

PATHOPHYSIOLOGY OF COMMON DISEASES

LEARNING OBJECTIVES

After the completion of this chapter, you should be able to,

- ◆ Explain the types, aetiology and pathogenesis of Parkinson's disease
- ◆ Describe the pathophysiology of schizophrenia and stroke
- ◆ Summarize the aetiology and pathophysiology of hypertension and ischaemic heart diseases
- ◆ Discuss the types, pathophysiology and complications of diabetes mellitus
- ◆ Elaborate on the various disorders of gastrointestinal system such as peptic ulcer, cirrhosis, alcoholic liver diseases, etc.
- ◆ Explain the aetiology, pathophysiology as well as signs and symptoms of acute and chronic renal failure
- ◆ Provide a note on causes and pathophysiology of respiratory disorders.

1. DISORDERS OF NERVOUS SYSTEM

1.1 PARKINSONISM

Introduction

Parkinsonism is a disorder caused by the degeneration of basal ganglia, causing impairment of the motor nerves and disabling motor functions. It is caused due to decreased activity of dopamine or increased activity of acetylcholine in striatum, present in the basal ganglia. Both, balance and imbalance in the extrapyramidal system is shown in the figure below.

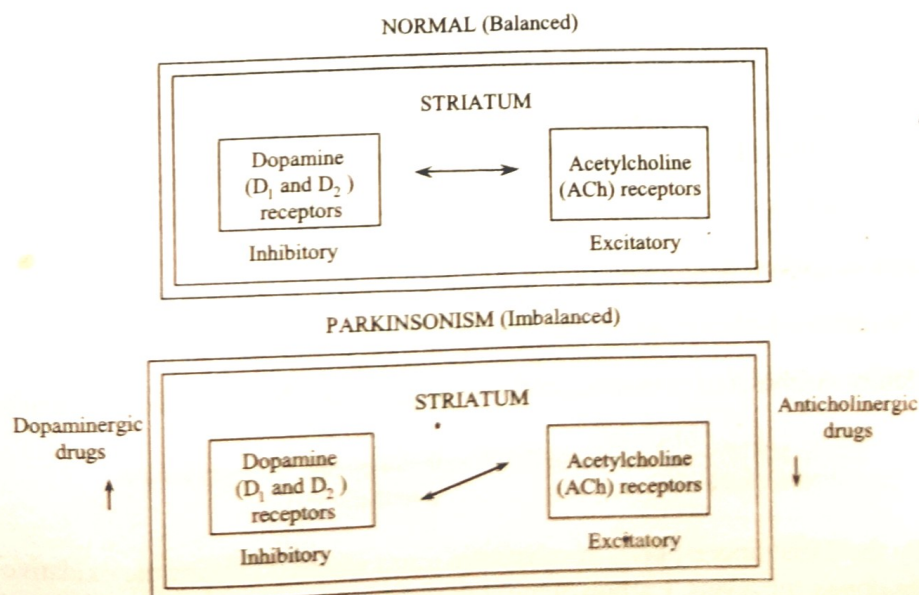


Figure: Balance and Imbalance in Extrapyramidal System

Dopaminergic neurons are present in the substantia nigra that synthesize dopamine and supply it to the striatum. Dopamine is synthesized in the terminals of dopaminergic neurons from tyrosine. Decrease in dopamine levels occur due to the loss of these dopaminergic neurons. This ultimately results in increased activity of acetylcholine (excitatory neurotransmitter).

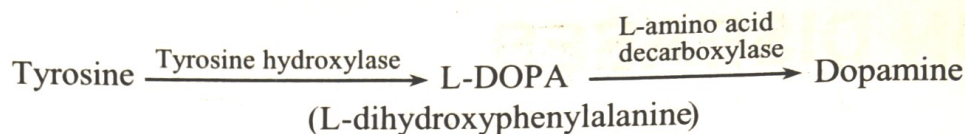
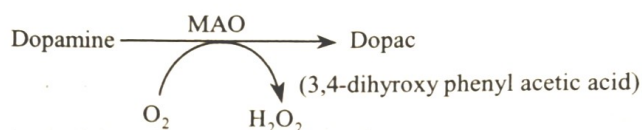


Figure: Synthesis of Dopamine

Types of Parkinsonism

1. Primary/Idiopathic Parkinsonism

As the name suggests, the cause of the disease remains unknown. Idiopathic parkinsonism is also termed as Parkinson's disease, predominantly affecting individuals over 60 years of age. Over the years, dopaminergic neurons degenerate due to H_2O_2 and free radicals such as O_2^- (superoxide) and OONO^- (peroxynitrite).



Free radicals are formed during the breakdown of dopamine by MAO enzyme. Toxic and degenerative moieties are also produced due to defective metabolism. These toxic moieties cause degeneration of dopamine. Disturbances in the motor control are seen when only about a quarter of normal dopamine levels reach the striatum.

2. Secondary/Drug Induced Parkinsonism

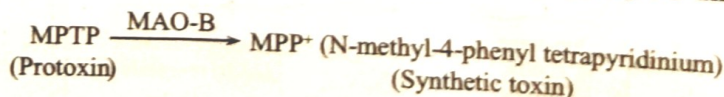
In this, there is no degeneration of dopamine as seen in the above case, but the decrease in dopamine is drug-induced. D_1 and D_2 are the two main dopaminergic receptors present in the striatum. D_1 receptors cause increased formation of cAMP and have stimulatory activity, while D_2 receptors cause decreased cAMP formation and have inhibitory activity. Prolonged use of antipsychotic drugs antagonize D_2 receptors and cause decreased dopamine levels. This can be treated by cessation of the offending drug.

Aetiology

The decrease in dopamine levels is due to the following reasons.

1. Ageing causes defective electron transfer in mitochondria, hence parkinsonism mostly occurs in individuals above 60 years of age
2. Genetic factors
3. Production of free radicals such as hydroxyl and peroxynitrite during the metabolism of neurotransmitters. These free radicals damage the brain cells and reduce dopamine levels
4. Poisons and poisonous environment
5. Intake of manganese or carbon monoxide
6. Neurotoxins like N-methyl-4-phenyl tetrahydropyridine (MPTP).

For example, the faulty synthesis of pethidine produces a byproduct, MPTP, CO and manganese.



MPP is taken up by the dopaminergic cells in substantia nigra where it inhibits the oxidative phosphorylation in the mitochondria and depletes dopamine levels. Carbon monoxide and manganese causes cell death and deposition of irregular proteins called *Lewy bodies* due to irregular functioning of the brain cells.

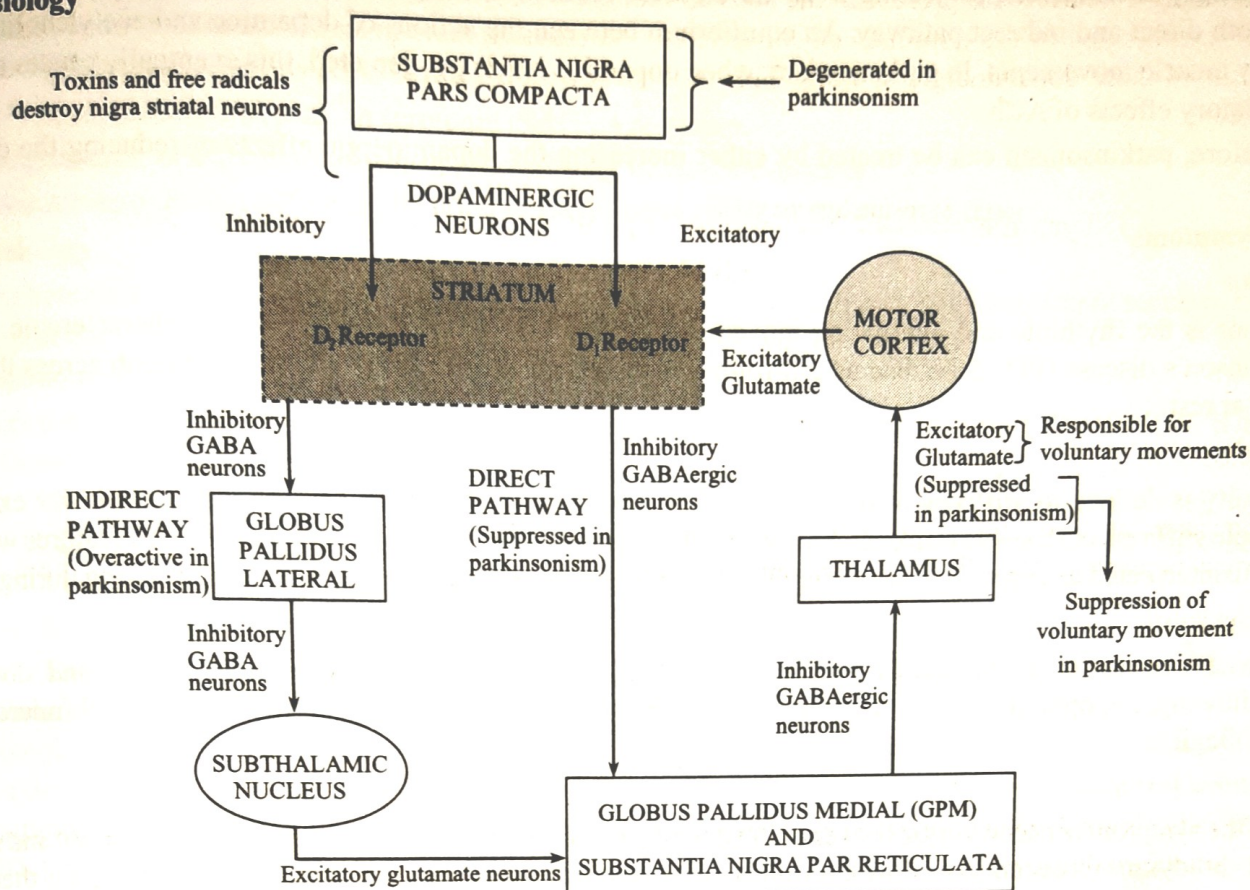


Figure: Pathogenesis of Parkinson's Disease

Dopaminergic neurons from substantia nigra pars compacta act on excitatory D₁ receptors (in the striatum) and causes excitation of the striatal neurons in the direct pathway. This excitation is neutralized when dopaminergic neurons from substantia nigra pars compacta act on inhibitory D₂ receptors (in the striatum) and cause inhibition of striatal neurons in the indirect pathway.

In the direct pathway, the globus pallidus medial and the substantia nigra par reticulata are innervated via inhibitory GABAergic neurons from the striatum. Similarly, the neurotransmission from these two regions to the thalamus is also carried out by inhibitory GABAergic neurons. However, the nervous innervation from thalamus to the cortex is via the excitatory glutaminergic neurons which result in voluntary movements.

In the indirect pathway, similar to the direct pathway, the nervous innervation from striatum to globus pallidus lateral and from these regions to subthalamic nucleus is through inhibitory GABAergic neurons. But the transmission from subthalamic nucleus to globus pallidus medial and substantia nigra par reticulata is through excitatory glutaminergic neurons. The basic difference between the two pathways is the type of innervation to the just two mentioned regions (globus pallidus medial and substantia nigra par reticulata). In direct pathway, the innervation is inhibitory, while in indirect pathway it is excitatory in nature. Hence, any alterations in the innervation to the globus pallidus medial and substantia nigra par reticulata ultimately affect the neurotransmission to the cortex, which results in either enhancement or suppression of voluntary movements.

Physiologically, dopamine causes activation of direct pathway and inhibition of the indirect pathway. This results in excitation of cortex, leading to voluntary movements. In parkinsonism, where the dopamine gets depleted due to destruction of dopaminergic neurons, the direct pathway gets suppressed, while the indirect pathway gets overstimulated. This leads to decreased excitatory outflow to the motor cortex resulting in the suppression of voluntary movements.

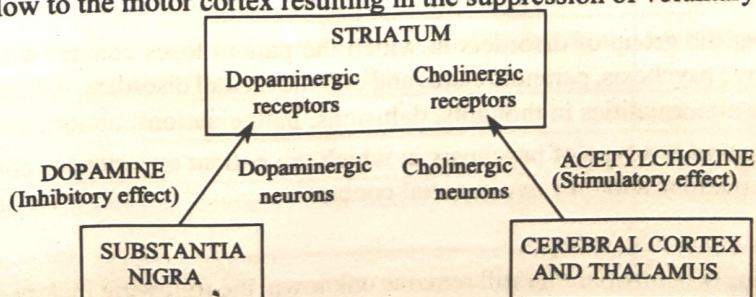


Figure: Dopaminergic and Cholinergic Nerve Supply to the Striatum

Cholinergic interneurons, projecting from the cerebral cortex and thalamus to striatum, oppose the dopaminergic activity in both direct and indirect pathway. An equilibrium between the actions of dopamine and acetylcholine controls the voluntary muscle movements. In parkinsonism, when dopamine levels get depleted, this eventually causes an increase in the stimulatory effects of ACh.

Therefore, parkinsonism can be treated by either increasing the dopaminergic effects or reducing the cholinergic effects.

Signs and Symptoms

1. Tremor

Tremor is the rhythmic and alternating movements of any body part. Rest tremors are characteristic feature of Parkinson's disease (PD) described as pill-rolling movements, mainly the movement of thumb across the fingers, seen at rest.

2. Rigidity

Rigidity is defined as stiffness of muscles, seen in axial regions (like face, trunk), upper and lower extremities. Muscle stiffness in face and trunk can be assessed by masked (expressionless) face and stooped features which may be misinterpreted as depression or unfriendliness. An early sign of rigidity is decrease in arm swing during walking.

3. Bradykinesia

Slowness in motion is defined as bradykinesia. It is associated with symptoms like difficulty and slowness in swallowing, hypophonic speech, difficulty in finger movements. Handwriting becomes very small (micrographia) and illegible.

4. Postural Instability

It is the symptom occurring in late stages of PD. It refers to poor balance which usually begins with slow and shuffling gait (bradykinesia accompanied with rigidity) and increased tendency to fall. This is resistant to drug therapy and hence cannot be easily treated.

5. Other Manifestations

- (a) Erectile dysfunction in males and urinary incontinence in both genders.
- (b) Postural hypotension may lead to falls.
- (c) Depression, dementia, visual hallucinations, delusions etc.

Progression of the disease can be evaluated by the use Hoehn and Yahr scale.

Table: Stages of Disability of PD

Stage	Disability
I	Unilateral disease with minimal or no functional impairment
II	Bilateral disease with preservation of balance
III	Mild to moderate bilateral disease with impairment of postural balance but can perform day-to-day chores independently
IV	Severe disability. Cannot work independently and require assistance
V	End stage disease. Paralysed to bed or wheel chair.

