cold viruses, are formed in saliva. Large salivary glycoproteins called mucins, appear to have antiviral properties as well.

*Oral fluid is also a mirror of the body*, containing many compounds that are indicator of health, disease status of a person. Also, like blood and urine, composition of oral fluid may be altered in the presence of disease. Saliva may be collected in a much less invasive fashion than blood or urine, and at times preferred over blood for analyzing analytes (Table 24.1).

**Table 24.1:** Saliva as diagnostic tool

| Analyte in saliva | Use |
|---|---|
| Alcohol | For alcohol screening at roadside emergency department—test cards are available |
| Free cortisol | Practical, convenient and accurate |
| Drug abuse testing | For therapeutic drug monitoring, detecting illicit drug use |
| Estrogen | Useful in diagnosis of and treatment of infertile women with anovulatory cycle during in vitro fertilization, monitoring hormone replacement therapy * and closely reflect free fraction of hormone |
| Progesterone | To investigate luteal defects in infertile female and reflect free unbound fraction |
| Protein | Screening IgA in infantile hypogammaglobulinemia and BMG in Sjogren's syndrome |
| Steroid hormones | Useful in frequent sampling |
| Testosterone | Indicator of androgen status |

*requires sensitive assay for accurate measurement.

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## Other Uses of Saliva Analysis

1. Diagnostic marker for early detection of cancer related protein in breast cancer.
2. Gene therapy using salivary glands offers hope in type I DM, GH deficiency and hypoparathyroidism.
3. In future, *Oral fluid chips* will be available for disease point-of-care diagnostic platform.
4. Nanotechnology based *salivary biosensor* for ultrasensitive salivary diagnostic analytes.

## Diagnostic Molecular Targets in Saliva

*Salivary transcriptome* consists of ~ 3000 mRNA that can be used for disease diagnostics. Although, salivary proteome is still several years away, the complete normal salivary transcriptome has been reported.

As a biomarker, RNA (in saliva) is as robust and as informative as any other analyte. Highly diagnostic RNA signatures have been identified for head and neck cancer and few major human systemic diseases. Latest target for candidates for salivary diagnostic are cardiovascular disease, cancer (lung, prostate, ovarian and colon), Alzheimer's disease, osteoporosis, cerebrovascular diseases, nephritis, septicemia, chronic respiratory diseases, chronic liver disease and pneumonitis.

**Questions:**

1. How is saliva used as diagnostic tool?
2. Explain diagnostic Molecular Targets in saliva.
3. What are the uses of saliva analysis?

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