KARPAGAM ACADEMY OF HIGHER EDUCATION
(Deemed to be University Established Under Section 3 of UGC Act 1956)
Coimbatore – 641 021.

LECTURE PLAN
DEPARTMENT OF BIOCHEMISTRY

STAFF NAME: Dr.S.PRIYANGA and Dr.M.SRIDHAR MUTHUSAMI
SUBJECT NAME: CLINICAL BIOCHEMISTRY SUB.CODE:15BCU601
SEMESTER: VI CLASS: III B.Sc (BC)

S.No	Lecture Duration Period	Topics to be Covered	Support Material/Page Nos
		UNIT-I	
1	1	Disorders of carbohydrate metabolism: Normal sugar level in blood	T1:318-319
2	1	Renal threshold	T1:319-320
3	1	Regulation of blood glucose concentration	T2:102-103
4	2	Diabetes Mellitus: Types, pathophysiology	T1:321-326
5	1	Diagnosis -OGTT, glycosylated hemoglobin, complications	T2:116-117
6	1	Diabetic ketoacidosis and diabetic coma	T2:165-168
7	1	Hypoglycemia: Definition and causes	T2:115-116
8	2	Renal glycosuria- fructosuria, pentosuria and galactosuria.	T1:319-321 T3:118,180
9	2	Disorders of Aminoacid metabolism: Cysteinurea. Hartnup disease. Fanconi syndrome	T1:440,452,638
10	1	Homocysteinuria, Alkaptonuria, Phenylketonuria, albinism and maple syrup urine disease	T2:194,201,206-207
11	1	Revision and discussion of possible question	

12	1	class test-I	
	Total No of Hours Planned For Unit 1=15		
		UNIT-II	
1	1	Disorders of Lipid metabolism: Introduction	T1:386-387
2	2	Clinical manifestation, biochemical abnormalities of lipoprotein, Abetalipoproteinemia,.	T1:387-389
3	1	Hyperlipoproteinemias,	T1:389-390
4	1	Hypobetalipoproteinemias	T1:390-391
5	1	Hyperlipidemia	T2:158-159
6	1	Hypercholesterolemia	T2:159-160
7	1	Cholesterol Acyl Transferase Deficiency	T1:388-389
8	1	Atherosclerosis	T1:389-392
9	2	Fatty liver, liver cirrhosis	T1:392-394
10	1	Revision and discussion of possible question	
11	1	class test-II	
	Total No of Hours Planned For Unit II=13		
		UNIT-III	
1	2	Disorders of Purine and Pyrimidine metabolism: Clinical manifestation, biochemical abnormalities	R3:875-876
2	1	Hyper uricemia- Gout	T3:356-357
3	2	Lesch-Nyhan syndrome, Von-Gierke's disease.	T3:357-358
4	1	Hypo uricemia – xanthinuria.	T3:358-359
5	1	Orotic aciduria.	T2:413-414
6	2	Disorders of Bilirubin metabolism: Definition, clinical manifestation	T1:580-581

7	1	Jaundice- types	T3:581-582
8	2	Biochemical abnormalities of Criggler-Najjar syndrome Gilbert's disease	T3:332-334
9	1	Dubin Johnson disease	W1
10	1	Revision and discussion of possible question	
11	1	Class test III	
	Total No of Hours Planned For Unit III=15		
		UNIT-IV	
1	2	Gastric, pancreatic and intestinal function Gastric function – Introduction-test of gastric function,	T1:593-594
2	1	Insulin stimulation test.	T1:597-598
3	1	Determination of gastrin in serum	T1:598-599
4	1	Tubeless gastric analysis.	T1:599-600
5	2	Pancreatic function- Introduction, pancreatic function test- serum amylase and lipase.	T4:517-519
6	1	Direct stimulation test-secretion of CCK	R1:199-201
7	1	Indirect stimulation test-lundh test.	R1:201-203
8	1	Intestinal function- Introduction, tests used in the diagnosis of malabsorption	T2:555-556
9	2	Determination of total fecal fat, xylose excretion test	R2:556-558
10	1	Determination of total protein	R2:558-559
11	1	Revision and discussion of possible question	
12	1	Class test IV	
	Total No of Hours Planned For Unit IV=15		

		UNIT-V	
1	1	Liver disease and liver function tests- Bilirubin metabolism and jaundice	T1:580-582
2	1	Liver function tests- Estimation of conjugated and total bilirubin in serum	T1:582-583
3	1	Detection of bilirubin and bile salts in urine	T1:583-584
4	1	Thymol turbidity test	T1:584-585
5	1	Serum enzymes in liver disease - Serum transaminases (SGOT and SGPT), and phosphatases.	T1:588-592
6	1	Kidney function tests – Introduction	T2:498-499
7	1	Physical examination of urine	T1:572-573
8	1	Elimination tests- clearance test, insulin clearance,	T1:574-575
9	1	Creatinine clearance ,urea clearance	T1:575-576
10	1	Renal blood flow and filtration fraction	T1:576-577
11	1	clinical significance of GGT, LDH and creatine phosphokinase in kidney function	T1:578-579
12	1	Coagulation tests- prothrombin time, Activated Partial Thromboplastin Time (APTT) and lupus anticoagulant.	T1:587-588
13	1	Revision and discussion of possible question	
14	1	Class test V	
	Total No of Hours Planned for unit V=14		
1	1	Previous year ESE question paper Discussion	
2	1	Previous year ESE question paper Discussion	
3	1	Previous year ESE question paper Discussion	

	Total No of Hours Planned = 3		
Total Planned Hours	**75**		

TEXT BOOK

1. Chatterjea MN, 2005, Text book of medical biochemistry, 6th edition, JB publisher. New Delhi.
2. D.M Vasudevan, 2007. Text book of biochemistry, 5th Edition, JB publisher. New Delhi
3. Harper's illustrated Biochemistry, 1988, 21st Edition, Lange medical publication, USA
4. U.satyanarayana. Biochemistry,2002. Arunabha sen, books and allied (p)Ltd. Vijayavada

REFERENCES

1. Tadataka Yamada, 2011. Text book of gasteroenterology, 5th Edition, volume 1,wiley and black well publishing Ltd. USA
2. Dinesh puri, 2014. Text book of medical biochemistry, Third Edition.Reed Elsevier India Pvt.Ltd.,Delhi
3. Nelson, D.L. and Cox, M.M., (2013). Lehninger: Principles of Biochemistry 6th ed., W.H. Freeman and Company (New York), ISBN:13:978-1-4641-0962-1 / ISBN:10:1-4641-0962.

WEBSITES

W1: https://ghr.nlm.nih.gov/condition/dubin-johnson-syndrome

15BCU601 **CLINICAL BIOCHEMISTRY** **Semester VI** **5H-5C**

SCOPE

A career in diagnostic laboratory or in Research laboratory is available. Students interested can continue their post graduation and research work.

OBJECTIVES

The knowledge acquired in clinical biochemistry shall help the students to understand the basics of life processes and function of the human body in health and disease, to integrate the various aspects of metabolism & their regulatory pathways.

UNIT I

Disorders of carbohydrate metabolism: Normal sugar level in blood, renal threshold, regulation of blood glucose concentration; Diabetes Mellitus: Types, pathophysiology; Diagnosis -OGTT, glycosylated hemoglobin, complications- diabetic ketoacidosis and diabetic coma. Hypoglycemia: Definition and causes. Renal glycosuria- fructosuria, pentosuria and galactosuria. Disorders of Aminoacid metabolism: Cysteinurea. Hartnup disease. Fanconi syndrome, Homocysteinuria, Alkaptonuria, Phenylketonuria, albinism and maple syrup urine disease.

UNIT II

Disorders of Lipid metabolism: Introduction, clinical manifestation, biochemical abnormalities of lipoprotein-Abetalipoproteinemia, Hyperlipoproteinemias, Hypobetalipoproteinemias; hyperlipidemia, hypercholesterolemia, Cholesterol Acyl Transferase Deficiency. Atherosclerosis, Fatty liver, liver cirrhosis.

UNIT III

Disorders of Purine and Pyrimidine metabolism: Clinical manifestation, biochemical abnormalities, Hyper uricemia- Gout, Lesch-Nyhan syndrome, Von-Gierke's disease. Hypo uricemia – xanthinuria; Orotic aciduria.

Disorders of Bilirubin metabolism: Definition, clinical manifestation, Jaundice- types, biochemical abnormalities of Criggler-Najjar syndrome. Gilbert's disease and Dubin Johnson disease.

UNIT IV

Gastric, pancreatic and intestinal function

Gastric function – Introduction- test of gastric function – insulin stimulation test, determination of gastrin in serum, tubeless gastric analysis.

Pancreatic function- Introduction, pancreatic function test- serum amylase and lipase, direct stimulation test-secretion of CCK, indirect stimulation test-lundh test.

Intestinal function- Introduction, tests used in the diagnosis of malabsorption, determination of total fecal fat, xylose excretion test and determination of total protein

UNIT V

Liver disease and liver function tests- Bilirubin metabolism and jaundice, liver function tests- Estimation of conjugated and total bilirubin in serum, Detection of bilirubin and bile salts in urine, Thymol turbidity test, serum enzymes in liver disease- Serum transaminases (SGOT and SGPT), and phosphatases.

Kidney function tests – Introduction, physical examination of urine, elimination tests- clearance test, insulin clearance, creatinine clearance and urea clearance: Renal blood flow and filtration fraction, clinical significance of GGT, LDH and creatine phosphokinase in kidney function.

Coagulation tests- prothrombin time, Activated Partial Thromboplastin Time (APTT) and lupus anticoagulant.

TEXT BOOKS

Ambika S. 2004, Fundamentals of Biochemistry for Medical Students, CIT Chennai.

Harper's illustrated Biochemistry, 2012, McGraw Hill publishers, New Delhi.

Chatterjea MN, 2011, Text book of medical biochemistry, 8th edition, JB publisher.

REFERENCES

Philip D.Mayne, 1994, Clinical Chemistry in Diagnosis and Treatment, ELBS Publications, New York.

Carl A. Burtis, Edward R. Ashwood and William Heinmann Teitz, 1999, Textbook of Clinical Biochemistry, W.B. Saunders Company, London.

Varley H 2003, Practical Clinical Biochemistry, CBS Publishing, New Delhi.

Macleod.J, C. wards and I. Bouchier.1995, Davidson's Principles and Practice of Micine, English Language Book Society.

Robert K. Murray, Daryl K. Granner, Peter A. Mayes, Victor W. Rodwell ,2012.
Harper's illustrated Biochemistry, Appleton and Lange Publishers, London, 29th edition

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DEPARTMENT OF BIOCHEMISTRY
III-B.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (15BCU601)
MULTIPLE CHOICE QUESTIONS

UNIT I

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Hypoglycemia is due to	Hypoinsulinemia	Hyperinsulinemia	Over excretion in urine	Utilization	Hyperinsulinemia
2	Fructosuria is due to deficiency of	Phospho frutokinase	Fructose 1,6diphosphatase	Fructokinase	Epimarase	Fructokinase
3	Severe diabetes patients excrete	Glucose only	Glucose and Ketoacids	Ketoacids only	Ketoacids without glucose	Glucose and Ketoacids
4	Inability to metabolize fructose due to absence of aldolase B enzyme is	galactose intolerance	sugar intolerance	fructose intolerance	carbohydrate intolerance	galactose intolerance
5	Hypoglycemia is due to	increased insulin	increased glucagon	decreased insulin	increased glucocorticoids	increased insulin
6	Ketosis is due to	Slow down in fat metabolism	An over utilization of Glucose	Under production of acetyl CoA	Over production of acetyl CoA	Over production of acetyl CoA
7	Galactose is present in urine under	normal condition	galactosemia	glycemia	galactorrhea	galactosemia
8	Hyperglycemia without glycosuria can occur if	the renal threshold is lowered	the renal threshold is raised	potentiation of insulinase activity	epinephrine like action	the renal threshold is lowered
9	Glucagon is produced by	α-cell	β-cells	γ-cells	all the above	α-cell
10	Hyper glycemia is due to	Hyper activity of thyroid	Hyper activity of pituitary	Hyper activity of adrenal	all the above	all the above
11	Increase in Blood glucose may be due to	Anaesthesia	asphysia	Pancreatitis	all the above	Pancreatitis
12	Galactosemia occurs in the deficiency of	Galactokinase	Galactose-1-phosphate uridyl transferase	Uridine diphosphogalactose 4-epimerase	All the above	Galactokinase
13	The ketone bodies which are excreted in diabetic ketoacidosis are	Acetoacetic acid and pyruvic acid	Acetoacetic acid & αhydroxy glutaric acid	Acetoacetic acid and β OH butyric acid	Acetoacetic acid and oxaloacetic	Acetoacetic acid and β OH butyric acid
14	Insulin decreases	Glycogenesis	glyolysis	gluconeogenesis	glucose transport	gluconeogenesis
15	obermeyer test can be used for the detection of which of the following	Acid maltase	Glucose-6-phosphatase	hartnups disease	Muscle phosphorylase	hartnups disease
16	In the normal resting state of humans, most of the blood glucose burnt as 'fuel' is consumed by	liver	Brain	Kidney	Adipose tissues	Brain
17	Von-Gierke disease is due to deficiency of	Glucose-6- phosphatase	Glucose -6-PO4 dehydrogenase	Gulcose-6-phophorylase	None of the above	Glucose-6-phosphatase
18	Galactosemia is due to the deficiency of	Galactose-1-PO4 uridyl transferase	Lactase	Galactase	Dulcitol	Galactose-1-PO4 uridyl transferase
19	The following hormones causes hypoglycemia except	Adrenaline	Insulin	Glucagon	Growth hormone	Glucagon
20	Insulin is essential in this type of diabetes mellitus	Type 1	Type 2	Gestational diabetes mellitus	All the above	Type 1
21	Diabetes mellitus is associated with	Polyphagia	Polydipsia	defective wound healing	all the above	all the above
22	Diabetes mellitus is confirmed if the fasting plasma concentration of glucose is	<140 mg/dl	>140 mg/dl	<80 mg/dl	< 120 mg/dl	<80 mg/dl
23	Which one of the following is an inborn error of carbohydrate metabolism?	galactosemia	ketoacidosis	hyperglycaemia	glycosuria	galactosemia
24	Galactokinase reacts with galactose to give	galactose 6-phosphate	galactose 1-phosphate	UDP galactose	Lactose	galactose 1-phosphate
25	Diabetes mellitus is due to	insulin deficiency	epinephrine deficiency	glucagon deficiency	antidiuretic hormone deficiency	insulin deficiency
26	Essential fructosuria is due to deficiency of	fructose 1,6-bisphosphatase	fructokinase	hexokinase	fructose 1-phosphate aldolase	fructokinase
27	Which of the following is not an hyperglycemic hormone	corticosteroids	insulin	glucagon	None of the above	insulin
28	Isomaltase is a / an	Pancreatic enzyme	Salivary enzyme	Intestinal enzyme	Gastric enzyme	Salivary enzyme
29	Formation of galactose 1 P from galactose and ATP is catalysed by	hexokinase	galactokinase	galactose 1 P uridyl transferase	glucokinase	galactokinase
30	Normal fasting blood sugar level is	< 60 mg / dl	< 100 mg / dl	< 140 mg / dl	< 200 mg / dl	< 100 mg / dl
31	The hormone that lowers blood glucose is	epinephrine	glucogan	insulin	thyroid hormone	insulin
32	Reducing sugar in the urine is detected by heating	5 ml of Benedict's reagent and 8 drops of urine	5 ml of urine and 8 drops of Benedict's reagent	3ml of Benedict's and 3ml of urine	None of the above	5 ml of urine and 8 drops of Benedict's reagent
33	Acetoacetic acid & β-OH butyric acid are produced by_____in uncontrolled diabetes mellitus	pancreas	liver	small intestine	kidneys	kidneys
34	An enzyme in saliva that hydrolyses starch is	pepsinogen	chymotrypsin	α - amylase	maltase	maltase
35	Starch is formed of	α-glucosidic chain	β-glycosidic chain	β – 1–glucosidic chain	α-glycosidic chain	α-glucosidic chain
36	_____can be used to monitor the control of diabetes	HbA1c	OGTT	benedicts test	GTT	HbA1c
37	There is polyuria without glycosuria inthis disorder	diabetes mellitus	diabetes insipidus	bronze diabetes	juvenile diabetes	diabetes insipidus

38	The deficient enzyme in essential pentosuria is	Glucose -6-phosphatase	Glucose-6-phosphate dehydrogenase	L-xylulose reductase	Glucose oxidase	L-xylulose reductase
39	Poly urea is encountered in	Diabetes insipidus	Nephrotic syndrome	Myxedema	infective hepatitis	Diabetes insipidus
40	Glucose tolerence is decreased in	Hypopituitorism	Addisons disease	Diabetes mellitus	Hypo thyroidism	Diabetes mellitus
41	alpha cells of langerhans produce the hormone	insulin	epinrphrine	glucagon	pancreatic polypeptide	glucagon
42	Alkaptonuria is due to the absence of	Dopa decarboxylase	Phenyl alanine hydroxylase	acid oxidase	transaminase	transaminase
43	Mousy odour is observed in	phenyl ketonuria	alkaptonuria	albinism	cystinuria	phenyl ketonuria
44	Phenylketonuria, an inborn error of metabolism is due to the absence of the enzyme which	deaminates tyrosine	hydrokylates phenyl alanine	oxidizes homogentisic acid	converts tyrosine to DOPA	hydrokylates phenyl alanine
45	Hartnup's disease is due to a defect in the transport of	Glycine	Tryptophan	Cystine	Lysine	Tryptophan
46	Which of the following amino acids give rise to α – keto acids that accumulate in the urine in maple syrup urine disease?	Lysine	Arginine	Valine	Phenylalanine	Valine
47	Maple syrup urine disease is due to defective metabolism of	aromatic amino acids	branched chain amino acids	lipoproteins	acids	amino acids
48	The primary symptom of Alkaptonuria is	Mental retardness	Growth failure	Vomit	Ochronosis	Ochronosis
49	Hartnup disease is an inborn error in the metabolism of	acids	Tryptophan	Cystine	None of the above	Tryptophan
50	Maple syrup urine disease is associated with the following amino acids	isoleucine, lysine, valine	isoleucine, leucine, valine	methionine, lysine, valine	alanine, leucine, valine	isoleucine, leucine, valine
51	The following is excreted in urine during cystinuria	cystine and cysteine	homocysteine and cystine	cystine,lysine, arginine, ornithine and a mixed sulphate	homocystine and cysteine	homocysteine and cystine
52	Homogenetisic acid oxidase deficiency results in	alkaptonuria	Hartnup disease	Fanconi syndrome	Hurler's syndrome	alkaptonuria
53	galactosemia occurs in the deficiency of	Galactokinase	Galactose-1-phosphate uridyl transferase	Uridine diphospho galactose 4-epimerase	(d) All the above	(d) All the above
54	Normal level of sugar in blood is _____ mg / 100ml	80 – 120	75 – 90	70 – 120	130 – 180.	80 – 120
55	Glucogon is secreted by _____ cell of pancreas.	Alpha cells	beta cells	Gamma cells	All the above	Alpha cells
56	Chronic disease due to disorder of carbohydrate metabolism _____	Diabetics mellitus	obesity	cancer	TB	Diabetics mellitus
57	The hormone which induces glycogenolysis & inhibit insulin production is _____	Glucagon	Insulin	Epinephrine	ACTH	Epinephrine
58	The condition in which glucose is excreted in urine is known as _____	Glycosuria	mellituria	Renal glucosuria	hyper glycemic glucosuria	Glycosuria
59	A man who has 50 kg weight can absorb _____ gm of glucose.	88.32	92	96.12	73	92
60	Hartnups disease is due to the defect in the transport of	Glycine	tryptophan	cysteine	lysine	tryptophan

UNIT-I

SYLLABUS

Disorders of carbohydrate metabolism: Normal sugar level in blood, renal threshold, regulation of blood glucose concentration; Diabetes Mellitus: Types, pathophysiology; Diagnosis -OGTT, glycosylated hemoglobin, complications- diabetic ketoacidosis and diabetic coma. Hypoglycemia: Definition and causes. Renal glycosuria- fructosuria, pentosuria and galactosuria. **Disorders of aminoacid metabolism:** Cysteinurea. Hartnup disease. Fanconi syndrome, Homocysteinuria, Alkaptonuria, Phenylketonuria, albinism and maple syrup urine disease.

Disorders of carbohydrate metabolism

Normal sugar level in blood

The blood sugar level, blood sugar concentration, or blood glucose level is the amount of glucose present in the blood of humans and other animals. Glucose is a simple sugar and approximately 4 grams of glucose are present in the blood of humans at all times. The body tightly regulates blood glucose levels as a part of metabolic homeostasis. Glucose is stored in skeletal muscle and liver cells in the form of glycogen; in fasted individuals, blood glucose is maintained at a constant level at the expense of glycogen stores in the liver and skeletal muscle.

In humans, glucose is the primary source of energy, and is critical for normal function, in a number of tissues, particularly the human brain which consumes approximately 60% of blood glucose in fasted, sedentary individuals. Glucose can be transported from the intestines or liver to other tissues in the body via the bloodstream. Cellular glucose uptake is primarily regulated by insulin, a hormone produced in the pancreas.

Glucose levels are usually lowest in the morning, before the first meal of the day, and rise after meals for an hour or two by a few millimoles. Blood sugar levels outside the normal range may be an indicator of a medical condition. A persistently high level is referred to as hyperglycemia; low levels are referred to as hypoglycemia. Diabetes mellitus is characterized by persistent hyperglycemia from any of several causes, and is the most prominent disease related to failure of blood sugar regulation. There are different methods of testing and measuring blood

sugar levels. The intake of alcohol causes an initial surge in blood sugar, and later tends to cause levels to fall. Also, certain drugs can increase or decrease glucose levels.

Normal values in humans

Normal value ranges may vary slightly among different laboratories. Many factors affect a person's blood sugar level. The body's homeostatic mechanism of blood sugar regulation (known as glucose homeostasis), when operating normally, restores the blood sugar level to a narrow range of about 4.4 to 6.1 mmol/L (70 to 110 mg/dL) (as measured by a fasting blood glucose test). The normal blood glucose level (tested while fasting) for non-diabetics, should be between 3.9 and 5.5 mmol/L (70 to 100 mg/dL).

The mean normal blood glucose level in humans is about 5.5 mmol/L (100 mg/dL); however, this level fluctuates throughout the day. Blood sugar levels for those without diabetes and who are not fasting should be below 6.9 mmol/L (125 mg/dL). The blood glucose target range for diabetics, according to the American Diabetes Association, should be 5.0–7.2 mmol/l (90–130 mg/dL) before meals, and less than 10 mmol/L (180 mg/dL) after meals (as measured by a blood glucose monitor).

Despite widely variable intervals between meals or the occasional consumption of meals with a substantial carbohydrate load, human blood glucose levels tend to remain within the normal range. However, shortly after eating, the blood glucose level may rise, in nondiabetics, temporarily up to 7.8 mmol/L (140 mg/dL) or slightly more. For people with diabetes maintaining 'tight diabetes control', the American Diabetes Association recommends a post-meal glucose level of less than 10 mmol/L (180 mg/dL) and a fasting plasma glucose of 3.9 to 7.2 mmol/L (70–130 mg/dL).

The actual amount of glucose in the blood and body fluids is very small. In a healthy adult male of 75 kg with a blood volume of 5 liters, a blood glucose level of 5.5 mmol/L (100 mg/dL) amounts to 5g, equivalent to about a teaspoonful of sugar. [10] Part of the reason why this amount is so small is that, to maintain an influx of glucose into cells, enzymes modify glucose by adding phosphate or other groups to it.

Renal threshold

The renal threshold refers to the blood glucose level at which the kidneys begin to extract glucose from the blood and excrete it into the urine, causing glycosuria, or glucose in the urine.

Polyuria in diabetes shows that the body is unable to metabolize carbohydrates properly. Carbohydrates are turned into glucose, which is sent into the blood to feed the cells. The cells, lacking insulin, can't accept the glucose, so it remains in the blood causing hyperglycemia. The

extra glucose in the blood accumulates there until the kidneys see it as an impurity to be filtered out and discarded. This point is known as the renal threshold.

When the renal threshold is exceeded, and the excess glucose begins to spill into the urinary tract, the glucose makes the urine attract water in what's known as the osmotic effect. This extra water in the urine causes the excessive urination, dehydrating the body, which in turn causes the excessive drinking of polydipsia.

Renal threshold values differ by species. While dogs and humans share the same renal threshold value of 180 mg/dl (10 mmol/L), the renal threshold of cats is 288 mg/dl (16 mmol/L); in cattle it's 108 mg/dl (6 mmol/L).

Glucose is filtered through the glomeruli in the kidney; for non-diabetics, all of the glucose is re-absorbed by the renal (kidney) tubules. This means there would be nothing present for a glucose urine test to detect. With hyperglycemia, the kidney tubules are unable to handle and process the amount of glucose they're being presented with, so the glucose winds up in the urine and can be detected in urine glucose testing.

The excess of glucose in the urine is the cause of excessive urination, or polyuria. Both glucose and water are leaving the body; the loss of water is what causes polydipsia, or excessive drinking. This is a vicious circle known as osmosis.

Regulation

The body's homeostatic mechanism keeps blood glucose levels within a narrow range. It is composed of several interacting systems, of which hormone regulation is the most important.

There are two types of mutually antagonistic metabolic hormones affecting blood glucose levels:

- Catabolic hormones (such as glucagon, cortisol and catecholamines) which increase blood glucose.
- One anabolic hormone (insulin), which decreases blood glucose.

These hormones are secreted from pancreatic islets which are bundles of endocrine tissues. There are four types of pancreatic islets, alpha (A) cells, beta (B) cells, Delta (D) cells and F cells. Glucagon is secreted from alpha cells, while insulin is secreted by beta cells. Together they regulate the blood-glucose levels through negative feedback, a process where the end product of one reaction stimulates the beginning of another reaction. In blood-glucose levels, insulin lowers the concentration of glucose in the blood. The lower blood-glucose level (a product of the insulin secretion) triggers glucagon to be secreted, and repeats the cycle.

In order for blood glucose to be kept stable, modifications to insulin, glucagon, epinephrine and cortisol are made. Each of these hormones has a different responsibility to keep blood glucose regulated; when blood sugar is too high, insulin tells muscles to take up excess glucose for storage. Glucagon responds to too low of a blood glucose level; it informs the tissue to produce more glucose. Epinephrine prepares the muscles and respiratory system for activity in the case of a "fight and flight" response. Lastly, cortisol supplies the body with fuel in times of heavy stress.

Abnormality in blood sugar levels

High blood sugar

If blood sugar levels remain too high the body suppresses appetite over the short term. Long-term hyperglycemia causes many of the long-term health problems including heart disease, eye, kidney, and nerve damage.

Blood sugar levels above 300 can cause fatal reactions. Ketones will be very high (a magnitude higher than when eating a very low carbohydrate diet) initiating ketoacidosis. The most common cause of hyperglycemia is diabetes. When diabetes is the cause, physicians typically recommend an anti-diabetic medication as treatment. From the perspective the majority of patients, treatment with an old, well-understood diabetes drug such as metformin will be the safest, most effective, least expensive, most comfortable route to managing the condition. Diet changes and exercise implementation may also be part of a treatment plan for diabetes.

Fasting blood glucose levels may be higher than the post meal blood glucose in many of the healthy subjects. Such individuals may be said to have physiological insulin resistance and may develop diabetes mellitus as long term complication. In clinical and laboratory practices, many of the time a healthy normal subject will present a fasting blood glucose value higher than the post meal blood glucose value. This creates confusion since there is a common perception that in blood, postprandial (PP) glucose level should be higher than fasting (F) glucose level. The repeated investigation subsequently yields somewhat similar type of result.

Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by alteration in the metabolism of carbohydrates, lipids and proteins. DM is probably one of the most terrible oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. It is well known that diabetes and hypertension are chief risk factors in the development of nephropathy, retinopathy, and cardiomyopathy which progress to myocardial infarction.

Types of Diabetes

During long standing hyperglycaemic state in diabetes mellitus, glucose forms covalent adducts with the plasma proteins through a non-enzymatic process known as glycation. Protein glycation and formation of advanced glycation end products (AGEs) play an important role in the pathogenesis of diabetic complications like retinopathy, nephropathy, neuropathy, cardiomyopathy along with some other diseases such as rheumatoid arthritis, osteoporosis and aging. Glycation of proteins interferes with normal functions by disrupting molecular conformation, altering enzymatic activity, and interfering with receptor functioning. AGEs form intra and extracellular cross linking not only with proteins, but with some other endogenous key molecules including like lipids and nucleic acids to contribute in the development of diabetic complications. Classification of diabetes mellitus is based on its etiology and clinical presentation. As such, there are four types or classes of diabetes mellitus; they are,

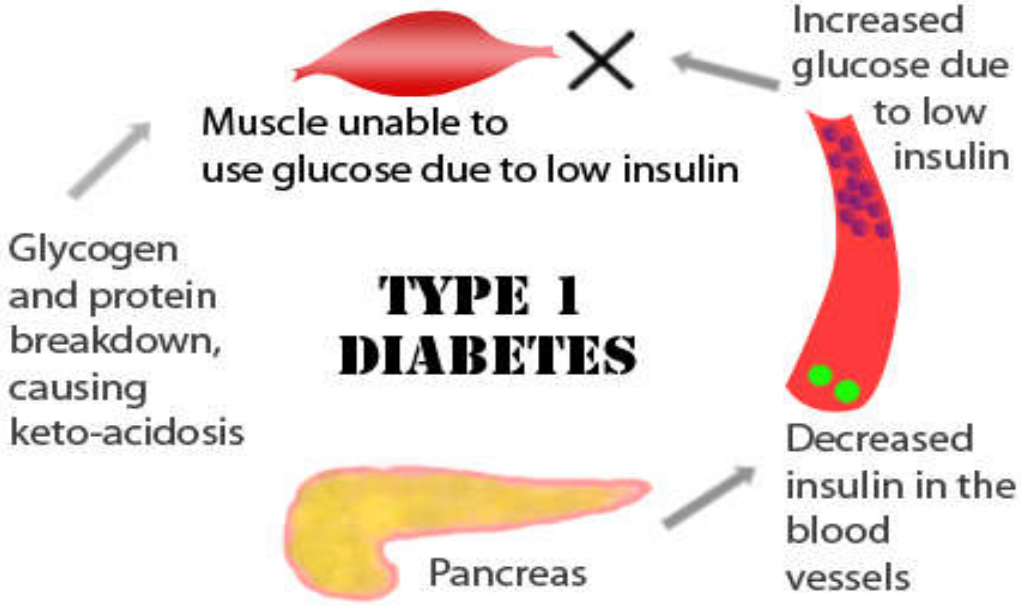
- **Type-1 (Insulin dependent diabetes mellitus)**
- **Type-2 (Non-insulin dependent diabetes mellitus)**
- **Gestational diabetes mellitus**
- **Other specific types**

The origin and etiology of DM can fluctuate greatly but constantly include defects in either insulin secretion or response or in both at some point in the course of disease. Mostly patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 DM (formerly known as non-insulin dependent DM) which is the most universal form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.