1.2 SCHIZOPHRENIA

Introduction

Psychosis is one among the group of disorders in which the patient loses contact with reality. Psychoses include schizophrenia, manic-depressive psychosis, paranoid states and organic mental disorders. All the psychotic disorders possess common clinical features like abnormalities in thoughts, delusions, hallucinations, abnormal behaviour etc.

Schizophrenia or *split mind* is a type of psychosis in which the patient experiences chronically impaired thinking, delusions and auditory hallucinations and may avoid social contact.

Aetiology

Although the exact cause of schizophrenia still remains unknown, the following factors are thought to be responsible for the disorder.

1. Genetic factors.
2. Imbalance of neurotransmitters in brain such as,
 - (a) Increase in dopamine (DA) levels
 - (b) Upregulation (increase) in serotonin (5-HT_{2A}) receptors.
3. Brain damage, enlargement of ventricles, widening of cerebral fissures.
4. Environmental factors affecting the brain in early stages of life or during pregnancy.

Pathophysiology

An abnormality in neurochemical transmitters like dopamine, glutamate and 5-HT (serotonin) seems to be responsible for schizophrenia.

1. Dopamine (DA) Hyperactivity Theory

According to this theory, excessive dopaminergic activity is responsible for schizophrenia. This is based on the following evidences.

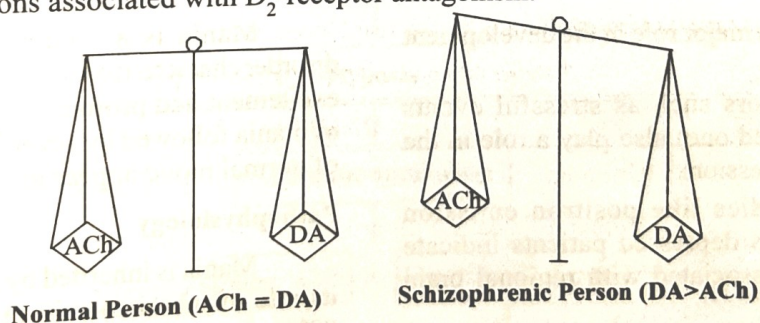
- (a) Drugs such as levodopa (dopamine precursor), amphetamine (releases DA in brain) or apomorphine (D_2 -receptor agonist) which increase DA activity can exacerbate the symptoms of schizophrenia in normal individuals.
- (b) Clinical antipsychotic efficacy is based on dopamine (D_2) receptor blocking potency.
- (c) Postmortem reports of schizophrenic brains showed an increased content of dopamine.

2. Glutamate Hypoactivity Theory

Another neurotransmitter believed to be involved in the pathogenesis of schizophrenia is glutamate. This is based on the evidence that glutamate-NMDA receptor antagonists (E.g.s: Phencyclidine, ketamine) exacerbate psychotic symptoms like hallucinations and impaired thoughts. Studies of postmortem brains of schizophrenics have revealed reduced levels of glutamate.

3. 5-HT Hyperactivity Theory

5-hydroxytryptamine is other neurotransmitter that may be involved in the pathogenesis of schizophrenia. This is based on the fact that LSD (lysergic acid diethylamide) which is a 5-HT_2 receptor agonist produces psychotic symptoms like hallucinations etc. Moreover, atypical antipsychotic drugs like clozapine, olanzapine which act as 5-HT receptor antagonists are effective antipsychotics but reports suggest that 5-HT receptor blockade merely reduces the extrapyramidal actions associated with D_2 -receptor antagonism.



Signs and Symptoms

1. Acute Psychotic Illness

Table : Positive and Negative Symptoms During Acute Psychotic Illness

Positive symptoms		Negative symptoms
1.	Hallucinations, especially auditory i.e., the patient hears voices which command him or comment on his actions.	Apathy (lack of interest in one's surroundings).
2.	Delusions, an absurd belief which cannot be changed by logical explanation. For example, the patient thinks that the aliens are after his life.	Lack of motivation.
3.	Disorganized thinking.	Social withdrawal.
4.	Agitation, anxiety or euphoria.	Emotional unresponsiveness.
5.	Initially, the speech becomes vague (unclear) followed by abnormality in thought process.	Abnormal behaviour and poor work record.
6.	Patient is responsive to neuroleptic drugs.	Patient shows poor response to neuroleptic drugs.

2. *Chronic Schizophrenia*

About 60-80% of patients with acute psychotic illness would progress to chronic schizophrenia. Here, the symptoms tend to worsen and the patient majorly expresses negative symptoms.

1.3 DEPRESSION

Introduction

Depression is the most common mood disorder (affective disorder). It is a severe mental disorder characterized by excessive sadness (depressed mood). It is a serious condition that can affect a person's normal social life, eating and sleeping habits and is associated with suicidal tendencies.

Types of Depression

There are two main types of depression.

1. *Unipolar Depression*

In this depression, the mood remains at one state or pole.

2. *Bipolar Depression*

Earlier it was known as manic-depressive psychosis. In this depression, mood swings from mania to depression in a cyclic manner over a period of few weeks i.e., the patient experiences episodes of mania and depression alternatively. It shows a strong hereditary tendency.

Aetiology

The exact cause of depression is not known, but some factors that are associated with increased risk have been identified.

1. Genetic factors play a major role in the development of depression.
2. Environmental factors such as stressful events (E.g: Death of a loved one) also play a role in the development of depression.
3. Brain imaging studies like positron emission tomography, MRI in depressed patients indicate that depression is associated with regional brain dysfunction.
4. Endocrine abnormalities like Cushing's syndrome and hypothyroidism may also contribute to the development of depression. Hyperactivity of hypothalamic-pituitary-adrenal axis is also reported in depressed patients.
5. Low concentration of neurotransmitters like serotonin (5-HT) or noradrenaline (NA) in the CNS has been found in the depressed patients.
6. Intake of drugs such as antihypertensives, steroids, anticonvulsants, antipsychotics etc., have also been found to be associated with depression.

Pathophysiology

Pathogenesis of depression is explained on the basis of monoamine/amine hypothesis. According to this theory, depression is a result of functional deficiency of monoamine (serotonin and/or noradrenaline) transmission in the brain.

This is based on the fact that drugs such as reserpine which inhibit noradrenaline and serotonin storage and methyldopa which inhibits noradrenaline synthesis induce depression. Therefore, it is believed that depression could be the result of functional deficit of amine transmission in the brain. This is known as amine hypothesis which provided the basis that the drugs which can increase the amine function in the brain could relieve depression. Accordingly, drugs such as monoamine oxidase inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) which increase aminergic transmission in one way or the other, have been developed and are being used effectively in the treatment of depression.

Signs and Symptoms

1. Sadness or low mood
2. Lack of interest and pleasure in all activities
3. Psychomotor agitation or retardation
4. Weight loss and anorexia
5. Sleep disturbances (insomnia or hypersomnia)
6. Suicidal thoughts
7. Decreased concentration and thinking
8. Reduced sexual activity
9. Fatigue
10. Gastric problems.

1.4 MANIA

Introduction

Mania is a bipolar manic-depressive psychotic disorder characterized by mood swings between pathological excitement and profound depression (i.e., cyclic episodes of mania followed by severe depression, where the periods of normal mood appear in between the extremes).

Pathophysiology

Mania is inherited by autosomal dominant genes and its rate of inheritance in monozygotic twin pair is about 80%.

Elevated levels of noradrenaline result in manic episodes whereas reduced levels result in depressive phase. Hence, stabilization of mood can be achieved by balancing the levels of neurotransmitters. The preponderance of noradrenaline or dopamine, exacerbates mania which may be relieved by reducing the activity of noradrenaline or dopamine. Mania is associated with the following changes.

1. Hyperfunctioning of noradrenergic or serotonergic activity.
2. Dysfunctioning of cholinergic transmission.

Signs and Symptoms

Pathological excitement includes excessive desire, euphoria, racing thoughts, pressured speech and little need for sleep.

1.5 STROKE

Introduction

According to World Health Organization, stroke is defined as "a neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours, with no apparent cause other than that of vascular origin".

Aetiological Classification

Based on the aetiology, stroke is classified into two types as follows,

1. Ischaemic Stroke

As the name suggests, ischaemic stroke occurs as a result of ischaemia (decreased supply of blood) in certain areas of the brain, which could occur due to the following reasons.

- Formation of a thrombus (blood clot) in a blood vessel might obstruct the flow of blood to the brain. In this case, it is referred as thrombotic stroke.
- It can occur as a result of an emboli/embolus reaching the brain, in which case it is referred as embolic stroke or cerebral embolism. An embolus is a clot of blood, fat, air or a foreign body that is carried by the blood from one point to another which finally lodges itself at a place.
- It can also occur as a result of decreased blood supply to the brain under certain circumstances such as shock. This phenomenon is referred as systemic hypoperfusion.

2. Haemorrhagic Stroke

As the name suggests, haemorrhagic stroke occurs as a result of haemorrhage i.e., escape or leakage of blood from a ruptured blood vessel in the brain, which can occur due to the following reasons,

- Use of certain drugs like anticoagulants, may lead to leakage of blood from the blood vessels
- Blood vessels may rupture due to highly elevated blood pressure
- Certain normalities of the blood vessels like presence of arteriovenous malformations (AVM) and aneurysm which are abnormal balloon-like swellings in the arteries may also lead to haemorrhagic stroke.

Pathophysiology of Ischaemic Stroke

Ischaemic stroke occurs due to decreased supply of blood to the brain due to various factors which have been discussed under the aetiological classification. This condition triggers an ischaemic cascade as described below.

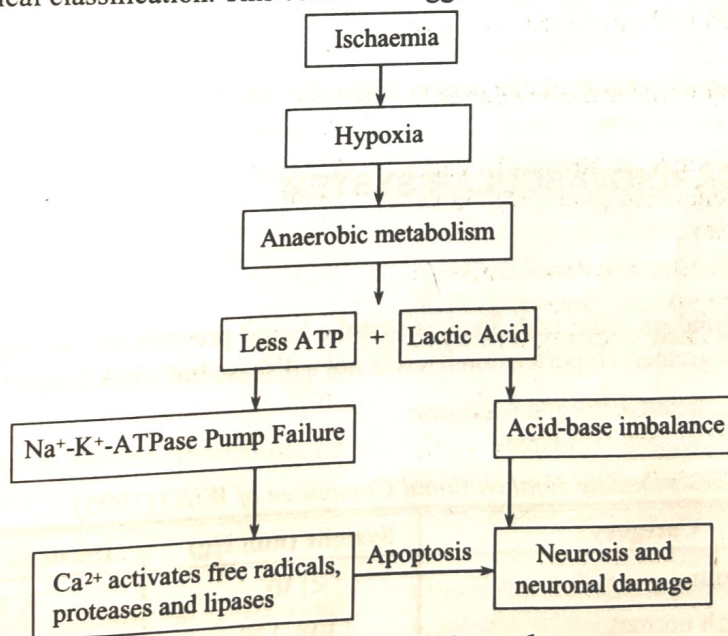


Figure: Ischaemic Cascade

Due to decreased supply of blood, the amount of oxygen the brain cells receive also decreases and eventually the brain cells resort to anaerobic metabolism to produce energy (ATP). The end products of anaerobic metabolism are lactic acid and very less amounts of ATP. Lactic acid disturbs the acid-base equilibrium in the brain and also damages the neurons. Due to decreased ATP production, the Na⁺-K⁺-ATPase pump fails leading to depolarization of the cell membrane resulting in an efflux of K⁺ and an influx of Ca²⁺ and Na⁺ ions into the neurons. Ca²⁺ activates proteases (enzymes that digest cell membranes) and free radicals. As a result, the cell membrane and mitochondria break down releasing toxins and apoptotic factors (substances that cause programmed cell death) into the cell, causing neurosis and neuronal damage.

Pathophysiology of Haemorrhagic Stroke

In haemorrhagic stroke, leakage of blood occurs from the blood vessels due to various aetiological factors as described previously. As a result, there is a formation of haematoma (accumulation of blood within the tissues that clots to form a solid swelling) is seen which keeps enlarging causing compression of the brain tissues, resulting in injury and development of an infarct (dead tissue) due to decreased supply of blood to the tissues.

Signs and Symptoms

Symptoms of stroke include headache, vomiting, unconsciousness, difficulty in swallowing, reading or writing, memory loss, urinary incontinence, dizziness, confusion, loss of vision or blurred vision, loss of balance, extreme weakness in the muscles of face, arms or legs, numbness and impaired co-ordination of the muscles.

Complications

1. Speech Problems

When certain parts of the brain that control facial muscles are affected, the person suffers from aphasia (disorder of language that affects the generation and content of speech).

2. Dysphagia

The person might face difficulty in swallowing in case the muscles of the neck are affected and this could lead to withdrawal of food particles into the lungs.

3. Memory Loss

Since stroke affects the brain, loss of memory is an obvious complication.

4. Parasthesias

The person experiences one sided or two sided numbness in the body.

5. Pain

The person might experience pain and numbness in the same area alternatively.

6. Paralysis

The person might experience paralysis which is loss of muscle control in specific area of the body or the entire body including the face.

7. Loss of Motor Function

Since the motor nerves are also affected, the person might face problems in walking, balancing, doing daily chores, etc.

2. DISORDERS OF CARDIOVASCULAR SYSTEM

2.1 HYPERTENSION

Introduction

Hypertension or high blood pressure is defined as systolic blood pressure of 140 mm Hg or greater and diastolic blood pressure of 90 mm Hg or greater. Hypertension itself is not a disease but a risk factor for several cardiovascular and renovascular diseases.

Types of Hypertension

1. Clinical Classification Described by Joint National Committee of WHO (1995)

Category	Systolic (mm Hg)	Diastolic (mm Hg)
1. Normal	<130	< 85
2. High normal	130 – 139	85 – 89
3. Hypertension		
(a) Mild (Stage 1)	140 – 159	90 – 99
(b) Moderate (Stage 2)	160 – 179	100 – 109
(c) Severe (Stage 3)	180 – 209	110 – 119
(d) Very severe (Stage 4)	≥ 210	≥ 120
4. Malignant hypertension	> 200	≥ 140

2. General Classification of Hypertension

- (a) **Primary or Essential Hypertension:** It is observed in 95% cases in which the cause is unknown i.e., idiopathic.
- (b) **Secondary Hypertension:** It is observed in 5-10% of the population and is caused due to kidney disease, endocrine abnormalities etc.

