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TOPIC: DIABETES

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ABSTRACT: In the scientific paper so we are present recalling information of whole reviews and update version of the diabetes conditions. Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders characterized by elevated levels of blood glucose (sugar). This occurs when the body either doesn't produce enough insulin (a hormone that regulates blood sugar) or cannot effectively use the insulin it produces.Type 1 diabetes cannot be prevented, but Type 2 diabetes can often be delayed or prevented through a healthy lifestyle, including a balanced diet and regular exercise.It's Important for individuals with diabetes to work closely with healthcare professionals to develop a personalized management plan to prevent complications and lead a healthy life. Regular check-ups, education, and support are crucial for successful diabetes management. Diabetes management in India faces several challenges, including limited healthcare resources, lack of awareness, and varying access to medical care in rural and urban areas.India has around 101 million people living with diabetes and another 136 million people in pre-diabetes stages, found a recently published study by the Madras Diabetes Research Foundation and Indian Council of Medical Research.Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycaemia, also called raised blood glucose or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes, and raised blood glucose causes around 20% of cardiovascular deaths Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increased 13%By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22% globally between 2000 and 2019.

I. INTRODUCTION :

[NIH]Pancreas is a compound gland, i.e. exocrine and endocrine glands. Islets of Langerhans comprise three types of cells (a, β and y cells) constituting 1-2% of pancreatic tissue.Annular pancreas is a congenital condition in which the head of the pancreas surrounds the second portion of the duodenum.[4]It may be associated with duodenal atresia. Infants present with feeding disorders and growth retardation (Fig. 26.1).Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders characterized by elevated levels of blood glucose (sugar).[3]This occurs when the body either doesn't produce enough insulin (a hormone that regulates blood sugar) or cannot effectively use the insulin it produces.[2]

II. FUNCTIONS OF ISLETS OF LANGERHANS:

Alpha Cells of PancreasLow blood glucose stimulates release of glucagon by a cells of pancreas.[1]Glucagon acts on liver and adipose tissue, increases blood sugar levels by glycogenolysis and gluconeogenesis. Hyperglycemia inhibits release of glucagon.[2][1]

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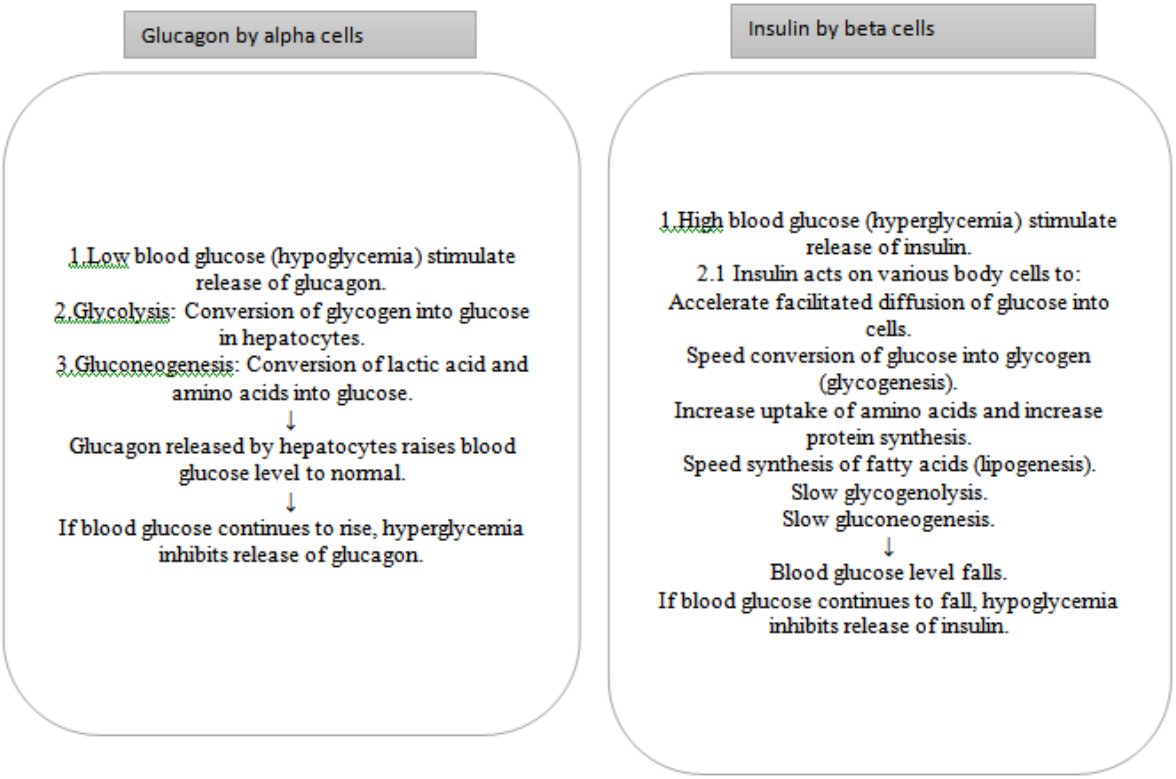