Type 1 diabetes

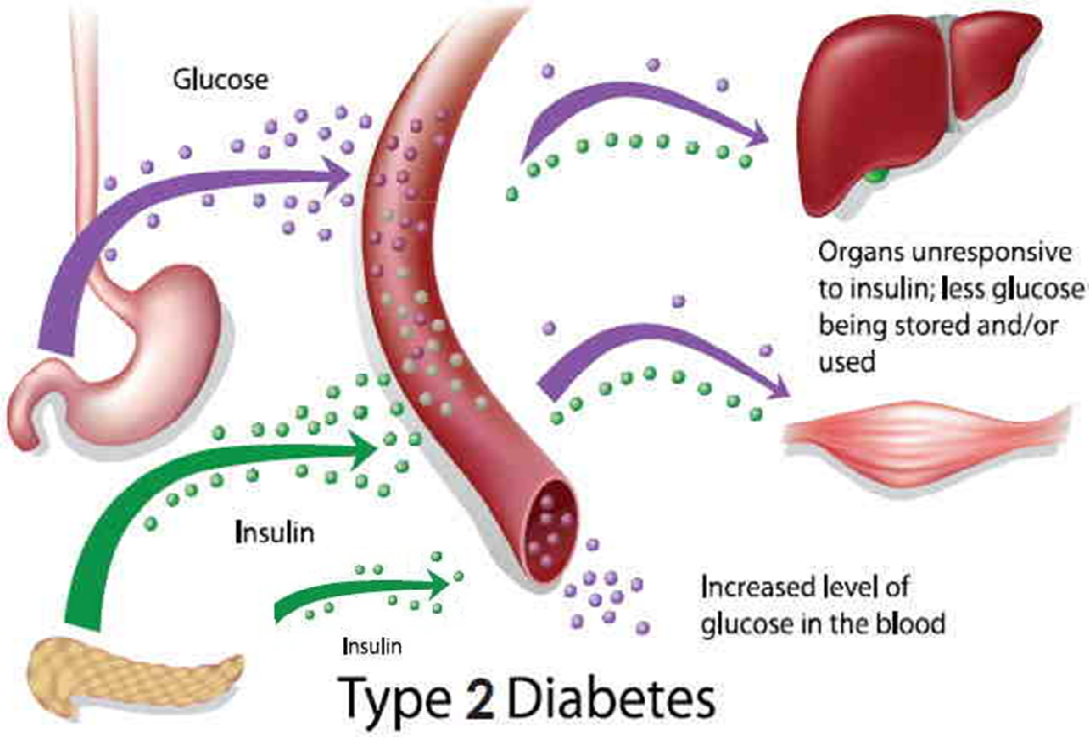
Type 1 Diabetes Mellitus (DM) is a catabolic disorder in which circulating insulin is very low or absent, plasma glucagon is elevated, and the pancreatic beta cells stop working to respond to all insulin secretory stimuli. The pancreas shows lymphocytic infiltration and destruction of insulin secreting cells of the islets of langerhans finally leads to insulin deficiency. Patients need exogenous insulin to overturn this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism. Type 1 diabetes leads to inability to discharge insulin that results in low down rates of glucose uptake into muscles and adipose tissue.

The usual rapid onset of the insulin dependent diabetes mellitus is due to the autoimmune attack on the pancreatic cells. Though the disease persists for several years the immune system slowly destroys the pancreatic cells. When >80% of the pancreatic cells have been damaged it leads to classic symptoms of diabetic disease. It usually occurs after 30 years of age, but the peak incidence of this disease occurs during puberty, around 12-14 years in boys and 10-12 years of age in girls. The major signs and symptoms include hyperglycemia, increased thirst, hunger, frequent urination, weight loss and ketoacidosis.



Type 2 diabetes

Type 2 diabetes is characterized by the combination of peripheral insulin resistance and also inadequate insulin secretion by the pancreatic beta cells. Insulin resistance, which has been accredited with elevated levels of free fatty acids in plasma. Type 2 diabetes mellitus is a clinical syndrome owing to relative or absolute deficiency of insulin or resistance to the action of insulin at the cellular level as a result hyperglycemia and glycosuria occurs. Patients with type 2 diabetes are more prone to Cardio Vascular Disease (CVD), which may be partially attributed to a higher occurrence of traditional risk factors like obesity, hypertension, and dyslipidaemia. However, factors closely related to diabetes may account for a substantial part of elevated cardiovascular risk. Recently, there are growing evidences for postprandial (post-challenge) glucose as an independent and strong risk factor for CVD, especially myocardial infarction. The pathophysiology of this relationship is not clearly elucidated, but different mechanisms like oxidant stress, activated inflammation with endothelial dysfunction and hypercoagulability have been suggested.



Gestational diabetes

Pregnancy induced diabetes or gestational diabetes is another important class of diabetes that has not received comparable level of attention, especially in the developing countries, despite its severity and increasing prevalence. It is characterized by carbohydrate intolerance of variable intensity with onset or first recognition during pregnancy.

Other specific types of diabetes

A few rare kinds of diabetes can result from specific conditions. These types of diabetes account for only 1% to 5% of all cases of diabetes.

- Diseases of the exocrine pancreas (e. g. pancreatitis, cystic fibrosis, hemochromatosis)
- Endocrinopathies (e. g. Cushing syndrome, acromegaly, pheochromocytoma)
- Drug induced (e. g. glucocorticoids, neuroleptics, alpha-interferons, pentamidine)
- Genetic defects of the β-cell function (e. g. MODY forms)
- Genetic defects of insulin action
- Infections

Rare forms of auto-immune mediated diabetes

Other genetic syndromes which can be associated with diabetes

Pathogenesis and Pathophysiology of Diabetes Mellitus

There is a direct link between hyperglycemia and physiological & behavioral responses. Whenever there is hyperglycemia, the brain recognizes it and send a message through nerve impulses to pancreas and other organs to decrease its effect.

Type 1 diabetes mellitus

Type 1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets. Several features characterize type 1 diabetes mellitus as an autoimmune disease:

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;

2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);

3. Presence of islet cell specific autoantibodies;

4. Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment;

5. The involvement of monokines and TH1 cells producing interleukins in the disease process;

6. Response to immunotherapy and;

7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members.

Approximately 85% of patients have circulating islet cell antibodies, and the majorities also have detectable anti-insulin antibodies before receiving insulin therapy. Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) within pancreatic B cells.

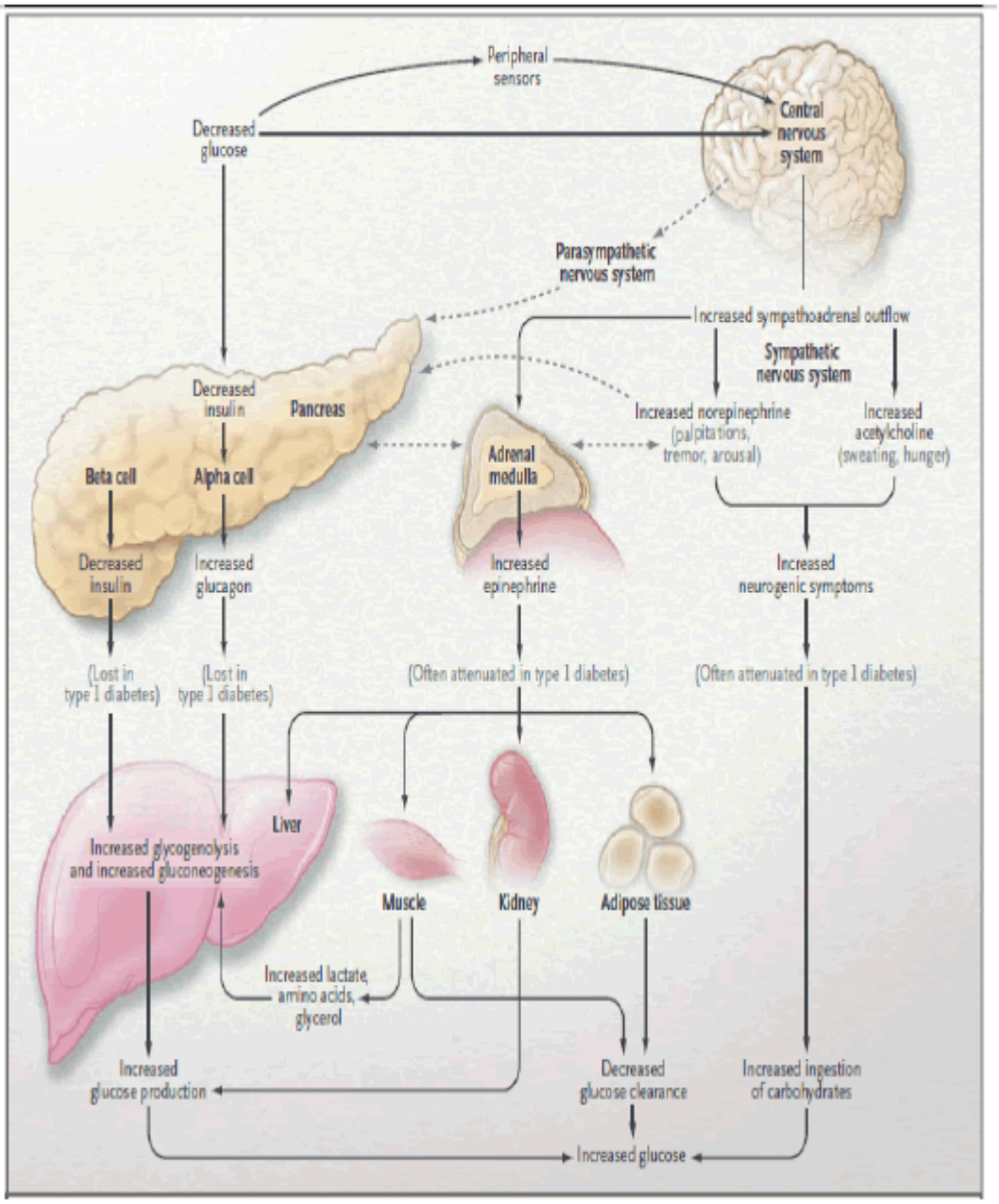
The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with T1DM. In addition to the loss of **insulin** secretion, the function of pancreatic α-cells is also abnormal and there is excessive secretion of glucagons in T1DM patients. Normally, hyperglycemia leads to reduced glucagons secretion, however, in patients with T1DM, glucagons secretion is not suppressed by

hyperglycemia. The resultant inappropriately elevated glucagons levels exacerbate the metabolic defects due to insulin defi-ciency. Although insulin deficiency is the primary defect in T1DM, there is also a defect in the administration of insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle. This impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue explained that the major metabolic derangements, which result from insulin deficiency in T1DM are impaired glucose, lipid and protein metabolism.

Type 2 diabetes mellitus

In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance. In situations where resistance to insulin predominates, the mass of β-cells undergoes a transformation capable of increasing the insulin supply and compensating for the excessive and anomalous demand. In absolute terms, the plasma insulin concentration (both fasting and meal stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis. Keeping in mind the intimate relationship between the secretion of insulin and the sensitivity of hormone action in the complicated control of glucose homeostasis, it is practically impossible to separate the contribution of each to the etiopathogenesis of DM2.

Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Except for maturity onset diabetes of the young (MODY), the mode of inheritance for type 2 diabetes mellitus is unclear. MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. MODY is defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies (ICA) are negative.



Diagnosis of both types of diabetes

Random plasma test

• The simplest test and doesn't require fasting before taking the test.

• If 200 or more than 200 mg/dl of blood glucose it probably indicates diabetes but has to be reconfirmed.

Fasting plasma glucose test:

• There should be eight hours fasting before taking this test. Blood glucose more than 126 mg/dl on two or more tests conducted on different days confirms a diabetes diagnosis.

Oral glucose tolerance test

• When random plasma glucose test is 160-200 mg/dl and the fasting plasma test is 110-125 mg/dl, then this test is conducted.

• This blood test evaluates body's response to glucose. This test requires fasting at least eight but not more than 16 hrs.

• Fasting glucose level is determined, and then gives 75 gm of glucose, 100 gm for pregnant women. The blood is tested every 30 minutes to one hr for two or three hrs.

• This test is normal if your glucose level at two hrs is less than 140 mg/dl. A fasting level of 126 mg/dl or greater and two hour glucose level of 200 mg/dl or Higher confirms a diabetes diagnosis.

Glycated proteins

Proteins react spontaneously in blood with glucose to form glycated derivatives. The extent of glycation of proteins is controlled by the concentration of glucose in blood and by the number of reactive amino groups present in the protein that are accessible to glucose for reaction. All proteins with reactive sites can be glycated and the concentration of the glycated proteins that can be measured in blood is a marker for the fluctuation of blood glucose concentrations during a certain period. From a clinical diagnostic point glycated proteins with a longer life time in blood are of interest, since they reflect the exposure of these proteins to glucose for longer periods

Glycated hemoglobin

The life span of hemoglobin in vivo is 90 to120 days. During this time glycated hemoglobin A forms, being the ketoamine compound formed by combination of hemoglobin A and glucose. Several subfractions of glycated hemoglobin have been isolated. Of these, glycated hemoglobin A fraction HbA1c is of most interest serving as a retrospective indicator of the average glucose Concentration. HbA1c is recommended as an essential indicator for the monitoring of blood glucose control. The blood HbA1c$\geq$ 6.5% is considered as diabetes.

Fructosamine test

Albumin is the main component of plasma proteins. As albumin also contains free amino groups, non-enzymatic reaction with glucose in plasma occurs. Therefore glycated albumin can similarly serve as a marker to monitor blood glucose. Glycated albumin is usually taken to provide a retrospective measure of average blood glucose concentration over a period of 1 to 3 weeks. Reference interval: 205- 285 micro mol/L.

Diagnosis of gestational diabetes mellitus

At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance or impaired fasting glucose. Women at high risk (positive family history, history of GDM, marked obesity, and high risk ethnic group) should be screened as soon as feasible. If the initial screening is negative, they should undergo retesting at 24-48 weeks. The diagnosis of GDM is made if two or more of the plasma glucose values in are met or exceeded.

Time	Plasma Glucose
Fasting	≥95mg/dl(5.3mmol/L)
1-hour	≥180mg/dl(10.0mmol/L)
2-hour	≥155mg/dl(8.6mmol/L)
3-hour	≥140mg/dl(7.8mmol/L)

It is unclear whether the risk of complications of diabetes differs according to whether the disease was diagnosed by means of fasting plasma glucose testing only or glycated hemoglobin testing only. Preliminary data from a large, community- based prospective cohort study suggest that the glycated hemoglobin level, which integrates fasting and postprandial glucose levels over a longer period, might be a better predictor of certain complications especially cardiovascular disease. It is also not known whether the risk of diabetes differs between patients identified as having pre-diabetes by means of glycated hemoglobin testing and those identified by means of fasting plasma glucose testing. Such risks probably vary according to which test is used ultimately to make the diagnosis. Ongoing research is assessing the value of risk scores that incorporate not only glycemic measures but also other biomarkers and risk factors to estimate diabetes risk.

Impaired fasting glucose (IFG) is defined as a fasting plasma glucose (FPG) level of 100 to 125 mg/dl (5.6 to 6.9 mmol/liter). Increased glycated hemoglobin (IGH) is defined as a

glycated hemoglobin level of 5.7 to 6.4%. The diagnosis of diabetes is confirmed with a repeat test on a separate day or by the alternative test (i.e. glycated hemoglobin instead of FPG or vice versa) on the same day or a separate day. If the result of the repeat test is in the prediabetic range, the patient should be counseled or treated for pre-diabetes. If the result of the repeat test is entirely normal (which is unlikely), rescreening in 6 months should be considered.

Glycemic Management

One of the biggest challenges for health care providers today is addressing the continued needs and demands of individuals with chronic illnesses like diabetes. The importance of regular follow-up of diabetic patients with the health care provider is of great significance in averting any long term complications. Studies have reported that strict metabolic control can delay or prevent the progression of complications associated with diabetes. Results of large randomized trials involving patients with type 1 diabetes or newly recognized or established type 2 diabetes show that control of glycemia delays the onset and slows the progression of micro vascular complications, including nephropathy, retinopathy, and neuropathy [52-54]. The needs of diabetic patients are not only limited to adequate glycemic control but also correspond with preventing complications; disability limitation and rehabilitation. Some of the Indian studies revealed very poor adherence to treatment regimens due to poor attitude towards the disease and poor health literacy among the general public.

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a life-threatening condition that develops when cells in the body are unable to get the sugar (glucose) they need for energy because there is not enough insulin. When the sugar cannot get into the cells, it stays in the blood. The kidneys filter some of the sugar from the blood. and remove it from the body through urine. Because the cells cannot receive sugar for energy, the body begins to break down fat and muscle for energy. When this happens, ketones, or fatty acids, are produced and enter the bloodstream, causing the chemical imbalance (metabolic acidosis) called diabetic ketoacidosis.

Causes

Ketoacidosis can be caused by not getting enough insulin, having a severe infection or other illness, becoming severely dehydrated, or some combination of these things. It can occur in people who have little or no insulin in their bodies (mostly people with type 1 diabetes but it can happen with type 2 diabetes, especially children) when their blood sugar levels are high.

Symptoms

- Flushed, hot, dry skin.

- Blurred vision.
- Feeling thirsty and urinating a lot.
- Drowsiness or difficulty waking up. Young children may lack interest in their normal activities.
- Rapid, deep breathing.
- A strong, fruity breath odor.
- Loss of appetite, belly pain, and vomiting.
- Confusion.

Causes and risk factors for diabetic ketoacidosis

As noted above, DKA is caused by the body having too little insulin to allow cells to take in glucose for energy.

This may happen for a number of reasons including:

- Having blood glucose levels consistently over 15 mmol/l
- Missing insulin injections
- If a fault has developed in your insulin pen or insulin pump
- As a result of illness or infections
- High or prolonged levels of stress
- Excessive alcohol consumption
- Illegal drug use

Diabetic Coma

Coma is relatively rare in diagnosed diabetes

Coma is relatively rare in diagnosed diabetes but it is very important to be aware of the situations that increase risk of coma.

Causes of diabetic coma

The main causes of coma occurring in people with diabetes are as a result of very low or very high blood glucose levels.

The three most common causes of coma in people with diabetes are:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Hyperglycaemic hyperosmolar state

Severe hypoglycemia and coma

Severe hypoglycemia (very low blood glucose levels) can lead to loss of consciousness and coma if not treated.

In most cases the body will restore blood sugar levels to normal by releasing glucagon to raise blood sugar levels.

Coma is more likely to occur from low blood glucose levels if:

- A large insulin overdose is taken
- Alcohol is in the body during hypoglycemia
- Exercise has depleted the body's glycogen supply

Diabetic ketoacidosis and coma

Diabetic ketoacidosis is a dangerous state of having very high blood glucose levels(typically above 17 mmol/L) in combination with high ketone levels.

Ketoacidosis is able to occur if the body runs out of insulin and is therefore a factor for people with type 1 diabetes to be aware of. Insulin can prevent ketone levels rising and this is the key reason why people with diabetes are advised never to miss their long term (basal) insulin injections.

The symptoms of ketoacidosis include nausea, vomiting, dehydration, disorientation and deep, laboured breathing.

If someone with diabetes is displaying these symptoms call for emergency medical help as loss of consciousness and coma could follow.

Illness in type 1 diabetes can lead to high blood glucose and ketone levels. It is advisable to test for ketones during periods of illness to prevent ketoacidosis developing.

Diabetic coma at diagnosis of type 1 diabetes

If the symptoms of type 1 diabetes are not spotted soon enough, ketoacidosis can develop leading to coma before a diagnosis is made.

It is possible that doctors may not correctly diagnose diabetes at first presentation. Approximately 1 in 4 patients diagnosed with type 1 diabetes are recorded as demonstrating signs of ketoacidosis.

Nonketotic hyperosmolar coma

In type 2 diabetes, insulin levels in the body are usually present to stop ketone levels rising too high. However, at very blood glucose levels (typically above 33 mmol/L) a dangerous condition called Hyperosmolar Hyperglycaemic State (HHS) can develop.

Periods of illness or lack of sufficient diabetes medication could lead to development of Hyperosmolar Hyperglycaemic State.

Symptoms of HHS include extreme thirst, disorientation, nausea and vomiting.

If someone with diabetes has the above symptoms call for medical help as losing consciousness and coma (hyperglycaemic hyperosmolar non-ketotic coma) can follow.

Preventing diabetic coma

The following recommendation can help to prevent diabetic coma from occurring:

- Be aware of the symptoms of high and low blood glucose
- Test blood sugar levels, particularly during periods of illness
- Drink alcohol responsibly
- Avoid alcohol after strenuous exercise
- Beware of hypoglycemia at night following exercise (if taking insulin or sulfonylureas)
- Test for ketones if blood glucose levels are high (type 1 diabetes)

Hypoglycemia

Hypoglycemia, also known as low blood sugar, is when blood sugar decreases to below normal levels. This may result in a variety of symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures, or death. A feeling of hunger, sweating, shakiness, and weakness may also be present. Symptoms typically come on quickly. The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin and sulfonylureas. Risk is greater in diabetics who have eaten less than usual, exercised more than usual, or have drunk alcohol. Other causes of hypoglycemia include kidney failure, certain tumors, such as insulinoma, liver disease, hypothyroidism, starvation, inborn error of metabolism, severe infections, reactive hypoglycemia, and a number of drugs including alcohol.

The glucose level that defines hypoglycemia is variable. In people with diabetes levels below 3.9 mmol/L (70 mg/dL) is diagnostic. In adults without diabetes, symptoms related to low blood sugar, low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis. Otherwise a level below 2.8 mmol/L (50 mg/dL) after not eating or following exercise may be used. In newborns a level below 2.2 mmol/L (40 mg/dL) or less than 3.3 mmol/L (60 mg/dL) if symptoms are present indicates hypoglycemia. Other tests that may be useful in determining the cause include insulin and C peptide levels in the blood. Hyperglycemia (high blood sugar) is the opposite condition.

Signs and symptoms

Hypoglycemic symptoms and manifestations can be divided into those produced by the counterregulatory hormones (epinephrine/adrenaline and glucagon) triggered by the falling glucose, and the neuroglycopenic effects produced by the reduced brain sugar. Shakiness, anxiety, nervousness

Palpitations, tachycardia

Sweating, feeling of warmth (sympathetic muscarinic rather than adrenergic)

Pallor, coldness, clamminess

Dilated pupils (mydriasis) Hunger, borborygmus

Nausea, vomiting, abdominal discomfort

Headache

Causes

The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin, sulfonylureas, and biguanides. Risk is greater in diabetics who have eaten less than usual, exercised more than usual, or drunk alcohol. Other causes of hypoglycemia include kidney failure, certain tumors, liver disease, hypothyroidism, starvation, inborn errors of metabolism, severe infections, reactive hypoglycemia, and a number of drugs including alcohol. Low blood sugar may occur in babies who are otherwise healthy who have not eaten for a few hours. Inborn errors of metabolism may include the lack of an enzyme to make glycogen (glycogen storage type 0).

Pathophysiology

Like most animal tissues, brain metabolism depends primarily on glucose for fuel in most circumstances. A limited amount of glucose can be derived from glycogen stored in astrocytes, but it is consumed within minutes. For most practical purposes, the brain is dependent on a continual supply of glucose diffusing from the blood into the interstitial tissue within the central nervous system and into the neurons themselves.

Therefore, if the amount of glucose supplied by the blood falls, the brain is one of the first organs affected. In most people, subtle reduction of mental efficiency can be observed when the glucose falls below 65 mg/dl (3.6 mM). Impairment of action and judgment usually becomes obvious below 40 mg/dl (2.2 mM). Seizures may occur as the glucose falls further. As blood glucose levels fall below 10 mg/dl (0.55 mM), most neurons become electrically silent and nonfunctional, resulting in coma. These brain effects are collectively referred to as neuroglycopenia.

The importance of an adequate supply of glucose to the brain is apparent from the number of nervous, hormonal and metabolic responses to a falling glucose level. Most of these are defensive or adaptive, tending to raise the blood sugar via glycogenolysis and gluconeogenesis or provide alternative fuels. If the blood sugar level falls too low, the liver

converts a storage of glycogen into glucose and releases it into the bloodstream, to prevent the person going into a diabetic coma, for a short period of time.

Treatment

Treatment of some forms of hypoglycemia, such as in diabetes, involves immediately raising the blood sugar to normal through the ingestion of carbohydrates, determining the cause, and taking measures to hopefully prevent future episodes. However, this treatment is not optimal in other forms such as reactive hypoglycemia, where rapid carbohydrate ingestion may lead to a further hypoglycemic episode.

Blood glucose can be raised to normal within minutes by taking (or receiving) 10–20 grams of carbohydrate. It can be taken as food or drink if the person is conscious and able to swallow. This amount of carbohydrate is contained in about 3–4 ounces (100–120 ml) of orange, apple, or grape juice although fruit juices contain a higher proportion of fructose which is more slowly metabolized than pure dextrose, alternatively, about 4–5 ounces (120–150 ml) of regular (non-diet) soda may also work, as will about one slice of bread, about 4 crackers, or about 1 serving of most starchy foods. Starch is quickly digested to glucose (unless the person is taking acarbose), but adding fat or protein retards digestion. Symptoms should begin to improve within 5 minutes, though full recovery may take 10–20 minutes. Overfeeding does not speed recovery and if the person has diabetes will simply produce hyperglycemia afterwards. A mnemonic used by the American Diabetes Association and others is the "rule of 15" – consuming 15 grams of carbohydrate followed by a 15-minute wait, repeated if glucose remains low (variable by individual, sometimes 70 mg/dl).

Renal glycosuria

Renal glycosuria, also known as renal glucosuria, is a rare condition in which the simple sugar (glucose) is excreted in the urine despite normal or low blood glucose levels. With normal kidney (renal) function, glucose is excreted in the urine only when there are abnormally elevated levels of glucose in the blood.

Renal glycosuria, also known as renal glucosuria, is a rare condition in which the simple sugar glucose is eliminated (excreted) in the urine despite normal or low blood glucose levels. With normal kidney (renal) function, glucose is excreted in the urine only when there are abnormally elevated levels of glucose in the blood. However, in those with renal glycosuria, glucose is abnormally eliminated in the urine due to improper functioning of the renal tubules, which are primary components of the filtering units of the kidneys (nephrons). In most affected individuals, the condition causes no apparent symptoms (asymptomatic) or serious effects. When renal

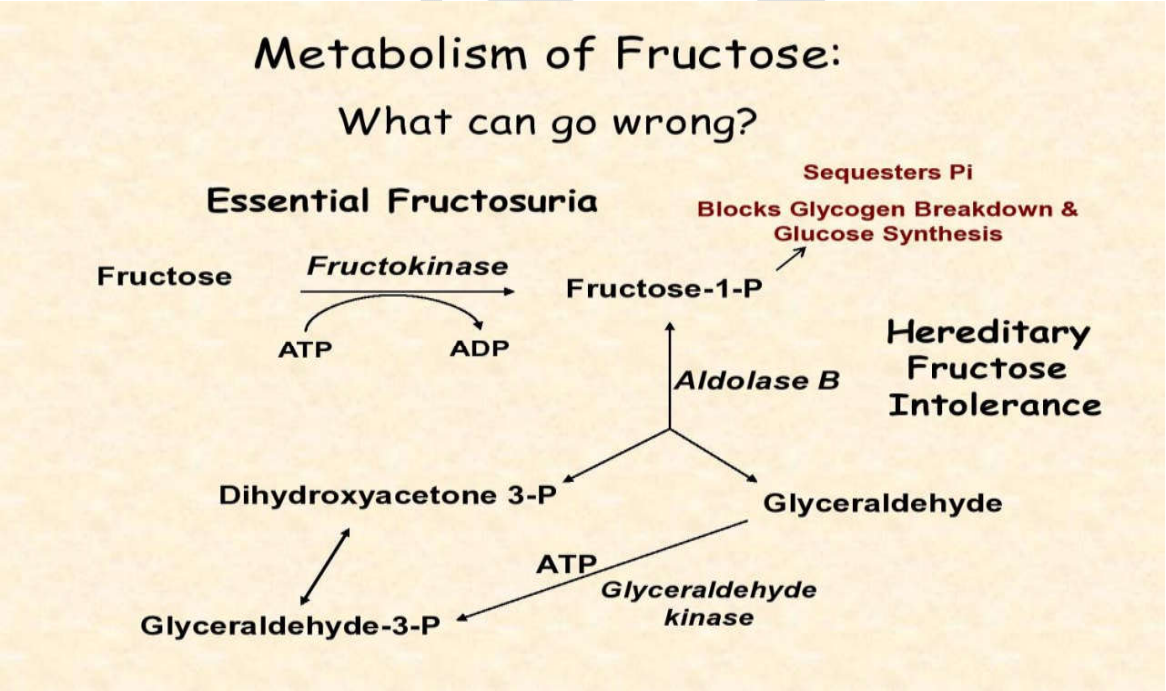
glycosuria occurs as an isolated finding with otherwise normal kidney function, the condition is thought to be inherited as an autosomal recessive trait.

Signs & Symptoms

In most affected individuals, renal glycosuria is a benign condition, resulting in no apparent symptoms (asymptomatic). However, in some cases, glycosuria may be pronounced enough to result in excessive urination (polyuria), excessive thirst (polydipsia), and other associated symptoms. Less commonly, under certain conditions, such as pregnancy or starvation, renal glycosuria may be associated with excessively low levels of bodily fluids (dehydration) or a condition in which there is an abnormal accumulation of certain chemical substances (ketone bodies) in bodily tissues and fluids due to excessive breakdown of fats (ketosis).

Fructosuria

Fructosuria is a rare but benign inherited metabolic disorder. It is characterized by the excretion of fruit sugar (fructose) in the urine. Normally, no fructose is excreted in the urine. This condition is caused by a deficiency of the enzyme fructokinase in the liver. This enzyme is needed for the synthesis of glycogen (the body's form of stored energy) from fructose. The presence of fructose in the blood and urine may lead to an incorrect diagnosis of diabetes mellitus.



Pentosuria

Essential pentosuria is a condition characterized by high levels of a sugar called L-xylulose in urine. The condition is so named because L-xylulose is a type of sugar called a pentose. Despite the excess sugar, affected individuals have no associated health problems. Essential pentosuria occurs almost exclusively in individuals with Ashkenazi Jewish ancestry. Approximately 1 in 3,300 people in this population are affected.

Genetic changes

Essential pentosuria is caused by mutations in the *DCXR* gene. This gene provides instructions for making a protein called dicarbonyl and L-xylulose reductase (DCXR), which plays multiple roles in the body. One of its functions is to perform a chemical reaction that converts a sugar called L-xylulose to a molecule called xylitol. This reaction is one step in a process by which the body can use sugars for energy.

DCXR gene mutations lead to the production of altered DCXR proteins that are quickly broken down. Without this protein, L-xylulose is not converted to xylitol, and the excess sugar is released in the urine.

While essential pentosuria is caused by genetic mutations, some people develop a non-inherited form of pentosuria if they eat excessive amounts of fruits high in L-xylulose or another pentose called L-arabinose. This form of the condition, which disappears if the diet is changed, is referred to as alimentary pentosuria. Studies show that some drugs can also cause a form of temporary pentosuria called drug-induced pentosuria. These non-inherited forms of the condition also do not cause any health problems.

Other names

- Essential benign pentosuria
- L-xylulose reductase deficiency
- L-xylulosuria
- Pentosuria
- Xylitol dehydrogenase deficiency

Galactosuria

Elevated concentration of galactose in the urine.