3. Clinical Classification of Primary and Secondary Hypertension

- (a) **Benign Hypertension:** It is observed in 95% patients in which there is a slow rise in blood pressure which may take years to develop.
- (b) **Malignant or Accelerated Hypertension:** It is observed in 5-10% of the population where there is rapid rise in blood pressure to 200/140 mm Hg or more. This type when left untreated, reduces the life expectancy of the patient.

Aetiology

On aetiological basis, hypertension is divided into two types.

1. Primary/Essential Hypertension

In majority of cases, hypertension is of unknown cause. However, a definite cause is known in primary hypertension. Following are the factors which may contribute to the elevation of BP.

- (a) Dietary intake of more sodium and less potassium.
- (b) Decrease in vascular synthesis of nitric oxide (NO) that is responsible for vasodilation.
- (c) In some cases primary hypertension may be hereditary.
- (d) Advancement of age may also be responsible for primary hypertension.

2. Secondary Hypertension

In some cases, hypertension may be secondary to other diseases like,

- (a) **Endocrine Disorders:** Pheochromocytoma and hyperaldosteronism
- (b) **Kidney Disorders:** Chronic glomerular nephritis
- (c) **Vascular Disorders:** Contraction (narrowing) of aorta and renal artery stenosis
- (d) **Drugs:** Drugs are also known to induce hypertension. These include oral contraceptives, NSAIDs, cyclosporin, erythropoietin, steroids, sympathomimetic amines, monoamine oxidase inhibitors etc.

Pathophysiology

Regulation of blood pressure is undertaken by various homeostatic reflexes. These include,

1. Baroreceptor reflexes which monitor the changes in blood pressure occurring per minute
2. Renin-angiotensin-aldosterone system which functions to regulate water, electrolyte and blood pressure
3. Atrial natriuretic peptide
4. Endothelins
5. Bradykinins
6. Antidiuretic hormone.

All these systems, in tandem, help to regulate the systemic blood pressure. Although the exact pathophysiology of primary (essential) hypertension is yet to be ascertained, the following theories have been put forward to explain the pathogenesis.

1. Increased renal retention of sodium elevates the blood volume which in turn increases the cardiac output. Such an increase results in the elevation of peripheral resistance and ultimately blood pressure. Later, it was found that sodium retention was influenced by natriuretic peptide.
2. Other postulation suggests that there are certain defects inherent to the cell which result in increased intracellular sodium leading to uptake of calcium ions. These calcium ions eventually increase the tone of the vasculature.
3. Certain genetic factors have also been associated with the development of hypertension.

Morphological Changes

Hypertension mainly effects the following organs.

1. Heart and its Blood Vessels

Prolonged systemic hypertension results in hypertensive cardiomyopathy (a condition affecting the cardiac muscles) which is the second most common type of heart disease after ischaemic heart disease. Manifestations include left ventricular hypertrophy and coronary atherosclerosis which may lead to ischaemic heart disease.

Morphological/Pathological Changes

Weight of the heart increases from 300 to 500 grams or more. Thickness of the left ventricular wall increases from 15 to 20 mm or more. Papillary muscles and trabeculae are rounded and become prominent. Cardiac failure, myocardial oedema and necrosis of myocardium are seen in advanced stages.

2. Nervous System

Hypertension leads to cerebrovascular diseases in which one or more blood vessels of the brain are involved.

(a) Ischaemic Brain Damage

It results from ischaemia which is caused due to reduction or complete lack of blood supply to the brain due to which it cannot meet its metabolic needs. Deprivation of oxygen and glucose for more than 3-4 minutes results in permanent damage.

(b) *Intracranial Haemorrhage*

Haemorrhage may be traumatic, nontraumatic or spontaneous. Intracranial haemorrhage is again of two types intracerebral haemorrhage and subarachnoid haemorrhage.

3. *Kidneys*

Hypertension results in the following two conditions.

(a) *Benign Nephrosclerosis*

It is a condition which describes kidney in benign phase of hypertension. It is usually seen in elderly persons and its severity increases in persons with medical history of hypertension and diabetes mellitus. High blood pressure with headache, dizziness, palpitation and nervousness are most commonly seen. Papilloedema is absent. Renal function tests and urine tests remain normal in the early stages. Mild proteinuria with some hyaline or granular casts are seen in advanced stages.

(b) *Malignant Nephrosclerosis*

It is usually associated with accelerated hypertension. It is uncommon and occurs as a result of pre-existing benign essential hypertension or in patients with secondary hypertension.

Headache, dizziness and impaired vision are most commonly seen. Presence of papilloedema differentiates malignant from benign phase hypertension. Urine analysis shows the presence of haematuria and proteinuria. Renal function tests show deterioration.

4. *Eyes*

Hypertension results in hypertensive retinopathy in which the diameter of retinal arterioles reduces, thereby resulting in retinal ischaemia.

Signs and Symptoms

High blood pressure can develop over many years with no noticeable symptoms. The symptoms appear when the elevation in blood pressure is severe. The warning signs include,

1. Nose bleeding
2. Irregular heart beat
3. Headache, dizziness and fatigue
4. Flushed face and blurred vision
5. Vertigo.

All the above symptoms of high blood pressure may vary from person to person.

Complications

Hypertension, if left untreated, results in the following complications.

1. *Blood Vessels*

- (a) Larger arterioles (> 1 mm diameter) dilate and become tortuous.
- (b) Smaller arterioles (< 1 mm diameter) develop atheroma.

2. *Central Nervous System*

Stroke is a common complication of hypertension which is due to cerebral haemorrhage or cerebral infarction.

3. *Eyes*

Central retinal vein thrombosis is associated with hypertension.

4. *Heart*

Hypertension causes ventricular hypertrophy, atrial fibrillation and left ventricular failure.

5. *Kidney*

Long standing hypertension causes chronic renal failure.

2.2 CONGESTIVE CARDIAC FAILURE (CCF)**Introduction**

Congestive heart failure (CHF) is defined as the inefficiency of the heart to pump sufficient amount of oxygenated blood to all the organs of the body to meet their metabolic demands.

Congestive heart failure is found to be one of the major contributors for morbidity and mortality.

Types of Congestive Heart Failure*Acute Heart Failure*

It is sudden and rapid development of heart failure due to decreased cardiac output leading to systemic hypotension. This leads to cardiogenic shock and cerebral hypoxia without any oedematous conditions.

Chronic Heart Failure

It develops slowly and gradually over a long period of time. It is observed in myocardial ischaemia, valvular heart diseases, systemic hypertension and chronic lung diseases. Oedema is also observed in chronic heart failure.

Left-sided Heart Failure

The failure of left ventricle to pump the entire blood present in it during systole results in retention of some amount of blood after every systole. Thus, blood is accumulated in the left ventricle after few systoles of the heart. Left ventricle fails to accept the blood from auricles and lungs thus the uncollected blood due to back-up pressure remains in the lungs resulting in pulmonary oedema.

Clinical Manifestations

1. Pulmonary oedema due to accumulation of fluid in the lungs.
2. Hydrostatic pressure within the pulmonary blood vessels leads to transfer of fluids and RBCs in interstitial spaces.
3. Decreased left ventricular output causes hypoperfusion (drastically decreased blood supply), kidneys (causes ischaemic tubular necrosis), brain (causes hypoxic injuries) and skeletal muscles (causes muscular weakness).

Right-sided Heart Failure

The failure of right ventricle to pump the entire blood present in it during systole results in retention of some amount of blood after every systole. Thus, blood is accumulated in right ventricle after few systoles. The left ventricle fails to accept blood from peripheral organs and ultimately results in generalized systemic oedema or peripheral oedema.

Clinical Manifestations

1. Venous congestion is seen in liver, spleen and kidneys.
2. Oedema occurs which deprives the system of normal oxygen content.
3. Accumulation of metabolic wastes which leads to circulatory stagnation. This in turn causes anoxia (total lack of oxygen), cyanosis (blue colouration due to accumulation of impure blood) and cold extremities.

Aetiology**1. Failure of the Pump**

It is the failure of ventricular muscles to supply adequate quantity of blood to the body due to ischaemic heart diseases, myocarditis, arrhythmias etc.

2. Excess Workload on Heart

Increased mechanical load on heart causes increased demand on cardiac muscles, resulting in myocardial failure.

- (a) Excess pressure load occurs in systemic and pulmonary hypertension, chronic lung diseases and valvular diseases.
- (b) Excess volume load is seen in valvular insufficiency, anaemia and hypoxia.

3. Defective Filling of Cardiac Chambers

Decreased cardiac output and heart failure occurs due to defects in filling of the heart.

4. Other Causes

- (a) Coronary artery disease (CAD) and hypertension
- (b) Congenital defects
- (c) Long term high blood pressure (which increases afterload)
- (d) Myocardial infarction
- (e) Valve disorders
- (f) Pulmonary oedema (due to failure of left ventricle)
- (g) Peripheral oedema (due to failure of right ventricle)
- (h) Cardiomyopathy
- (i) Hyperthyroidism
- (j) Severe anaemia
- (k) Left ventricular systolic dysfunction.

Pathophysiology

A failing heart is characterized by its inability to pump adequate blood for the metabolic needs of the body tissues. It is of two types. In systolic failure, the mechanical pumping action (i.e., myocardial contractility) is impaired and ejection fraction is also reduced (<45%). This ultimately results in reduced cardiac output. In diastolic failure, there is loss of adequate ventricular relaxation and filling which leads to reduced cardiac output (but the ejection fraction is normal in diastolic failure).

Compensatory Mechanisms During CHF

To enhance the cardiac output, several compensatory mechanisms are activated. If the cardiac output gets restored by these mechanisms, then the cardiac failure is said to be compensated.

1. Increased Sympathetic Discharge

To compensate for decreased blood pressure, baroreceptors located in the arch of aorta, carotid sinuses and walls of the heart get stimulated and cause activation of β -adrenergic receptors, leading to an increase in the rate and force of myocardial contraction.

An increase in the venous return (preload) is also seen due to the activation of α -adrenergic receptors which brings about vasoconstriction. Increased rate and force of contraction together with increased preload results in an initial increase in the cardiac output. Vasoconstriction of the arteries due to α -stimulation also causes an increase in the afterload and a fall in the ejection fraction. As a result, the cardiac output decreases and this in turn decreases renal perfusion followed by down regulation of β -receptors. Persistent sympathetic activity increases the work load (preload and afterload) on the failing heart, which adversely affects the cardiac activity.

2. Activation of Renin-Angiotensin-Aldosterone (RAA) Axis

A fall in the cardiac output decreases the rate of renal perfusion, due to which the RAA system gets activated. Angiotensin II causes vasoconstriction and an increase in the peripheral vascular resistance (PVR), while aldosterone leads to increased retention of sodium and water, thereby increasing the blood volume i.e., preload increases.

PVR also enhances the afterload due to which the heart is unable to pump the extra blood volume and this leads to the development of back-up pressure causing pulmonary and peripheral oedema.

3. Cardiac Remodelling

This is the most important mechanism by which body compensates for the intrinsic cardiac effects. Cardiac remodelling involves changes in the shape of the heart (from normal to spherical) due to myocardial hypertrophy. During cardiac

remodelling, the connective tissue cells as well as abnormal myocardial cells undergo proliferation and dilation (instead of stretching) under the influence of angiotensin II.

During early stages, the remodelled heart maintains the cardiac performance. But eventually, hypertrophy may exert certain adverse effects like ischaemic changes, increase in the ventricular wall tension, decrease in the rate and force of contraction of heart (mechanical performance), which further exacerbates the remodelling process. After sometime, the myocytes also begin to die subjecting the other myocytes to heavy work load.

Phenomenon of Decompensated Heart Failure

Body is said to compensate the failing cardiac effects, if these compensatory mechanisms are able to adequately restore the cardiac output. However, it so happens that these compensatory mechanisms get exhausted after a certain period of time and may ultimately worsen the cardiac performance. Stress on heart increases and a stage is reached where these mechanisms fail to maintain adequate cardiac output. At this stage, heart failure is said to be decompensated and produces characteristic signs and symptoms of heart failure.

Signs and Symptoms

1. Generalized oedema is the characteristic feature of CHF.
2. Decreased cardiac output.
3. Impaired oxygenation and decreased blood supply causes muscle fatigue.
4. Dyspnoea (difficulty in breathing).
5. Orthopnoea (shortness of breath in lying posture).
6. Sleep disturbance due to cough and nocturia (increased frequency of urination during night).
7. Attacks of paroxysmal nocturnal dyspnoea (PND).
8. Patients appear pale and hands are cold and sweaty.
9. Poor circulation results in confusion, dizziness and sweating.

2.3 ISCHAEMIC HEART DISEASES

2.3.1 Angina

Introduction

Angina is the classical symptom of myocardial ischaemia. It refers to severe pain in the middle of the chest during exercise or effort due to decreased supply of oxygenated blood to the heart.

Types of Angina

1. *Stable (Exertional) Angina*

It is provoked by physical exertion. The patient feels heaviness, squeezing and sensation of strangling or constriction in the chest. The pain fades quickly after rest. During the attack, ST segment in the ECG

is depressed. No elevation of enzymes in the blood is observed as there is no irreversible myocardial injury.

2. *Unstable (Pre-infarction) Angina*

It is characterized by frequent onset of pain which occurs even at rest. The attack lasts for a longer duration. It is an indication of myocardial infarction.

3. *Variant/Prinzmetal Angina*

It is characterized by pain at rest and has no relationship with physical activity. It occurs because of coronary artery spasm which in turn occurs because of the release of vasoconstrictors by mast cells in the coronary adventitia. The attacks are very painful and usually occur between midnight and 8.00 a.m. ECG shows ST segment elevation during pain. It occurs more commonly in women. The patient responds well to vasodilators (like nitroglycerine).

4. *Microvascular Angina*

The patient experiences chest pain but there is no apparent coronary artery blockage. Pain results due to poor functioning of tiny blood vessels nourishing the heart, arms and legs. It occurs during exercise (due to reduced vasodilator activity) or at rest.

Aetiology

1. Atherosclerosis of large coronary arteries
2. Heart valve diseases (aortic stenosis)
3. Thickening of heart muscles (hypertrophic cardiac myopathy)
4. Coronary artery disease (CAD)
5. Coronary artery spasm
6. Hypertension
7. Cigarette smoking.

All the above said diseases increase the cardiac work due to which oxygen demand by the heart also increases. This ultimately results in an imbalance between supply and demand of oxygen finally causing angina.

Pathophysiology

Heart works to meet the metabolic demands of the body. Energy for this work is obtained from the oxygen carried to the heart via the coronary blood flow.

In certain situations like the release of adrenaline, during physical stress etc., heart has to perform some extra work due to increased heart rate, arterial pressure, contraction, ventricular volume etc. Due to such increase in the cardiovascular performance, energy required to perform the metabolic activity also increases. Therefore, oxygen supply to the heart should also increase.

The amount of oxygen required by the myocardium can be interpreted by the double product or angina index which is represented as follows,

$$\text{Double product} = \text{Heart rate} \times \text{Systolic blood pressure} \\ (\text{Angina index})$$

People suffering from coronary artery diseases exhibit impaired coronary arteries because of their blockade due to atherosclerotic plaque, coronary spasm, coronary artery embolism etc. In such conditions, an imbalance occurs between the cardiovascular performance (demand) and the coronary blood flow (supply) leading to ischaemia.

Myocardial ischaemia results in decreased coronary sinus blood pH, cellular loss of K^+ ions, increased production of lactate, impaired ventricular functioning and consequent chest discomfort (angina).

Signs and Symptoms

1. Gripping or central chest pain.
2. Increased shortness of breath on exercise.
3. Sense of heaviness or numbness in the arm, shoulder, elbow or hand (usually on the left side).
4. Pain may radiate to both the arms, neck, jaws, teeth, or between the shoulder blades.
5. Occasionally, the pain is epigastric.
6. Nausea, vomiting, light headedness, shortness of breath, bluish discolouration of skin etc.

2.3.2 Arteriosclerosis

Arteriosclerosis literally means hardening of arteries. The term arteriosclerosis was first used by Jean Frederic Martin Lobestein. It is a generic term encompassing several diseases that cause thickening and hardening of the arterial walls. It can occur in the arteries of the heart, kidneys, brain abdominal aorta or legs. It includes three types of vascular diseases that are characterised by thickening of the arterial wall and loss of elasticity. These vascular diseases have been discussed below.

1. Atherosclerosis

It is the most common type of arteriosclerosis and mainly affects intima of large and medium sized arteries. It is characterised by build up of fatty material (atheromas) in the arterial walls, leading to decreased blood flow.

This topic has been discussed in detail in the upcoming section.

2. Monckeberg's Medial Sclerosis

It is a non-inflammatory, degenerative disorder affecting media of small and medium size muscular arteries. It is characterised by deposition of calcium in the arterial walls making them stiff but not narrow. The exact pathogenesis is not known. It is common with advancing age, diabetes and chronic renal diseases.

3. Arteriolosclerosis

It is characterised by thickening and hardening of small arteries and arterioles. The kidneys are most commonly affected. It is associated with hypertension and diabetes. It occurs in following two forms.

(a) Hyaline Arteriolosclerosis

It is described as hyaline thickening of the arteriolar walls and luminal narrowing as a result of accumulation of plasma components on the walls. It is seen in conditions like hypertension, diabetic microangiopathy, benign nephrosclerosis and also in elderly.

(b) Hyperplastic Arteriolosclerosis

Onion-skin laminated thickening of the arteriolar walls occurs due to concentric proliferation of smooth muscle cells. This leads to progressive luminal narrowing. It is associated with necrotising arteriolitis.

2.3.3 Atherosclerosis

Introduction

Atherosclerosis or atheroma is a condition in which there occurs patchy thickening of the intimal (inner most) layer of arterial wall mainly due to lipid deposition and fibrous tissue formation. Atherosclerosis is derived from two Greek words, *Athero* meaning porridge and *sclerosis* meaning scarring.

Aetiology

Risk factors associated with atherosclerosis act in combination rather than alone.

1. Major Constitutional Risk Factors

(a) Age and Sex: It is an age-related disease because the plaques (deposits of fatty substances, cholesterol, cell debris, calcium and fibrin deposits) begin to develop as the age advances. Fully developed atheromatous plaques are seen at the age of 40 years and above. The risk of atherosclerosis is more in men than in women.

(b) Family History and Genetic Factors : Abnormalities in lipid metabolism lead to hypercholesterolaemia. It also occurs due to diabetes, hypertension, obesity and hyperlipoproteinaemia.

(c) Racial Factors: Whites are at a greater risk of atherosclerosis when compared to blacks.

2. Major Acquired Risk Factors

(a) Excess Lipid Deposition: Increase in low density lipoproteins (LDL), cholesterol, very low density lipoprotein (VLDL), triglycerides and decreased high density lipoprotein (HDL) are associated with atherosclerosis.

(b) Hypertension: It causes mechanical injury to the arterial wall as blood pressure is increased.

(c) Smoking: Atherosclerosis is commonly seen in smokers due to, decreased levels of HDL and/or accumulation of carbon monoxide in blood, thus producing carboxyhaemoglobin which favours atherosclerosis.

- (d) **Diabetes Mellitus:** People with diabetes mellitus develop atherosclerosis early due to increased platelet aggregation and LDL but decreased HDL.

Table: Types of Cholesterol and their Values

Cholesterol type	Normal values
HDL cholesterol	> 40 mg/dl
LDL cholesterol	< 130 mg/dl
VLDL triglycerides	< 160 mg/dl

3. Minor Risk Factors

- Obesity
- Usage of oral contraceptives by women
- Lack of exercise
- Sedentary life-style
- Consumption of alcohol
- Dietary factors
- Stressful life-style (type A behavioural pattern)
- Viral infections.

Pathophysiology

Atherosclerosis depends on many factors therefore it is a multifactorial disease.

1. Endothelial Injury

It is a major contributory factor in the initiation of atherosclerosis due to the formation of plaques in large and medium sized arteries. The causes include cigarette smoking, hypertension and chronic hyperlipidaemia.

2. Intimal Smooth Muscle Cell Proliferation

It is seen due to endothelial injury. Proliferation of smooth muscle cells is due to various mitogens like platelet derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factors, transforming growth factor (TGF- α) and synthesis of matrix proteins like collagen, elastic fibres, proteins and proteoglycans.

3. Lipoproteins Entry into the Intima

Plasma LDL enters the intima and gets oxidized. The oxidized LDL attracts monocytes which are activated and transformed into lipid-laden foam cells. Death of the foam cells by apoptosis releases the lipid core.

Pathological Changes

The early lesions of diffuse intimal thickenings, fatty streaks and gelatinous lesions lead to the development of atherosclerotic lesions. However, clinical symptoms are observed only in fully developed atheromatous plaques and complicated plaques.

1. Atheromatous Plaques

These are also called fibrous plaque, fibrofatty plaque or atheroma. These are white to yellowish-white lesions, 1-2 cm in diameter. The plaque shows variation in appearance as it depends upon the age of the lesion.

- Fibrous Cap :** It is seen externally and is covered by endothelium. It comprises smooth muscle cells, dense connective tissue and extracellular matrix.
- Cellular Area :** It is present beneath the fibrous cap and comprises macrophages, foam cells, lymphocytes and lipid containing smooth muscle cells.
- Central Core :** It is the deepest layer of atheromatous plaque which comprises lipid material, cholesterol clefts, fibrin, necrotic debris and lipid-laden foam cells.

2. Complicated Plaques

These are developed atheromatous plaques which lead to death. The changes include calcification, ulceration, thrombosis, haemorrhage and aneurysm.

Signs and Symptoms

Symptoms are not observed until the arteries get clogged with plaque and blood supply gets reduced to the organ. Symptoms show variation depending on the organ involved.

1. Heart

Restricted blood supply to the heart causes angina pectoris and myocardial infarction. The other symptoms include shortness of breath, sweating, nausea, dizziness, breathlessness and palpitations (awareness of the heart beat).

2. Brain

Narrowing of brain arteries in atherosclerosis leads to transient ischaemic attacks, headache, dizziness, paralysis of one side of body (hemiplegia), numbness, visual disturbances, improper gait and stroke.

3. Abdomen

Dull or crampy pain is felt in the abdomen due to blockage of intestinal arteries. The patient also experiences vomiting, diarrhoea or constipation.

4. Legs

Narrowing of leg arteries leads to pain in the leg muscles, hair loss on the legs and thickening of toe nails.

2.3.4 Myocardial Infarction

Introduction

Myocardial infarction (MI) is the irreversible necrosis of heart muscle due to prolonged ischaemia. It occurs when the vessel supplying the myocardium remains completely occluded for 15-20 minutes.

Myocardial infarction or acute myocardial infarction (AMI) commonly referred as *heart attack* is now being termed as ST Segment Elevation Myocardial Infarction (STEMI) in modern medical terminology.

Aetiopathogenesis

The causes are divided into two types.

1. Atherosclerotic Causes

These account for 90% of the cases. Atherosclerosis is a gradual process of build up of cholesterol, lipids and fibrous tissue in the inner walls of the coronary artery. This ultimately results in the formation of plaque which narrows the lumen of the coronary artery and reduces the flow of blood to heart muscles.

Atherosclerotic plaques become unstable and rupture, exposing the soft fatty deposition inside. When this occurs, platelets reach the site, stick to the vessel and form a blood clot (coronary thrombosis). The blood clot further narrows the arteries. Eventually, the narrowed arteries develop new blood vessels to supply blood to the heart. However, during stressful conditions, the new arteries fail to supply adequate blood to the heart muscles resulting in ischaemia followed by diastolic and systolic dysfunction, elevation of filling pressures, electrocardiographic changes, chest discomfort (*angina*) and then myocardial necrosis (*infarction*).

2. Non-Atherosclerotic Causes

These account for 10% of the cases of myocardial infarction (MI).

- (a) Coronary Vasospasm: Spasm of medium or large-sized coronary arteries.
- (b) Arteritis: Inflammation of arteries.
- (c) Coronary Stenosis: Narrowing or constriction of coronary artery.
- (d) Coronary Embolism: Obstruction of coronary blood vessels by an embolus.
- (e) Thrombotic Disorders: Occur due to development of thrombus.

Types of Infarcts

Infarct is an area of necrosis formed due to insufficient blood supply. Infarcts are classified based on,

1. Type of Anatomical Region Involved

Depending upon the affected area of the left ventricle, infarct is called anterior, posterior, lateral, septal and circumferential and their combinations are known as anterolateral, posterolateral and anteroseptal.

2. Ventricular Wall Thickness

- (a) Transmural: Entire thickness of the ventricular wall.
- (b) Subendocardial/Laminar: Involves half of the myocardial wall.

3. Age of Infarct

- (a) Acute, recent or fresh (newly formed infarcts).
- (b) Old, healed or organized (advanced infarcts).

Location of Infarcts

1. Ventricles

Left ventricle is more prone to infarction than right ventricle. Thin walls of the right ventricle and its less metabolic requirements makes it less susceptible to infarcts.

2. Atria

Right atria is more prone to infarction than left atria. Oxygenated blood is supplied to the left atria, hence it is protected from infarction.

Pathological Changes

Table: Gross and Microscopic Changes Seen in Myocardial Infarction

Time	Gross (Macroscopic) changes	Microscopic Changes
After 6 hrs	Swollen and paler myocardium	Onset of coagulative necrosis and oedematous fluid between the myocardial fibres
At 24 hrs	Cyanotic, red-purple areas of haemorrhage due to blood stagnation	Necrotic tissue appears deeply stained
10 th day	Bright yellow and soft with red-purple periphery.	Inflammatory reaction develops and infiltration of macrophages, eosinophils, lymphocytes and plasma cells occurs.
Third week		Necrosed muscle is removed and there is more ingrowth of fibrocollagenous tissue.
Fourth to sixth week	Infarcted tissue turns grayish-white, harder, shrunken with fibrous scar	Increase in collagen connective tissue, decreased vascularity, fewer macrophages, plasma cells and lymphocytes.

Signs and Symptoms

1. Severe chest pain (similar to exertional angina)
2. Sweating
3. Dyspnoea
4. Chest pain radiating to jaws, shoulder, arms and back
5. Epigastric discomfort with or without nausea and vomiting
6. Frothy and blood-stained sputum
7. Dizziness, weakness, irregular heart beat, anxiety, heartburn and indigestion
8. 20% of the patients experience no pain, hence called silent MI which occurs in diabetics and elderly.

Complications

1. Acute left ventricular failure with pulmonary oedema
2. Pericarditis
3. Cardiac arrhythmia and heart block due to interruption of the conduction system of heart
4. Rupture of the infarcted ventricular wall into the pericardial cavity causing haemopericardium
5. Cardiac aneurysm
6. Cardiogenic shock
7. Systemic venous thrombosis caused due to slowing of blood.

3. DISORDERS OF ENDOCRINE SYSTEM

3.1 DIABETES MELLITUS

Introduction

Diabetes mellitus (DM) is defined as a heterogeneous metabolic syndrome characterized by chronic hyperglycaemia i.e., increase in blood glucose (sugar) levels with disturbances in carbohydrate, fat and protein metabolism. It is the most commonly occurring chronic endocrinal disorder which affects almost each and every cell of the human body. Insulin is the chief hormone which plays a pivotal role in the occurrence of DM. It results either due to,

1. Insufficient insulin production
2. Inability of the body to utilize the insulin produced
3. Increased synthesis of glucose in the body.

Epidemiology

Approximately 5-10% of patients suffer from type-1 DM and majority (90-95%) suffer from type-2 DM. Type-1 usually occurs in younger population, below 30 years of age, the incidence being very high in girls between 10-12 years of age and in boys between 12-14 years of age.

Type-2 DM mainly occurs in older population i.e., above 40 years. About half of the total patients newly diagnosed with type-2 DM are above 55 years and approximately 18% are of 60 years or above.

Types of Diabetes Mellitus

1. Type-1 DM/Insulin Dependent DM (IDDM)/Juvenile Onset DM

Type-1 DM mainly occurs due to the destruction of insulin secreting pancreatic β -cells of islets of Langerhans. The onset of symptoms is rapid in type-1 DM.

(a) Type-1A

This type of DM mainly develops due to autoimmune T-cell mediated destruction of insulin secreting β -cells. Almost 90% of the patients diagnosed with type-1 DM are associated with type-1A.

(b) Type-1B/Idiopathic

The cause of this type of DM is yet to be established. It is characterized by deficiency of insulin with a tendency to develop ketosis.

2. Type-2/Non-insulin Dependent DM (NIDDM)/Maturity Onset DM

This type of DM occurs due to relative insulin deficiency or resistance or both. The onset of symptoms is slower and less marked than in type-1DM. The disease usually progresses to such an extent that it requires external supply of insulin in order to maintain blood-glucose levels.

3. Gestational DM

This type of DM mainly occurs during pregnancy and is caused due to carbohydrate intolerance.