Disorders of aminoacid metabolism

Disorder	Metabolic defect (enzyme/other)
I. Phenylalanine and tyrosine	
1. Phenylketonuria	Phenylalanine hydroxylase
2. Tyrosinemia type II	Tyrosine transaminase
3. Neonatal tyrosinemia	p-Hydroxy phenylpyruvate dioxygenase
4. Alkaptonuria	Homogentisate oxidase
5. Tyrosinosis (tyrosinemia type I)	Maleyl acetoacetate isomerase or fumaryl acetoacetate hydrolase
6. Albinism	Tyrosinase
II. Sulfur amino acids (methionine, cysteine and cystine)	
7. Cystinuria	Defect in renal reabsorption
8. Cystinosis	Impairment in cystine utilization (defect in lysosomal function)
9. Homocystinuria type I	Cystathionine synthetase
10. Homocystinuria type II	N^5, N^{10}-Methylene THF reductase
11. Homocystinuria type III	N^5-Methyl THF-homocysteine methyltransferase
12. Cystathionuria	Cystathioninase
III. Glycine	
13. Glycinuria	Defect in renal reabsorption
14. Primary hyperoxaluria	Glycine transaminase
IV. Tryptophan	
15. Hartnup's disease	Defective intestinal absorption
V. Branched chain amino acids (valine, leucine and isoleucine)	
16. Maple syrup urine disease	Branched chain α-keto acid dehydrogenase
17. Intermittent branched chain ketonuria	Variant of the above enzyme (less severe)
18. Hypervalinemia	Valine transaminase
19. Isovaleric acidemia	Isovaleryl CoA dehydrogenase
VI. Histidine	
20. Histidinemia	Histidase
VII. Proline	
21. Hyperprolinemia type I	Proline oxidase

Cystinuria

Cystinuria is an inherited disease that causes stones made of the amino acid cystine to form in the kidneys, bladder, and ureters. Inherited diseases are passed down from parents to children through a defect in their genes. To get cystinuria, a person must inherit the defect from both parents.

The defect in the gene causes cystine to accumulate inside the kidneys, which are the organs that help regulate what goes in and out of your bloodstream. The kidneys have many functions, including:

- reabsorbing essential minerals and proteins back into the body
- filtering the blood to remove toxic waste
- producing urine to expel waste from the body

In someone who has cystinuria, the amino acid cystine builds up and forms stones instead of going back into the bloodstream. These stones can get stuck in the kidneys, bladder, and ureters. This can be very painful until the stones pass through urination. Very large stones may need to be surgically removed.

The stones can recur many times. Treatments are available to manage pain and to prevent more stones from forming.

Symptoms

The symptoms may include:

- blood in the urine
- severe pain in the side or the back, almost always on one side
- nausea and vomiting
- pain near the groin, pelvis, or abdomen

Cystinuria is asymptomatic, meaning it causes no symptoms, when there are no stones. However, the symptoms will recur each time stones form in the kidneys. The stones commonly occur more than once.

Causes

Defects, also called mutations, in the genes called *SLC3A1* and *SLC7A9* cause cystinuria. These genes provide the instructions for your body to make a certain transporter protein found in the kidneys. This protein normally controls the reabsorption of certain amino acids.

Amino acids are formed when the body digests and breaks down proteins. The amino acids are used to perform a wide variety of bodily functions. They are important to body and are not considered waste. Therefore, when they enter the kidneys, the amino acids are normally absorbed

back into the bloodstream. In people with cystinuria, their genetic defect interferes with the transporter protein's ability to reabsorb the amino acids.

One of the amino acids — cystine — is not very soluble in urine. If it isn't reabsorbed, it will accumulate inside the kidney and form crystals, or cystine stones. The rock-hard stones then get stuck in the kidneys, bladder, and ureters. This can be very painful.

Hartnup's disease:

Hartnup disease is an autosomal recessive disorder caused by impaired neutral (ie, monoaminomonocarboxylic) amino acid transport in the apical brush border membrane of the small intestine and the proximal tubule of the kidney. Patients present with pellagra like skin eruptions, cerebellar ataxia, and gross aminoaciduria.

Prognosis:

Hartnup disease is manifested by a wide clinical spectrum. Most patients remain asymptomatic, but, in a minority of patients, skin photosensitivity and neurologic and psychiatric symptoms may have a considerable influence on quality of life. Rarely, severe CNS involvement may lead to death. Mental retardation and short stature have been described in a few patients. Malnutrition and a low-protein diet are the primary factors that contribute to morbidity.

Signs and symptoms

Hartnup disease manifests during infancy with variable clinical presentation: failure to thrive, photosensitivity, intermittent ataxia, nystagmus, and tremor.

Nicotinamide is necessary for neutral amino acid transporter production in the proximal renal tubules found in the kidney, and intestinal mucosal cells found in the small intestine. Therefore, a symptom stemming from this disorder results in increased amounts of amino acids in the urine.

Pellagra, a similar condition, is also caused by low nicotinamide; this disorder results in dermatitis, diarrhea, and dementia.

Hartnup disease is a disorder of amino acid transport in the intestine and kidneys; otherwise, the intestine and kidneys function normally, and the effects of the disease occur mainly in the brain and skin. Symptoms may begin in infancy or early childhood, but sometimes they begin as late as early adulthood. Symptoms may be triggered by sunlight, fever, drugs, or emotional or physical stress. A period of poor nutrition nearly always precedes an attack. The attacks usually become progressively less frequent with age. Most symptoms occur sporadically and are caused by a deficiency of niacinamide. A rash develops on parts of the body exposed to the sun. Mental

retardation, short stature, headaches, unsteady gait, and collapsing or fainting are common. Psychiatric problems (such as anxiety, rapid mood changes, delusions, and hallucinations) may also result.

Treatment

A high-protein diet can overcome the deficient transport of neutral amino acids in most patients. Poor nutrition leads to more frequent and more severe attacks of the disease, which is otherwise asymptomatic. All patients who are symptomatic are advised to use physical and chemical protection from sunlight: avoid excessive exposure to sunlight, wear protective clothing, and use chemical sunscreens with a SPF of 15 or greater. Patients also should avoid other aggravating factors, such as photosensitizing drugs, as much as possible. In patients with niacin deficiency and symptomatic disease, daily supplementation with nicotinic acid or nicotinamide reduces both the number and severity of attacks. Neurologic and psychiatric treatment is needed in patients with severe central nervous system involvement.

Fanconi syndrome

- Fanconi syndrome or Fanconi's syndrome is a syndrome of inadequate reabsorption in the proximal renal tubules of the kidney.
- The syndrome can be caused by various underlying congenital or acquired diseases, by toxicity (for example, from toxic heavy metals), or by adverse drug reactions.
- It results in various small molecules of metabolism being passed into the urine instead of being reabsorbed from the tubular fluid (for example, glucose, amino acids, uric acid, phosphate, and bicarbonate).
- Fanconi syndrome affects the proximal tubules, namely, the proximal convoluted tubule (PCT).
- Different forms of Fanconi syndrome can affect different functions of the proximal tubule, and result in different complications.
- The loss of bicarbonate results in type 2 or proximal renal tubular acidosis.
- The loss of phosphate results in the bone diseases rickets and osteomalacia (even with adequate vitamin D and calcium levels), because phosphate is necessary for bone development in children and even for ongoing bone metabolism in adults.

The clinical features of proximal renal tubular acidosis are:

- Polyuria, polydipsia and dehydration
- Hypophosphatemic rickets (in children) and osteomalacia (in adults)
- Growth failure
- Acidosis
- Hypokalemia
- Hyperchloremia
- Other features of the generalized proximal tubular dysfunction of the Fanconi syndrome are:
- Hypophosphatemia/hyperphosphaturia
- Glycosuria
- Proteinuria/aminoaciduria
- Hyperuricosuria

Causes

- In contrast to Hartnup disease and related tubular conditions, Fanconi syndrome affects the transport of many different substances, so is not considered to be a defect in a specific channel, but a more general defect in the function of the proximal tubules.
- Different diseases underlie Fanconi syndrome; they can be inherited, congenital, or acquired.

Inherited

- Cystinosis is the most common cause of Fanconi syndrome in children.
- Other recognised causes are Wilson's disease (a genetically inherited condition of copper metabolism), tyrosinemia , galactosemia, glycogen storage diseases, and hereditary fructose intolerance.

Acquired

- It is possible to acquire this disease later in life.
- Causes include ingesting expired tetracyclines (where tetracycline changes to form epitetracycline and anhydrotetracycline which damage proximal tubule)

- In the HIV population, Fanconi syndrome can develop secondary to the use of an antiretroviral regimen containing tenofovir and didanosine.
- Lead poisoning also leads to Fanconi syndrome.
- Multiple myeloma or monoclonal gammopathy of undetermined significance can also cause the condition.
- Treatment
- Treatment of children with Fanconi syndrome mainly consists of replacement of substances lost in the urine (mainly fluid and bicarbonate).

Homocystinuria

Homocystinuria is caused by lack of the enzyme needed to metabolize homocysteine. This disorder can cause a number of symptoms, including decreased vision and skeletal abnormalities. Children with homocystinuria are unable to metabolize the amino acid homocysteine, which, along with certain toxic by-products, builds up to cause a variety of symptoms. Symptoms may be mild or severe, depending on the particular enzyme defect.

Infants with this disorder are normal at birth. The first symptoms, including dislocation of the lens of the eye, causing severely decreased vision, usually begin after 3 years of age. Most children have skeletal abnormalities, including osteoporosis. Children are usually tall and thin with a curved spine, chest deformities, elongated limbs, and long, spiderlike fingers. Without early diagnosis and treatment, mental (psychiatric) and behavioral disorders and intellectual disability are common. Homocystinuria makes the blood more likely to clot spontaneously, resulting in strokes, high blood pressure, and many other serious problems.

Since 2008, nearly every state in the United States has required that all newborns be screened for homocystinuria with a blood test. A test measuring enzyme function in liver or skin cells confirms the diagnosis.

Some children with homocystinuria improve when given vitamin B_6 (pyridoxine) or vitamin B_{12} (cobalamin).

Alkaptonuria

Biochemical Defect

1. Alkaptonuria is an autosomal recessive condition with an incidence of 1 in 250,000 births.

2. The metabolic defect is the deficiency of homogentisate oxidase

3. This results in excretion of homogentisic acid in urine.

4. It is compatible with fairly normal life. The only abnormality is the blackening of urine on standing. The homogentisic acid is oxidized by polyphenol oxidase to benzoquinone acetate. It is then polymerized to black colored alkaptone bodies.

5. By the 3rd or 4th decade of life, patient may develop ochronosis (deposition of alkaptone bodies in intervertebral discs, cartilages of nose, pinna of ear) . Black pigments are deposited over the connective tissues including joint cavities to produce arthritis.

6. No specific treatment is required. But minimal protein intake with phenylalanine less than 500 mg/day is recommended.

Diagnosis of Alkaptonuria

1. Urine becomes black on standing when it becomes alkaline. Blackening is accelerated on exposure to sunlight and oxygen. The urine when kept in a test tube will start to blacken from the top layer .

2. Ferric chloride test will be positive for urine.

3. Benedict's test is strongly positive. Therefore, alkaptonuria comes under the differential diagnosis of reducing substances in urine.

Alkaptonuria

Alkaptonuria is a rare inherited disorder. It occurs when your body can't produce enough of an enzyme called homogentisic dioxygenase (HGD). This enzyme is used to break down a toxic substance called homogentisic acid. When you don't produce enough HGD, homogentisic acid builds up in your body.

The buildup of homogentisic acid causes your bones and cartilage to become discolored and brittle. This typically leads to osteoarthritis, especially in your spine and large joints. People with alkaptonuria also have urine that turns dark brown or black when it's exposed to air.

Symptoms:

Dark stains on a baby's diaper are one of the earliest signs of alkaptonuria. There are few other symptoms during childhood.

Symptoms become more obvious as you age. Your urine may turn dark brown or black when it's exposed to air. By the time you reach your 20s or 30s, you may notice signs of early-onset osteoarthritis. For example, you may notice chronic stiffness or pain in your lower back or large joints.

Other symptoms of alkaptonuria include:

- dark spots in the sclera (white) of your eyes
- thickened and darkened cartilage in your ears
- blue speckled discoloration of your skin, particularly around sweat glands
- dark-colored sweat or sweat stains
- black earwax
- kidney stones and prostate stones
- arthritis (especially hip and knee joints).

Alkaptonuria can also lead to heart problems. The buildup of homogentisic acid causes your heart valves to harden. This can keep them from closing properly, resulting in aortic and mitral valve disorders. In severe cases, heart valve replacement may be necessary. The buildup also causes your blood vessels to harden. This raises your risk of high blood pressure**.**

Causes:

Alkaptonuria is caused by a mutation on your homogentisate 1,2-dioxygenase (HGD) gene. It's an autosomally recessive condition**.**

Treatment:

No treatment modality has been unequivocally demonstrated to reduce the complications of alkaptonuria. Main treatment attempts have focused on preventing ochronosis through the reduction of accumulating homogentisic acid. Such commonly recommended treatments include large doses of ascorbic acid (vitamin C) or dietary restriction of amino acids phenylalanine and tyrosine. However, vitamin C treatment has not shown to be effective, and protein restriction (which can be difficult to adhere to) has not shown to be effective in clinical studies.

Several recent studies have suggested that the herbicide nitisinone may be effective in the treatment of alkaptonuria. Nitisinone inhibits the enzyme, 4-hydroxyphenylpyruvate dioxygenase, responsible for converting tyrosine to homogentisic acid, thereby blocking the

production and accumulation of HGA. Nitisinone has been used for some time at much higher doses in the treatment of type I tyrosinemia. Nitisinone treatment has been shown to cause a larger than 95% reduction in plasma and urinary HGA. The main drawback is accumulation of tyrosine, the long-term risks of which are unknown; there is a particular concern about damage to the cornea of the eye. Long-term use would require frequent monitoring for complications.

Phenylketonuria (PKU)

Phenylketonuria occurs in infants born without the ability to normally break down an amino acid called phenylalanine. Phenylalanine, which is toxic to the brain, builds up in the blood.

- Phenylketonuria is caused by lack of the enzyme needed to convert phenylalanine to tyrosine.
- Symptoms include intellectual disability, seizures, nausea, vomiting, an eczema-like rash, and a mousy body odor.
- The diagnosis is based on a blood test.
- A strict phenylalanine-restricted diet allows for normal growth and development.

Phenylketonuria (PKU) is a disorder that causes a buildup of the amino acid phenylalanine, which is an essential amino acid that cannot be synthesized in the body but is present in food. Excess phenylalanine is normally converted to tyrosine, another amino acid, and eliminated from the body. Without the enzyme that converts it to tyrosine, phenylalanine builds up in the blood and is toxic to the brain, causing intellectual disability.

Symptoms

Newborns with PKU rarely have symptoms right away, although sometimes they are sleepy or eat poorly. If not treated, affected infants progressively develop intellectual disability over the first few years of life, eventually becoming severe. Other symptoms include seizures, nausea and vomiting, an eczema-like rash, lighter skin and hair than their family members, aggressive or self-injurious behavior, hyperactivity, and sometimes psychiatric symptoms. Untreated children often give off a mousy body and urine odor as a result of a by-product of phenylalanine (phenylacetic acid) in their urine and sweat.

Diagnosis

PKU is usually diagnosed with a routine screening test.

PKU occurs in most ethnic groups. If PKU runs in the family and DNA is available from an affected family member, amniocentesis or chorionic villus sampling with DNA analysis can be done to determine whether a fetus has the disorder.

Parents and siblings of children with PKU can be tested to find out whether they carry the gene that causes the disease. If two carriers conceive a child, that child has a 1 in 4 chance of being born with the disease.

Prognosis

A phenylalanine-restricted diet, if started early and maintained well, allows for normal development. However, if very strict control of the diet is not maintained, affected children may begin to have difficulties in school. Dietary restrictions started after 2 to 3 years of age may control extreme hyperactivity and seizures and raise the child's eventual intelligence quotient (IQ) but do not reverse intellectual disability. Recent evidence suggests that some intellectually disabled adults with PKU (born before newborn screening tests were available) may function better when they follow the PKU diet.

A phenylalanine-restricted diet should continue for life, or intelligence may decrease and neurologic and mental problems may ensue.

Prevention and Treatment

To prevent intellectual disability, people must restrict phenylalanine intake (but not eliminate it altogether because people need some phenylalanine to live) beginning in the first few weeks of life. Because all natural sources of protein contain too much phenylalanine for children with PKU, affected children cannot have meat, milk, or other common foods that contain protein. Instead, they must eat a variety of processed foods, which are specially manufactured to be phenylalanine-free. Low-protein natural foods, such as fruits, vegetables, and restricted amounts of certain grain cereals, can be eaten. Special nutritional products, including infant formula without phenylalanine, are also available. Future treatments may include cell transplantation and gene therapy.

Albinism

1. The Greek word, albino means white. Albinism is an autosomal recessive disease with an incidence of 1 in 20,000 population .

2. Tyrosinase is completely absent, leading to defective synthesis of melanin.

3. The ocular fundus is hypopigmented and iris may be gray or red. There will be associated photophobia, nystagmus and decreased visual acuity.

4. The skin has low pigmentation, and so skin is sensitive to UV rays. The skin may show presence of nevi and melanomas. Hair is also white.

5. Manifestations are less severe in tyrosinase positive type, where the abnormality is in the uptake of tyrosine by melanocytes.

6. Albinism may be produced by the following causes:

a. Melanocyte deficiency secondary to a failure of melanoblasts to colonize the skin.

b. Failure of melanocytes to form melanosomes

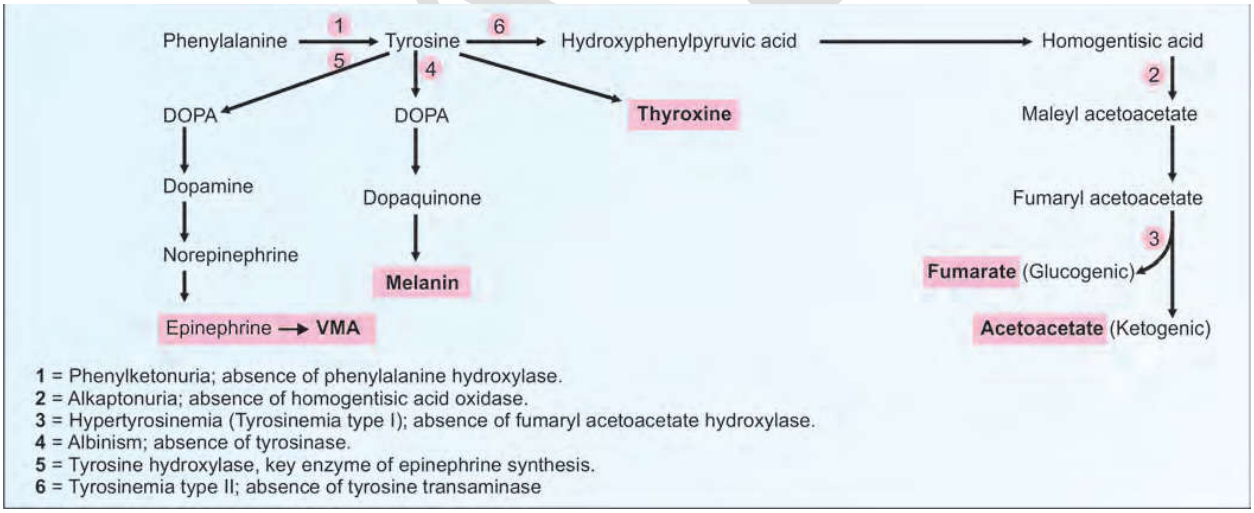
c. Due to tyrosinase deficiency, melanin is not produced in the melanosomes

d. Failure of melanosomes to form melanin owing to substrate deficiency

e. Failure of melanosomes to store melanin or to transport melanin to keratinocytes

f. Excessive destruction of functional melanosomes.

Summary of tyrosine metabolism



MAPLE SYRUP URINE DISEASE

Maple syrup urine disease is caused by lack of the enzyme needed to metabolize amino acids. By-products of these amino acids cause the urine to smell like maple syrup.

Children with maple syrup urine disease are unable to metabolize certain amino acids. By-products of these amino acids build up, causing neurologic changes, including seizures and intellectual disability. These by-products also cause body fluids, such as urine and sweat, to smell like maple syrup. This disease is most common among Mennonite families.

There are many forms of maple syrup urine disease. In the most severe form, infants develop neurologic abnormalities, including seizures and coma, during the first week of life and can die within days to weeks. In the milder forms, children initially appear normal but during infection, surgery, or other physical stress, they can develop vomiting, staggering, confusion, and coma.

Since 2007, nearly every state in the United States has required that all newborns be screened for maple syrup urine disease with a blood test.

Infants with severe disease are treated with dialysis. Some children with mild disease benefit from injections of vitamin B_1 (thiamin). After the disease has been brought under control, children must always consume a special artificial diet that is low in three amino acids (leucine, isoleucine, and valine). During times of physical stress or flare-ups, it may be necessary to monitor blood tests and give fluids by vein.

POSSIBLE QUESTIONS

1. Describe the regulation of blood glucose concentration.
2. Write a note on Diabetes Mellitus: types, pathophysiology and complications.
3. Give an account of GTT and its interpretation.
4. What are the methods used for diagnosis of diabetes?
5. Discuss on various types of renal glycosurias.
6. Write a note on cysteinuria, homocysteinuria, fanconi syndrome and MSUD.
7. Write a note on disorders of aromatic amino acids.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III-B.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (15BCU601)
MULTIPLE CHOICE QUESTIONS

UNIT II

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Chylomicron hyper lipoprotenemia is associated with deficiency of ------ lipase	adipolytic	lipoprotein	pancreatic	hepatic	lipoprotein
2	Increased fat accumulation in liver is noted in which of the following conditions ?	Lipoprotein lipase deficiency	Obesity	Juvenile diabetes mellitus	Deficiency of choline	Lipoprotein lipase deficiency
3	The lipoprotein that delivers cholesterol to tissues is	VLDL	LDL	HDL	Chylomicron	LDL
4	Lipoprotein lipase deficiency in blood leads to	Type I primary hyperlipoproteinemia	Type II primary hyperlipoproteinemia	Type III primary hyperlipoproteinemia	Type IV primary hyperlipoproteinemia	Type I primary hyperlipoproteinemia
5	In Tay Sach's disease _____ accumulates	sphingomyelins	glycolipids	gangliosides	cerebrosides	gangliosides
6	Chylomicron hyperlipoproteinemia is associated with a deficiency of _____lipase	adipolytic	lipoprotein	pancreatic	hepatic	lipoprotein
7	Fatty liver occurs in	chronic alcoholism	high fat diet	atheroselerosis	essential fatty acid deficiency	chronic alcoholism
8	Gaucher's disease is a	Glycogenesis	Lipidosis	Dysproteinemia	Chronic renal disease	Lipidosis
9	The plasma lipoprotein that transports hepatic- synthesised triglycerides and cholesterol is	LDL	HDL	VLDL	IDL	LDL
10	The enzyme that hydrolyses triglyceride to glycerol and fatty acids is	lecithin-cholesterol acyl transferase	lipoprotein lipase	HMG-CoA reductase	none of the above	lipoprotein lipase
11	The low density lipoprotein contains more amount of	lipids	proteins	glycoproteins	carbohydrates	lipids
12	The normal level of blood cholesterol in an adult man is	150-250 mg/dl	300-450 mg/dl	60-90 mg/dl	40-55 mg/dl	150-250 mg/dl
13	Tay Sach's disease is due to the deficiency of	B-N-acetyl glucosaminilase A	Sphingo myclinase	Aryl sulphatase	Hexoaminadase A	Hexoaminadase A
14	The following are true with the LCAT	LCAT is lecithin cholesterol acyl transferase	LCAT is responsible for most of the plasma cholesteryl esters	LCAT absence leads to block in reverse cholesterol	All the above	LCAT is lecithin cholesterol acyl transferase
15	VLDL is rich in	Free cholesterol	Triglyceride	Phospholipid	Protein	Triglyceride
16	Substance which prevent the accumulation of lipid in the liver is called	Lipophilic factor	Lipophobic factor	Lipotropic factor	Lipidosis	Lipotropic factor
17	LDL fraction is relatively rich in	Cholesterol	Triglyceride	Free fatty acids	Phospholipids	Cholesterol
18	Phosphatic acid is a precursor of	Phosphotidyl Inositol	Phosphotidyl ethanolamine	Phosphotidyl choline	Phosphatidyl glycerol	Phosphatidyl glycerol
19	Good cholesterol is named as	LDL	VLDL	HDL	IDL	HDL
20	The defect in hyperlipoproteinemia type 1 is	Deficiency of LPL	Production of abnormal LPL	APO C-11 deficiency causing inactive LPL	All the above	Deficiency of LPL
21	In Tay Sach's disease the following are true except one	Accumulation of ganglioside occurs in brain and spleen	Lysosomal hexosaminidase A is absent	Sphingomyelinase is absent	Leads to death by the age of 3 or 4 years	Accumulation of ganglioside occurs in brain and spleen
22	Blood cholesterol level is raised in	hyper thyroidism	hypothyroidism	hypo insulinism	pernicious anemia	hypothyroidism
23	Substance which prevent the accumulation of lipid in the liver is called	Lipophilic factor	Lipophobic factor	Lipotropic factor	Lipidosis	Lipophilic factor
24	Lipoprotein lipase deficiency in blood leads to	Type I primary hyperlipoproteinemia	Type II primary hyperlipoproteinemia	Type III primary hyperlipoproteinemia	Type IV primary hyperlipoproteinemia	Type I primary hyperlipoproteinemia
25	Tangires disease is due to the deficiency of	HDL	Sphingo myclinase	Aryl sulphatase	alphalipoprotein	alphalipoprotein
26	The normal level of total fecal fat excreated is	2-6 g/day	7 - 10 g/day	12-14 g/day	1 - 2 g/day	2-6 g/day
27	The following may lead to fatty liver except one	Alcoholism	Starvation	Carbohydrate rich diet	Uncontrolled diabetes mellitus	Alcoholism

28	The poison causes inhibition of fatty acid oxidation	Hypotaurin	Hypoglycine	Puromycin	Hyposederine	Puromycin
29	Acanthosis -abnormality of	RBC	WBC	Platelets	Phagocytes	RBC
30	The normal level of total cholesterol in blood is	75-300mg/dl	250-400mg/dl	150-250mg/dl	200-350mg/dl	150-250mg/dl
31	The biochemical defect in Type I hyperlipoproteinemia is	Deficiency of LPL	Absence of HDL	Absence of bete lipoprotein	defective LDL receptor	Deficiency of LPL
32	A high blood cholesterol and diminished serum proteins are encountered in	Nephrotic syndrome	Acute nephritis type II	atheroselerosis	Myxedema	atheroselerosis
33	Hypercholesterolemia is due to	Increased synthesis	Increased bile acid formation	Increased dietary fat	Both a and b	Both a and b
34	Niemann-pick leads to acumulation of	Ceramide	Cerebroside	Sphingomyelin	Sulphatides	Sphingomyelin
35	The lipoprotein which contains more protein	Chylomicron	VLDL	LDL	HDL	HDL
36	Fatty liver is caused by	CH3CL	CCl4	MgSO4	CH_3COOH	CH3CL
37	Increased in blood of this class of lipoprotein is benefical to ward off coronary heart diseases	HDL	LDL	VLDL	IDL	LDL
38	High affinity LDL receptor is	apo E	apo B-100	apo C	none of the above	apo B-100
39	In Tangiers disease there is	Deficiency of alpha lipoprotein	Deficiency of cholesterol	Increase in phospholipid	Increase in free fatty acids	Deficiency of alpha lipoprotein
40	LCAT is	Lactose-choline alanine transferase	Lecithin-cholesterol acyl transferase	Lecithin-carnitine acyl transferase	Linoleate carbamoyl acyl transferase	Lecithin-cholesterol acyl transferase
41	Zellweger's syndrome is characterised by absence of	Peroxisomes	Glyoxysomes	Ribosomes	Lysosomes	Peroxisomes
42	Carnitine palmitoyl transferase deficiency results in	hypoglycaemia and low plasma ketone bodies	hyperglycaemia and high plasma ketone bodies	low plasma TG and lipoproteins	high plasma TG and lipoproteins	low plasma TG and lipoproteins
43	Diets having high P:S ratio (polyunsaturated :saturated FA) has the effect of	increasing serum cholesterol and LDL level	decreasing serum cholesterol and LDL level	increasing TG in blood	decreasing TG in blood	increasing TG in blood
44	Which of the following hormone decreases cholesterol synthesis	Insulin	Throid hormones	Glucagon	ADH	Glucagon
45	The major source of cholesterol in aorta	LDL	HDL	VLDL	IDL	LDL
46	Scavenging action is one of the chief function of	LDL	HDL	VLDL	Chylomicron	HDL
47	Wolman's Disease is characterised by	Increased levels of cholesterol	Increased levels of triglyceride	Decreased levels of cholesterol	Decreased levels of triglyceride	Increased levels of cholesterol
48	Cardiolipin is a phospholipid present in	mitochondria	microsome	Ribosomes	ER	mitochondria
49	Combination of sphingosine and acyl-coA results in the formation of	Ceramide	Sphingomyelin	cerebroside	lecithine	Ceramide
50	Which of the following hormones promote lipolysis	Epinephrine	Norepinephrine	Glucagon	All the above	Glucagon
51	CCl4 poisoning causes	Artherosclerosis	Fatty liver	Myocardial infarction	all the above	Fatty liver
52	Lipotrophic agents	choline	Methionine	Valine	Choline and methionine	Choline and methionine
53	Pathological liver may be due to	Deficiency of EFA,	Deficiency of Pantothenic acid,	Deficiency of Pyridoxine	Deficiency of EFA, deficiency of pantothenic acid and deficiency of pyridoxine	Deficiency of EFA, deficiency of pantothenic acid and deficiency of pyridoxine
54	Hard yellow plaque of lipoid which is found in inner most layer of arteries is called	Carcinomas	Pace maker	Atheroma	Atherosclerosis	Atheroma
55	All veins in body carry deoxygenated blood except	Aorta	Inferior venacava	Superior venacava	Pulmonary vein	Pulmonary vein
56	Constriction and hardening of arteries occur in a condition known as	Arteriosclerosis	Atherosclerosis	Both of them	Venusclerosis	Arteriosclerosis
57	Veins collects blood from body and send it to	Liver	Lungs	Heart	Arteries	Heart
58	Prime contributor of atherosclerosis is	Accumulation of monocytes	Accumulation of mesophyll	Accumulation of albumin	Accumulation of cholesterol	Accumulation of mesophyll
59	Arteriosclerosis occurs due to presence of	Phosphorus in arteries	Potassium in arteries	Magnesium in arteries	Calcium in arteries	Potassium in arteries
60	When thrombus becomes free-floating and dislodges then thrombus becomes	Embolus	Bolus	Acidosis	Hypnosis	Hypnosis

Unit II

Syllabus

Disorders of Lipid metabolism: Introduction, clinical manifestation, biochemical abnormalities of lipoprotein-Abetalipoproteinemia, Hyperlipoproteinemias, Hypobetalipoproteinemias; hyperlipidemia, hypercholesterolemia, Cholesterol Acyl Transferase Deficiency. Atherosclerosis, Fatty liver, liver cirrhosis.

DYSLIPOPROTEINEMIA

Inherited disorders of lipoproteins are encountered in some individuals resulting in primary hyper- or hypolipoproteinemias. These are due to genetic defects in lipoprotein metabolism and transport. The secondary acquired lipoprotein disorders are due to some other diseases(e.g.d iabetes mellitus, nephritic syndrome,atherosclerosis,hypothyrodism e tc.), resulting in abnormal lipoprotein pattern which often resembles the primary inherited condition.