Aetiology

1. Damage to pancreatic β -cells of islets of Langerhans leads to deficiency of insulin (type 1 DM).
2. Secretory problems leading to insulin deficiency or resistance or both (type-2 DM).
3. Genetic Factors
 - (a) Genetic disorders pertaining to functioning of β -cells, which mainly involve chromosome-12, hepatocyte nuclear factor (HNF)-1- α , 7, 20, HNF-4 α , 13, 17 and 2.
 - (b) Down's syndrome, Turner's syndrome and Klinefelter's syndrome may also lead to DM.
4. Diseases
 - (a) Cystic fibrosis, neoplasia, trauma or pancreatectomy etc., can cause DM.
 - (b) Certain endocrinopathies like acromegaly, pheochromocytoma, Cushing's syndrome etc., may also lead to DM.
 - (c) Uncommon forms of immune mediated diabetes is caused by anti-insulin receptor antibodies, Stiff-man syndrome, etc.
5. Infections caused by viruses like cytomegalovirus, congenital rubella virus etc., may also lead to DM.
6. Drugs or chemicals such as atypical antipsychotics, corticosteroids, diazoxide, nicotinic acid, thiazides, pentamidine, interferon- α , phenytoin, acetazolamide, caffeine, glycerol, lithium salts, niacin, rifampin, oral contraceptives, clonidine, sympathomimetics etc., may also induce DM.
7. Other factors like obesity, advancing age, emotional stress and vasculitis in highly perfused tissues like kidneys, eyes, etc., may also cause DM.
8. Increased secretion of counter-regulatory hormones (glucagon, growth hormone, catecholamines) is also a cause of DM.

Pathophysiology

Type-1 DM

Type-1 DM occurs due to complete deficiency of insulin as β -cells of pancreas are destroyed. The mechanisms which explain the pathogenesis of type-1 DM are as follows.

1. Autoimmunity

Immunological destruction of β -cells can be supported by the following evidences.

- (a) Presence of lymphocyte infiltration around islets of Langerhans (insulinitis).
- (b) Occurrence of islet cell antibodies against insulin and glutamic acid decarboxylase (GAD).

- (c) T-cell mediated cytotoxicity or apoptosis which selectively destroys insulin secreting β -cells.

2. Metabolic Abnormalities

Increased secretion of counter regulatory hormones of insulin like glucagon, growth hormone, cortisol and catecholamines increases the production of glucose from liver. This condition mainly arises due to acute infections or diseases.

3. Environmental Factors

Environmental conditions do not actually cause DM but aggravate the disease. Certain viruses (like cytomegalovirus, Coxsackie β -virus, measles, mumps), chemicals (pentamidine, alloxan, streptozocin), bovine milk proteins and geographical as well as seasonal changes may initiate autoimmune destruction of β -cells.

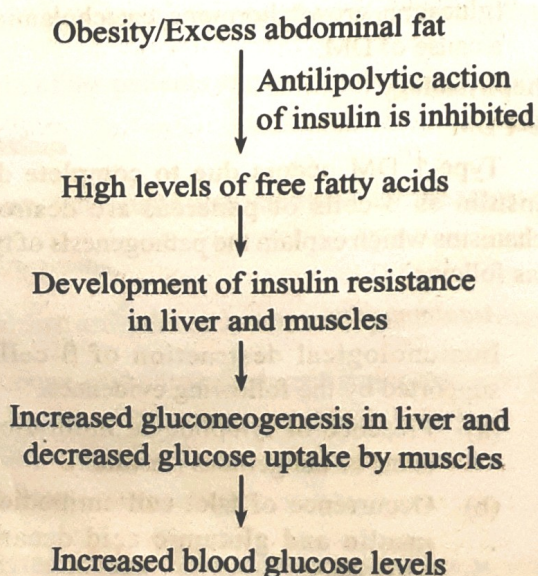
4. Genetic Factors

Genetical predisposing factors of type-1 DM are associated with 2 genes i.e., DR3 and DR4 on chromosome 6 present on Human Lymphocyte Antigen (HLA) region. An individual with one or both the genes is relatively more prone to DM. About 95% people suffering from DM show the presence of either one or both the genes. In them β -cells act as autoantigens, stimulate CD4⁺ T-lymphocytes and bring about their own immune mediated destruction.

Type-2 DM

1. Insulin Resistance

The basic underlying cause for the occurrence of type-2 DM is insulin resistance (peripheral tissues do not respond to insulin). This mainly occurs due to obesity.



2. Impaired Insulin Secretion

Impaired insulin secretion and insulin resistance are interlinked with each other in pathogenesis of DM.

The effect of insulin resistance in early stages of the disease is compensated by hyperinsulinaemia. This helps in maintaining blood glucose levels for time. However, β -cell function impairs eventually, required amount of insulin is not secreted leading to insulin deficiency. The cause for the deterioration in the levels of insulin is not clearly established, but it may be due to,

- Glucose toxicity around islets of Langerhans which may impair the functioning of β -cells
- Lipotoxicity i.e., increased free fatty acid levels
- Deposition of fibrillary proteins around islets of Langerhans by amylin (an islet-amyloid polypeptide) which may impair the functioning of β -cells.

3. Genetic Factors

Occurrence of type-2 DM is linked with the presence of metabolic syndrome or syndrome X. Additionally, individuals with paternal history are at a higher risk of developing type 2 DM.

4. Constitutional Factors

Certain diseases like hypertension, high physical exercise or obesity may contribute to the occurrence of type-2 DM.

Signs and Symptoms

The major difference lies in the appearance of symptoms in type-1 and type-2 DM. These are rapid in type-1 DM but slow and gradual in type 2 DM.

Common signs and symptoms associated with both types of DM are polyuria, polydipsia, polyphagia, fatigue, weight loss, ketonemia, ketonuria, azoturia, blurred vision, tingling sensation or numbness of the extremities, itching, irritability, drowsiness, skin infections, slow healing of wounds, impaired growth, glucosuria, hyperglycaemia and hyperlipidaemia.

Complications

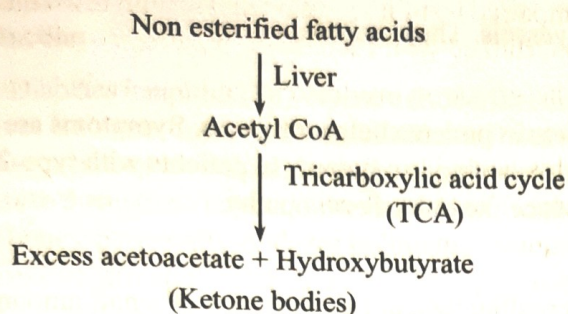
Short Term Complications

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) or hyperosmolar non-ketotic hyperglycaemia are the two life-threatening acute metabolic complications associated with DM which require immediate medical intervention.

1. Diabetic Ketoacidosis (DKA)

DKA is one of the major causes of death in 5-10% of patients suffering from DM. It is a secondary condition arising due to deficiency of insulin. It is usually associated with type-1 DM and very rarely seen in type-2 DM.

Pathophysiology



The ketone bodies are released into the circulation in excess amounts because the restraining effect of insulin on lipolysis is eliminated due to its deficiency. It may also occur due to discontinuation of insulin therapy or due to stressful conditions like stroke, acute myocardial infarction or trauma.

Manifestations

- Osmotic diuresis occurring due to hyperglycaemia results in dizziness, fatigue and weakness.
- Fatigue is increased because of excess potassium loss due to polyuria and vomiting stimulated by ketone bodies.
- Ketoacidosis aggravates dehydration and hyperosmolarity causing nausea, vomiting and anorexia.
- High plasma osmolarity results in mild to severe impairment of consciousness. About 10% of the cases develop coma.
- Kussmaul respiration i.e., deep and rapid breathing due to stimulation of respiratory centre by metabolic acidosis.
- Patients exhibit fruity breath (of acetone) due to the presence of excess of ketones. It usually smells like nail polish remover.
- Other symptoms like dry skin, tachycardia and hypotension may also occur.

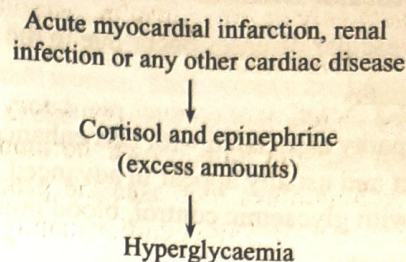
Management

- Fluid correction by infusing 0.9% NaCl.
- Hyperglycaemia treated by administering insulin.
- Identification and subsequent treatment of any infection.

2. Hyperosmolar Hyperglycaemic State (HHS) / Hyperosmolar Non-Ketonic Hyperglycaemia

In HHS, the blood glucose levels are higher than 33.3 mmol/l or 600 mg/dL. It mainly occurs in middle aged and older people suffering from type-2 DM. It has a high death rate of 15-30%.

Pathophysiology



Other factors that cause HHS are poor compliance with dosage regimens or use of diuretics or drug which cause impairment in glucose tolerance (glucocorticoids).

Manifestations

Hyperglycaemia occurs in a gradual manner for a prolonged period, causing dehydration due to osmotic diuresis, further leading to hyperosmolarity. Hyperosmolarity may precipitate thromboembolism as it increases the viscosity of blood.

Management

- Fluid replacement with 0.9% NaCl to improve circulation and to stabilize BP.
- Intravenous infusion of insulin in moderate doses.
- Prophylaxis or treatment of thromboembolism.

Long term Complications

Chronic complications occur slowly and gradually and are usually not noticed. They include macrovascular and microvascular disorders arising due to the damage to large and small blood vessels respectively.

1. Macrovascular Diseases

These diseases arise from damage to large blood vessels. They mainly include cardiovascular diseases and peripheral vascular diseases.

(a) Cardiovascular (CVS) Diseases

Approximately 80% of deaths in patients suffering from type-2 DM is due to CVS diseases. The risk of occurrence of CVS diseases is increased by smoking, presence of hyperlipidaemia and nephropathy.

- Hypertension
- Silent myocardial infarction usually occurs with diabetes.
- Atherosclerosis and atherosclerotic lesions are common in both type-1 and type-2 DM. It occurs due to dyslipidaemia, decrease in the levels of high density lipoproteins (HDL), obesity, hypertension and excessive platelet aggregation.

(b) Peripheral Vascular Disease (PVD)

In this, arteries of the legs are affected leading to claudication, and cramping pain while walking. Iliac vessels may also be affected leading to buttock pain and erectile dysfunction.

2. Microvascular Diseases

Microvascular diseases occur due to the damage to small blood vessels. They include,

(a) Retinopathy

Retinopathy associated with DM enhances the chances of blindness in patients below 60 years. Symptoms are slow in onset and usually appear in advanced stages, therefore regular screening is required. In patients with type-2 DM along with glycaemic control, blood pressure control helps to reduce the risk of retinopathy.

(b) Nephropathy

Nephropathy can be evaluated by detecting the presence of microalbuminuria i.e., presence of small amounts of albumin in urine and proteinuria i.e., presence of excess amounts of albumin in urine. Proteinuria usually occurs in the advanced stages of disease.

(c) Peripheral Neuropathy

Progressive loss of peripheral nerve fibres leading to nerve dysfunction is called peripheral neuropathy. Generally, distal sensory symptoms appear in the feet leading to initial loss of sensation which may progress to loss of feeling.

Distal motor neuropathy leads to muscle pain (mainly in thighs), weakness, wasting and impaired fine co-ordination of hands, foot or both.

3. Macro and Microvascular Diseases

Infected diabetic foot ulcers are common. The risk of incidence increases with the presence of PVD, neuropathy and hyperglycaemia.

4. Formation of Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are compounds that are formed when sugars react with proteins or lipids through glycation reaction. They are present in animal derived foods and are further formed when these foods are cooked. AGEs have been implicated in aging process and in pathogenesis of several degenerative diseases including diabetes, atherosclerosis, Alzheimer's disease and chronic renal diseases.

About 20 AGEs have been characterised in human tissues such as carboxy methyl lysine, carboxy ethyl lysine, pentosidine, methyl glyoxal lysine dimer, glyoxal lysine dimer etc. They can be exogenously ingested through food or endogenously formed. The process by which AGEs are formed was discovered by Louis Camille Maillard in the year 1912. Hence the chemical reaction by which AGEs were formed was named Maillard reaction.

AGE products are formed by a series of slow, non-enzymatic reactions that begins when carbonyl groups of sugars react with amino groups of proteins, lipids or nucleic acids. This leads to formation of a Schiff's base (unstable) which then undergoes irreversible rearrangement to form a stable ketoamine (Amadori product). Amadori product then undergo a series of modifications including dehydration, oxidation, rearrangement and fragmentation to form a heterogeneous group of adducts which are collectively called advanced glycation end products (AGEs).

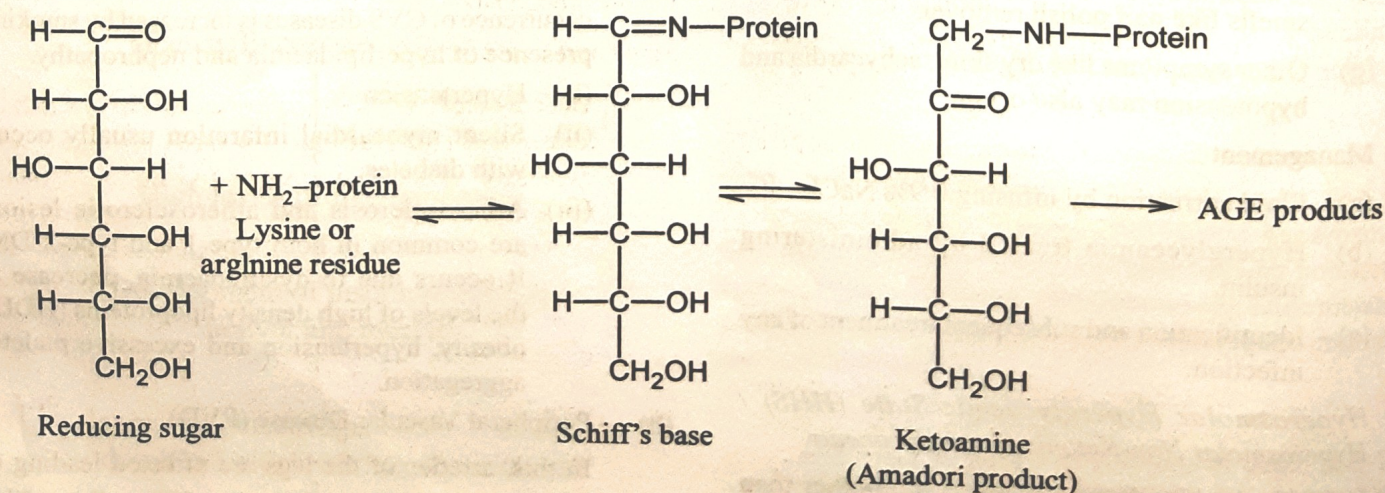


Figure: Formation of AGE Products (Maillard Reaction)

Endogenous formation of AGE products increases in conditions like persistent hyperglycaemia, dyslipidaemia and oxidative stress. Factors like diet, smoking etc., also influence their formation rate.

3.2 DIABETES INSIPIDUS

Introduction

Diabetes insipidus (DI), is a rare endocrinal disorder. It derives its name from the combination of two words, *diabetes* meaning overflowing and *insipidus* signifying tasteless to distinguish it from diabetes mellitus, where *melli* means honey. Essentially, diabetes insipidus is characterized by excessive urination (polyuria) and thirst (polydipsia). In normal individuals, the volume of water reabsorbed at the collecting ducts is regulated by a hormone called antidiuretic hormone (ADH), also referred as vasopressin. This hormone is released from the posterior lobe of pituitary in response to an increase in the plasma osmolarity or hypovolaemia (reduced blood volume). In certain patients with diabetes insipidus, either the hypothalamus or the posterior pituitary may get damaged due to certain reasons, thus resulting in hyposecretion of vasopressin. On the other hand, in certain patients, vasopressin receptors in the kidneys become unresponsive towards the released hormone.

Aetiology

There are basically 4 forms of diabetes insipidus, which differ in their aetiology.

1. Central (Neurogenic) Diabetes Insipidus

This form, also termed as neurohypophyseal diabetes insipidus, occurs as a result of damage to the hypothalamus or posterior pituitary. The source for damage can range from being a brain tumour, shock, head injury, brain surgery or very rarely due to syphilis, sarcoidosis, genetic disorders etc. Such injury results in hyposecretion of vasopressin.

2. Nephrogenic Diabetes Insipidus

This form of DI occurs more rarely than the neurogenic DI. In this form, although the posterior pituitary releases normal levels of antidiuretic hormone (ADH) but its receptors in the kidney are unresponsive to it. Other causes of nephrogenic DI include kidney damage, hypokalaemia, hypercalcaemia etc. Additionally, it may be hereditary i.e., restricted to certain families and transmissible to generations or may even be idiopathic i.e., of unknown cause.

3. Dipsogenic Diabetes Insipidus

Normally, the action of fluid (water) consumption is regulated by the hypothalamus via its thirst centre. When this centre gets damaged or there occurs a defect in the thirst mechanism, the patient feels excessively thirsty, consumes lots of water and thereby experiences polyuria as the secretion of antidiuretic hormone has been impaired.

4. Gestational (Gestogenic) Diabetes Insipidus

This form of diabetes insipidus is predominant in pregnant women. Such women are known to produce a placental enzyme termed vasopressinase which catalyses the degradation of maternal ADH, thus reducing its levels.

Pathogenesis

Diabetes insipidus is caused due to hyposecretion of ADH or unresponsiveness of the renal ADH receptors towards the hormone. Physiologically, in response to an increase in the plasma osmolarity or hypovolaemia, the hypothalamic osmoreceptors bring about activation of certain neurosecretory cells. These cells synthesize and release vasopressin. ADH stored in the axon terminals of the neurosecretory cells get released in the blood. Though the released hormone acts on 3 sites i.e., kidneys, sweat glands and vascular endothelium, only the action of vasopressin pertaining to kidneys has been described. On reaching the kidneys via blood, the hormone binds to V_2 receptors and reduces the water permeability of the collecting ducts. This results in retention of water and decreased urine output. This reduces the plasma osmolarity which results in cessation of ADH release.

However, in neurogenic diabetes insipidus, damage to either hypothalamus or posterior pituitary impairs their function and results in hyposecretion of ADH. One of the causes of nephrogenic DI is the unresponsiveness of ADH receptors towards the normal hormonal levels. Although, the regulation of electrolyte balance is given priority over volume regulation, but in case of diabetes insipidus where there is drastic reduction of body fluids, the body attempts to conserve water which is achieved at the cost of already reduced electrolyte levels. Hence, the patient may exhibit severe signs of dehydration if he is deprived of fluids for longer time period.

Signs and Symptoms

1. The classical symptoms of diabetes insipidus in both infants and adults are excessive urination along with excessive thirst. The extent of urination depends upon the severity of the disease. A patient with mild DI may produce about 2.5 litres of urine per day while almost 15 litres may be excreted in chronic conditions in contrast to normal value which ranges in between 1.5-2.5 litres/day.
2. Adults with DI exhibit the following symptoms,
 - (a) Nocturia i.e., urination at night
 - (b) Bed-wetting
 - (c) Dehydration in some individuals as the loss of fluids exceeds the fluid intake.

3. Infants and children with DI experience the following symptoms,
 - (a) Fever
 - (b) Emesis (vomiting)
 - (c) Diarrhoea
 - (d) Persistent crying
 - (e) Dry and cool extremities.
4. Complications of DI include severe dehydration and electrolytic imbalance which can prove fatal unless treated.

4. DISORDERS OF GASTROINTESTINAL SYSTEM

4.1 PEPTIC ULCER

Formation of sores or erosions in the lining of stomach and duodenum are referred as *peptic ulcers*. Stomach ulcers are referred as *gastric ulcers* while ulcers occurring in the duodenum are known as *duodenal ulcers*. Together, they are known as *peptic ulcers*.

Types of Ulcers

1. *Esophageal Ulcers*
Ulcers in the lower sections of the esophagus are known as esophageal ulcers. They occur due to defective sphincter. These ulcers are also known to occur when the gastric acid (HCl) from the stomach, refluxes back into the esophagus.
2. *Gastric Ulcers*
Ulcers occurring in the upper curve (antrum) of the stomach are referred to as gastric ulcers.
3. *Duodenal Ulcers*
Ulcers occurring in the duodenum are known as duodenal ulcers. They occur either at the duodenal bulb or at the pyloric channel.
4. *Stress-Induced Ulcers*
Ulcers in stomach and duodenum occurring due to injury, burns, emotional stress or illness are referred to as stress-induced ulcers.
5. *Marginal or Anastomotic Ulcers*
After gastrectomy (removal of a part of the stomach), the remaining part of the stomach gets connected to the intestine. Ulcers occurring at the margin where stomach connects to the intestine are referred to as marginal ulcers.
6. *Drug or NSAID-Induced Ulcers*
Occurrence of ulcers due to prolonged use of NSAIDs are referred to as drug-induced ulcers.

Aetiology

Peptic ulcers occur due to the imbalance between the protective factors (mucus production, mucosal blood flow) and destructive factors of the stomach (excess acid production, NSAIDs, pepsin). This imbalance occurs due to multiple reasons such as,

1. *Infection Caused by Helicobacter pylori*
Infection due to *H.pylori* is the most common cause for the development of peptic ulcers. It is a Gram-negative bacterium found in the gastric mucosa. It disrupts the mucosal barrier resulting in the formation of ulcers. About 80-85% of the gastric ulcers and about 90-95% of the duodenal ulcers are associated with *H.pylori*. The infection is transmitted through faeco-oral route.
2. *Excessive Use of NSAIDs*
Use of NSAIDs for prolonged periods alter the balance of mucosal barrier. They block the prostaglandin synthesis which is necessary for the formation of mucosal barrier.
3. *Excess Secretion of Gastric Acid*
Certain cases like Zollinger-Ellison's syndrome is characterized by the presence of gastrinoma (gastrin producing tumour) that causes excessive gastric acid secretion and ultimately results in peptic ulcers.
4. *Other Related Factors*
Smoking, genetic factors, chronic disorders like cirrhosis, Zollinger-Ellison syndrome, arthritis etc., might precipitate peptic ulcers.

Pathophysiology**Gastric Acid Secretion**

Stomach maintains a pH of 1-2 and secretes 2.5 litres of gastric juice per day. This gastric juice is composed of hydrochloric acid, pepsin, renin, mucus, neutral chlorides, intrinsic factor and also traces of potassium, ammonium and calcium ions. Hydrochloric acid is secreted by the parietal cells of the stomach and pepsinogen by the chief or peptic cells. Apart from these, protective factors like mucus and bicarbonate ions are also secreted, which tend to form a protective layer over the mucosa in order to protect it from the deleterious effects of gastric acid.

H.pylori-induced Ulcers

H.pylori is a spiral bacteria localized in the gastric antrum of the stomach. The steps involved in *H.pylori*-induced peptic ulcers are,

1. *H.pylori* attaches to the epithelial surface of the mucosa and causes injury to the cells by releasing a vacuolating toxin called vac A.
2. It also secretes an enzyme urease which hydrolyses urea to toxic products like ammonium chloride and bicarbonate. These along with bacterial phospholipases and proteases break the glycoprotein-lipid complexes of gastric mucosa and induce an inflammatory response.
3. Now, the organism penetrates into the mucosa and enhances gastric acid production. The organism is able to withstand high acidic environments due to the release of ammonia.
4. It also affects the bicarbonate production in duodenum and thus decreases the luminal pH of duodenum. This acidic environment favours the presence of gastric epithelium in the duodenum (gastric metaplasia).
5. Because of the growth of gastric metaplasia in the duodenum, the organism tends to localize here and results in mucosal inflammation that ultimately leads to the formation of peptic ulcers.

NSAID-induced Ulcers

NSAIDs induce peptic ulcers in the following ways.

1. NSAIDs increase the gastric acid secretion, which tends to disrupt the mucosal lining and results in ulcers.
2. *Inhibition of PG*

NSAIDs are known to inhibit COX-1 and COX-2 which are responsible for the formation of prostaglandins. Inhibition of PG formation prevents mucus and bicarbonate secretion that ultimately creates an imbalance between protective and deleterious factors resulting in ulcer formation.

3. *NSAID-related Mucosal Injury*

A decrease in mucosal blood flow is seen when NSAIDs are administered. This is due to an increase in the production of TNF- α which in turn stimulates the migration of neutrophils to the gastric mucosa. These neutrophils disrupt the endothelium and decrease the blood flow. Endothelium disruption can also occur due to the release of oxygen-derived free radicals and proteases by neutrophils.

4. *Superficial Damage*

Weakly acidic drugs like aspirin gain entry into the gastric mucosa. Inside the cell, dissociation of H^+ ions occurs because of neutral pH. As a result, NSAIDs get accumulated in the mucosa and damage the mucosal lining resulting in peptic ulcers.

NSAIDs also prevent the repair process of damaged cells and platelet aggregation that plays a role in aggravating peptic ulcers.

Signs and Symptoms

The main clinical manifestation of peptic ulcers is pain in the abdomen with burning sensation which increases after 2-3 hours of food consumption. Other symptoms include heartburn, indigestion, belching, nausea, vomiting, loss of appetite, weight loss, black tarry stools, blood vomiting and pain during night time. It is not necessary that all patients suffering from peptic ulcers should experience symptoms as some patients are asymptomatic. Moreover, symptoms may vary depending upon the type of ulcer.

Table: Difference Between Duodenal and Gastric Ulcers

Feature	Duodenal ulcer	Gastric ulcer
Occurrence	It occurs mostly in males and is more common than gastric ulcers	It occurs mostly in males and is less common than duodenal ulcers
Aetiology	1. Infection of <i>H. pylori</i> 2. Hyperacidity 3. Decreased resistance to pepsin. 4. Alcohol, tobacco, caffeine 5. Assumed causes are : (a) Anxiety (b) Release of gastrin (c) 'O' blood group people suffers from duodenal ulcer known as Zollinger Ellison syndrome in which a tumour in the pancreas secretes a substance that causes ulcers throughout the stomach and duodenum. (d) Decreased food intake. (e) Decreased blood circulation. (f) Decreased motility of stomach (g) Decreased prostaglandin synthesis.	
Specific aetiology	1. People with 'O' blood group are highly susceptible 2. Due to disorder of pancreas. 3. Hyperparathyroidism.	1. Damage of mucosal barrier by gastric acid. 2. Gastritis 3. Bile reflux 4. Pancreatic enzyme reflux 5. Radiation.
Symptoms	1. Abdominal pain occurs between meals; hence known as pain-food relief pattern. 2. Abdominal pain is common at night. 3. There is no vomiting. 4. Melena i.e., tarry, foul smelling bloody faeces is common. 5. The patient does not lose any weight. 6. There is no dietary restrictions. 7. The patient experiences extreme tenderness in the right hypochondrium. 8. Seen mostly in people who are under stressful conditions.	1. Abdominal pain occurs after 30 minutes of meal which exists for 2-3 hours depending on the meal type and quantity, hence known as food pain pattern. 2. Abdominal pain does not occur at night 3. Vomiting is common. 4. Haematemesis (blood vomiting) is more common. 5. The patient loses weight. 6. The patient is given bland diet without spicy stuff. 7. The patient experiences extreme tenderness in the midline of epigastrium. 8. Mostly seen in labourers.
Pathogenesis	It is common in the first part of the duodenum	It is common along the lesser curvature of pyrolic antrum in stomach.
1. Ulcer site		
2. Microscopy	1. Duodenal ulcers are benign but gastric ulcers may become malignant 2. Both duodenal and gastric ulcers are round to oval shaped 3. They are smaller in size (1.2.5 cm in diameter). 4. They bear a depression 5. The depth of ulcers vary from being superficial to deep i.e., from mucosal to muscular layer.	
Complications	1. Duodenal stenosis 2. Haemorrhage 3. Perforations (more common) 4. Benign type of ulcers	1. Pyrolic steanosis 2. Haemorrhage 3. Perforations (less common) 4. Malignant type of ulcers

4.2 INFLAMMATORY BOWEL DISEASES

4.2.1 Ulcerative Colitis

Introduction

Ulcerative colitis (UC) is one of the two types of inflammatory bowel diseases, the other being Crohn's disease. The exact cause and pathogenesis of UC remains unknown. It commonly initiates in mucosa of rectum and sigmoid colon and may later spread to the entire colon, ulcerate and become infected. It is commonly seen in young adults. It is characterized by repeated acute inflammatory episodes followed by periods of remission.

Epidemiology

Incidence of UC is approximately between 20 and 40 years of age. Females are at a higher risk than males.

Aetiology

Factors that are thought to play an important role in the occurrence of UC are as follows.

1. Patients with a family history of UC are at higher risk of developing the disease.
2. The concordance rate of ulcerative colitis in identical twins is 10% whereas it is 3% in dizygotic twins.
3. Smoking reduces the risk of UC probably due to nicotine. Ex-smokers are at higher risk when compared to non-smokers.
4. Emotional and psychological factors such as stress may result in UC.
5. The conditions that may be associated with UC are arthritis, haemolytic anaemia, iritis as well as certain skin lesions and drug sensitivities.

Pathophysiology

Although the exact pathology of UC remains unknown, injury to colon appears to be due to immune mediated inflammatory reaction. Genetically susceptible human beings cannot down regulate immune or non-specific inflammatory responses. It is also thought that the primary failure of regulatory lymphocytes and cytokines to control inflammation and effector pathways may result in UC.