HYPOLIPOPROTEINEMIAS

Although low levels of plasma lipids (not HDL!) within the normal range may be beneficial to the body, very low lipid levels are undesirable. These are commonly associated with certain abnormalities

Abetalipoproteinemia

All apo-B containing lipoproteins are reduced since microsomal triglyceride transfer protein is defective. Hence TAG is not incorporated into VLDL and chylomicrons.. Beta lipoprotein (LDL) is absent. Fat-soluble vitamins are not absorbed, causing mental and physical retardation. Serum levels of triglycerides, cholesterol and phospholipids are extremely low. Blindness may occur as a result of degenerative changes in retina. Erythrocytes have spiny projections (acanthocytes).

Familial hypobetalipoproteinemia:

lt is an inherited disorder probably due to an impairmenti n the synthesiso f apoproteinB . The plasma LDL concentration in the affected individuals is between 10 to 50% of normal values. This disorder is harmless, and,the individuals have healthy and long life.

Familial alpha-lipoprotein deficiency (Tangier disease):

It was first described in patients from Tangier island in North-West Africa. It is a relatively benign, autosomal recessive condition. It is characterized by a defect in the efflux (flowing out) of cholesterol from cells, and reduction of HDL levels in the blood. The biochemical defect is the absence of "ATP-Binding Cassette Transporter-1" (ABC- 1), which is involved in transferring cellular cholesterol to HDL. So, plasma HDL is low and alpha band is nost seen in electrophoresis. Cholesterol esters are accumulated in tissues. Manifestations are large orange yellow tonsils, muscle atrophy, recurrent peripheral neuropathies and atherosclerosis.

Hypo-alpha-lipoproteinemia

This is inherited as an autosomal dominant trait. Serum HDL is decreased. There is increased risk for coronary artery diseases

Disease	*Lipoproteins*	*Cholesterol*	*Triacylglycerols*	*Clinical findings*
Familial hypo beta lipoproteinemia	LDL decreased B-100 decreased	Decreased	Normal disease	Decreased risk of coronary artery
Abeta lipoproteinemia	VLDL↓; LDL↓↓ B-48↓; B-100↓↓	Markedly decreased	Decreased	Malabsorption; mental and physical retardation; acanthocytosis
Hypo alpha lipoproteinemia	HDL↓ A-I↓	Normal	Normal	Increased risk of coronary artery disease
Familial alpha Lp-deficiency	HDL↓↓ A-I↓↓	Normal	Normal	Increased risk of CAD

Hyper

Elevation in one or more of the lipoprotein fractions constitutes hyperlipoproteinemias. These disorders may be either primary or secondary. Some authors use hyperlipidemias or Dyslipidemias instead of hyperlipoproteinemias. Frederickson's classification of hyperliporoteinemias-based on the electrophoretic patterns of plasma lipoproteins-is widely accepted to understand these disorders.

- In all cases of hyperlipidemias, the elevated lipid fraction is either cholesterol or TAG or both.
- The elevation of lipids in plasma leads to the deposition of cholesterol on the arterial walls, leading to atherosclerosis.
- The coronary and cerebral vessels are more commonly affected.
- Thromboembolic episodes in these vessels lead to ischemic heart disease and cerebrovascular accidents. The deposition of lipids in subcutaneous tissue leads to xanthomas.
- The type of xanthoma depends on the nature of lipid deposited.
- Eruptive xanthomata are small yellow nodules associated with deposition of triglycerides.
- They disappear when the lipid level falls.
- Tuberous xanthomata are yellow plaques containing triglycerides and cholesterol, found mainly over the elbows and knees.
- Xantheslasma are lipid deposits under the periorbital skin and contain mainly cholesterol.
- Tendinous xanthomata are found over the tendons.
- Deposits of lipids in cornea lead to corneal arcus; indicating hyper cholesterolemia.

Hyperlipidemias, in the order of highest to lowest incidence are described below.

Type II A (Primary Familial Hypercholesterolemia)

- There is elevation of LDL.
- Patients seldom survive the second decade of life due to ischemic heart disease
- The cause is **LDL receptor** defect.
- Receptor deficiency in liver and peripheral tissues will result in the elevation of LDL levels in plasma, leading to hypercholesterolemia. The LDL receptor defect may be due to the following reasons.

1. LDL receptor deficiency.

2. Defective binding of B-100 to the receptor. A substitutionof glutamine for arginine at 3500th amino acid results in poor binding to LDL receptors. This defect is known as B-3500 or familial defective apo B.

3. Receptor-LDL complex is not internalized

Secondary type II hyperlipoproteinemia is seen in hypothyroidism, diabetes mellitus, nephrotic syn drome and cholestasis

Type II B Hyperlipoproteinemia

- There is elevation of both cholesterol and triglycerides with excessive production of apo-B. Therefore, LDL and VLDL are elevated. The abnormalities are manifested only by the third decade of life..

Type IV (Familial Endogenous type)

- This is due to over production of triglycerides by liver.
- The VLDL level in plasma is elevated.
- Cardiac manifestations are seen in the 4th decade of life.
- It may be associated with diabetes mellitus, obesity and impaired glucose tolerance.

Type I

- It is rare.
- It is due to lipoprotein lipase deficiency.
- It usually manifests in young age.
- A chylomicron band in fasting plasma is the characteristic finding. Hepatomegaly, eruptive xanthoma and abdominal pain are seen.

Type III

- It is very rare.
- It is due to increased levels of LDL and IDL.
- Palmar xanthomas and vascular disease are noticed.

Type V

- Chylomicrons and VLDL are increased.
- Hypertriglyceridemia, usually secondary to other disorders like obesity, excessive alcohol intake, renal failure, pancreatitis, etc. are common

Other causes of hyperlipoproteinemias include hepatic lipase defect, LCAT defect and Lp(a) excess and Wolman's disease

Type	*Lipoprotein fraction elevated*	*Cholesterol level*	*TAG level*	*Appearance of plasma after 24 hr*	*Metabolic defect*	*Features*	*Management*
Type I	Chylomicrons	N	↑↑	Creamy layer over clear plasma	Lipoprotein lipase deficiency	Eruptive xanthoma; hepatomegaly; Pain abdomen.	Restriction of fat intake. Supplementation with MCT
Type II A	LDL	↑↑	N	Clear	LDL Receptor defect; Apo B ↑	Atherosclerosis, coronary artery disease, Tuberous xanthoma	Low cholesterol diet. Decreased intake of saturated fat. Give PUFA and drugs like statins.
Type II B	LDL and VLDL	↑↑	↑	Slightly cloudy	Apo B ↑ Apo CII	Corneal arcus	Do
Type III	Broad beta-VLDL and Chylomicrons	↑↑	↑	Cloudy	Abnormal apo-E; Apo CII ↑	Palmar xanthoma. High incidence of vascular disease	Reduction of weight, restriction of fat and chol. Give PUFA and drugs
Type IV	VLDL	↑	↑↑	Cloudy or milky	Over production of VLDL; Apo CII ↑	Associated with diabetes, heart disease, obesity.	Reduction of body weight. Restrict carbo hydrate and cholesterol
Type V	VLDL Chylomicrons	N	↑↑	Creamy layer over milky plasma	Secondary to other causes	Chronic pancreatitis	High PUFA intake, hypocholipidemic drug

	premature coronary heart diseases
Wolman's disease	Deficiency of cholesterol ester hydrolase in lysosomes; VLDL

Lecithin cholesterol acyltransferase deficiency (LCAT deficiency)

It is a disorder of lipoprotein metabolism.

Autosomal recessive

Lecithin cholesterol acyltransferase catalyzes the formation of cholesterol esters in lipoproteins

A deficiency of LCAT causes accumulation of unesterified cholesterol in certain body tissues. Cholesterol effluxes from cells as free cholesterol and is transported in HDL as esterified

cholesterol. LCAT is the enzyme that esterifies the free cholesterol on HDL to cholesterol ester and allows the maturation of HDL. LCAT deficiency does not allow for HDL maturation resulting in its rapid catabolism of circulating apoA-1 and apoA-2. The remaining form of HDL resembles nascent HDL

Symptoms include visual impairment caused by diffuse corneal opacities, target cell hemolytic anemia, and renal failure. Less common symptoms include atherosclerosis, hepatomegaly (enlarged liver), splenomegaly (enlarged spleen), and lymphadenopathy.

	Serum cholesterol	*Serum triglyceride*
Diabetes	Increased	Increased
Nephrotic syndrome	Increased	Increased
Hypothyroidism	Increased	Increased
Biliary obstruction	Increased	Normal
Pregnancy	Normal	Increased
Alcoholism	Normal	Increased
Oral contraceptives	Normal	Increased

HYPERCHOLESTEROLEIMA

Increase in plasma cholesterol (> 200 mg/dl) concentration i s known as hypercholesterolemia and is observed in many disorders

1. Diabetes mellitus : Due to increased cholesterol synthesis since the availability of acetyl CoA is ncreased.
2. Hypothyroidism (myxoedema) : This is believed to be due to decrease in the HDL receptors on hepatocytes
3. Obstructive jaundice : Due to an obstruction in the excretion of cholesterol through bile.
4. Nephrotic syndrome : Increase in plasma globulin concentration is the characteristic feature of nephrotic syndrome. Cholesterol elevation is due to increase in plasma lipoprotein fractions in this disorder

Hypercholesterolemia is associated with atherosclerosis and coronary heart disease.

Bad cholesterol and good cholesterol :

Cholesteroli s a natural metabolite performing a wide range of functions (membrane structure, precursor for steroid hormones, bile acids).The cholesterol in high concentration present in LDL,i s considered bad due to its involvement in altherosclerosis and related complications. Thus, LDL may be regarded as lethally dangerous Iipoprotein. On the other hand, HDL cholesterol is good since its high concentration counter acts atherogenesis. HDL may be considered as highly desirable lipoprotein

Control of hypercholesterolemia

Severalmeasures a re advocated to lower the plasma cholesterol level

1. Consumption of PUFA :

   Dietary intake of pofyunsaturated fatty acids (PUFA) reduces the plasma cholesterol level. PUFA will help in transport of cholesterol by LCAT mechanism and its excretion from the body. The oils with rich PUFA content include cottonseedo il, soyab eano il, sunflowero il, corn oil, fish oils etc. Chee and coconut oil are poor sources of PUFA.

2. Dietary cholesterol :

   Cholesterol is found mainly in animal foods and not in plant foods. Dietary cholesterol influence on plasma cholesterol is minimal. However, avoidance of cholesterol-rich foods is advocated to be on the safe side

3. Plant sterols :

   Certain plant sterols and their esters(e.g.sitostanol esters) reduce plasma cholesterol levels. They inhibit the intestinal absorption of dietary cholesterol

4. Avoiding high carbohydrate diet :

   Diets rich in carbohydrates (particularly sucrose) should be avoided to control hvpercholesterolemia.

5. lmpact of lifestyles :

   Elevation in plasma cholesterol is obseved in people with smoking, abdominal obesity,I ack of exercise,stress,high blood pressure,c onsumptiono f soft water etc. Therefore adequate changesi n the lifestyles will bring down plasma cholesterol.

6. Dietary fiber :

   Fiber present in vegetables decreases the cholesterol absorption from the intestine.

7. Moderate alcohol cosumption :

   The beneficial effects of moderate alcohol intake are masked by the ill effects of chronic alcoholism. Red wine is particularly beneficial due to its antioxidants,besides low alcohol content.

8. Use of drugs :

   Drugs such as lovastatin which inhibit HMC CoA reductase and decrease cholesterols synthesis are used. Statins currently in use include atorvastatin, simvastatin and pravastatin. Certain drugs-cholestyramine and colestipol-bind with bile acids and decrease their intestinal reabsorption. This helps in the conversion of more cholesterol to bile acids and its excretion through feces. Clofibrate increases the activity of lipoprotein lipase and reduces the plasma cholesterol and triacylglycerols.

ATHEROSCLEROSIS

- Atherosclerosis (Greek athere-mush) is a complex disease characterized by thickening or hardening of arteries due to the accumulation of lipids (particularly cholesterol) collagen, fibrous tissue, proteoglycans, calcium deposits etc. in the inner arterial wall.
- Atherosclerosis is a progressive disorder that narrows and ultimately blocks the arteries. lnfarction is the term used to indicate the stoppage of blood flow resulting in the death of affected tissue.
- Coronary arteries--the arteries supplying blood to heart-are the most commonly affected leading to myocardial infarction or heart attacks.

Atherosclerosis and LDL

Stage I: Formation of foam cells:

- Increased levels of cholesterol for prolonged periods will favour deposits in the subintimal region of arteries.
- Aorta, coronary arteries and cerebral vessels are predominantly affected by the atherosclerotic process.
- The LDL cholesterol, especially oxidized LDL particles are deposited in the walls of arteries.
- Plasma LDL is mainly catabolized via apo-B LDL receptor pathway.
- But a small part of LDL particles are degraded by nonspecific uptake of macrophages.
- Free radical induced oxidative damage of LDL will accelerate this process.
- Later, the macrophages become overloaded with cholesterol, and these are then called "foam cells".
- These form the hallmark of atherosclerotic plaques.

Stage II: Progression of atherosclerosis:

- Smooth muscle cells containing lipid droplets are seen in the lesion.
- During early stages of atherosclerosis, the condition is reversible if plasma lipid levels, especially LDL-cholesterol levels are lowered.
- But when lipid accumulates, the lesion progresses unchecked and the arterial changes become irreversible.

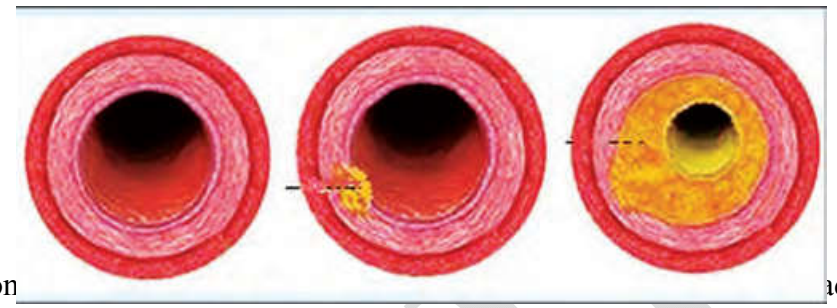
Stage III: Fibrous proliferation:

- Due to liberation of various growth factors by macrophages and platelets.
- Lipoproteins, glycosaminoglycans and collagen are accumulated.
- Thus there is a definite component of inflammation in atherosclerosis.
- This chronic infection leads to increased plasma high sensitive C-reactive protein (hs-CRP)

Stage IV: Advancing fibrous plaque:

- This leads to narrowing of vessel wall (Fig. 25.3).

- The blood flow through the narrow lumen is more turbulent and there is tendency for clot formation.
-



Left, cut section advanced plaque formation

Myocardial Infarction (MI)

- Finally, a clot is formed which obstruct one of the major vessels.
- Thrombosis in coronary artery leads to ischemia of the tissue supplied, due to hindrance to oxygen supply
- Finally infarction (death of tissue) occurs.
- Along with this ischemia (decreased blood supply), instead of the normal aerobic conditions, anerobic glycolysis takes preponderance.
- This leads to decreased ATP, increased NADH, accumulation of lactic acid and decreased pH in cardiac muscle cells.
- Net result is inefficient contraction of heart muscle, and if allowed to progress further, death of the muscle cells in the affected region.

- Usually the diagnosis can be made from the clinical history, the electrocardiogram and cardiac markers (troponin T, CK-MB, etc,
- Size of the infarct may be reduced by immediate administration of Tissue plasminogen activator (t-PA)

PLASMA LIPID PROFILE

- The sample of serum should be taken after 12–14 hours of fasting. In laboratories, lipid profile is assessed by estimating the following fractions in plasma.
  1. Total cholesterol
  2. HDL-cholesterol
  3. LDL-cholesterol
  4. Triglycerides
- In special cases, the following apoproteins are also estimated.
  5. Apo-B level
  6. Apo-A-I level
  7. Lp(a) level
- Abnormal levels of serum cholesterol are seen is certain conditions; these are listed below

  1.Diabetes mellitus: Acetyl CoA pool is increased and more molecules are channeled to cholesterol.

  2. Obstructive jaundice: The excretion of cholesterol through bile is blocked.

  3. Hypothyroidism:

  4. Nephrotic syndrome: Albumin is lost through urine, globulins (including lipoproteins) are increased as a compensatory mechanism.

  5. Familial hyper lipoproteinemias:

RISK FACTORS FOR ATHEROSCLEROSIS

Total Cholesterol

level below 200 mg/dl (In healthy persons, cholesterol level varies from 150 to 200 mg/dL . If other risk factors are present, cholesterol level should be kept preferably below 180 mg/dL. Values around 220 mg/dL will have moderate risk and values above 240 mg/dL will need active treatment)

LDL cholesterol

Should be below 130mg/dL

HDL-cholesterol

The atheroprotective HDL-cholesterol should be more than 40mg/dL in males and >50 mg/dL in females

Serum Triglyceride

Normal level is 50–150 mg/dL. Blood level more than 150 mg/dL is injurious to health.

Apoprotein Levels and Ratios

Apo A-I is a measure of HDL-cholesterol (good) and apo B measures LDL-cholesterol (bad). Ratio of Apo B : A-I is the most reliable index. The ratio of 0.4 is very good; the ratio 1.4 has the highest risk of cardiovascular accidents

.

Lp(a)

Lp(a) inhibits fibrinolysis. Levels more than 30 mg/dL increase the risk 3 times; and when increased Lp(a) is associated with increased LDL, the risk is increased 6 times. Nicotinic acid will reduce serum

Non-HDL Cholesterol

A value of more than 160 mg/dL carries high risk

High Sensitivity C Reactive Protein (hsCRP)

It is a marker for risk for atherosclerosis and is used as a predictor for future myocardial infarction within the next 12 months. Less than 1 mg/L (0.1 mg/dL) is considered as low risk and single measurement is sufficient. Levels between 1–3 mg/L are border line, indicating some risk, and will need assessment of serial samples at 1 week intervals. Levels more than 3 mg /L is having high risk for future MI, and will need active medical intervention

Homocysteine Level

Plasma homocysteine above 15 m/L will increase the riskof coronary artery disease and stroke at a younger age.

Administration of pyridoxine, vitamin B12 and folic acid may lower the homocysteine level, but may not have any substantial benefit on clinical outcome.

Diabetes Mellitus

Diabetes is associated with an increase in small LDL particles, high TAG and low HDL levels. In the absence of insulin, hormone sensitive lipase is activated, more free fatty acids are formed, which are catabolized to produce acetyl CoA. These cannot be readily utilized, as the availability of oxaloacetate is reduced and citric acid cycle is sluggish. So acetyl CoA pool is increased, and it is channelled to cholesterol synthesis

Other factors

- Cigarette smoking
- Hypertension
- Obesity and sedentary Life style
- Long chain saturated fatty acid

PREVENTION OF ATHEROSCLEROSIS

Almost 90% of CAD is predictable, preventable and curable. Lifestyle changes are require, which include regular exercise, balanced diet, cessation of smoking, maintaining proper weight, control of hypertension, diabetes and dyslipidemia. The aim is to reduce total cholesterol below 180 mg/dL; to decrease LDL-cholesterol below 130 mg/dl and to keep HDL-cholesterol above 35 mg/dL

(refer measures advocated to lower the plasma cholesterol level above)

FATTY LIVER

- Fatty liver is a reversible condition wherein large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis (i.e., abnormal retention of lipids within a cell).
- Excessive alcohol intake and the obesity (with or without effects of insulin resistance) are the leading cause of this disease
- The condition is also associated with other diseases that influence fat metabolism. When this process of fat metabolism is disrupted, the fat can accumulate in the liver in excessive amounts, thus resulting in a fatty liver
- It is difficult to distinguish alcoholic FLD from nonalcoholic FLD, and both show microvesicular and macrovesicular fatty changes at different stages.
- Accumulation of fat may also be accompanied by a progressive inflammation of the liver (hepatitis), called steatohepatitis.

By considering the contribution by alcohol, fatty liver may be termed alcoholic fatty liver or nonalcoholic fatty liver disease (NAFLD), and the

more severe forms as alcoholic steatohepatitis (part of alcoholic liver disease) and non-alcoholic steatohepatitis (NASH).

Causes

Fatty liver (FL) is commonly associated with alcohol or metabolic syndrome (diabetes, hypertension, obesity, and dyslipidemia), but can also be due to any one of many causes

Metabolic

abetalipoproteinemia, glycogen storage diseases, , acute fatty liver of pregnancy, lipodystrophy

Nutritional

Drugs and toxins like methotrexate, expired tetracycline, highly active antiretroviral therapy, glucocorticoids, environmental hepatotoxins (e.g., phosphorus, mushroom poisoning)

Alcoholic

Alcoholism is one of the major cause of fatty liver due to production of toxic metabolites like aldehydes during metabolism of alcohol in the liver. This phenomenon most commonly occurs with chronic alcoholism.

Other

celiac disease,[inflammatory bowel disease, HIV, hepatitis C and alpha 1-antitrypsin deficiency

Mechanism leading to hepatic steatosis

Defects in fatty acid metabolism are responsible for pathogenesis of FLD, which may be due to imbalance in energy consumption and its combustion, resulting in

lipid storage, or can be a consequence of peripheral resistance to insulin, whereby the transport of fatty acids from adipose tissue to the liver is increased

Impairment or inhibition of receptor molecules (PPAR-α, PPAR-γ and SREBP1) that control the enzymes responsible for the oxidation and synthesis of fatty acids appears to contribute to fat accumulation.

In addition, alcoholism is known to damage mitochondria and other cellular structures, further impairing cellular energy mechanism.

On the other hand, non-alcoholic FLD may begin as excess of unmetabolised energy in liver cells. Hepatic steatosis is considered reversible and to some extent nonprogressive if the underlying cause is reduced or removed.

steatohepatitis

Severe fatty liver is sometimes accompanied by inflammation, a situation referred to as steatohepatitis.

Steatosis (retention of lipid) and onset of steatohepatitis may represent successive stages in FLD progression.

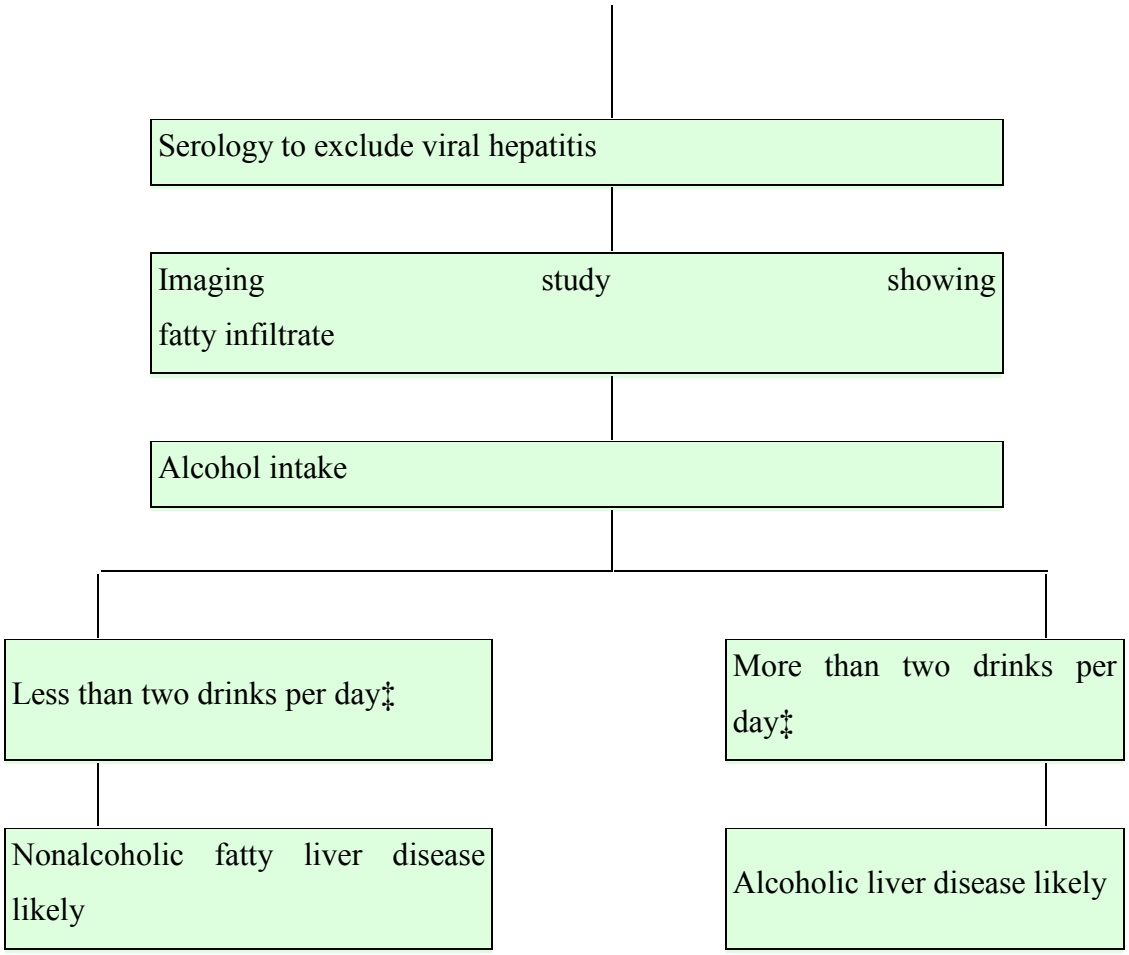
Liver disease with extensive inflammation and a high degree of steatosis often progresses to more severe forms of the disease

It can lead to hepatic fibrosis or cirrhosis

The progression to cirrhosis may be influenced by the amount of fat and degree of steatohepatitis and by a variety of other sensitizing factors. In alcoholic FLD, the transition to cirrhosis related to continued alcohol consumption is well-documented, but the process involved in non-alcoholic FLD is less clear.

Flow chart for diagnosis, modified from

Elevated liver enzyme



‡ Criteria for nonalcoholic fatty liver disease: consumption of ethanol less than 20 g/day for women and 30 g/day for men

- Most individuals are asymptomatic and are usually discovered incidentally because of abnormal liver function tests or hepatomegaly noted in unrelated medical conditions.
- Elevated liver biochemistry is found in 50% of patients with simple steatosis.

- The serum alanine transaminase level usually is greater than the aspartate transaminase level in the nonalcoholic variant and the opposite in alcoholic FLD (AST:ALT more than 2:1).
- Imaging techniques

Treatment

- The treatment of fatty liver depends on its cause, and, in general, treating the underlying cause will reverse the process of steatosis if implemented at an early stage.
- Two known causes of fatty liver disease are an excess consumption of alcohol and a prolonged diet containing foods with a high proportion of calories coming from lipids
- For the patients with non-alcoholic fatty liver disease with pure steatosis and no evidence of inflammation, a gradual weight loss is often the only recommendation
- In more serious cases, medications that decrease insulin resistance, hyperlipidemia, and those that induce weight loss have been shown to improve liver function

LIVER CIRRHOSIS

A chronic disease of the liver marked by degeneration of cells, inflammation, and fibrous thickening of tissue. It is typically a result of alcoholism or hepatitis. It is a condition in which the liver does not function properly due to long-term damage. Early on, there are often no symptoms.

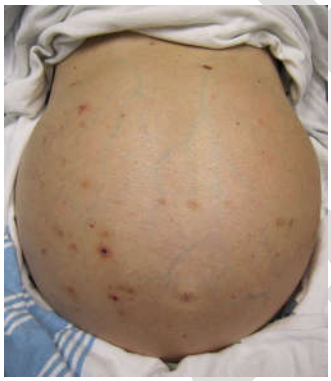
As the disease worsens, a person may become tired, weak, itchy, have swelling in the lower legs, develop yellow skin, bruise easily, have fluid build up in the abdomen, or develop spider-like blood vessels on the skin.

The fluid build-up in the abdomen may become spontaneously infected.

Other complications include hepatic encephalopathy, bleeding from dilated veins in the esophagus or dilated stomach veins, and liver cancer.

Hepatic encephalopathy results in confusion and possibly unconsciousness.

- Cirrhosis is most commonly caused by alcohol, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease.
- Typically, more than two or three drinks per day over a number of years is required for alcoholic cirrhosis to occur.
- Non-alcoholic fatty liver disease is due to a number of reasons, including being overweight, diabetes, high blood fats, and high blood pressure. A number of less common causes include autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, certain medications, and gallstones.
- Cirrhosis is characterized by the replacement of normal liver tissue by scar tissue. These changes lead to loss of liver function. Diagnosis is based on blood testing, medical imaging, and liver biopsy.



SIGNS AND SYMPTOMS

Liver cirrhosis.

Cirrhosis has many possible manifestations.

These signs and symptoms may be either as a direct result of the failure of liver cells or secondary to the resultant portal hypertension.

Weakness and loss of weight may be early symptoms.

Liver dysfunction

- The following features are as a direct consequence of liver cells not functioning.
- Spider angiomata
- Palmar erythema
- Gynecomastia,
- Hypogonadism,.
- Liver size can be enlarged, normal, or shrunken in people with cirrhosis.
- Ascites, accumulation of fluid in the peritoneal cavity (space in the abdomen),
- Fetor hepaticus is a musty breath odor resulting from increased dimethyl sulfide.
- Urine may also appear dark.

Portal hypertension

- Liver cirrhosis increases resistance to blood flow and higher pressure in the portal venous system, resulting in portal hypertension. Effects of portal hypertension include:
- Splenomegaly
- Esophageal varices result from collateral portal blood flow through vessels in the stomach and esophagus (a process called portacaval anastomosis). When these blood vessels become enlarged, they are called varices and are more likely to rupture. Variceal rupture often leads to severe bleeding, which can be fatal.

TREATMENT

Some causes of cirrhosis, such as hepatitis B, can be prevented by vaccination. Treatment partly depends on the underlying cause. The goal is often to prevent worsening and complications. Avoiding alcohol is recommended. Hepatitis B and C may be treatable with antiviral medications. Autoimmune hepatitis may be treated with steroid medications. In severe cirrhosis, a liver transplant may be an option

Lipotropic Factors

They are required for the normal mobilization of fat from liver. Therefore deficiency of these factors may result in fatty liver. They can afford protection against the

development of fatty liver.

1. Choline: Feeding of choline has been able to reverse
fatty changes in animals.

2. Lecithin and methionine. They help in synthesis of apoprotein and choline formation. The deficiency of methyl groups for carnitine synthesis may also hinder
fatty acid oxidation.

3. Vitamin E and selenium give protection due to their antioxidant effect.

4. Omega-3 fatty acids present in marine oils have a protective effect against fatty liver. Methionine levels also affect the amount of sulfur-containing compounds, such as glutathione, in the liver. Glutathione and other sulfur-containing peptides (small proteins) play a critical role in defending against toxic compounds. When higher levels of toxic compounds are present, more methionine is needed.

Choline assists detoxification reactions in the liver. Though choline can be synthesized from methionine or serine, recent evidence indicates that choline is an essential nutrient.

Betaine hydrochloride is a powerful lipotropic and increases gastric acid.[2] Betaine itself (in a non-hydrochloric form, also known as TMG or Trimethylglycine) also has a lipotropic effect.[3]

Oxibetaine is another agent listed as a lipotropic compound.

POSSIBLE QUESTIONS

1. Explain the types and causes of hyperlipoproteinemia.
2. Write a note on hypolipoproteinemias.
3. Explain the causes, clinical manifestations diagnosis of atherosclerosis.
4. Write a note on liver cirrhosis.
5. Write a note on fatty liver.
6. Discuss on the biochemical abnormalities of lipoprotein.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III-B.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (15BCU601)
MULTIPLE CHOICE QUESTIONS

UNIT III

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	The drug of choice for the treatment of primary gout is	Allopurinol	Xanthine	Lysine	Paracetamol	Allopurinol
2	_____ is a structural analog of hypoxanthine that competitively inhibits the enzyme xanthine oxidase	Leucine	Allopurinol	Tyrosine	Hypoxanthine	Allopurinol
3	The antiinflammatory drug colchicine is used for the treatment of	Rheumatoid arthritis	Goutyarthritis	Alloxanthine	Xanthinuria	Goutyarthritis
4	Lesh-Nyhan syndrome is due to the deficiency of	Xanthine oxidase	Purine nucleoside phosphorylase	Hypoxanthine - guanine phosphoribosyl transferase	Adenosine deaminase	Hypoxanthine - guanine phosphoribosyl transferase
5	Lesh-Nyhan syndrome is a	Chromosomal abnormality	Immunodeficiency disease	Sex linked metabolic disorder	Hereditary disorder	Immunodeficiency disease
6	Structural gene for HGPRT is located on the	Y chromosome	X chromosome	X and Y chromosome	Z chromosome	X chromosome
7	Lesh-Nyhan syndrome is commonly seen in	Females	Males	Male and Female	Monkey	Males
8	The symptoms of Lesh-Nyhan syndrome are	Mental retardation	Aggressive behavior	Learning disability	Mental retardation, aggressive behavior and learning disability	Mental retardation, aggressive behavior and learning disability
9	The patients of lesch - Nyhan syndrome have an irrestible urge to	Bite their hands	Bite their fingers and lips	Bite their legs	Bite their fingers, hands and lips	bite their fingers and lips
10	orotic aciduria is characterized by the excretion of _____ in urine	Xanthine	Urea	Uricacid	Oroticacid	Oroticacid
11	Severe anemia and retarded growth are seen in	Gout	Lesch-Nyhan syndrome	Oroticacid urea	Hyperuricemia	Oroticacid urea
12	The deficiency of orotate phospho ribosyl transferase causes _____	Feeding diet rich in uridine/cytidine	Feeding diet rich in alanine	feeding diet rich in Xanthine	Feeding diet rich in guanine	Feeding diet rich in uridine/cytidine
13	Secondary orotic aciduria is otherwise called as	Lesch - Nyhan syndrome	Reyes syndrome	Xanthinuria	Reyes syndrome and Xanthinuria	Reyes syndrome
14	_____ deficiency causes secondary orotic aciduria	Ornithine transcarbamoylase	HGPRT	Deaminase	Transaminase	Ornithine transcarbamoylase
15	xanthinuria frequently causes the formation of _____stress in urinary tract	Xanthine stores	Cobalt	Magnesium	Calcium	Xanthine stores
16	The deficiency of xanthine oxidase causes	Xanthinuria	Hypouricemia	Xanthinuria and hypouricemia	Reyes syndrome	Xanthinuria
17	Decreased uric acid in the serum represent	Hypouricemia	Hyperuricemia	Xanthinuria	Oroticaciduria	Hypouricemia
18	Hypo xanthine and xanthine are ---------- --- hence easily excreted	Soluble	Insoluble	Not soluble	Sparingly soluble	Soluble
19	Name of the structural analog of hypoxanthine	Xanthine	Allopurinol	Glutamine	Xanthine, allopurinol and glutamine	Allopurinol
20	The normal serum total bilirubin concentration is in the range of	0.4 - 0.8 mg/dl	0.4 - 1.0 mg/dl	0.2 - 0.8 mg/dl	0.5 - 0.7 mg/dl	0.4 - 1.0 mg/dl
21	Jaundice is a clinical condition characterized by yellow colur of the _____ and _____	Eyes and skin	Face	Hands	Head	Eyes and skin
22	The term hyperbilirubenemia is often used to represent the increased concentration of	Serum bilirubin	Serum creatinine	Serum urea	Serum uric acid	Serum bilirubin
23	hemolytic jaundice is a condition associated with increased hemolysis of	Erythrocytes	WBC's	Platelets	Macrophages	Erythrocytes
24	Dysfunction of the liver causes	Hemolytic jaundice	Hepatic jaundice	Obstructive jaundice	Hemolytic and hepatic jaundice	Hepatic jaundice
25	Hepato cellular jaundice is due to damage to	Mast cells	Hepatocytes	Neutrophils	Macrophages	Hepatocytes
26	Hepatitis B virus produces a disease known as	Homologous serum jaundice	Heterologous	Wilson's disease	Chronic alcoholism	Homologous serum jaundice
27	Post hepatic jaundice is due to an obstruction of bile flow between the	Liver and duodenum	Liver and intestine	Small intestine and ileum	Liver and jejunum	Liver and duodenum
28	Obstructive jaundice is otherwise called as	Regurgitation jaundice	Retardation jaundice	Hemolytic jaundice	Hepatic jaundice	Regurgitation jaundice
29	The othername of jaundice is called as	Icterus	jaune - yellow	Icterus and Jaune yellow	Albinism	Icterus and Jaune yellow
30	crigler - Najjar syndrome type I is also known as	congenital non-hemolytic jaundice	obstructive jaundice	neo-natal physiologic jaundice	All the above	congenital non-hemolytic jaundice
31	crigler - Najjar syndrome type I is caused by the defect of the enzyme	udp-glucuronyl transferase	UTP -glucuronyl transferase	bilirubin glucuronyl transferase	biliverdin glucuronyl transferase	udp-glucuronyl transferase
32	The children affected with crigler - Najjar syndrome I die within the first _____ of life	2	5	4	3	2
33	crigler najjar syndrome type II is due to severe defect in the	biliverdin conjugation	bilirubin conjugation	bilirubin diglucuronide	all the above	bilirubin conjugation
34	Gilberts disease is a disease with combination of	single disorder	multiple disorders	tripe disorders	All the above	tripe disorders

35	crigler najjar syndrome the bilirubin concentration falls within	20 mg/dl	50 mg/dl	60 mg/dl	10 mg/dl	20 mg/dl
36	_____ is the end product of purine metabolism in human	urea	creatine	orotic acid	uric acid	uric acid
37	The normal serum uric acid concentration is in the range of	3 - 7 mg/dl	9 - 10mg/dl	11 - 12 mg/dl	1- 2 mg/dl	3 - 7 mg/dl
38	Hyper uricemia refers to an elevation in the serum _____ concentration	ammonia	urea	uric acid	creatinine	uric acid
39	The excretion of uric acid is otherwise called as	glycosuria	uricosuria	anemia	emotional glycosuria	uricosuria
40	Deposits of uric acid in the joints is called as	uricosuria	goutyarthritis	tophi	arthritis	tophi
41	Historically gout was found to be often associated with	high living	over eating	alcohol consumption	High living, over eating and alcohol consumption	High living, over eating and alcohol consumption
42	primary gout is _____ due to over production of uric acid	in born error of metabolism	impairment of kidneys	increase in the synthesis of uric acid	liver impairment	in born error of metabolism
43	HGPRT is an enzyme of	purine salvage pathway	pyrimidine biosynthesis	denovo pathway of purine synthesis	All the above	purine salvage pathway
44	The end product of purine metabolism in humans is	xanthine	uric acid	urea	allantoin	uric acid
45	An enzyme of purine metabolism associated with immunodeficiency disease	adenosine deaminase	xanthine oxidase	PRPP synthetase	HGRPT	adenosine deaminase
46	_____ the drug used for effective treatment for gout	ibuprofen	paracetamol	avil	amoxilin	ibuprofen
47	In crigler -Najjar syndrome the bilirubin concentration falls within	20 mg/dl	50mg/dl	100 mg/dl	10 mg/dl	20 mg/dl
48	gilberts syndrome is a _____ group of diseases	homogenous	hetrogenous	mixed	single	hetrogenous
49	gilberts syndrome is associated with	uncojugated hyper bilirubinaemia	hypouricemia	conjugated hyper bilirubinaemia	hyperuricemia	uncojugated hyper bilirubinaemia
50	The causes for gilberts syndrome include	reduced glucuronyl transferase activity	defect in hepatic clearance of bilirubin	defect in uptake of bilirubin by liver cells	All the above	All the above
51	the bilirubin level in gilberts syndrome is	<3 mg /dl	<6mg/dl	< 4mg/dl	< 5mg/dl	<3 mg /dl
52	Dubin - johson syndrome is characterised by	conjugated hyper bilirubinaemia	child hood jaundice	adult life jaundice	Conjugated hyper bilirubinaemia, child hood jaundice and adult life jaundice	Conjugated hyper bilirubinaemia, child hood jaundice and adult life jaundice
53	The symptoms of gilbert syndrome is	fatigue	weakness	abdominal pain	Fatigue, weakness and abdominal pain	Fatigue, weakness and abdominal pain
54	In gilberts disease there is defect in secretion of _____ in bile	unconjugated bilirubin	conjugated bilirubin	direct bilirubin	total bilirubin	conjugated bilirubin
55	Hemolysis is the one of the symptom of	gilberts syndrome	jaundice	Dubin - johnson syndrome	gout	gilberts syndrome
56	_____ therapy has been found useful in curing crigler - NAjjar syndrome	Radiation	photo	chemo	Radiation and chemo	photo
57	Type II crigler - Najjar syndrome is a _____	Mutation	hereditary disorder	rare inherited disorder	none of the above	rare inherited disorder
58	Bile of type II crigler - Najjar syndrome patients found to contain _____	bilirubin diglucuronide	bilirubin monoglucuronide	biliverdin	bile pigments	bilirubin monoglucuronide
59	Patients with crigler Najjar syndrome repond to treatment with large doses of	aspirin	acetamide	phenobarbitone	chloroform	phenobarbitone
60	Type II crigler Najjar syndrome is characterised by _____ in bilirubin conjugating system	chronic defect	severe defect	moderate defect	mild effect	mild effect

UNIT-III

SYLLABUS

Disorders of Purine and Pyrimidine metabolism: Clinical manifestation, biochemical abnormalities, Hyper uricemia- Gout, Lesch-Nyhan syndrome, Von-Gierke's disease. Hypo uricemia – xanthinuria; Orotic aciduria.

Disorders of Bilirubin metabolism: Definition, clinical manifestation, Jaundice- types, biochemical abnormalities of Criggler-Najjar syndrome. Gilbert's disease and Dubin Johnson disease.

Disorders of Purine and Pyrimidine metabolism

Uric acid metabolism:

Uric acid exists as sodium ureate in plasma. Maximum amount of sodium ureate that can dissolve in the blood plasma is about 7 mg/100 ml. At this point there will be saturation of blood with sodium ureate. Above this it gets precipitated. Uric acid concentration does not vary with greater intake of uric acid in the diet because on intake of higher concentration in the diet the synthesis of uric acid in the body will be inhibited. Hence there is a balanced amount of uric acid in the body.

Miscible pool of uric acid:

Total amount of uric acid present in the body in the dissolved state in males is 3.4 to 7.0 mg/dl and in females it is 2.4 to 5.7 mg/dl.

Modes of excretion:

It is excreted in urine by glomerular filtration. Amount excreted is 250 to 750 mgs/day. It is also excreted through bile, to about $1/5^{th}$ of the total amount into the intestine. In the intestine it will be converted to CO_2 and NH_3 either by action of intestinal flora or autoxidation of the uric acid.

Estimation of blood uric acid in ureotelic animals has importance in the diagnosis of gout and Von-Gierke's disease.

Purine & Pyrimidine Nucleotide

Biosynthesis Are Coordinately Regulated

Purine and pyrimidine biosynthesis parallel one another mole for mole, suggesting coordinated control of their biosynthesis. Several sites of cross-regulation characterize purine and pyrimidine nucleotide biosynthesis. The PRPP synthase reaction, which forms a precursor essential for both processes, is feedback-inhibited by both purine and pyrimidine nucleotides.

Humans catabolize purines to uric acid

Humans convert adenosine and guanosine to uric acid. Adenosine is first converted to inosine by adenosine deaminase. In mammals other than higher primates, uricase converts uric acid to the watersoluble product allantoin. However, since humans lack uricase, the end product of purine catabolism in humans is uric acid.

Conditions varying the blood levels of uric acid:

Gout:

If the concentration of uric acid exceeds 7 mg/100 ml in the blood plasma, the uric acid gets precipitated as sodium ureate crystals that cannot be excreted hence gets deposited in the soft tissues. There is abnormal deposition in joints and tendons. This abnormal deposition of sodium ureate crystals in soft tissue is known as TOPHI. Because of this the tissue gets degraded or degenerated at the bone joints leading to degeneration of neighbouring tissues as well. Degeneration causes inflammation of the joint.

Gouty arthritis:

Generally the metacarpal phalangeal joints and metatarsal phalangeal joints are affected by this gout. Knee joint is also affected.

There are two types of gout:

1. Primary Gout:

Enzyme 'PRPP synthetase' shows altered kinetics leading to overproduction of PRPP and hence overproduction of purines.

2. Secondary gout:

This is due to—

(i) Excess catabolism of purine as in polycythemia.

(ii) Decreased excretion of uric acid as in renal failure.

Gout can be controlled by—

1. Uricosuric drugs like salicylates, cinchopher, adrenal cortical hormones, which cause increased excretion of uric acid in urine by decreasing its re-absorption.

2. Allopurinol (Allantoin) a structural analogue to hypoxanthine which competitively inhibits xanthine oxidase and decreases the production of uric acid.

Von-Gierke's disease:

In this disease there is an overproduction of uric acid. The HMP shunt pathway is overactive due to the deficiency of glucose-6-phosphatase thereby producing excessive amounts of ribose-5-phosphate. This leads to the overproduction of PRPP, hence the uric acid.

Purine overproduction and hyperuricemia in von Gierke's disease (glucose-6-phosphatase deficiency) occurs secondary to enhanced generation of the PRPP precursor ribose 5-phosphate. An associated lactic acidosis elevates the renal threshold for urate, elevating total body urates

Methods of estimation:

Phosphotungstic acid method, Fehling's method and Auto analyzer.

Conditions varying the blood level of uric acids:

Whenever there is cell death, the nucleic acids are released and converted to purines and finally uric acid is formed.

The conditions where uric acid level increases in the blood are:

(a) Excessive tissue destruction and

(b) Gout.

Excessive tissue destruction:

Is seen in—

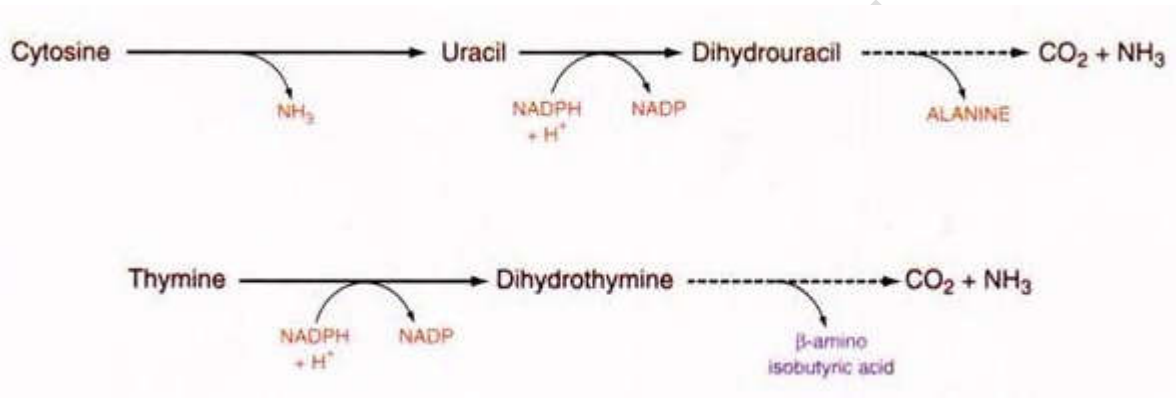
1. Old age
2. Febrile diseases
3. Hypoxia
4. Trauma

5. Kidney dysfunction or total renal failure

6. High non-vegetarian diets

2. Pyrimidine Nucleoside:

Pyrimidine nucleosides are catabolized in the liver. The products of breakdown of pyrimidine ring are ammonia and CO_2 which are converted into urea for excretion.



Lesch-Nyhan syndrome

Lesch-Nyhan syndrome is a condition that occurs almost exclusively in males. It is characterized by neurological and behavioral abnormalities and the overproduction of uric acid. Uric acid is a waste product of normal chemical processes and is found in blood and urine. Excess uric acid can be released from the blood and build up under the skin and cause gouty arthritis (arthritis caused by an accumulation of uric acid in the joints). Uric acid accumulation can also cause kidney and bladder stones.

The nervous system and behavioral disturbances experienced by people with Lesch-Nyhan syndrome include abnormal involuntary muscle movements, such as tensing of various muscles (dystonia), jerking movements (chorea), and flailing of the limbs (ballismus). People with Lesch-Nyhan syndrome usually cannot walk, require assistance sitting, and generally use a wheelchair. Self-injury (including biting and head banging) is the most common and distinctive behavioral problem in individuals with Lesch-Nyhan syndrome. Frequency The prevalence of Lesch-Nyhan syndrome is approximately 1 in 380,000 individuals. This condition occurs with a similar frequency in all populations. Genetic Changes Mutations in the HPRT1 gene cause Lesch-Nyhan syndrome. The HPRT1 gene provides instructions for making an enzyme called hypoxanthine phosphoribosyltransferase 1.

This enzyme is responsible for recycling purines, a type of building block of DNA and its chemical cousin RNA. Recycling purines ensures that cells have a plentiful supply of building blocks for the production of DNA and RNA. HPRT1 gene mutations that cause Lesch-Nyhan syndrome result in a severe shortage (deficiency) or complete absence of hypoxanthine phosphoribosyltransferase 1. When this enzyme is lacking, purines are broken down but not recycled, producing abnormally high levels of uric acid. For unknown reasons, a deficiency of hypoxanthine phosphoribosyltransferase 1 is associated with low levels of a chemical messenger in the brain called dopamine. Dopamine transmits messages that help the brain control physical movement and emotional behavior, and its shortage may play a role in the movement problems and other features of this disorder. However, it is unclear how a shortage of hypoxanthine phosphoribosyltransferase 1 causes the neurological and behavioral problems characteristic of Lesch-Nyhan syndrome. Some people with HPRT1 gene mutations produce some functional enzyme. These individuals are said to have Lesch-Nyhan variant.

The signs and symptoms of Lesch- Nyhan variant are often milder than those of Lesch-Nyhan syndrome and do not include self-injury. Inheritance Pattern This condition is inherited in an X-linked recessive pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Hypouricemia

Hypouricemia and increased excretion of hypoxanthine and xanthine are associated with xanthine oxidase deficiency due to a genetic defect or to severe liver damage. Patients with a severe enzyme deficiency may exhibit xanthinuria and xanthine lithiasis.

Orotic Acidurias

The orotic aciduria that accompanies Reye's syndrome probably is a consequence of the inability of severely damaged mitochondria to utilize carbamoyl phosphate, which then becomes

available for cytosolic overproduction of orotic acid. Type I orotic aciduria reflects a deficiency of both orotate phosphoribosyltransferase and orotidylate decarboxylase, the rarer type II orotic aciduria is due to a deficiency only of orotidylate decarboxylase.

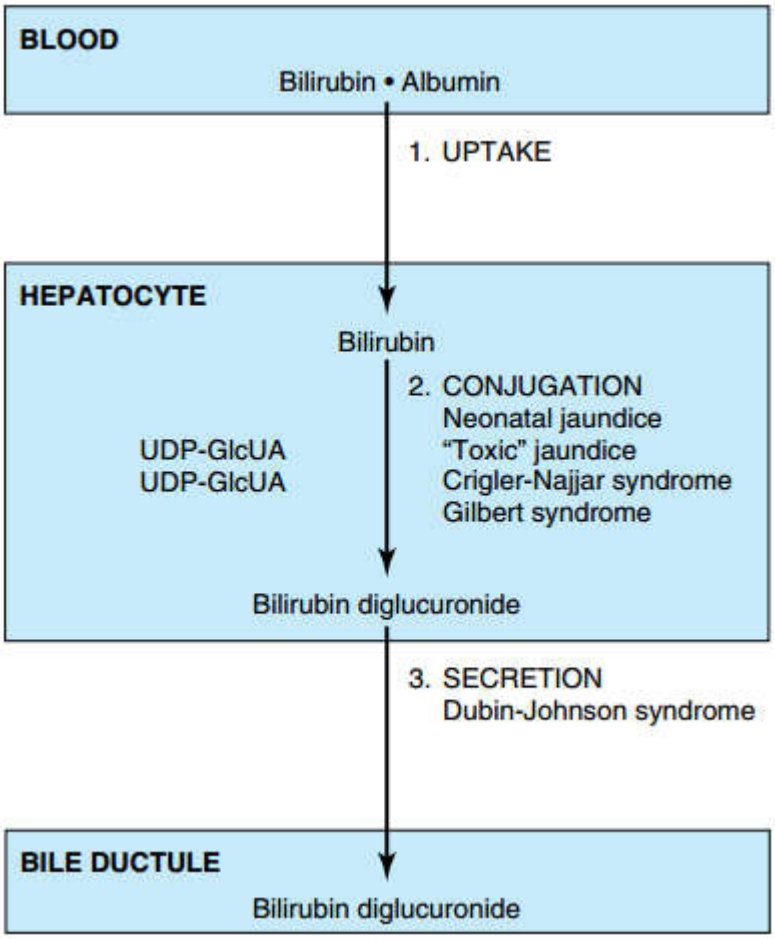
Disorders of Bilirubin metabolism

Bilirubin is only sparingly soluble in water, but its solubility in plasma is increased by noncovalent binding to albumin. Each molecule of albumin appears to have one high-affinity site and one low-affinity site for bilirubin. In 100 mL of plasma, approximately 25 mg of bilirubin can be tightly bound to albumin at its highaffinity site. Bilirubin in excess of this quantity can be bound only loosely and thus can easily be detached and diffuse into tissues. A number of compounds such as antibiotics and other drugs compete with bilirubin for the high-affinity binding site on albumin. Thus, these compounds can displace bilirubin from albumin and have significant clinical effects.

In the liver, the bilirubin is removed from albumin and taken up at the sinusoidal surface of the hepatocytes by a carrier-mediated saturable system. This facilitated transport system has a very large capacity, so that even under pathologic conditions the system does not appear to be rate-limiting in the metabolism of bilirubin.

Since this facilitated transport system allows the equilibrium of bilirubin across the sinusoidal membrane of the hepatocyte, the net uptake of bilirubin will be dependent upon the removal of bilirubin via subsequent metabolic pathways. Once bilirubin enters the hepatocytes, it can bind to certain cytosolic proteins, which help to keep it solubilized prior to conjugation. Ligandin (a family of glutathione S-transferases) and protein Y are the involved proteins. They may also help to prevent efflux of bilirubin back into the blood stream.

Diagrammatic representation of the three major processes (uptake, conjugation, and secretion) involved in the transfer of bilirubin from blood to bile.



Hyperbilirubinemia causes jaundice

When bilirubin in the blood exceeds 1 mg/dL (17.1 μmol/L), hyperbilirubinemia exists. Hyperbilirubinemia may be due to the production of more bilirubin than the normal liver can excrete, or it may result from the failure of a damaged liver to excrete bilirubin produced in normal amounts. In the absence of hepatic damage, obstruction of the excretory ducts of the liver—by preventing the excretion of bilirubin—will also cause hyperbilirubinemia. In all these situations, bilirubin accumulates in the blood, and when it reaches a certain concentration (approximately 2–2.5 mg/dL), it diffuses into the tissues, which then become yellow. That condition is called jaundice or icterus.

In clinical studies of jaundice, measurement of bilirubin in the serum is of great value. A method for quantitatively assaying the bilirubin content of the serum was first devised by van den

Bergh by application of Ehrlich's test for bilirubin in urine. The Ehrlich reaction is based on the coupling of diazotized sulfanilic acid (Ehrlich's diazo reagent) and bilirubin to produce a reddish-purple azo compound. In the original procedure as described by Ehrlich, methanol was used to provide a solution in which both bilirubin and the diazo regent were soluble. Van den Bergh inadvertently omitted the methanol on an occasion when assay of bile pigment in human bile was being attempted. To his surprise, normal development of the color occurred "directly." This form of bilirubin that would react without the addition of methanol was thus termed "directreacting." It was then found that this same direct reaction would also occur in serum from cases of jaundice due to biliary obstruction. However, it was still necessary to add methanol to detect bilirubin in normal serum or that which was present in excess in serum from cases of hemolytic jaundice where no evidence of obstruction was to be found. To that form of bilirubin which could be measured only after the addition of methanol, the term "indirect-reacting" was applied.

It was subsequently discovered that the indirect bilirubin is "free" (unconjugated) bilirubin en route to the liver from the reticuloendothelial tissues, where the bilirubin was originally produced by the breakdown of heme porphyrins. Since this bilirubin is not water-soluble, it requires methanol to initiate coupling with the diazo reagent. In the liver, the free bilirubin becomes conjugated with glucuronic acid, and the conjugate, bilirubin glucuronide, can then be excreted into the bile. Furthermore, conjugated bilirubin, being water soluble, can react directly with the diazo reagent, so that the "direct bilirubin" of van den Bergh is actually a bilirubin conjugate (bilirubin glucuronide).

Depending on the type of bilirubin present in plasma—ie, unconjugated or conjugated—hyperbilirubinemia may be classified as retention hyperbilirubinemia, due to overproduction, or regurgitation hyperbilirubinemia, due to reflux into the bloodstream because of biliary obstruction.

Because of its hydrophobicity, only unconjugated bilirubin can cross the blood-brain barrier into the central nervous system; thus, encephalopathy due to hyperbilirubinemia (kernicterus) can occur only in connection with unconjugated bilirubin, as found in retention hyperbilirubinemia. On the other hand, because of its water-solubility, only conjugated bilirubin can appear in urine. Accordingly, choluric jaundice (choluria is the presence of bile pigments in the urine) occurs only

in regurgitation hyperbilirubinemia, and acholuric jaundice occurs only in the presence of an excess of unconjugated bilirubin.

Elevated Amounts of Unconjugated Bilirubin in Blood Occur in a Number of Conditions

A. HEMOLYTIC ANEMIAS

Hemolytic anemias are important causes of unconjugated hyperbilirubinemia, though unconjugated hyperbilirubinemia is usually only slight (< 4 mg/dL; < 68.4 μmol/L) even in the event of extensive hemolysis because of the healthy liver's large capacity for handling bilirubin.

B. NEONATAL "PHYSIOLOGIC JAUNDICE"

This transient condition is the most common cause of unconjugated hyperbilirubinemia. It results from an accelerated hemolysis around the time of birth and an immature hepatic system for the uptake, conjugation, and secretion of bilirubin. Not only is the bilirubin-UGT activity reduced, but there probably is reduced synthesis of the substrate for that enzyme, UDP-glucuronic acid. Since the increased amount of bilirubin is unconjugated, it is capable of penetrating the blood-brain barrier when its concentration in plasma exceeds that which can be tightly bound by albumin (20–25 mg/dL). This can result in a hyperbilirubinemic toxic encephalopathy, or kernicterus, which can cause mental retardation. Because of the recognized inducibility of this bilirubin-metabolizing system, Phenobarbital has been administered to jaundiced neonates and is effective in this disorder. In addition, exposure to blue light (phototherapy) promotes the hepatic excretion of unconjugated bilirubin by converting some of the bilirubin to other derivatives such as maleimide fragments and geometric isomers that are excreted in the bile.

C. CRIGLER-NAJJAR SYNDROME, TYPE I; CONGENITAL NONHEMOLYTIC JAUNDICE

Type I Crigler-Najjar syndrome is a rare autosomal recessive disorder. It is characterized by severe congenital jaundice (serum bilirubin usually exceeds 20 mg/dL) due to mutations in the gene encoding bilirubin-UGT activity in hepatic tissues. The disease is often fatal within the first 15 months of life. Children with this condition have been treated with phototherapy, resulting in some reduction in plasma bilirubin levels. Phenobarbital has no effect on the formation of bilirubin glucuronides in patients with type I Crigler-Najjar syndrome. A liver transplant may be curative.

D. CRIGLER-NAJJAR SYNDROME, TYPE II

This rare inherited disorder also results from mutations in the gene encoding bilirubin-UGT, but some activity of the enzyme is retained and the condition has a more benign course than type I. Serum bilirubin concentrations usually do not exceed 20 mg/dL. Patients with this condition can respond to treatment with large doses of phenobarbital.

E. GILBERT SYNDROME

Again, this is caused by mutations in the gene encoding bilirubin-UGT, but approximately 30% of the enzyme's activity is preserved and the condition is entirely harmless.

F. TOXIC HYPERBILIRUBINEMIA

Unconjugated hyperbilirubinemia can result from toxin-induced liver dysfunction such as that caused by chloroform, arsphenamines, carbon tetrachloride, acetaminophen, hepatitis virus, cirrhosis, and Amanita mushroom poisoning. These acquired disorders are due to hepatic parenchymal cell damage, which impairs conjugation.

Obstruction in the Biliary Tree Is the Commonest Cause of Conjugated hyperbilirubinemia

A. OBSTRUCTION OF THE BILIARY TREE

Conjugated hyperbilirubinemia commonly results from blockage of the hepatic or common bile ducts, most often due to a gallstone or to cancer of the head of the pancreas. Because of the obstruction, bilirubin diglucuronide cannot be excreted. It thus regurgitates into the hepatic veins and lymphatics, and conjugated bilirubin appears in the blood and urine (choluric jaundice).

The term cholestatic jaundice is used to include all cases of extrahepatic obstructive jaundice. It also covers those cases of jaundice that exhibit conjugated hyperbilirubinemia due to micro-obstruction of intrahepatic biliary ductules by swollen, damaged hepatocytes (eg, as may occur in infectious hepatitis).

B. DUBIN-JOHNSON SYNDROME

This benign autosomal recessive disorder consists of conjugated hyperbilirubinemia in childhood or during adult life. The hyperbilirubinemia is caused by mutations in the gene encoding MRP-2 (see above), the protein involved in the secretion of conjugated bilirubin into bile. The centrilobular hepatocytes contain an abnormal black pigment that may be derived from epinephrine.

C. ROTOR SYNDROME

This is a rare benign condition characterized by chronic conjugated hyperbilirubinemia and normal liver histology. Its precise cause has not been identified, but it is thought to be due to an abnormality in hepatic storage.