Signs and Symptoms

Bloody diarrhoea with mucus and abdominal pain with fever are the characteristic symptoms of ulcerative colitis. The symptoms vary depending on the severity of the disease.

4.2.2 Crohn's Disease

Introduction

It is an inflammatory disorder of the alimentary tract commonly affecting the terminal ileum and the rectum. It can affect the entire length of the alimentary tract (from mouth to anus) but terminal ileum is the common site of infection.

Epidemiology

Young adults of age group 20-40 years of either sex are prone to Crohn's disease with higher incidence among those who smoke.

Aetiology

Crohn's disease is characterized by chronic patchy inflammation of the tissue involved and oedema of the entire thickness of the intestinal wall. This results in the formation of skin lesions which are characterized by partially obstructed luminal regions interspersed with regions of normal tissue.

Pathogenesis

Though the exact cause of the disease remains unclear, weak immunological response of an individual against certain viral infections is conceded as a contributing factor in developing Crohn's disease.

Signs and Symptoms

Ulcers and fistulae are important hallmarks of this disease. Surgical intervention is beneficial, however in severe cases the condition may relapse even after surgery.

Complications

- Complications of Crohn's disease are manifested by,
1. Formation of fistula around the anal region
 2. Megaloblastic anaemia due to malabsorption of vitamin B₁₂ and folic acid from the intestine
 3. Formation of fistulae between the intestinal region and associated adjacent regions like loop of bowel or skin surface
 4. Secondary infection due to ulceration of the inflamed areas
 5. Cancer of the small and large intestine.

4.3 CIRRHOSIS

Introduction

Cirrhosis may be defined as the chronic injury of liver involving fibrosis of hepatocytes (functional units of the liver) within the liver accompanied with regenerative nodule formation. The nodules protrude and make the surface of liver uneven and turn it to pale brown. Cirrhosis may be due to various causes and leads to decreased hepatic function. Almost all chronic diseases progress to cirrhosis.

Epidemiology

Cirrhosis is more common in men aged between 40 and 60 years.

Aetiology

Many causes are associated with the development of cirrhosis.

1. Alcohol Consumption

The most common cause of cirrhosis is alcohol consumption. Chronic alcoholism can induce fatty changes, inflammation and progressive fibrosis of liver leading to alcoholic cirrhosis.

2. *Chronic Hepatitis C*

About 20-30% of patients infected with hepatitis C virus (HCV) develop cirrhosis. Hepatic steatosis (infiltration of hepatocytes with fat or abnormal entry of fat into the liver), increased iron content, oxidative stress, etc., are the few proposed mechanisms by which HCV causes liver damage.

3. *Chronic Hepatitis B*

Chronic infection with hepatitis B virus (HBV) can cause hepatic inflammation and injury which progresses to cirrhosis over several years. HBV is the next common cause of cirrhosis.

4. *Autoimmune Hepatitis*

It is an immunologic disease of unknown cause. It involves inflammation of the liver that ultimately leads to cirrhosis.

5. *Primary Biliary Cirrhosis (PBC)*

It is also an autoimmune disease of liver, mostly seen in women. It occurs as a result of chronic cholestasis (obstruction of bile flow in hepatocytes) that causes chronic hepatic inflammation and scarring which ultimately leads to cirrhosis.

6. *Primary Sclerosing Cholangitis (PSC)*

Cholangitis is the inflammation of bile ducts. Sclerosing cholangitis is caused due to chronic ulcerative colitis in which all the bile ducts become narrow. This leads to cholestasis and ultimately cirrhosis. It typically occurs in young males.

7. *Metabolic Disorders*

- (a) Hereditary Haemochromatosis (HH)
- (b) Wilson's Disease
- (c) α_1 -antitrypsin Deficiency

Pathophysiology

Cirrhosis initiates with the release of cytokines during inflammation and necrosis of hepatocytes. These cytokines stimulate fibrogenesis. After the inflammation subsides, the destroyed liver tissue gets replaced by fibrous tissue. Consequently, there is loss of normal architecture of liver along with loss of normal function. Later hyperplasia of hepatocytes (adjacent to damaged cells) occurs that leads to the formation of nodules consisting of hepatocytes confined within sheets of fibrous tissue.

As the condition progresses, there is decreased flow of blood through the liver leading to a rise in the portal pressure. This is known as portal hypertension which can lead to severe complications such as ascites, oesophageal varices, hepatic encephalopathy and rarely hepatorenal syndrome.

Signs and Symptoms

Cirrhosis is usually asymptomatic until the disease progresses to an advanced stage. The major complication is portal hypertension which can lead to the following conditions.

1. *Ascites*

It is characterized by accumulation of fluid in the abdominal cavity (peritoneum). Patients with ascites may experience symptoms such as weight gain, abdominal pain and gastroesophageal reflux.

2. *Esophageal Varices*

Portal hypertension causes backflow of blood from portal system to the systemic circulation via the coronary, gastric and inferior mesenteric veins leading to esophageal varices, gastric varices and hemorrhoids respectively.

3. *Porto-systemic Encephalopathy*

It is a condition in which CNS function is impaired due to the presence of toxic products of protein metabolism, particularly ammonia which is normally metabolized by liver. Symptoms include altered mental state, sleep reversal, apathy, hypersomnia, intellectual deterioration, slurred speech etc.

- 4. Other clinical manifestations include jaundice, splenomegaly, thrombocytopenia, leukopenia and excess feminization (due to inability of the cirrhotic liver to metabolize steroidal hormones).

4.4 ALCOHOLIC LIVER DISEASES

Introduction

Cirrhosis refers to the structural damage of the liver by scarring and fibrosis (thickening) wherein the liver tissue is substituted by scar tissue as a result of long-term inflammation and injury. Alcohol abuse is the most common cause of cirrhosis and the condition is called *Alcoholic Liver Disease* (ALD). It is also known as Laennec's Cirrhosis.

ALD refers to the liver damage that occurs as a result of sudden and intense or long-term alcohol abuse.

Stages in ALD

1. *Alcoholic Steatosis (Fatty Liver)*

In this stage, neutral fat collects in the cytoplasm of the parenchymal cells in the form of microvesicular and macrovesicular globules, pushing the nucleus to the boundaries of the cell. Sometimes, lipogranulomas which are yellowish nodules formed due to lipid metabolism abnormalities may be present which contain lymphocytes, macrophages and large cells with multiple nucleoli. Cysts containing fat may also form and the liver increases in size, acquires a lemony tinge, becomes oily and hardened, resembling a shiny capsule.

2. *Alcoholic Hepatitis*

After a sudden and intense episode of alcohol consumption, alcoholic hepatitis develops. In alcoholic hepatitis, the following features are observed.

(a) *Necrosis of Liver Cells*

The liver cells deteriorate, become functionless and eventually die.

(b) *Mallory Bodies*

Presence of Mallory bodies, which are eosinophilic particles present in the cytoplasm near the nucleus, may indicate alcoholic hepatitis.

(c) *Inflammatory Response*

Substance containing cells with a single nucleus and WBCs with lobed nucleus, which causes inflammation is found in regions where Mallory bodies are present and where the cells have died and this substance may cover the complete lobule in case of rampant necrosis or cell death.

(d) *Fibrosis*

Areas around the veins and cells thicken leading to a web-like appearance which is referred to as 'creeping collagenosis'.

3. *Alcoholic Cirrhosis*

Initially, nodules less than 3 mm in diameter called micronodules are formed which eventually increase in size with time to form macronodules, while the liver which was big, contained fat and weighed more than 2 kgs, drops to less than 1 kg in weight and becomes fat deprived. Fat containing nodules which have a lemony tinge with very less proportional difference are embedded on the liver's surface making the liver look bulgy and knobby. The following features are seen.

(a) *Nodule Formation*

The lobules disappear, nodules are formed and the central veins become inconspicuous.

(b) *Fibrous Septa*

In the beginning, septa made up of fibres, that splits the liver parenchyma into nodules is very fine but over time it becomes thick and confluent as the scarring intensifies.

(c) *Liver Parenchyma*

Initially, liver cells present in the living parenchyma transform into restorable nodules and exhibit high levels of fatty change but the fat percentage gradually decreases as the fibrous septa becomes dense.

(d) *Cell Death, Inflammation and Proliferation of Bile Duct*

Infiltrate containing cells with single nucleus is found in fibrous septa and there is rapid reproduction and growth of the bile duct cells along with stoppage in bile production and enhanced accumulation of iron storage compound called hemosiderin in the cytoplasm due to increased absorption of iron. In highly progressed cases of alcoholic cirrhosis, it is difficult to spot Mallory bodies.

Aetiology

10-15 out of 100 individuals who consume alcohol develop cirrhosis. Following are the few risk factors.

1. *Alcohol Consumption*

Alcoholic cirrhosis may occur as a result of consuming 60,000-80,000 mg of ethyl alcohol daily in the form of any drink for 10 years. The extent of damage to the liver depends on the ethanol content in the drink, which may vary with the type of the drink and on the period for which it is taken, whereas consuming alcohol irregularly for prolonged periods allows the liver to recuperate and hence is less injurious. A majority of the individuals who consume large amounts of alcohol for prolonged periods develop fatty liver and this might advance into alcoholic hepatitis in 10-20% of the individuals and into alcoholic cirrhosis after a decade.

2. *Sex*

With a daily consumption of less than 20,000-40,000 mg of females are still at a higher risk of developing alcohol progressive ALD as compared to males, most likely due to oestrogen's influence.

3. *Malnutrition*

Long-term alcoholism in people with deficiency of proteins and vitamins can lead to ALD and malnutrition since the nutrients get dislodged due to the heat evolved from the metabolism of alcohol. Inflammation of the gastric mucosa and pancreas also plays a part in causing malnutrition in alcohol abusers.

4. *Infection*

The progression of ALD may speed up by the occurrence of bacterial and viral infections.

5. *Hereditary Factors*

Different individuals have varied elimination rates of ethanol because of genetic polymorphism for MEOS (Microsomal P-450 oxidases) and ADH (alcohol dehydrogenase) enzyme systems and individuals show varied sensitivity to liver damage due to difference in HLA histocompatibility.

6. *Hepatitis C-Virus (HCV)*

If a person with long term alcohol abuse contracts hepatitis C, then daily consumption of just 20,000-50,000 mg of alcohol may accelerate the advancement of ALD, with higher intensity even in young individuals. There is an increase in the probability of development of cancer of liver cells, mortality rate and progression of ALD to cirrhosis.

Pathogenesis

Long-term alcohol abusers with risk factors (which were discussed previously) develop ALD due to the hazardous influence of ethanol and its metabolites. The pathogenesis may be explained as under.

1. *Direct Toxicity of Liver Cells by Ethanol*

Direct toxicity of the liver cells may occur after continuous consumption of ethanol daily, for more than a week, which might lead to the deposition of fat in the liver cells.

2. *Toxicity of Liver Cells by Ethanol Metabolites*

Acetaldehyde which is one of the metabolite of alcohol, produces majority of toxic effects on the cells of liver by forming two adducts. They include,

(a) Protein-aldehyde Adduct

These adducts may bring about injury to the membranes and cytoskeleton and cause death of the cells of liver due to their poisonous nature.

(b) Malon-dialdehyde acetaldehyde (MAA) Adduct

They play a part in the process of fibrogenesis of liver cells via peroxisome proliferator-activated receptor (PPAR- γ) present on the liver cells and produce autoantibodies and trigger an autoimmune cascade.

3. *Oxidative Stress*

Free radicals are formed as a result of oxidation of ethanol by mitochondrial cytochrome-450 oxidases (MEOS) which result in injury to the proteins and membranes.

4. *Immunological Mechanisms*

Liver cells suffer invasion by the immune system. Although ingestion of alcohol is discontinued, liver damage progresses in many cases due to weakened cell-mediated immunity.

5. *Inflammation*

Cells of the intestine are injured due to long-term alcohol abuse, which in turn expands the endotoxins to unleash IL-6, IL-1 (interleukins), TNF- α (tumour necrosis factor) and TGF- β (transforming growth factor), which are cytokines which stimulate inflammation, cause cell death and programmed cell death.

6. *Fibrogenesis*

Pericytes found in perisinusoidal space of the liver called *stellate cells* get activated in response to liver cell injury, by stimulation of malon dialdehyde-acetaldehyde adducts, acetaldehyde and by activation of phagocytic cells of the liver called Kupffer cells, leading to fibrogenesis. 'Lto' cells change into cytoplasmic filaments and inactive cells and there is a rise in collagen.

7. *Rise in the Redox Ratio*

Plasma acidity rises due to enhanced lactate-pyruvate redox ratio, which occurs as a consequence of enhanced NADH:NAD redox ratio in the liver cells.

8. *Hepatocyte Water and Proteins Retention*

Water and proteins which are freshly produced by the liver are held back in the liver cells as alcohol hampers their release leading to enlargement of the liver due to bulging of the liver cells.

9. *Hypoxia*

Liver cells die due to lack of oxygen. This happens as a result of long-term alcohol abuse, which might lead to increased need for oxygen by the liver cells.

10. *Increased Liver Fat*

During long-term alcohol abuse there is deposition of fat in the liver cells, which may be derived from food by enhanced formation of lipids by the liver or by increased stimulation of the fat containing tissues.

5. DISORDERS OF RENAL SYSTEM

5.1 ACUTE RENAL FAILURE

Introduction

Renal failure is a disorder of the kidneys characterized by reduced or diminished glomerular filtration. Depending upon the severity, it is divided as acute and chronic renal failure.

An individual is said to suffer from acute renal failure when the glomerular filtration rate has undergone a sudden and drastic reduction. The condition responds well to therapy and the normal renal function is restored within few days or weeks.

Aetiology and Pathophysiology

The causes are divided as,

1. Prerenal changes that include

- (a) Decreased blood flow to nephron
- (b) Renal ischaemia

2. Intrinsic renal changes that include

- (i) Glomerular disease
- (ii) Disease of artery and arterioles within the kidney
- (iii) Disease of renal tubules
- (iv) Acute tubulointerstitial nephritis
- (v) Pyelonephritis.

3. Postrenal changes cause obstruction to the urine flow along the renal tract leading to post renal disease of the kidney.
4. Other causes include low blood volume (due to haemorrhage), decreased cardiac output, kidney stones, haemolytic uraemic syndrome, NSAIDs and antibiotics.

Signs and Symptoms

They vary depending upon the etiological factors.

1. Acute Nephritis

It is associated with

- (a) Acute post-streptococcal glomerulonephritis.
- (b) Glomerulonephritis

Kidney failure is due to excess proliferation of epithelial cells in the glomerulus leading to alteration in the permeability (slight increase) with decrease in glomerular filtration rate (GFR).