POSSIBLE QUESTIONS

1. Write notes on symptoms, causes and types of jaundice
2. Write a note on

   i) Lesch-Nyhan syndrome ii) Von-Gierke's disease
3. Explain in detail the causes, clinical manifestation and treatment of gout
4. Write a note on hypouricemia
5. Explain biochemical abnormalities of Criggler-Najjar syndrome, Gilbert's disease and Dubin Johnson disease.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III-B.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (15BCU601)
MULTIPLE CHOICE QUESTIONS

UNIT IV

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	who was the first to study concentation of urea in blood and its excretion in urine	Louis pasteur	Ambard	Wilson	Edward	Ambard
2	If the urea volume exceeds 2ml/mt, the rate of urea elimination is at	minimum	normal	maximum	steady	maximum
3	volume of blood cleared of urea per minute can be calculated by the following formula	CX V/A	AXV/B	CXV/B	UxV/B	UxV/B
4	The clearance which occurs when the urinary volume exceeds 2ml/mt is termed as	maximum urea clearance	minimum urea clearance	standard urea clearance	all the above	maximum urea clearance
5	The average normal value for standard urea clearance is	54 ml	64 ml	44 ml	33 ml	54 ml
6	The average normal value for maximum urea clearance is	75 ml	85 ml	65 ml	40 ml	75 ml
7	The urea clearance is proportional to the	surface area of head	surface area of body	surface area of neck	surface area of lungs	surface area of body
8	urea clearance of _____ % indicates normal excretion of kidneys	60	80	70	20	70
9	values of urea clearance between 20 - 40% indicates	mild impairment	severe impairment	moderate impairment	all the above	moderate impairment
10	urea clearance values between_____ indicate mild impairment of excretion of kidneys	40 -70%	20 - 40%	50-60%	20 - 30 %	40 -70%
11	normal values for creatine clearance varies from	95-105 ml/mt	100 -105 ml/mt	10 -150 ml/mt	5-60 ml/mt	95-105 ml/mt
12	Endogenous creatinine is a _____of body	substrate	product	normal metabolite	all the above	normal metabolite
13	creatinine is neither secreted nor reabsorbed by the tubules. So its clearance gives	Renal function	liver function	glomerular filteration rate	Excretory function of kidney	glomerular filteration rate
14	patients with mild renal disease are recommended to take	high protein diet	moderate protein diet	low protein diet	High fat diet	low protein diet
15	In terminal uraemia , the urea clearance fallsto about _____ of the normal values	5%	10%	15%	11%	1%
16	Crystals of ammonium magnesium phosphate found in	acid urine	alkaline urine	neutral urine	Acid and alkaline urine	alkaline urine
17	phosphate crystals of urine deposits are in _____ form	amorphous	crystalline	colourless	powder	colourless
18	name the type of phosphate crystals which are much commonly seen in urine deposits	coffin lid type	feathery	fernlike	needle shape	coffin lid type
19	calcium hydrogen phosphate most often found crystalline in the form of	rosettes	clusters	Rosettes and star shape	star shape	Rosettes and star shape
20	Magnesium phosphate is found as _____ in alkaline to weakly acid urines	rhombic plates	diagonal shape	rectangular shape	needle shape	rhombic plates
21	Amorphous phosphates are found in the form of	fine granules	crystals	paste	clusters	fine granules
22	crystals of uric acid are found frequently in the deposits from _____ urines	alkaline	slightly acidic	slightly alkaline	acid urines	acid urines
23	pure uric acid crystals are _____ in nature	colored	colourless	red color	brown color	colourless
24	The pigment found in urine deposit containing uric acid crystals is due to the	inclusion of urinary pigments in the crystals	bile pigments	skin pigments	UTI	inclusion of urinary pigments in the crystals
25	uric acid crystals dissolve in	acetic acid	hydrochloric acid	sodium hydroxide	ethanol	sodium hydroxide
26	uric acid crystals are found in normal people	after sweating	fevers	After sweating and fever	Cold	After sweating and fever
27	_____ urates are found in urine deposits	ammonium and sodium	potassium	calcium and magnesium	Ammonium, sodium, potassium, calcium and magnesium	Ammonium, sodium, potassium, calcium and magnesium
28	calcium oxalate may be found in the deposit from both	acid urine	alkaline urine	acid and alkaline urine	all the above	acid and alkaline urine
29	the commonest forms of calcium crystals include	octahedral	ellipsoidal	dumb - bell shapes	Octahedral, ellipsoidal and dumb bell shapes	Octahedral, ellipsoidal and dumb bell shapes
30	crystals of calcium sulphate have been reported in acid urine as	long needles	short needles	medium needles	thread like needles	long needles
31	epithelial cells may be found more common in the deposit from normal urines of _____	men	child	women	adults	women
32	_____ gives a characteristic appearance to the urine	redblood cells	pus	epithelial cells	cast	redblood cells
33	hyaline casts are found in increased numbers in the majority of cases of	albuminuria	glycosuria	gout	renal disease	albuminuria
34	_____ type of casts are found when there is damage to tubular epithelium	epithelial cells	hyaline casts	granule cast	fatty casts	epithelial cells
35	stones from the kidney and renal pelvis are	harder	softer	larger	smaller	smaller
36	largest stones are found in the	liver	kidney	gallbladder	renal pelvis	gallbladder
37	uric acid stones are always coloured varying shades of	black	green	brown	blue	brown
38	_____ calculi contain a single urinary constituents	foreign	simple	mixed	Mild	simple
39	the substances introduced in to the body from outside is called as	native substances	foreign body	antigens	antibodies	foreign body
40	_____ are found in calculi	uric acid and urates	calcium oxalate	alkaline phosphates	Uric acid, urates, calcium oxalate and alkaline phosphates	Uric acid, urates, calcium oxalate and alkaline phosphates

41	_____are the stones are hardest found and not crushed easily	phosphate	oxalate	carbonate	xanthine	oxalate
42	phosphate calculi are _____	hard	soft and whitest	rough and dark colored	Semi solid	soft and whitest
43	xanthine stones are _____ in colour	yellowish brown	blue	green	red	yellowish brown
44	_____ calculi are found either at operation or post mortem	gall bladder	liver	kidney	pancreatic	pancreatic
45	most of the stones found in human beings are combined with	cholesterol	sterol	stigma sterol	lanosterol	cholesterol
46	_____ are the rare stones	calcium carbonate	cystine stones	xanthine stone	all the above	all the above
47	Urinary buffer is	Bicarbonate buffer	Peptide chain	Polypeptide chain	Non-protein compound	Bicarbonate buffer
48	Which one of the following is not a ketone body?	Acetic acid	Acetone	β –hydroxy butyric acid	Acetoaceticacid	Acetone
49	Ketone bodies are intermediary products in	Carbohydrate metabolism	Lipid metabolism	Nucleic acid metabolism	None of the above	None of the above
50	Fatty liver is due to	Deficiency of lipoprotein factors	Starvation	Ketosis	Ketosis, starvation and deficiency of lipoprotein factors	Ketosis, starvation and deficiency of lipoprotein factors
51	Accumulation of ketone bodies in the urine	Hyperglycemia	Ketoacidosis	ketonuria	Hypocalcemia	ketonuria
52	An enzyme which is excreted in urine is	Lactase dehydrogenase	Amylase	Ornithine transcarbamoylase	Hexokinase	Amylase
53	Oliguria can occur in	Diabetes mellitus	Diabetes insipidus	Acute glomerulonephritis	Chronic glomerulonephritis	Acute glomerulonephritis
54	Polyuria can occur in	Diabetes mellitus	Diarrhoea	Acute glomerulonephritis	High fever	Diabetes mellitus
55	Normal specific gravity of urine is	1.000-1.010	1.012-1.024	1.025-1.034	1.035-1.045	1.012-1.024
56	Bence-Jones proteinuria occurs in	Nephrotic syndrome	Renal cancer	Multiple myeloma	Chronic glomerulonephritis	Multiple myeloma
57	Bence-Jones protein precipitates at	$20^{o}C$-$40^{o}C$	$40^{o}C$- $60^{o}C$	$60^{o}C$-$80^{o}C$	$80^{o}C$-$100^{o}C$	$40^{o}C$- $60^{o}C$
58	Renal glycosuria occurs due to	Increased filtration of glucose in glomeruli	Increased secretion of glucose by renal tubular cells	Decreased reabsorption of glucose by renal tubular cells	Increased conversion of glycogen into glucose in tubular cells	Decreased reabsorption of glucose by renal tubular cells
59	Haematuria can occur in	Haemolytic anaemia	Mismatched blood transfusion	Yellow fever	Stone in urinary tract	Stone in urinary tract
60	Normal range of serum urea is	0.6-1.5mg/dl	9-11mg/dl	20-45mg/dl	60-100mg/dl	20-45mg/dl

Unit IV

Syllabus

Gastric function – Introduction- test of gastric function – insulin stimulation test, determination of gastrin in serum, tubeless gastric analysis.

Pancreatic function- Introduction, pancreatic function test- serum amylase and lipase, direct stimulation test-secretion of CCK, indirect stimulation test-lundh test.

Intestinal function- Introduction, tests used in the diagnosis of malabsorption, determination of total fecal fat, xylose excretion test and determination of total protein.

Gastric function test

Tests for Determining Gastric Function:

1. Examination of Resting Contents
2. Fractional Gastric Analysis using Test Meals
3. Examination of Contents after Stimulation
4. Tubeless Gastric Analysis

1. Examination of Resting Contents:

After a night's fast the stomach contents are completely removed by passing the tube

Types of Stomach Tubes

1. The stomach tube is made of rubber or plastic and has an external diameter of 4 mm.

2. Two types of tubes are in use:

(a) Rehfuss tube: This has an uncovered metal end with openings about the size of the bore of the tube

(b) Ryle's tube: This is commonly used. It has a covered end containing a small weight of lead, the holes being in the tube a short distance from the end.

The follow-ing characteristics are important in the diagnosis of diseases of stomach:
i)Volume:

(a) Only 20 to 50 ml of resting contents are obtained in normal cases.

(b) An increase in volume may be due to hyper-secretion of gastric juice, retention of gastric contents owing to delayed emptying of the stomach, and regurgitation of the duodenal contents

ii. Consistency:

(a) The normal gastric juice is fluid in consistency and does not contain any food residue and may contain small amounts of mucus

(b) Food residues are present in case of carcinoma of the stomach

iii. Colour:

(a) In case of normal person, the gastric residue is clear or it may slightly yellow or green due to regurgitation of bile from duodenum.

(b) A dark red or brown colour may be observed due to the presence of altered blood or fresh-blood.

iv. Bile:

Increased quantities of bile shows abnormality which is a result of intestinal obstruction or ideal stasis.

v. Blood:

(a) Blood is not present in normal cases

(b) Presence of small amount of fresh blood may be traumatic.

(c) Brown or reddish-brown blood may occur in gastric ulcer and sometimes in gastric carcinoma due to the formation of dark brown acid hematin as a result of the hemolysis of red blood cells by HCl.

(d) Bleeding may also occur from gastritis.

vi. Mucus:

(a) A small amount of mucus may be present in normal cases.

(b) Increased amount of mucus is present in gastritis and in gastric carcinoma. Pres-ence of mucus is inversely proportional to the amount of HCl present.

(c) Swallowed saliva may contain excess of mucus.

vii. Free and Total Acidity:

(a) The acidity is determined by titration with a standard solution of NaOH using methyl orange or Topfer's reagent which indicates end point by the change of red to yellow colour or using phenolphthalein indicator which shows end point by the change of yellow to red colour.

(b) The presence of the amount of free HCl is free acidity; the complete titration shows the total acidity which is composed of protein hydrochloride and any organic acid; the difference between two titrations gives the combined acid.

(c) The result is expressed as ml of 0.1 N HCl per 100 ml of gastric contents. This is same as mEq/litre.

(d) The normal values of free acid is 0 to 30 mEq/L and that of total acid is 10 to 40 mEq/L.

viii. Organic Acids:

(a) The presence of large amounts of lactic acid and butyric acid in achlorhydria and hypochlorhydria indicates the remaining of residual foods in the stomach. In ab-sence of HCl, the microorganisms ferment the food residues producing lactic acid and butyric acid,

(b) Achlorhydria is associated with retention of food residues and is found in carcinoma stomach

Test 2. Fractional Gastric Analysis using Test Meals:

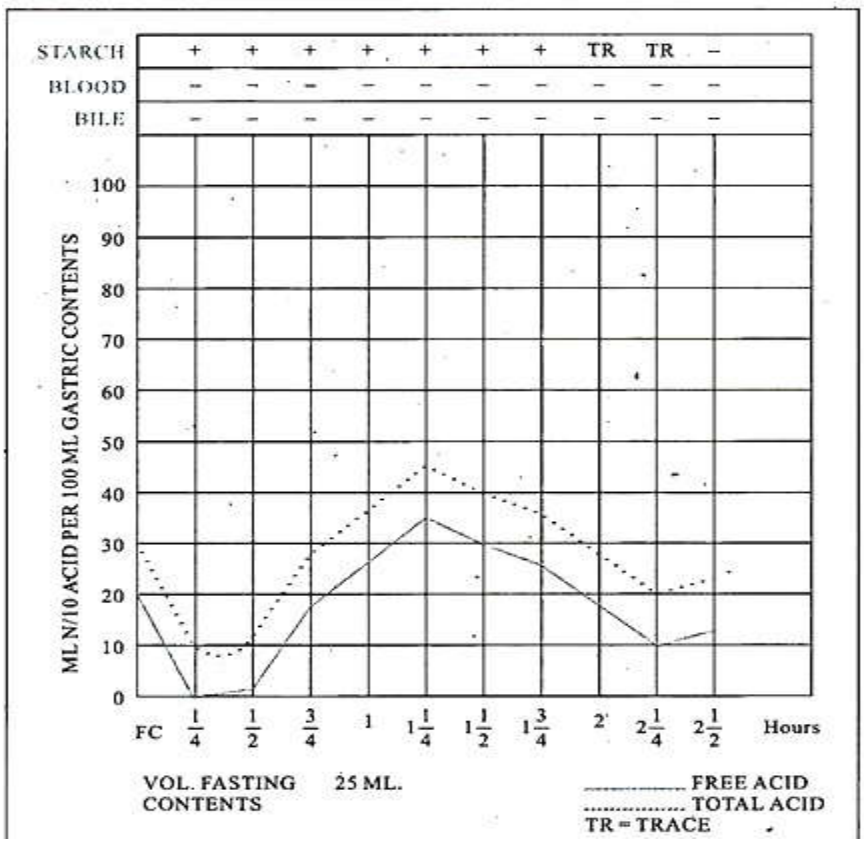
This consists of:

i. Introduction of Ryle's tube in stomach of a fasting individual.
ii. Analysis of residual gastric contents after collection.
iii. Ingestion of test meal.
iv. Collection of 5 to 6 ml gastric contents after meal by aspiration using a syringe and analysis of the samples.

i) Test Meals:

(a) Oatmeal is prepared by adding 2 tablespoonful's of oat meal to one quart of boiling water.

(b) **"Ewald"** test meal consists of two pieces (35 gm.) of toast and 250 ml light tea.



(ii) Collection of Samples:

(a) About 10 ml gastric contents are collected at an interval of exactly 15 minutes by means of syringe attached to the tube.

(b) If the stomach is not empty at the end of 3 hours, the remaining stomach contents are removed and the volume is also noted.

(c) Each sample is strained through a fine cloth.

(d) The strained samples are analysed for free and total acidity and the residue on the cloth is examined for mucus, bile, blood, and starch.

(iii) Results and Interpretation:

(a) In normal health, after taking the meal, the free acid is found after 15 to 45 minutes (See figure below). The free acid then steadily rises to reach the maximum at about 15 minutes to 1/2 hour, after which the concentration of free acid begins to fall. The free acid ranges from 15 to 45

mEq/litre at the maximum with total acid at about 10 units higher. Blood is not present and appreciable amount of bile is also not present.

(b) In hyperchlorhydria- free acidity exceeds 45 mEq/litre but the combined acidity remains the same as in normal persons. Hyperacidity is found in duodenal ulcer in which a climbing type of curve is formed in gastric ulcer in which 50 per cent cases give normal results, and blood may be present, in gastric carcinoma in which small percentage show hyperacidity and blood, in jejunal and gastrojejunal ulcers in which there may be hyperacidity after operation.

(c) In hypochlorhydria- low acidities are found in carcinoma of stomach in atonic dyspepsia. Free HCl is absent in gastric secretion in pernicious anemia.

(d) In achlorhydria, no HCl secretion but pepsin is present.

(e) In achylia gastrica, gastric secretion is completely absent due to advanced cases of cancer of stomach, advanced cases of gastritis, and acute pernicious anemia.

Test 3. Examination of Contents after Stimulation:

A. Alcohol Stimulation:

(i) The Ryle's tube is passed into the stomach after overnight fast and resting contents are collected for analysis.

(ii) 100 ml of 7 per cent ethyl alcohol is administered. Samples of gastric contents are collected at an interval of 15 minutes and all the samples are analysed for free and total acidity, peptic activity, presence of bile, blood and mucus.

(iii) **The advantages of alcohol test meal are the followings:**

(a) More easily administered and prepared.

(b) Consumed better.

(c) The gastric response is more rapid and more intense.

(d) Quick emptying of the stomach.

(e) Specimens are clear and easily analysed.

(iv) The disadvantages of this test are:

(a) Stimulus with alcohol is more vigorous.

(b) Stimulus is not so strictly physiological.

(c) Free acidity levels are higher and normal limits are wider.

B.Caffeine Stimulation:

(i) The Ryle's tube is introduced into the stomach after overnight fast and the resting gastric contents are collected and analysed.

(ii) Caffeine sodium benzoate (500 mg dissolved in 200 ml of water) is administered orally. Samples of stomach contents are collected at an interval of 15 minutes and analysed for free and total acidity, peptic activity, presence of bile, blood and mucus.

(iii) Advantages of this stimulation is similar to that of alcohol stimulation.

C. Histamine Stimulation test:

Histamine is a powerful stimulant for the secretion of HCl in the normal stomach. It increases the cAMP level which causes the increased secretion of highly acidic gastric juice with low pepsin content.

(i) Standard histamine test:

(a) The Ryle's tube is passed into the stomach after overnight fast and the stomach contents are collected for analysis.

(b) A subcutaneous injection of histamine (0.01 mg/kg body weight) is inserted. 10 ml stomach contents are collected at an interval of 10 minutes for one hour and samples are analysed for free and total acidity, peptic activity, presence of bile, blood and mucus.

(c) Achylia gastrica ("true" achlorhydria) is indicated by the absence of free HCl in the secretion after histamine administration. More juice may be secreted in duodenal ulcer.

ii) Augmented histamine test:

It is a more powerful stimulus test and it shows an inability to secrete acid. Larger doses of histamine sometimes causes an unwanted severe reactions.

(a) The Ryle's tube is introduced after an overnight fast and the gastric contents are collected for analysis. The resting contents are collected at an interval of 20 minutes for an hour. Halfway of this period, 4 ml anthisan (antihistamine) is given intramuscularly.

(b) At the end of the hour, histamine (0.04 mg histamine acid phosphate per kg body weight) is given subcutaneously and gastric contents are collected at an interval of 15 minutes for one hour for analysis.

(c) In pernicious anemia, no free HCl is secreted after histamine stimulation. In duodenal ulcers, higher values of acid are obtained.

(d) Recently, histalog is used in place of histamine. No side effects like histamine are observed by its use. The recommended dose of histamine is 10 to 50 mg. This histalog is highly effective in stimulating gastric secretion

D. Insulin Stimulation Test:

Hypoglycemia due to insulin administration is an active stimulus of gastric acid secretion. The blood sugar level below 45 mg per cent is essential for a reliable test.

(i) The Ryle's tube is passed into the stomach after an overnight fast and the stomach is made empty.

(ii) 15 units of soluble insulin is injected intravenously and about 10 ml gastric contents are collected at an interval of 15 minutes for 2 ½ hours. The samples are analysed for free and total acidity, peptic activity, and presence of blood, bile, starch. Starch should not be present.

(iii) In duodenal ulcer, acid level is more in response to insulin. The concentration of free acid may be over 100 mEq/litre. After vagotomy no response of insulin is found and the gastric acidity remains at 15 to 20 mEq/litre before and after insulin injection.

E. Pentagastrin Test:

Pentagastrin is a synthetic peptide and it is butyl-oxy-carbonyl β-alanine. It is an active stimulator.

(i) The Ryle's tube is passed into the stomach after an overnight fast and the resting contents are completely removed. After emptying the stomach two 15 minute specimens are collected to have the **"basal secretion"**.

(ii) Pentagastrin (6μg/kg body weight) is injected subcutaneously and specimens are collected at an interval of 15 minutes for analysis.

(iii) The normal basal secretion rate is 1 to 2.5 mEq/hour. The maximum secretion in normal person after pentagastrin stimulus varies from 20 to 40 mEq/hour.

(iv) In duodenal ulcer, the range is 15 to 83 mEq/hour. This test is of little value in gastric ulcer. The **"true"** achlorhydria is found in cancer of the stomach. The reduced acid level is observed in acute gastritis. The **"true"** achlorhydria is also noted in Pernicious anemia. The Zollinger-Ellison syndrome is characterised by a high basal secretion usually above 10 mEq/hour and no further rise is found after giving Pentagastrin.

This syndrome is characterised by peptic ulcer, gastric hyper-secretion and diarrhoea. This syndrome is also accompanied by parathyroid adenomas with hyperparathyroidism. The secretion of pepsin occurs after stimulation with pentagastrin.

Test 4. Tubeless Gastric Analysis:

DiagnexBlue test

The modified test is done with the introduction of "DiagnexBlue" prepared by reacting carbacrylic cation exchange resin with **"Azure A"** an indicator. The hydrogen ions of the resin is exchanged with **"Azur A"** ions.

The reaction is reversed in the stomach when acid is in a concentration having pH less than 3.0. The indicator **"Azur A"** is released by the action of acid. The released one is absorbed in the small intestine and excreted in the urine, the colour of which is matched with known standards.

This test is valuable if it is used as **"screening test"** only. A positive result indicates the secretion of acid by the stomach. A negative result is an unreliable indicator of **"true"** achlorhydria.

This test is not reliable in patients suffering from renal diseases, urinary retention, malabsorption, pyloric obstruction. Vitamin preparation should not be taken on the day proceeding the test which may contain substances decolorized by vitamin C.

Serum Gastrin - *for diagnosis of the Zollinger-Ellison syndrome.*

Serum gastrin concentration is determined by radioimmunoassay.

Highest serum gastrin concentrations are found in cases of the Zollinger-Ellison syndrome.

High serum gastrin concentrations are also found in cases of fundal atrophic gastritis with

Condition	serum gastrin (pg/ml)
normal	< 500
antral gastritis	low to normal
duodenal ulcer	300 - 500
fundal gastritis	300 - 60,000
Z.E. syndrome	3,500 - 60,000

achlorhydria .

Pancreatic Function Tests

- The exocrine pancreas secretes about 1000–2500 mL of juice in 24 hours.
- The fluid is alkaline and contains bicarbonate and enzymes.
- This secretion is under the control of the hormones, Secretin and Cholecystokinin.
- Secretin is produced under the stimulation of gastric HCl.
- Secretin produces a secretion with high bicarbonate content.
- Gastrin stimulates production of cholecystokinin (CCK), which in turn produces pancreatic secretion rich in enzymes.
- The major enzymes present in pancreatic juice are amylase, lipase and proteolytic enzymes (trypsin, chymotrypsin, carboxypeptidase, elastase) as their zymogens

- **Assessment of Pancreatic Function**

  Measurement of pancreatic enzymes:

  Amylase or alpha-1,4-glucosidase is the major enzyme which digests starch .

  - The serum amylase contains the P (pancreatic) and S (salivary) iso-enzymes.
  - These two can be distinguished by the inhibition test.
  - A protein inhibitor, present in alcoholic extracts of wheat will selectively inhibit the S isoenzyme.

- Normal amylase level in serum is 50–120 units.
- The level rises within 5 hours of the onset of **acute pancreatitis** and the level reaches a peak within 12 hours.
- But the level need not parallel the severity of the disease. Within 2–4 days of the attack, the level returns to normal.
- As the serum amylase level starts falling, urinary amylase level rises.
- If the sample is collected too early, the serum amylase levels may not show the expected rise.
- If the sample is collected too late, again serum amylase may be low due to necrosis of the pancreatic tissue.
- Calculation of clearance ratio will avoid these defects.

$$CR = \frac{\text{Urine amylase level}}{\text{Serum amylase level}} \times \frac{\text{Scr}}{\text{Ucr}} \times 100$$

CR is clearance ratio, Scr is serum creatinine level and Ucr is urinary creatinine level.

- In patients with acute pancreatitis, the ratio varies from 7 – 15%.
- The normal ratio is 1 – 4.4%
- Amylase level in blood is mildly increased in cases of cholecystitis, peptic ulcer, diseases of mesentery and obstruction of intestine.
- A small percentage of patients with acute pancreatitis fails to show any rise.
- No significant change or only mild elevation is noticed in chronic pancreatitis.
- Macroamylasemia is a condition characterized by persistent elevation of serum amylase activity with no apparent clinical symptoms of pancreatic disease.
- The amylase complexes with immunoglobulins, which prevents renal excretion.

- Macroamylasemia by itself is not a disease. But it may be an early marker of pancreatic disease.

Serum lipase is the major lipolytic enzyme which hydrolyzes glycerol esters of long chain fatty acids.

- The level in blood is highly elevated in acute pancreatitis and this persists for 7 – 14 days. Thus lipase remains elevated longer than amylase.
- Moreover, lipase is not increased in salivary diseases.
- Therefore, lipase estimation has advantage over amylase.
- Normal lipase level is 0-160U/L

Pancreatic elastase: Another test for the diagnosis of pancreatic insufficiency is pancreatic elastase.

- ELISA test kits are available; a value of >200 mg in stool sample indicates normal exocrine pancreatic function and values <200 mg indicates exocrine pancreatic insufficiency.

Other pancreatic enzymes: A simple screening test for tryptic activity of feces may be done using serial dilutions of stool extract.

- Drops of serially diluted extract is placed on a piece of X-ray film along with a control sample. After an hour at 37°C, the extract is washed off, and the film examined for tryptic activity by noting translucency of the film.

Secretin-cholecystokinin test: In the fasting condition, the duodenal contents are first aspirated. Then secretin 1 unit/kg body weight is given followed by CCK.

- Again the duodenal contents are aspirated for 80 minutes at 10 minutes intervals.
- Each sample is analyzed for volume, bicarbonate content and amylase activity.
- If the bicarbonate secretion is more than 15 mmol/L at 30 minutes, the secretory capacity is normal

Lundh test: The test meal is composed of milk powder, vegetable oil and glucose to make 6% fat, 5% protein and 15% carbohydrate.

- After aspirating the duodenal contents, 500 mL of fluid meal is given.
- Then duodenal secretions are collected at 30 minutes intervals for 2 hours.
- The tryptic activity of duodenal aspirates are measured.
- Benzoyl arginine ethyl ester (BAEE) is incubated with the aspirate.
- The benzoic acid liberated after tryptic hydrolysis of the substrate is calculated.
- In chronic pancreatitis, the tryptic activity is decreased, but not in carcinoma of pancreas.

Indirect tests of pancreatic function include (a) Measurement of tumor markers like carcino-embryonic antigen (CEA), alpha feto protein (AFP), and pancreatic oncofetal antigen. (b) Fat balance studies. (c) Measurement of leucine aminopeptidase which is usually elevated in pancreatic carcinoma.

Fat balance studies:

The estimation of fat in stool is done. When feces contains split fatty acids, it points to a normal pancreatic function, but defective absorption. On the other hand, if the fat excreted is neutral fat, it is due to defective digestion, and is more in favor of pancreatic disease.

Estimation of **sweat electrolytes**: In pancreatic **fibrocystic disease**, sodium and chloride are increased in sweat. The disease is characterized by thick viscous secretion of exocrine glands, including pancreas, salivary, tracheal, bronchial and sweat glands.

- Pilocarpine is given into the skin to stimulate the secretion of sweat glands.
- The sweat is absorbed into a filter paper, which is weighed before and after the absorption.
- The difference in weight of the filter paper gives the weight of the sweat.
- From the specific gravity and weight, the volume is determined.

- Then sodium and chloride are eluted from the filter paper and separately determined.
- Sweat chloride levels of more than 60 mmol/L, on two separate occasions, is diagnostic of cystic fibrosis.

	Volume (mL/h)	*HCO_3^- (mmol/L/h)*	*Amylase (Unit/h)*
Normal	150–200	70	200
Chronic pancreatitis	Decrease	Decrease	Decrease
Pancreatic	Normal	Decrease	Decrease carcinoma
Obstruction to pancreas duct	Decrease	Normal	Normal

Intestinal function test

Studies On Malabsorption

Malabsorption may result from defective digestion or faulty absorption or from both.

Reduction of absorptive surface may result from

i) Celiac disease;
ii) Gluten sensitive enteropathy;
iii) Tropical sprue;
iv) Ideopathic steatorrhea;
v) Extensive surgical removal of ileum;
vi) Crohn's disease or vii) Whipple's disease.

1. **D-Xylose absorption test**:

Xylose is absorbed easily, but not rapidly metabolized. Hence its blood level is an index of the rate of absorption. An oral dose (25 g) of xylose is given to the fasting patient. In normal subjects, more than 23% of the administered dose should be excreted during the 5 hours, out of which 50% excretion should occur within the first 2 hours. In severe malabsorption, the total excretion is low. In mild malabsorption, it may only be delayed.

2. **Starch tolerance test**:

A usual GTT is done on the first

On the following day, 100 g soluble starch is given and the rise in glucose level is noted. In normal cases, the peak level in the starch test will be at least 80% of the peak level of usual GTT.

3. Schilling test

The Schilling test is a medical investigation used for patients with vitamin B_{12} (cobalamin) deficiency. Vitamin B12 deficiency may be due to pernicious anemia (lack of gastric secretion of intrinsic factor from fundal gastritis) or to intestinal malabsorption or, rarely, to dietary deficiency. The purpose of the test is to determine whether the patient has pernicious anemia

1st Stage

A 1 mg loading dose of vitamin B12 is administered IM to saturate tissue stores.

50 ug of radioactive cobalt labeled vitamin B12 is administered orally.

The total radioactivity in a 24-48 hour urine collection is determined.

Interpretation of 1st Stage Results:

normal: - 8 - 40% of the administered radioactivity is found in the urine collection

vitamin B12 malabsorption: - < 8% of the administered radioactivity is found in ……..the urine collection

2nd Stage

If vitamin B12 malabsorption is found, then the test is repeated three days later (second stage), but with the administration of intrinsic factor along with radiolabeled B12.

Interpretation of Second Stage Results

- atrophic gastritis with pernicious anemia: - radiolabeled vitamin B12 is absorbed and the content of radiolabeled vitamin B12 in the urine collection becomes normal
- intestinal malabsorption: - the content of radiolabeled vitamin B12 in the urine collection remains abnormally low.

4. Tests for steatorrhea

Absorption of dietary fat requires bile salts, pancreatic lipase, formation of bile salt/fatty acid micelles and intestinal absorption. Malabsorption of fat may result from bile duct obstruction, pancreatic in sufficiency or intestinal disease.

a. Indirect indications from decreased absorption of fat soluble vitamins:

- decreased vitamin D absorption ==> negative calcium balance ==> secondary hyperparathyroidism ==> osteomalacia
- decreased vitamin K absorption ==> prolonged prothrombin time ==> susceptibility to hemorrhage
- decreased carotene absorption

b.Microscopic examination of neutral fat stained stool smear.

c.Quantitative fecal fat determination on a 72 hr. stool specimen with 100 g/day …….dietary fat:

- Normal < 5 g/day

- Steatorrhea > 7

Note: Total fat (including both triglyceride and free fatty acid) is measured, so that steatorrhea from intestinal or pancreaic origin is not distinguished.*Determination of the fatty acid/triglyceride composition of a stool specimen might conceivably differentiate pancreatic insufficiency and intestinal malabsorption as the cause, but bacterial lipolytic activity precludes the differentiation.*

When feces contains split fatty acids, it points to a normal pancreatic function, but defective absorption. On the other hand, if the fat excreted is neutral fat, it is due to defective digestion, and is more in favor of pancreatic disease.

Nevertheless, **the quantitative fecal fat determination provides the most definitive criterion for steatorrhea**.

Determination Of Total Protein

Normal total protein level in blood is 6-8g/dl

Low level is found in malabsorption conditions, such as celiac disease or inflammatory bowel disease

CLASS: III BSC BC **COURSE NAME: CLINICAL BIOCHEMISTRY**
COURSE CODE: 15BCU601 **BATCH-2015-2018**
UNIT: IV (GASTRIC, PANCREATIC AND INTESTINAL FUNCTION)

POSSIBLE QUESTIONS

1. Write a note on gastric function test.
2. Describe in detail tubeless gastric analysis.
3. Write a note on pancreatic function test.
4. What are the types of indirect pancreatic stimulation test?
5. Write a note on the role of serum amylase and lipase in pancreatic function.
6. What is the test used for the diagnosis of malabsorption?
7. Write a note on intestinal function test.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III-B.Sc., BIOCHEMISTRY
CLINICAL BIOCHEMISTRY (15BCU601)
MULTIPLE CHOICE QUESTIONS

UNIT V

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Plasma derived enzymes act on substrates in	plasma	serum	blood	lymph	plasma
2	Example of plasma derived enzyme is	soluble protein fraction	liver marker enzymes	coagulation enzymes	serum cancer marker enzymes	coagulation enzymes
3	The substrate for creatine phosphokinase is	creatine	phosphate	ATP	creatine phosphate	creatine phosphate
4	The other name of creatine phosphokinase is	oxido reductase	creatine kinase	phosphokinase	hydroperoxidase	creatine kinase
5	Normal value of CPK is	4 - 60 Iu/l	5 - 60 Iu/l	6 - 60 Iu/l	2 - 40 Iu/l	4 - 60 Iu/l
6	After myocardial infarction, serum value of CPK is found to increase within _____ hours	3	4	6	5	6
7	Serum CPK activity is a more senstive indicator in early stage of	liver disorders	Kidney failure	Intestinal disorder	myocardial ischaemia	myocardial ischaemia
8	The level of CPk comes to normal within _____ hours after myocardial infarction	3	4	6	5	6
9	The determination of CPk activity is more useful in	myocardial infarction	Kidney failure	Intestinal disorder	myocardial ischaemia	myocardial ischaemia
10	CPk is found in higher concentration in	lungs	thyroid	adrenal gland	skeletal muscle	thyroid
11	Serum glutamate oxaloacetate transaminase is otherwise called as	aspartate transaminase	alanine transaminase	lactate dehydrogenase	CPk	alanine transaminase
12	Concentration of serum glutamate oxaloacetate transaminase is high in	skeletal muscle	myocardium	liver	bones	bones
13	Serum activity of SGOT varies from	5-15 Iu/l	6-12Iu/l	4 - 17 IU/l	10 -12 Iu/l	5-15 Iu/l
14	In acute myocardial infarction serum glutamate oxaloacetate transaminase activity rises sharply within the first ----------	3 to 5 days	2 to 4 days	1 to 2 days	3 to 4 days	2 to 4 days
15	serum oxaloacetate transaminase activity returns to normal within____after acute myocardial infarction	1st day of infarction	2nd day of infarction	3rd day of infarction	last day of infarction	3rd day of infarction
16	Highest levels of SGOT was found after	4	5	11	12	12
17	LDH catalyzes the reversible conversion of	pyruvic acid	lacticacid	Both a and b	none of the above	lacticacid
18	In acute myocardial infarction serum LDH rises sharply within the first _____ hours	12 to 14 hrs	10 -12 hrs	11 - 12 hrs	5 - 6 hrs	10 -12 hrs
19	The LDH atains peak at 48 hours reaching about the concentration of	500 IU/L	1000 IU/L	1500IU/L	700 IU/L	1500IU/L
20	The peak rises in serum LDH is _____ proportional to the extent of injury to the myocardial tissue	sparingly	steadily	roughly	fairly	sparingly
21	In acute myocardial infarction , serum LDH returns to normal within	8th -14th day	7th to 15th day	6th to 14th day	9th to 10th day	7th to 15th day
22	Serum LDH elevation may persist for more than a week after _____ having returned to normal levels	CPK and SGOT	CPK and SGPT	LDH and SGOT	Acid phosphatase and LDH	LDH and SGOT
23	LDH is widespread in body cells and its levels are raised in	carcinomatosis	acute leukaemias	granulocytic leukaemia	all the above	carcinomatosis
24	The only enzyme of GI origin which is regularly assayed is	serum amylase	serum lipase	cholineesterase	histaminase	serum amylase
25	Normal value of serum amylase is	80 to 180 somogy units/100ml	10 -100 somogy units/100ml	5 - 50 somogy units/100ml	2-25 somogy units/ml	80 to 180 somogy units/100ml
26	Coagulation enzymes are	plasma derived enzymes	cell derived enzymes	Secretory enzymes	Metabolic enzymes	plasma derived enzymes
27	Aminotransferase is the other name of	LDH	CPK	SGOT	SGPT	SGOT
28	In myocardial infrarction there is no rise of	SGOT	SGPT	LDH	CPK	SGPT
29	Extra cardiac factors for the elevation of SGOT are	muscle disease and hepatic disease	pulmonary embolism	Heart attack	Hypercholesterolemia	muscle disease and hepatic disease
30	Normal serum LDH ranges from	60 to 250 IU/L	150 to 300 IU/L	50 to 100 IU/L	1 to 5 IU/L	60 to 250 IU/L
31	Isoenzymes differ from each other	structurally	electrophoretically	immunologically	Structurally, electrophoretically and immunologically	Structurally, electrophoretically and immunologically
32	There are _____physically distinct isoenzymes for LDH	three	five	four	six	five
33	Which of the following has the highest negative charge	LDH -1	LDH -2	LDH - 3	LDH - 4	LDH -1
34	Which of the following is slowest moving LDH	LDH - 5	LDH -2	LDH - 1	LDH - 4	LDH - 5
35	Isoenzymes have diferent	optimal pH	Km values	physical structure	Optimal pH, Km values and physical structure	Optimal pH, Km values and physical structure
36	Myocardium is rich in	LDH - 5	LDH -1	LDH -2	LDH - 3	LDH -1
37	In human tissues CPK exists as _____different isoenzymes	three	five	two	four	three
38	Malignant tumors of testes and ovary show rise of	LDH 2	LDH 3	LDH 4	LDH 2, 3 and 4	LDH 2, 3 and 4
39	CPK is found in serum only in case of	cellular damage	hepatic disorders	kidney disease	none of the above	cellular damage
40	CPK is not found at	liver	kidney	RBC	all the above	kidney
41	CPK-Mi is a atypical CPK isoenzyme found in	liver	RBC	mitochondria	none of the above	mitochondria
42	In myocardial infarction_____ increases and acounts for 4.5 to 20% of the total CK	CK 1	CK 2	CK 3	CK-Macro	CK 2
43	The normal level of Cholinesterase is	2.17 to 5.17 IU/ml	1.57 to 5.57 IU/ml	5.17 to 6.17 IU/ml	1.0 to 8.0 IU/ml	2.17 to 5.17 IU/ml
44	Serum Cholinesterase increases in	acute myocardial infarction	liver disorders	pancreatitis	all the above	acute myocardial infarction

45	True Cholinesterase is found in	intestine	Liver	Heart muscle	Nerve tissues and RBC	Nerve tissues and RBC
46	Which Cholinesterase is found in plasma	True Cholinesterase	Pseudo cholinesterase	Both	None	Pseudo cholinesterase
47	Serum Cholinesterase is decreased in	Acute hepatitis	Acute myocardial infarction	Nephrotic syndrome	Nephrosis	Acute hepatitis
48	Serum Lipase assay is more specific in	nervous disorder	Kidney disorders	Pancreatic disorders	Hepatic disorders	Pancreatic disorders
49	Isoenzymes of ALP are found in	bone	liver	placenta	Bone, liver and placenta	Bone, liver and placenta
50	ALP is a most valuable index of	osteoblastic activity	Hepatic activity	Renal activity	None of the above	osteoblastic activity
51	The normal level of serum ALP in children is	12-30 K.A.	20-40 K.A.	5-7K.A.	1-10 K.A.	12-30 K.A.
52	The normal level of acid phosphatase	0.6-3.1 KA units/100ml	0.2-0.5 KA units/100ml	1-5 KA units/100ml	0.5-1.0 KA units/100ml	0.6-3.1 KA units/100ml
53	ACP found in erythrocytes are active in pH of	6	5	3	4	6
54	The chief enzyme assay useful in cancer of prostate is	ALP	ACP	LDH	CPK	ACP
55	Decreased synthesis of _____ is seen in Hypophosphatasia	ACP	ALP	CPK	LDH	ALP
56	Serum amylase is decreased in patients with	chronic hepatic disease	chronic pancreatic disease	severe malnourishment	Severe malnourishment, chronic hepatic and pancreatic disease	Severe malnourishment, chronic hepatic and pancreatic disease
57	Decreased serum pseudocholinesterase is seen in	severe malnourishment	chronic hepatic disease	insecticide poisoning	Chronic nervous disease	chronic hepatic disease
58	The enzyme assay that are carried out in myocardial infarction are	CK	AST	LDH	CK, AST and LDH	CK, AST and LDH
59	The enzyme assay that are carried out in muscle diseases are	SGOT / SGPT	Aldolase	CPK	SGOT, SGPT, aldolase and CPK	SGOT, SGPT, aldolase and CPK
60	Essential element for blood clotting is	chloride	calcium	sulphate	phosphate	calcium

UNIT-V

SYLLABUS

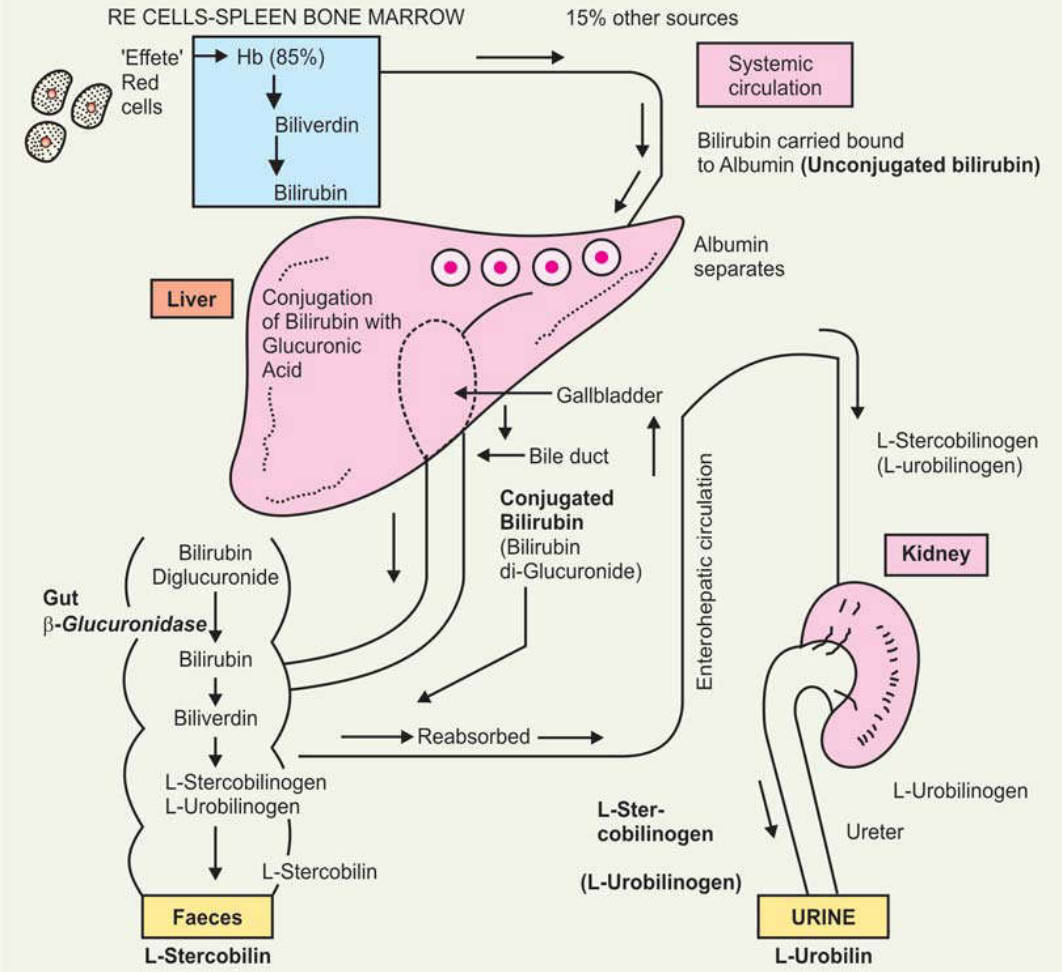
Liver disease and liver function tests- Bilirubin metabolism and jaundice, liver function tests- Estimation of conjugated and total bilirubin in serum, Detection of bilirubin and bile salts in urine, Thymol turbidity test, serum enzymes in liver disease- Serum transaminases (SGOT and SGPT), and phosphatases.

Kidney function tests – Introduction, physical examination of urine, elimination tests- clearance test, insulin clearance, creatinine clearance and urea clearance: Renal blood flow and filtration fraction, clinical significance of GGT, LDH and creatine phosphokinase in kidney function.

Coagulation tests- prothrombin time, Activated Partial Thromboplastin Time (APTT) and lupus anticoagulant.

Bilirubin metabolism and jaundice

Bilirubin metabolism



Bilirubin Metabolism

- The heme present in the hemoglobin and other proteins/enzymes (e.g. cytochromes) are eliminated only through liver
- The lysis of red blood cells releases hemoglobin which splits to release globin and heme.
- The heme part is catabolized by microsomal heme oxygenase system of reticuloendothelial system to produce bilirubin.
- The bilirubin (unconjugated) thus formed is hydrophobic in nature hence it is transported in the blood by binding with albumin to reach the liver.

- In the liver, it is conjugated with glucuronic acid to form hydrophilic conjugated bilirubin and is excreted in bile into the intestine.
- Bacterial action (deconjugation and reduction) forms bilinogens (stercobilinogen, mesobilinogen and urobilinogen).
- About 20% of the urobilinogen is reabsorbed daily from the intestine to enter enterohepatic circulation to get re excreted into the intestinal lumen (enterohepatic circulation).
- A small fraction of urobilinogen enters the systemic circulation and gets filtered at the glomerulus and excreted in urine.

Plasma Bilirubin

i. Normal plasma bilirubin level ranges from 0.2–0.8 mg/ dL.
ii. The unconjugated bilirubin is about 0.2–0.6 mg/dL, while conjugated bilirubin is only 0–0.2 mg/dL.
iii. If the plasma bilirubin level exceeds 1 mg/dL, the condition is called hyperbilirubinemia. Levels between 1 and 2 mg/dL are indicative of latent jaundice.
iv. When the bilirubin level exceeds 2 mg/dL, it diffuses into tissues producing yellowish discoloration of sclera, conjunctiva, skin and mucous membrane resulting in jaundice.
v. Icterus is the Greek term for jaudice.

Liver function test

Biochemical tests are of immense value in diagnosis and monitoring of liver diseases. These tests are usually referred to as "liver function tests" (LFT). LFTs are the most widely performed biochemical tests in the laboratory. Important liver functions are.

1. Synthetic function
   a. Synthesis of plasma proteins (albumin, coagulation factors, many globulins)
   b. Synthesis of cholesterol
   c. Synthesis of triacyl glycerol
   d. Lipoprotein synthesis
2. Metabolic function
   a. Carbohydrates : Glycolysis; glycogen synthesis; glycogen breakdown; gluconeogenesis
   b. Ketogenesis; fatty acid synthesis and breakdown
   c. Protein catabolism
   d. Citric acid cycle, production of ATP
3. Detoxification and excretion
   a. Ammonia to urea
   b. Bilirubin (bile pigment)
   c. Cholesterol
   d. Drug metabolites
4. Homeostasis: Blood glucose regulation
5. Storage function : Vitamin A, D, K, B_{12}
6. Production of Bile salts; help in digestion

CLINICAL MANIFESTATIONS OF LIVER DYSFUNCTION

1.Jaundice

Jaundice is the yellowish discoloration of sclera, skin and mucous membrane.

It is characteristic of liver disease but it will occur when rate of hemolysis is increased leading to

elevation of serum bilirubin.

Physiological Jaundice

- It is also called as neonatal hyperbilirubinemia.
- In all new born infants after the 2nd day of life, mild jaundice appears.
- This transient hyperbilirubinemia is due to an accelerated rate of destruction of RBCs and also because of the immature hepatic system of conjugation of bilirubin.
- In such cases, bilirubin does not increase above 5 mg/dL.
- It disappears by the second week of life.

Breast Milk Jaundice

- In some breast-fed infants, prolongation of the jaundice has been attributed to high level of an estrogen derivative in maternal blood, which is excreted through the milk.
- This would inhibit the glucuronyl transferase system.

Sulfa and such other drugs may release bilirubin from albumin, and may cause jaundice in newborn.

Hemolytic Jaundice

- Hemolytic Disease of the Newborn
  - This condition results from incompatibility between maternal and fetal blood groups.
  - Rh positive fetus may produce antibodies in Rh negative mother.

    In Rh incompatibility, the first child often escapes.
  - But in the second pregnancy, the Rh antibodies will pass from mother to the fetus. They would start destroying the fetal red cells even before birth.
  - Sometimes the child is born with severe hemolytic disease, often referred to as **erythroblastosis fetalis**.
  - When blood level is more than 20 mg/dL, the capacity of albumin to bind bilirubin is exceeded.
  - In young children before the age of 1 year, the blood-brain barrier is not fully matured, and therefore free bilirubin enters the brain **(Kernicterus)**. It is deposited in brain, leading to mental retardation, fits, toxic encephalitis and spasticity.
  - If the child develops hemolytic disease, child may be given exchange transfusion along withpphototherapy and barbiturates. **Phototherapy** with blue light (440nm wavelength) isomerize insoluble ……..bilirubin to more soluble isomers. These can be excreted through urine without conjugation.

Hemolytic Diseases of Adults

This condition is seen in increased rate of hemolysis. It usually occurs in adults.

The characteristic features are increase in **unconjugated bilirubin** in blood, absence of bilirubinuria and excessive excretion of UBG in urine and SBG in feces .

Common causes are:

i. Congenital spherocytosis

ii. GPD deficiency

iii. Autoimmune hemolytic anemias

iv.Toxins like carbon tetrachloride.

Hepatocellular Jaundice

- The most common cause is viral hepatitis, caused by Hepatitis Viruses A, B, C, D or E.
- In pure hepatocellular disease, conjugation in liver is decreased and hence **free bilirubin** is increased in circulation.
- However, inflammatory edema of cell often compresses intracellular canaliculi at the site of bile formation and this produces an element of obstruction.
- When conjugated bilirubin level also increases, mixed type of jaundice results.
- Bilirubinuria also occurs.
- The UBG level in urine may be normal or decreased in hepatocellular jaundice

Obstructive Jaundice

Conjugated bilirubin is increased in blood, and it is excreted in urine. If there is complete obstruction, UBG

will be decreased in urine or even absent and . In total obstruction of biliary tree, the bile does not enter the intestine. Since no pigments are entering into the gut, the feces become clay colored.

The common causes of obstructive jaundice are:

a. Intrahepatic cholestasis. This may be due to:

i. Chronic active hepatitis

ii. Biliary cirrhosis

iii. Lymphomas

iv. Primary hepatoma

v. Obstructive stage of viral hepatitis.

b. Extrahepatic obstruction. This may be due to:

i. Stones in the gallbladder or biliary tract

ii. Carcinoma of head of pancreas

iii. Enlarged lymph glands in the porta hepatis

Type of bilirubin	*Class of jaundice*	*Causes*
Unconjugated	Prehepatic or hemolytic	Abnormal red cells; antibodies; drugs and toxins; thalassemia; hemoglobinopathies. Gilbert's syndrome; Crigler-Najjar syndrome
Unconjugated and conjugated	Hepatic or hepatocellular	Viral hepatitis; toxic hepatitis; intrahepatic cholestasis
Conjugated or obstructive	Post-hepatic	Extrahepatic cholestasis; gallstones; tumors of bile duct; carcinoma of pancreas; lymph node enlargement in porta hepatis

2. Portal Hypertension

3. Ascites

1. *Viruses:* HAV, HBV, HCV, Herpes, Adenovirus
2. Alcohol
3. *Toxins:* Carbon tetracholoride, Chloroform, Mushroom, Aflatoxin, Arsenic
4. *Immunological:* Autoimmune hepatitis, NASH
5. *General diseases:* Wilson's disease, Hemochromatosis, AAT deficiency, Porphyrias, Sarcoidosis, Amyloidosis
6. *Neoplasm:* Hepatocellular carcinoma, Metastatic liver disease, Lymphoma
7. *Bacterial infections:* TB, Leptospirosis, Brucella, Abscesses
8. *Parasites:* Helminths, Amebiasis, Plasmodia, Leishmania
9. *Drugs:* Salicylate, Tetracyclines, Methotrexate, Isoniazid, Rifampicin, Halothane, Methyldopa, Valproate

A. Classification based on laboratory findings	
Group I (tests of hepatic excretory function)	
i.	Serum—bilirubin; total, conjugated, and unconjugated
ii.	Urine—bile pigments, bile salts and urobilinogen
Group II: Liver enzyme panel (see Chapter 23) (These are markers of liver injury and/	
i.	Alanine amino transferase (ALT)
ii.	Aspartate amino transferase (AST)
iii.	Alkaline phosphatase (ALP)
iv.	Gamma glutamyl transferase (GGT)
Group III: Plasma proteins (see Chapter 28) (Tests for synthetic function of liver)	
i.	Total proteins
ii.	Serum albumin, globulins, A/G ratio
iii.	Prothrombin time
Group IV: Special tests	
i.	Ceruloplasmin (see Chapters 28 and 39)
ii.	Ferriti
iii.	ypsin (AAT)
iv.	Alpha fetoprotein (AFP) (see Chapter 57)
B. Classification l	**al aspects**
Group I: Markers of Liver Dysfunction	
i.	Serum bilirubin, total, conjugated
ii.	Urine: Bile pigments, bile salts and UBG
iii.	Total protein, serum albumin and A/G ratio
iv.	Prothrombin time
v.	Blood ammonia, when indicated
Group II: Markers of hepatocellular injury	
i.	Alanine amino transferase (ALT)
ii.	Aspartate amino transferase (AST)
Group III: Markers of cholestasis	
i.	Alkaline phosphatase
ii.	Gamma glutamyl transferase

:**Markers of Hepatic Dysfunction**

(Test of Excretory Function of Liver)

1.Measurement of Bilirubin

Bilirubin is the excretory product formed by the catabolism of heme.

It is conjugated by the liver to form bilirubin diglucuronide and excreted through bile Measurements of bilirubin as well as detection of bilirubin and urobilinogen in urine are important tests of liver function.

i. Normal serum bilirubin level varies from **0.2 to 0.8 mg/dL.**

The unconjugated bilirubin (bilirubin-albumin complex) (free bilirubin) (indirect bilirubin) varies from 0.2–0.7 mg/dL and conjugated bilirubin (direct bilirubin) 0.1–0.4 mg/dL.

A rise in serum bilirubin above 1 mg/dL is abnormal (latent jaundice); but jaundice appears only if the level goes above 2 mg/dL.

ii The bilirubin is estimated by **van den Bergh reaction,** where diazotized sulfanilic acid (sulfanilic acid in HCl and sodium nitrite) reacts with bilirubin to form a purple colored complex, azobilirubin. Normal serum gives a positive van den Bergh reaction.

iii. When bilirubin is **conjugated**, the purple color is produced immediately on mixing with the reagent, the

response is said to be van den Bergh **direct positive.**

iv. When the bilirubin is **unconjugated**, the color is obtained only when alcohol is added, and this response

is known as **indirect positive**.

v. If both conjugated and unconjugated bilirubin are present in increased amounts, a purple color is produced

immediately and the color is intensified on adding alcohol. Then the reaction is called **biphasic**.

vi. In **Hemolytic** jaundice, unconjugated bilirubin is increased. Hence van den Bergh test is indirect

positive. In **obstructive** jaundice, conjugated bilirubin is elevated, and van den Bergh test is direct positive.

In **hepatocellular** jaundice, a biphasic reaction is observed, because both conjugated and unconjugated bilirubins are increased

2.Urinary Bilirubin

i. In all cases of jaundice, urine should be examined for the presence of bile pigments (bilirubin), bile salts and

urobilinogen.

ii. Only conjugated bilirubin is soluble in water and is excreted in urine. Hence in prehepatic jaundice, when

the unconjugated bilirubin is increased in blood, it does not appear in urine; hence called acholuric jaundice.

iii. But in obstructive jaundice, conjugation of bilirubin is taking place, which cannot be excreted through the normal passage, and so it is regurgitated back into bloodstream; this is then excreted through urine. So in

obstructive jaundice, urine contains bilirubin; hence in old literature, it is called choluric jaundice

3.Urinary Urobilinogen

i. In cases of obstruction, bile is not reaching the intestine and so urobilinogen may be decreased or absent in

urine.

ii. In hepatocellular jaundice, urobilinogen is initially elevated, then decreases or disappears when the

obstructive stage sets in and reappears when obstruction is cleared.

iii. Urobilinogen is absent in urine, when there is obstruction to bile flow. The **first indication of recovery is**

the reappearance of urobilinogen in urine.

iv. In hemolytic anemias, urobilinogen is increased.

v. Bilirubin is detected by Fouchet's test and urobilinogen by Ehrlich's test.

4.Urine Bile Salts

Normally bile salts (sodium salts of taurocholic acid and glycocholic acid) are present in the bile; but are not seen in urine.

Bile salts in urine are detected by **Hay's test**.

Positive Hay's test indicates the obstruction in the biliary passages causing regurgitation of bile salts into the systemic circulation leading to its excretion in urine.

Obstruction can occur in obstructive jaundice and also in hepatic jaundice due to obstruction of micro biliary channels caused by inflammation.

Type of jaundice	*Bile pigment*	*Bile salt*	*Urobilinogen*
Pre-hepatic (hemolytic)	Nil	Nil	++
Hepatocellular	++	+	Normal
Post-hepatic (obstructive)	+++	++	Nil

Specimen	*Test*	*Pre-hepatic or hemolytic or retention jaundice*	*Hepatocellular jaundice*	*Post-hepatic or obstructive or regurgitation jaundice*
Blood	Unconjugated bilirubin (van den Bergh indirect test)	++	++	Normal
	Conjugated bilirubin (van den Bergh direct test)	Normal	Excretion is rate-limiting. It is the first impaired activity. In early phase, it is increased	++
	Alkaline phosphatase (40–125 U/L)	Normal	2–3 times increased	10–12 times
Urine	Bile salt (Hay's test)	Absent	Absent	Present
	Conjugated bilirubin (Fouchet's)	Absent	Present	Present
	Urobilinogens (Ehrlich test)	+++	Increased in early cholestatic phase; Absent later decreased as production is low. Earliest manifestation of recovery is presence of bilinogen in urine	Absent
Feces	Urobilins	++	Normal or decreased	Clay colored

Tests Based on Synthetic Function of Liver

1.Serum Albumin Level

Almost all the plasma proteins except immunoglobulins are synthesized by the liver.

Serum **albumin** is quantitatively the most important protein synthesized by the liver, and reflects the extent of functioning liver cell mass.

Since albumin has a fairly long half-life of 20 days, in all chronic diseases of the liver, the albumin level is decreased.

A reversal in A/G ratio is often the rule in cirrhosis, due to hypoalbuminemia and associated hypergammaglobulinemia

Normal albumin level in blood is 3.5 to 5 g/dL; and globulin level is 2.5 to 3.5 g/dL.

2.Serum Globulins

They constitute immunoglobulins (gamma) produced by B lymphocytes as well as alpha and beta globulins synthesized mainly by hepatocytes.

Gamma globulins in the serum are increased in chronic liver diseases (chronic active hepatitis, cirrhosis).

In cirrhosis, antibodies against intestinal bacteria are seen, since the cirrhotic liver cannot clear the bacteria reaching through circulation.

3.Prothrombin Time (PT)

Since prothrombin is synthesized by the liver, it is a useful indicator of liver function.

The half life of prothrombin is 6 hours only; therefore PT indicates the present function of the liver.

PT is prolonged only when liver loses more than 80% of its reserve capacity.

Vitamin K deficiency is also a cause for prolonged prothrombin time.

In case of liver disease, the PT remains prolonged even after parenteral administration of vitamin K.

4.Alpha fetoprotein (AFP)

5.Ceruloplasmin (Cp)

6.Transthyretin (Pre-albumin)

7.Alpha-1 Antitrypsin (AAT)

8.Haptoglobin

Thymol turbidity test

It is the laboratory test for the nonspecific measurement of globulins, that appear in abnormally high concentration in association with a wide variety of diseased states, notably those affecting the liver. The test consists of adding 1 volume of blood serum to 60 volumes of a buffer supersaturated with thymol; the thymol–globulin interaction results in turbidity, the degree of which thymol–globulin interaction results in turbidity, the degree of which varies with the concentration of globulins. High turbidity is observed in approximately 80 to 90 percent of individuals with acute viral hepatitis and in 20 to 70 percent of those with cirrhosis. The test is also useful in the differential diagnosis of the two main types of jaundice. A negative thymol test in the presence of jaundice is very useful for distinguishing between hepatic and extrahepatic jaundice.

Tests Based on Serum Enzymes (Liver Enzyme Panel)

The enzymes used in the assessment of hepatobiliary disease may be divided into two groups:

(a) Those indicating hepatocellular damage and;

(b) Those indicating cholestasis (obstruction).

Enzymes Indicating Hepatocellular Damage

i. Normal serum ALT (alanine amino transferase) is 10–35 IU/L and Normal serum level of AST is 8–20 U/L

ii. The levels of **amino transferases** (ALT and AST) in serum are elevated in all liver diseases

iii. **Very high levels** (more than 1000 units) are seen in acute hepatitis (viral and toxic).

iv. The degree of elevation may reflect the extent of hepatocellular necrosis.

v. In most cases the lowering of the level of transaminases indicates recovery

vi. Elevation of ALT is more in cases of hepatic disease compared to AST. But AST may be more than ALT in **alcoholic liver disease**. In alcoholic liver disease, AST/ALT ratio is more than two is quite

vii. **Moderate elevation** of amino transferases often between 100–300 U/L is seen in **alcoholic** hepatitis, autoimmune hepatitis, Wilson's disease and nonalcoholic chronic hepatitis

viii. **Minor elevation** less than 100U/L is seen in chronic viral hepatitis (hepatitis C), fatty liver and in nonalcoholic steatohepatitis (**NASH**).

ix. In chronic hepatitis and cirrhosis of liver, serum ALT poorly correlates with the degree of liver cell damage.

Normal AST: ALT ratio is 0.8. A ratio >2 is seen in
- Alcoholic hepatitis
- Hepatitis with cirrhosis
- Non-alcoholic steatohepatitis (NASH)
- Liver metastases
- Myocardial infarction
- Erythromycin treatment

A low ratio (ALT is higher) is seen in
- Acute hepatocellular injury
- Toxic exposure
- Extrahepatic obstruction (cholestasis)

Markers of Obstructive Liver Disease

Alkaline Phosphatase (ALP)

i. Very high levels of alkaline phosphatase (ALP) are noticed in patients with cholestasis or hepatic carcinoma. Bile duct obstruction induces the synthesis of the enzyme by biliary tract epithelial cells

ii. In **parenchymal diseases** of the liver, mild elevation of ALP is noticed. But in hepatitis, inflammatory edema produces an obstructive phase, during which ALP level **Liver** is elevated.

iii. Very high levels of ALP (10–12 times of upper limit) may be noticed in extrahepatic **obstruction** (obstructive jaundice) caused by gallstones or by pressure on bile duct by carcinoma of head of pancreas. Intrahepatic cholestasis may be due to virus (infective hepatitis) or by drugs (chlorpromazine).

iv. ALP is produced by epithelial cells of biliary canaliculi and obstruction of bile with consequent irritation of epithelial cells leads to secretion of ALP into serum.

v. . Drastically high levels of ALP (10–25 times of upper limit) are seen in **bone diseases** where osteoblastic activity is enhanced. For example, Paget's

(Note. There are 6 iso-enzymes for ALP. The one, which is inhibited by phenylalanine is of placental origin. It is found in blood in normal pregnancy. An isoenzyme closely resembling the placental form is characteristically seen in circulation in about 15% cases of carcinoma of lung, liver and gut and named as **Regan iso-enzyme** or carcinoplacental iso-enzyme)

Gamma Glutamyl Transferase (GGT)

i. GGT is clinically important because of its sensitivity to detect **alcohol abuse**.