Main characteristic features are

- (a) Proteinuria (presence of proteins in urine)
- (b) Haematuria (blood in urine)
- (c) Oedema
- (d) Mild hypertension

Fluid retention in acute nephritis is due to :

- (a) Decreased GFR
- (b) Accumulation of salt and water due to increased reabsorption in the distal convoluted tubules.

2. Tubular Pathology

The renal failure occurs due to acute tubular necrosis which is due to dysfunction of renal tubular cells. In acute tubular necrosis, all the cells of renal tubules get destroyed which progresses in three stages.

- (a) Oliguric Phase - Normal urine excreted per day is 1.5 liters. In oliguria, the urine output is less than 400 ml/day and this phase lasts for 7 to 10 days. Decrease in urine formation leads to
 - (i) Accumulation of waste products in blood.
 - (ii) Metabolic acidosis
 - (iii) Hyperkalaemia
 - (iv) Hypernatraemia
 - (v) Hypervolaemia (increase in blood volume), which affects the cardiovascular system by increasing the work load and leading to cardiac failure.
- (b) Diuretic Phase - Indicates increase in urine formation hence healing of oliguric phase occurs. This is due to drawing of sodium and water into the renal tubules and kidneys.
- (c) Recovery Phase - In this phase, healing of tubular epithelial cells occurs with restoration of normal tubular function. The healing may take around one year.

3. Pre-renal Symptoms

In this, neither the glomerulus nor the tubules are damaged.

5.2 CHRONIC RENAL FAILURE

Introduction

It is characterized by decreased glomerular filtration. This condition is progressive and the damage done is irreversible. The disease is very slow in its onset, consuming several years and therefore the patient remains asymptomatic until considerable damage has been done.

Aetiology

1. Glomerulonephritis (inflammation of the renal glomeruli)
2. Diabetes mellitus
3. Pyelonephritis (inflammation of the kidneys)
4. Hypertension
5. Polycystic kidney disease.

Pathophysiology

Clinical features vary with different stages of chronic renal failure.

1. First Stage

It is called as diminished renal reserve. However, no symptoms indicative of renal failure are evident. The reason is that the damage to renal parenchyma is marginal.

2. Second Stage

This stage is characterized by renal insufficiency and reduced GFR. The clinical manifestations include,

- (a) Polyuria (passing of large volumes of dilute urine)
- (b) Metabolic acidosis, caused due to accumulation of H^+ ions because of the failure on the part of the kidney to work as a buffering system.
- (c) Hypertension
- (d) Anaemia, due to decrease in renal-induced erythropoietin production.
- (e) Increased levels of creatinine and other waste products of protein metabolism.

3. Third Stage

It is called as renal failure wherein about 90% of the nephrons are irreversibly damaged. Decrease in the number of nephrons occurs along with further reduction in the GFR. An individual with renal failure exhibits symptoms such as loss of appetite, hiccups, vomiting, muscle twitching, drowsiness, convulsions, coma etc.

4. Fourth Stage (End Stage Kidney Failure)

Almost all the renal parenchyma is destroyed, GFR is about 5% of the normal filtration rate, complete accumulation of metabolic waste products occurs and extra renal symptoms are observed. Damage caused to nephron increases gradually and GFR decreases gradually stage by stage. Diagnosis of CRF occurs in the second and third stage. People with end stage renal failure require dialysis therapy and kidney transplant operation as well.

Stage	Synonym	Reduction in GFR
1.	Diminished renal reserve	35-50% of normal
2.	Renal insufficiency	20-35% of normal
3.	Renal failure	72% of normal
4.	End stage kidney disease	75% of normal

6. DISORDERS OF RESPIRATORY SYSTEM

6.1 ASTHMA

Introduction

Asthma is defined as an inflammatory condition where there is an increased responsiveness of trachea and bronchi to various stimuli resulting in narrowing of airways (bronchoconstriction). It is a clinical syndrome characterized by difficulty in breathing (dyspnoea), cough, wheezing (abnormal sound during breathing) accompanied with increased mucosal secretion and increased respiratory rate (tachypnoea).

Types of Asthma

1. Based on Severity of Attack

Mild intermittent asthma	Chronic asthma	Severe persistent asthma or Status asthmaticus
- Number of attacks per week ≤ 2 and patient remains asymptomatic in between the attacks. - Exercise tolerance is very good.	- Patients suffer from daily attacks of asthma which lasts for several days. - Exercise tolerance is very less.	- Patients suffer from continuous attacks of asthma which is fatal. - Exercise tolerance is very less.
Forced expiratory volume FEV_1 (the air which is exhaled in 1 second) $\geq 80\%$ of the normal value and variation is less.	FEV_1 is around 60-80%. - Nocturnal attacks occur 2-3 times per month.	$FEV_1 < 60\%$ - Nocturnal attacks are observed every day.

2. Based on Causes

Extrinsic asthma	Intrinsic (idiosyncratic) asthma	Mixed type
- It is a common type of asthma manifested by hypersensitivity reaction. - IgE levels are increased. - Family history is present. - It is triggered due to allergens. - Incidence of attacks is more in children.	- Its exact cause is unknown and it is triggered by infectious agents. - Levels of IgE are normal. - Family history is not seen. - It is non-immune in nature and may be caused by exercise and stress. - Incidence of attacks is seen in adults.	- It includes both features of extrinsic and intrinsic asthma. - Asthma when developed in early stages of life is of extrinsic type and which develops in later stages of life is of intrinsic type. - This type of asthma is caused by stress, cold and exercise.

Aetiology

Factors responsible for asthmatic attacks are as follows:

- Genetic factors.
- Exposure to allergens, dust, pollen, moulds, house dust, mites etc.
- Viral respiratory tract infections may precipitate exercise-induced asthma.
- Exposure to irritants like strong odour, vapours, chemicals etc.
- Environmental exposure i.e., changes in weather and cigarette smoke.
- Seasonal variations also precipitate asthmatic attack.
- Dietary changes i.e., high intake of tinned food, low antioxidant intake, low intake of omega-3-fatty acids.
- Lack of exercise which leads to less stretching of the airways. This contracts the muscles of the airways upon exposure to minor irritants.
- Occupational exposure at work place.

Pathophysiology

The attacks of asthma are triggered by various allergenic extracts, exposure to which brings about mast cell sensitization and mast cell degranulation.

Mast Cell Sensitization : Mast cells play an important role in the pathogenesis of asthma. Any allergen when gains access into the body through the mucous membrane, stimulates monocytes, macrophages and B-lymphocytes to produce antigen-specific immunoglobulins (IgE).

IgE attaches to the surface of the mast cell and sensitizes it. This sensitization is observed during the first exposure to allergens. Hence, upon first exposure to allergen there is no attack but only development of antibodies.

Mast Cell Degranulation : During the second exposure to the same allergen, the antigens bind to it to form antigen-antibody complex which leads to degranulation of mast cells. The chemical substances which are released from degranulated mast cells are,

- (a) Histamine : It causes mucus secretion, contraction of smooth muscles and oedema leading to narrowing of airways.
- (b) Serotonin : Stimulates the smooth muscles and causes vasoconstriction.
- (c) Leukotrienes : Cause smooth muscle contraction and are regulators of allergic and inflammatory reactions.
- (d) Prostaglandins : Cause mucosal oedema.

1. Pathogenesis of Allergic Asthma

Pathogenesis of allergic asthma occurs in two phases.

(a) Early (Acute) Phase

It lasts for 30-60 minutes. During this phase, mast cells get activated due to allergic or non-specific stimulus and cause the release of spasmogenic mediators (histamine, serotonin etc.,) which bring about bronchoconstriction. The constriction of bronchial muscles is followed by excess mucus production which narrows the airways thereby worsening the attack.

(b) Late (Chronic) Phase

It is seen upon exposure to allergen for 4-8 hours. During this phase, WBCs migrate to the site of attack. Eosinophils release major basic proteins which cause bronchospasm, vasodilation and excess mucus production. This phase is characterized by inflammation, fibrosis, oedema and necrosis of bronchial epithelial cells. Inflammatory reaction occurs due to the release of leukotrienes, prostaglandins, TXA_2 and histamine.

2. Pathogenesis of Non Allergic Asthma

In this type, the levels of IgE are normal but various skin tests show negative response.

Signs and Symptoms

Asthma is characterised by difficulty in breathing (dyspnoea), cough, wheezing (abnormal sound during breathing) accompanied with increased mucosal secretion and increased respiratory rate (tachypnoea).

6.2 CHRONIC OBSTRUCTIVE AIRWAY DISEASE

Introduction

Chronic obstructive airway disease (COAD) commonly known as chronic obstructive pulmonary disease (COPD) is one of the most prevalent pulmonary disorders. It can be defined as a chronic progressive lung disease in which airflow obstruction occurs due to the narrowing of airways. It mainly involves lung parenchyma, small bronchioles and large airways. It is also known by other names such as chronic obstructive lung disease (COLD), chronic obstructive respiratory disease (CORD), and chronic airflow limitation (CAL).

COPD exists mainly in two forms, viz chronic bronchitis and emphysema. In clinical terms, chronic bronchitis can be defined as chronic productive cough on most days for at least 3 months during 2 successive years, for which other causes identified to cause phlegm (sputum) production have been excluded. On the other hand, emphysema is manifested by enlargement of the air spaces distal to the terminal bronchioles with damage to alveolar walls.

Epidemiology

It is one of the leading causes of death in industrialized nations such as USA, England and Scotland. It was ranked as the sixth major cause for world wide mortality in 1990, and is expected to reach fourth place by 2030 due to rise in smoking rates and demographic variations in most of the nations.

Aetiology

Smoking is the major cause for the development of COPD. The more a person smokes, the more likely is the risk of developing COPD. However in rare cases, non-smokers also develop COPD due to the deficiency of α_1 -antitrypsin that protects the lungs against damage caused by proteases.

Exposure to tobacco smoke is measured in terms of 'pack-years' using the following expression.

$$\text{Total pack year} = \frac{\text{No. of cigarettes smoked/day}}{20} \times \text{No. of years of smoking}$$

A person with 1-20 pack years of exposure has 10% risk of developing mild COPD and 4% risk of severe COPD.

Other risk factors include,

1. Exposure to dust, chemicals and fumes
2. Air pollution
3. Presence of autoimmune component of COPD
4. Bronchial hyper responsiveness and allergy.

Pathophysiology

Chronic Bronchitis

It results due to pulmonary damage and inflammation in large airways. It is characterized by increase in the number and size of mucus secreting glands and goblet cells in the bronchial epithelium. As a result, there is hypersecretion of thick and viscous mucus which leads to increased expectoration and consequent distention of alveoli followed by loss of their gas exchange function. The body compensates with increased cardiac output and hypoventilation. All these changes contribute to hypoxaemia and polycythaemia (increase in number of RBCs) followed by hypercapnia and respiratory acidosis. This in turn causes pulmonary vasoconstriction leading to increase in right ventricular pressure, followed by right ventricular hypertrophy and progressive right ventricular failure (cor pulmonale).

Microscopically, there occurs inflammation in the airway walls followed by scarring and remodelling that thickens bronchioles and alveolar walls, thus resulting in blocking and obstruction of the airways. As the disease progresses, there is further scarring of the airway walls, ultimately leading to limitation to airflow, which is the pathologic mechanism underlying COPD. Patients with advanced chronic bronchitis are called "blue boaters" because of the presence of cyanosis, hypoxia and fluid retention observed in them.

Emphysema

Emphysema results due to enlargement of the air spaces and destruction of the alveolar walls (i.e., narrowing of airways). This reduces the surface area available for the exchange of O_2 and CO_2 during breathing and also decreases the elasticity of the lung, resulting in loss of support for the airways present in the lungs. This contributes to hyperinflation of the lungs (i.e., increase in volume of air in the lungs) and subsequent dyspnoea. Limitation to airflow is the primary mechanism underlying emphysema. Emphysema is mainly of two types.

(i) Centriacinar Emphysema

It is characterized by destructive enlargement of central portions of acini (a small sac surrounded by secretory cells of the gland) and respiratory bronchioles. It is most severe in upper lung lobes and is commonly seen in smokers and coal miners.

(ii) Panacinar Emphysema

It is characterized by destruction of entire alveolus distal to terminal bronchioles. It is severe in lower lung lobes and is commonly seen in patients with deficiency of α_1 -antitrypsin.

In response to smoke in smokers, macrophages and neutrophils release large amounts of elastase and matrix metalloproteinases which cleave elastin of alveoli and matrix respectively. As these proteases are produced in large amounts in smokers, they are not counteracted effectively by antiproteases.

This results in loss of elastic recoil in the airways and impairment of matrix repair. This in turn destroys pulmonary capillary bed, leading to decrease in ability to oxygenate the blood. The body compensates by increasing ventilation (hyperventilation) and decreasing cardiac output. This results in relatively slow circulation through a fairly well oxygenated lung. Hypoxia and pulmonary cachexia (weight loss of lungs) occurs due to decrease in cardiac output and this eventually leads to muscle wasting and weight loss. Patients with emphysema are called "*pink puffers*" as they appear to have pink complexion and breathe in short puffs to compensate hypoxia.

Signs and Symptoms

Chronic bronchitis is characterized by the presence of following symptoms.

1. Persistent cough with sputum production
2. Bronchospasm
3. Wheezing
4. Dyspnoea
5. Cyanosis
6. Pulmonary hypertension
7. Cor pulmonale
8. Severe recurrent lower respiratory tract infections characterized by discharge of thick, viscous, yellow or green sputum. Emphysema is characterized by the following signs and symptoms.
 - (a) Dyspnoea
 - (b) Cough with scanty and mucoid sputum
 - (c) Thin and pursed lips
 - (d) Mild pulmonary hypertension
 - (e) Cor pulmonale only in terminal stage of the disease
 - (f) Lower incidence of bronchial infections.

Complications

1. Sleep Apnoea Syndrome

It is a respiratory disease in which the patient takes frequent or prolonged pauses while breathing during sleep. This leads to decrease in arterial blood gases and consequent decrease in oxygenation of haemoglobin. Hypoxaemia along with pulmonary hypertension and cardiac arrhythmias may result in premature cardiac failure.

2. Acute Respiratory Failure

Acute progress in chronic bronchitis together with rise in volume and viscosity of phlegm further impairs ventilation and produces severe hypoxaemia and hypercapnia. Acute respiratory failure is said to occur if the blood gas levels show low oxygen, high carbon dioxide and low pH (7.3 or less). It is characterized by confusion, cyanosis, hypotension, restlessness, sweating, tachycardia and eventual unconsciousness.