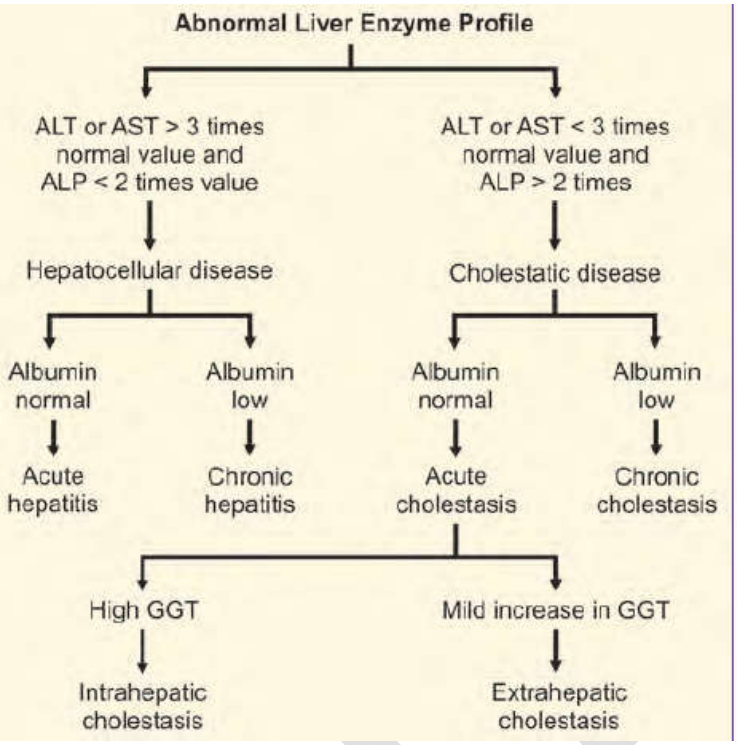
ii. GGT level in alcoholic liver disease roughly parallels the alcohol intake

iii. Elevated levels of GGT are observed in chronic alcoholism, pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease and in diabetes mellitus.

iv. In liver diseases, GGT elevation parallels that of ALP and is very sensitive of biliary tract disease. Recent studies have shown elevated GGT levels in NASH also

5'-Nucleotidase

It is also called Nucleotide phosphatase (NTP). The level is increased in hepatobiliary disease and closely parallels the ALP levels



Tests for Metabolic Capacity of Liver

Blood Ammonia

The ammonia level is an indicator of the capacity of the liver to eliminate ammonia generated in intestine. Raised ammonia in the serum/ plasma is suggestive of **cirrhosis**

Liver function test

Parameter	*Remarks*
Serum albumin	In chronic liver disease
Serum globulins	Increase in chronic hepatitis
PT	Prolonged in liver disease
PT + vitamin K	Prolonged in hepatocellular If PT normal, cholestasis
Alpha fetoprotein	Increase in carcinoma
Ceruloplasmin	Decrease in Wilson's disease, Menke's disease
Transthyretin	To assess nutritional status
Alpha-1antitrypsin	Decrease in neonatal cholestasis, progressive juvenile cirrhosis, micronodular cirrhosis
Haptoglobin Transferrin	Severe hepatocellular disease cirrhosis.
Lipoprotein X	Increase in cholestasis
Galactose	Half-life >12 minutes in tolerance test cirrhosis, infective hepatitis
Amino acids	Increased aromatic amino acids + branched chain aminoacids in hepatic coma; both increased in cirrhosis
Serum bilirubin	See Table 26.4.
Urine bilirubin	See Table 26.4
Urine urobilinogen	See Table 26.2
Plasma bile acids	Post-prandial rise in hepatic dysfunction; increased fasting level in portosystemic shunting
Urine bile salts	Positive in post-hepatic jaundice and hepatic jaundice
Ammonia	Increase in cirrhosis, portocaval anastamosis
Transaminases	
Viral hepatitis	ALT and AST increased
Chronic active hepatitis	N or slight increase
Cholestasis	Slight increase
Alcoholic hepatitis	ALT/AST ratio reversed
ALP	Increase in cholestasis
GGT	Increase in cholestasis

Kidney function test

- The major functions of the kidneys are to excrete metabolic waste products as well as to maintain water, pH, electrolyte balance, production of calcitriol and erythropoietin
- A decrease in kidney function is due to a reduction in the performance of nephrons.
- The functional unit of the kidney is the nephron, which is composed of the Bowman's capsule with the glomerular tuft of capillaries, the proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT) and collecting tubules.

Functions of Kidney

•Maintenance of Homeostasis

Excretion of Metabolic end products

•Elimination of Foreign materials

•Regulation of Acid –base balance

•Retention of vital substances

•Regulation of arterial pressure

•Production of Hormones:

□Erythropoietin

□Calcitriol

□Renin

Filtration: 180 liters/day of water with all sodium, chloride, sugar and amino acids

Reabsorption: 178.5 liters reabsorbed; all glucose and amino acids reabsorbed; most of sodium and chloride reabsorbed.

Classification of Renal Function Test

I. Urine Analysis

Physical Examination

Chemical Examination

Microscope Examination

II. Blood Analysis

Estimation of Plasma proteins

Estimation of NPN

III. Tests for Glomerular Function

Creatinine clearance

Urea clearance

Inulin clearance

IV. Test to Measure RPF

PAH Test

V. Test for Tubular Function

Urine concentration test

Urine dilution test

Acid load test

Phenol –sulphophthalein test

I. Urine Analysis

Physical Examination

Urine analysis

Urinary Output Volume: 1,500 ml / day

(a) Polyuria -2,500 ml / day

Diabetes Mellitus

Diabetes insipidus

Chronic glomerulonephritis

(b) Oliguria-500ml1day

Fever

Diarrhea

Acute renal failure

(c) Anuria -Complete cessation of urine

Acute tubular Necrosis

Bilateral renal stones

Prostate enlargement

(ii) pH:

Urine is normally acidic with a pH of 4.5 to 6.0 Alkaline urine is found in cases of UTI

(iii) Specific Gravity:

1.010 to 1.025 Indicates the concentrating ability of kidney

(iv) Osmolality:

Urine osmolality depends on the state of hydration. After excessive fluid intake the osmotic concentration may fall as low as 50 m osm/kg, where as with restricted fluid intake, it is up to 1,200 m osm/kg. On average fluid intakes, 300 to 900 m osm / kg are found.

(v). Colour:

Urine is transparent, pale yellow (or) amber in colour.

(vi). Odour:

Fresh urine is normally aromatic. Foul smell indicated bacterial Infection

Chemical Examination

(i)

Glucose:

Normal urine contains small amounts of glucose, which cannot be detected by routine test.

Presence of detectable amounts of glucose in urine is called glycosuria.

Protein:

The glomerular basement membrane does not usually allow passage of albumin and large proteins.

Increased amounts of protein in urine is called proteinuria.

Proteinuria –Indication of leaky glomerulli.

Most common type of proteinuria is due to albumin.

(iii)Blood:

Intact glomerulus does not allow the passage of RBC's

But, with severe glomerular damage, RBC leakage occurs –Hematuria.

v. KetoneBodies:

Ketone Bodies

They are acetoacetic acid, beta hydroxybutyric acid and acetone.

Ketonuria is seen in diabetes mellitus, starvation, persistent vomiting, von Gierke's disease and in alkalosis.

Ketone bodies are analyzed by **Rothera's test**.

Bile Salts

Bile salts are present in urine during the early phase of obstructive jaundice Their presence is identified by Hay's test..

Bile Pigments-obstructive jaundice

Urobilinogen-hemolytic jaundice

Microscopic Examination

- Urine sample is collected
- Subjected to centrifugation
- Microscopic Examination of the centrifuged
- Urinary sediment defects the following.

(i) Cells –RBC, WBC, pus cells

(ii) Crystals –Calcium phosphate, Calcium oxalate, Amorphous phosphate

(iii) Casts –Hyaline casts, granular casts, Red blood casts.

Estimation of Blood

Estimation of Plasma Proteins:

NormalValue:6.4 to 8.3 gm%

Components:

(i) Albumin :3 –5 gm%

(ii) Globulin :2 –3 gm %

(iii) Fibrinogen:0.3 gm%

A/G ratio: 1.7:1

Estimation of Non –Protein Nitrogenous Substances

Normal Value: 28 to 40 mg%

Components:

(i) Urea : 15–40 mg/dL

(ii) Uric acid: 3–7 mg/dL (M)

2–5 mg/dL (F)

(iii) Creatinine : 0.7–1.4 mg/dL(M)

0.4–1.3 mg/dL(F)

Normal blood levels of these substances are ↑sed in case of impairment of renal function.

An Increase of these end products in blood -Azotaemia.

Tests for Glomerular Function -Renal Clearance Tests

•A renal clearance test is employed to assess the rate of glomerular filtration.

Normal GFR for young adults is 120–130 mL/mt/1.73M^2.

GFR is also affected by age, sex, body size, protein intake and pregnancy.

•Renal clearance is defined as the volume of plasma from which the substance is completely cleared by the kidneys per minute. (ml/min)

$$\text{Clearance} = \frac{U \times V}{P}$$

Where, U -Concentration of substance in urine (mg/dl)

V -Volume of urine excreted (ml/min)

P -Concentration of substance in plasma(mg/dl)

- If the substance is freely filtered across the capillary wall, and neither secreted nor reabsorbed, then its clearance is equal to glomerular filtration rate.
- A substance which meets these requirements is an ideal filtration marker.
- If the substance is also secreted by the tubules, the clearance exceeds GFR.
- For those which are reabsorbed by tubules, clearance is less than GFR

Creatinine Clearance Test

Importance of Creatinine Clearance

i. Creatinine is a waste product, formed from creatine phosphate.
ii. This conversion is **spontaneous, non-enzymatic,** and is dependent on total muscle mass of the body.

iii. It is not affected by diet, age or exercise. Women and children excrete less creatinine than men, because of their smaller muscle mass. rapidly excreted

iv. Since the production is continuous, the blood level **will not fluctuate** much, making creatinine an ideal substance for clearance test.

.

Reference Values of Creatinine

Adult males, 0.7 – 1.4 mg/dL

Adult females, 0.6 – 1.3 mg/dL

Children, 0.4 – 1.2 mg/dL.

About 50% kidney function must be lost before creatinine level in blood is raised. Serum level usually parallels the severity of the disease. *Creatinine level more than 1.5 mg/dL indicates impairment*

of renal function. Creatinine is quantitated by **Jaffe's test** (alkaline picrate).

Procedure for Creatinine Clearance Test

Give 500 mL of water to the patient, to promote good urine flow.

After about 30 minutes, ask to empty the bladder and discard the urine.

Exactly after 60 minutes, again void the bladder and collect the urine, and note the volume.

Take one blood sample. Creatinine level in blood and urine are tested and calculated.

Un corrected clearance = $(U/P) \times V$

where U is the urine creatinine concentration,

P is theplasma creatinine concentration and

V is the urine flow in mL/min

It is useful to correct the clearance value with body surface area. This is important, especially in children, and persons with short or tall frame. Creatinine clearance corrected for surface area could be calculated as:

$$\frac{U \times V \times 1.73}{P \times A}$$

When corrected for surface area, the creatinine clearance value will become comparable between males, females and children, which is about 100 mL/min/1.73 sq meter.

Normal value=95-105ml/min/1.73m^2

Interpretation of Creatinine Clearance

i. A decreased creatinine clearance is a very sensitive indicator of reduced **glomerular filtration rate**.

ii. Clearance value up to 75% of the average normal value may indicate adequate renal function.

In older people, the clearance is decreased.

iii The importance of creatinine clearance is in the **early detection** of functional impairment of kidney

without overt signs and symptoms. Changes in plasma creatinine which may not apparently indicate

abnormal function may show gross changes in the value of clearance.

iv. The test is very helpful in long term monitoring of patients with renal insufficiency (ups and downs) under a protein restricted diet.

Urea Clearance Test

Importance of Urea Clearance

The urea clearance is less than GFR, because urea is partially reabsorbed .Urea clearance is the number of mL of blood, which contains the urea excreted in a minute by kidneys.

Procedure

Allow the patient to have a normal breakfast. At 9 AM give a cup of water and the patient is instructed to void

the bladder, and urine is discarded. At 10 AM bladder is completely emptied and the volume of urine is measured and the urine urea is estimated. A blood sample is taken and blood urea is also estimated.

Maximum Urea Clearance

The urea clearance is calculated by the formula

$U \times V/P$

where U = mg of urea per mL of urine;

P = mg of urea per mL of plasma and

V = mL of urine excreted per minute.

This is called maximum urea clearance and the normal value is found to be 75 mL/min

Standard Urea Clearance

But the clearance value is decreased when V, the volume of urine, is less than 2 mL/min. Then, it is called standard urea clearance, where the normal value is found to be 54 mL/min, and is calculated as:

$$\frac{U \times \sqrt{V}}{P}$$

Interpretation of Urea Clearance Value

i. If the value is below 75% of the normal, it is considered to be **abnormal**.

ii. The values fall progressively with failing renal function.

ii. The clearance value may be abnormal even though the plasma urea values are within normal limits. The

plasma urea values will start to rise only when the clearance value falls below 50% of the normal.

iii. Urea is normally reabsorbed from renal tubules and therefore, tubular function also affects urea clearance. Hence, creatinine clearance test is more preferred.

iv. Urea is freely filtered by the glomerulus and passively reabsorbed in both PCT and DCT. Urea clearance is less than GFR

Inulin Clearance

Inulin is a polysaccharide of fructose.

It is not appreciably metabolized by the body.

It is neither absorbed nor secreted by the tubules.

Therefore, inulin clearance is a measure of GFR.

The value of inulin clearance is 125 mL/min.

About 100 mL of sterile 10% solution of inulin is given as slow intravenous drip within 2 hours. Urine specimen formed during this period is collected totally.

Blood sample is taken at the middle of the test.

Inulin is estimated by resorcinol giving a red color.

The test needs continuous infusion of inulin so as to keep the plasma level adequate.

Since it involves administration of an extraneous compound, this procedure is not used routinely.

IV. Test To Measure Renal Plasma Flow

Renal plasma flow (RPF), which is the volume of blood plasma delivered to the kidneys per unit time

Para –Aminohippurate Test

(i) PAH: Filtered and secreted

(ii) Not reabsorbed

(iii) PAH clearance is defined as the amount of plasma passed through kidneys.

(iv) Known amount of PAH is injected into the body

(v) Concentration of PAH in plasma and urine volume of urine Excreted.

$$RPF = \frac{U \times V}{P}$$

(vi) Normal Value: 600ml/min

Filtration fraction

Filtration Fraction (FF): The filtration fraction (FF) is the fraction of plasma passing through the kidney which is filtered at the glomerulus and is obtained by dividing the inulin clearance by the PAH clearance.

Filtration Fraction is the ratio of the glomerular filtration rate (GFR) to the renal plasma flow (RPF).

Filtration Fraction, FF = GFR/RPF

The GFR on its own is the most common and important measure of renal function.

However, in a condition such as renal artery stenosis, the blood flow to the kidneys is reduced. The filtration must therefore be increased in order to perform the normal tasks of the kidney in balancing fluid and electrolytes in the body. This would be reflected by a high filtration fraction, showing that the kidneys have to do more work with the fluid they are receiving.

- Diuretics such as loops and thiazides decrease the filtration fraction.
- Catecholamines (Norepinephrine and Epinephrine) increase the filtration fraction
- Severe haemorrhage will also result in an increased filtration fraction

Normal range: 0.16 to 0.21 in an adult.

V. Test For Tubular Function

a) Urine Concentration Test:

(i) Fluid intake is withheld for 15 hours.

(ii) Early morning urine sample is collected.

(iii) Specific gravity is measured.

(iv) It specific gravity exceeds 1.025, the renal concentrating ability is considered normal. If not, indicates renal impairment.

(v) Clinically, the loss of concentrating ability is manifested by nocturia (passage of urine at night)

b) Urine Dilution Test

(i)Bladder is Emptied.

(ii) 1,000 to 1,200 ml of water is given to the patient.

(iii) Urine sample is collected every hour for the next 4 hours.

(iv) Specific gravity is measured

(v) If the functioning of renal tubule is normal, the urinary specific gravity should fall to 1.005 or less.

(vi) It the renal tubules are diseased, the concentration of the solutes in urine will remain constant irrespective of excess water intake.

c)Acid Load Test

(i) Acid load test is used for the diagnosis of renal tubular acidosis.

(ii) Ammonium chloride is administered orally in a gelatin capsule (0.1g/kg body wt)

(iii) Ammonium chloride Dissociates into:

(iii) Ammonium chloride Dissociates into:

NH4 + Cl-

(liver) ↓ ↓

Hcl (counted balanced by H+)

Urea

↓

urine acidification

(iv) Urine is collected 2 –8 hours after ingestion

(v) PH below 5.5 : Normal

Between 5.5 to 7.0 : Renal tubular acidosis

d)Phenolsulfophthalein Test

(i) Non –toxic dye

(ii)Excreted by kidneys

(iii) Intravenous injection of 6mg of PSP in /ml of saline is given.

(iv) Urine specimen collected at 15,30,60 and 120 minutes

(v)Rate of excretion of the dye is measured.

(iv) 15 minutes urine : 25% PSP

(vii) Excretion less than 23% in 15 minutes urine sample indicates impaired Renal excretory function

Serum enzymes in patients with renal failure

The serum enzymes of patients with end-stage renal disease (ESRD) are commonly abnormal. This is due in part to the absence of renal excretion and to the frequent presence of multiple comorbid conditions. Since the diagnosis of many diseases is based upon the detection of elevated levels of these enzymes, the accurate clinical assessment of the patient with ESRD is not possible.

LIVER ENZYMES IN RENAL DISEASE

The serum enzymes most commonly used to help assess the diagnosis of hepatobiliary disease include the aminotransferases, alkaline phosphatase, and gammaglutamyl transpeptidase (GGT).

Aminotransferases — Serum concentrations of aspartate and alanine aminotransferase (AST [SGOT] and ALT [SGPT]) are routinely measured to assess liver function in patients with and without renal failure.

The concentrations of serum aminotransferases in both chronic dialysis and chronic renal failure patients most commonly fall within the lower end of the range of normal values Although the exact cause is unknown, possible underlying reasons may be related to pyridoxine deficiency (pyridoxal phosphate is a necessary coenzyme for ALT and AST) and/or the presence of an inhibitory substance in the uremic milieu

Creatine Kinase is assayed in blood tests as a marker of damage of CK-rich tissue such as in myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, and acute kidney injury

LDH is found to be elevated in chronic renal failure

Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells and its level is found to be elevated kidney disease

Renal Failure –Disorders

Failure of excretory functions of kidney

↓se GFR

ACUTE RENAL FAILURE	CHRONIC RENAL FAILURE
CAUSES:	CAUSES:
(i) Acute Nephritis	(i) Chronic Nephritis
(ii) Acute Tubular Necrosis	(ii) Polycystic kidney
(iii) Renal calculi	(iii) Renal calculi
(iv) Damage of Renal tissue	(iv) Urethral constriction
Features	
(i) Oliguria	(i) Uremia
(ii) Anuria	(ii) Acidosis

(iii) Proteinuria	(iii) Edema
(iv) Hematuria	(iv) Anemia
(v) Edema	(v) Hyperparathyroidism

Coagulation Tests

- The process of hemostasis occurs in three phases:

1. The vascular platelet phase, which assures primary hemostasis;
2. Activation of the coagulation cascade, which assures formation of the clot;
3. Activation of a series of control mechanisms, which stop propagation of the clot and limit activation of the coagulation cascade to the region of endothelial rupture.

Tests of the Vascular Platelet Phase of Hemostasis

Bleeding Time

Definition

Bleeding time is a medical test done on someone to assess their platelets function. It involves making a patient bleed then timing how long it takes for them to stop bleeding. Without the aid of external pressure, bleeding usually stops within 7 to 9 minutes.

It involves cutting the underside of the subject's forearm, in an area where there is no hair or visible veins. The cut is of a standardized width and depth, and is done quickly by an automatic device.

A blood pressure cuff is used above the wound, to maintain venous pressure at a specified value. The time it takes for the bleeding to stop (i.e. the time it takes for a platelet plug to form) is measured. Cessation of bleeding can be determined by blotting away the blood every several seconds until the site looks "glassy".

Basic Science

The vascular platelet phase of hemostasis consists of a primary vasoconstriction that serves to decrease blood flow, followed by adherence of platelets to the ruptured endothelium (adhesion) and each other (aggregation). This platelet aggregate, called the platelet plug, stops the bleeding and forms a matrix for the clot. The bleeding time is an excellent screening test for the vascular platelet phase of hemostasis.

Clinical Significance

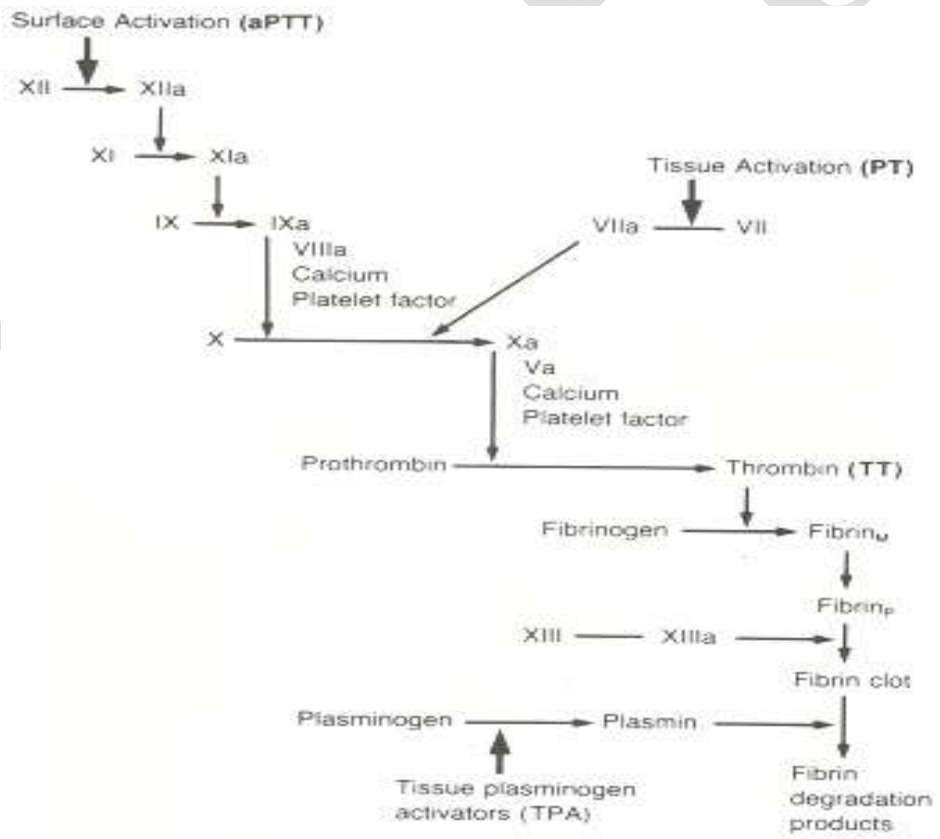
Patients with abnormalities of the vascular platelet phase of hemostasis present with purpura (petechiae and ecchymoses) and spontaneous bruising. They may have mucosal bleeding and fundus hemorrhages. Commonly, the problem is either thrombocytopenia, easily evaluated by a platelet count, or abnormal platelet function, which can be diagnosed with platelet function studies.

Tests of the Coagulation Cascade

These in vitro tests—

- the activated partial thromboplastin time (aPTT),
- prothrombin time (PT)
- thrombin time (TT)—

measure the time elapsed from activation of the coagulation cascade at different points to the generation of fibrin.



Activated Partial Thromboplastin Time

Definition

The aPTT measures the time necessary to generate fibrin from initiation of the intrinsic pathway . Activation of factor XII is accomplished with an external agent (e.g., kaolin) capable of activating factor XII without activating factor VII.

Blue Top Vacutainer tube used for PT and PTT blood tests. It is filled with buffered tri-sodium citrate solutions

Partial thromboplastin time is typically analyzed by a medical technologist or a laboratory technician on an automated instrument at 37 °C (as a nominal approximation of normal human body temperature). The test is termed "partial" due to the absence of tissue factor from the reaction mixture.

Blood is drawn into a test tube containing oxalate or citrate, molecules which act as an anticoagulant by binding the calcium in a sample. The blood is mixed, then centrifuged to separate blood cells from plasma (as Partial thromboplastin time is most commonly measured using blood plasma).

A sample of the plasma is extracted from the test tube and placed into a measuring test tube.

Next, an excess of calcium (in a phospholipid suspension) is mixed into the plasma sample (to reverse the anticoagulant effect of the oxalate enabling the blood to clot again).

Finally, in order to activate the intrinsic pathway of coagulation, an activator (such as silica, celite, kaolin, ellagic acid) is added, and the time the sample takes to clot is measured optically. Some laboratories use a mechanical measurement, which eliminates interferences from lipemic and icteric samples

Normal Level-30-40 Sec

Basic Science

This test is abnormal in the presence of reduced quantities of factors XII, IX, XI, VIII, X, V, prothrombin, and fibrinogen (all integral parts of the "intrinsic" and "common" pathway. It is usually prolonged if a patient has less than approximately 30% normal activity. It can also be abnormal in the presence of a circulating inhibitor to any of the intrinsic pathway factors.

(Notably, deficiencies in factors VII or XIII will not be detected with the PTT test.)

Clinical Significance

The aPTT is a good screening test for inherited or acquired factor deficiencies. Inherited disorders including classic hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency, or Christmas disease) are well-known diseases in which the aPTT is prolonged.

Acquired factor deficiency is common. Vitamin K deficiency, liver dysfunction, and iatrogenic anticoagulation with warfarin are most common.

A prolonged aPTT that cannot be completely normalized with the addition of normal plasma can be explained only by the presence of a circulating inhibitor of coagulation.

The most common inhibitors should be considered antithrombins. These compounds inhibit the activity of thrombin on the conversion of fibrinogen to fibrin .The two most common inhibitors are heparin, and fibrin degradation products (FDP).

Other inhibitors appear to be antibodies. The easiest to understand is the antibody against factor VIII in patients with hemophilia A treated with factor VIII concentrate. Inhibitors against other factors have been described with a variety of diseases

A particular problem may be seen in patients suffering from systemic lupus erythematosus. These patients may present with a prolonged aPTT without evidence of bleeding. Some present with thrombosis. The abnormality cannot be corrected with normal plasma and has been referred to as the "lupus anticoagulant." This phenomenon does not represent an in vivo problem with the coagulation cascade. Rather, it is a laboratory abnormality caused by the presence of a serum constituent that interferes with the in vitro partial thromboplastin test.

Occasionally the reported value of the aPTT will be lower than normal. This "shortened" time may reflect the presence of increased levels of activated factors in context of a "hypercoagulable state." It is seen in some patients in the early stages of DIC (Disseminated intravascular coagulation)

Prothrombin Time

Definition

The PT measures the time necessary to generate fibrin after activation of factor VII. It measures the integrity of the "extrinsic" and "common" pathways (factors VII, V, X, prothrombin, and fibrinogen).

Technique

Citrated plasma and an activating agent (usually thromboplastin extracted from animal brain) are incubated at 37°C. The plasma is recalcified and the time is measured until fibrin filaments are observed. Each laboratory has its own normal value, usually between 12 and 15 seconds.

Basic Science

As with the interpretation of a prolonged aPTT, a prolonged PT may reflect either factor deficiency or a circulating inhibitor of coagulation. The distinction is made by repeating the test after a 1:1 mix with normal plasma.

The test is more sensitive than the aPTT for deficient levels of factors, and a relatively small drop in factor VII levels may prolong the PT.

Clinical Significance

Inherited deficiency of factor VII is a rare bleeding disorder characterized by a prolonged PT and a normal aPTT. The PT completely corrects when mixed with normal plasma. Acquired deficiencies are usually related to liver disease, warfarin therapy, or depletion secondary to consumptive coagulopathy, severe bleeding, or massive transfusion.

Circulating inhibitors are most often directed at factor X or thrombin. Most common are heparin or products of fibrinolysis. In their presence the prolonged PT cannot be completely corrected to normal in a 1:1 mixing study.

PT test may also be called an INR test. INR (international normalized ratio) stands for a way of standardizing the results of prothrombin time tests, no matter the testing method. It lets your doctor understand results in the same way even when they come from different labs and different test methods. In some labs, only the INR is reported and the PT is not reported.

Formula:

$(INR=(PT\ patient/PT\ normal)^{ISI})$

PT patient = patient's measure PT (seconds)

PT normal = laboratory's geometric mean value for normal patients (seconds)

ISI = International Sensitivity Index

In healthy people an INR of 1.1 or below is considered normal

Thrombin Time

Definition

This test measures the time necessary to drive the reaction of fibrinogen to fibrin in the presence of thrombin. It measures the integrity of this reaction and isolates an abnormality to either a decrease in normal fibrinogen or an inhibitor to its activation.

Technique

Citrated plasma is incubated at 37°C and thrombin is added to the solution. Time is measured from the addition of thrombin to the generation of fibrin filaments. Calcium is unnecessary.

Normal level -12-14 sec

Basic Science

Abnormalities can be explained in one of three ways: deficient fibrinogen (< 100 mg/dl), abnormal fibrinogen, or an inhibitor to the reaction. As with other tests of the coagulation cascade, if a 1:1 mixing study normalizes the prolonged time, one is dealing with factor deficiency. As it pertains to fibrinogen, however, one must distinguish a decrease in normal fibrinogen from the production of an abnormal fibrinogen (dysfibrinogenemia).

Clinical Significance

Acquired deficiency of fibrinogen is usually due to a consumptive coagulopathy or, less often, severe liver disease. Hereditary deficiencies exist, but with variable clinical presentations. Afibrinogenemia is an often fatal childhood condition.

Abnormal fibrinogen (dysfibrinogenemia) can be acquired or inherited. The acquired form is usually found in association with severe liver disease, but has been reported in other diseases. The congenital form is rare, usually autosomal dominant. A discordance between immunologic and physiologic measurements of fibrinogen is the key to diagnosis.

The most common acquired inhibitors of this reaction are heparin and fibrin degradation products (FDP). The effect of heparin can be eliminated by catalyzing the reaction with reptilase, which, unlike thrombin, is insensitive to heparin. FDP are commonly seen in consumptive coagulopathies and primary fibrinolytic states.

POSSIBLE QUESTIONS

1. Explain the significance of estimation of conjugated and total bilirubin in serum.
2. Write a note on bilirubin metabolism.
3. Describe the various renal function tests.
4. Explain the various stages of blood coagulation.
5. Discuss the clinical significance of partial thromboplastin time and APTT.
6. Write the clinical significance of Phosphatases.
7. Write the clinical significance of transaminases.
8. Describe Insulin clearance test.
9. Describe urea and creatinine clearance test.
10. Discuss about Liver Function Test.
11. Explain the clinical manifestations of liver disease.
12. Discuss on liver enzyme panel and their role in clinical diagnosis.
13. Explain the clinical significance of GGT, LDH and creatine phosphokinase in kidney function