III. NOGLUCOGENESIS:

Lactic acid and certain amino acids are converted into glucose in liver by glucagon.[4][1]

3.1Beta Cells of Pancreas:cells situated around capillaries within pancreatic bules synthesize insulin.High blood glucose level (hyperglycemia) stimulates eleas of insulin, Insulin acts on principal target tilates.[6]Example :liver, adipose tissue and skeletal muscles.It accelerates facilitated diffusion of glucose into the cells resulting in decreased blood sugar levels.Action of insulin and glucagon on glucose fat and proteins metabolism are given in Table A.[7][1]

3.2Carbohydrate metabolism:Insulin speeds conver sion of glucose into glycogen (glycogenesis) in Liver nd muscles. It inhibits glycolysis and neogenesis.[11][1]

3.3Fat metabolism:Insulin speeds synthesis of fatty acids (lipogenesis) from glucose derived from adipose tissue. It inhibits metabolic breakdown of fat.[3][2]

3.4Protein metabolism:Insulin increases uptake of amino acids and protein synthesis by liver. It inhibits protein breakdown.[14]

3.5Alpha Cells of Pancreas:These cells secrete somatostatin hormone, and inhibit the release of insulin by pancreas.[10][7]It decreases secretion, motility and absorption in the digestive tract somatostatin also inhibits the pituitary release of growth hormone.[18]

IV. SYNTHESIS OF INSULIN:[CENTERS DISEASE CONTROL]

•Rough endoplasmic reticulum of pancreatic ß cellsSynthesize inactive form pre-proinsulin. It is transferred to Golgi apparatus. Pre-proinsulin gets cleaved into insulin and C-peptide.[18][10]

• C peptide levels are marker of endogenous synthesis of insulin.[13]Its estimation is used to distinguish type 1 diabetes mellitus from type 2 diabetes mellitus (Table B). Pathogensis of type 1 diabetes mellitus is shown in Table C.[18]

4.1Function of Insulin:

Normally, insulin molecules bind to the receptors on the body's cells. It allows glucose entry into the cells, where it is converted to glycogen to be utilized forenergy.[13]It also stimulates protein synthesis and free fatty acid storage in adipose tissue. Ittsulin deficiency blocks tisstes access to essential nutrients for fuel and storage.[12]

4.2Insulin Receptor Substrate Molecules:[Article]Insulin receptor substrate molecules (IRS-1, IRS-2, IRS 3 and IRS-4) play central role in insulin signaling and maintenance of basic cellular functions, i.e. growth, survival and metabolism.[9]

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IRS-1 and IRS-2 participale in glucose production in liver, glucose uptake in skeletal muscle and adipose tissue; and insulin synthesis by pancreatic ß cells.[4]
IRS-1 plays central role in glucose production skeletal muscle. IRS-2 participates in regulation insulin uptake by liver.[2]It also takes part in development and survival of pancreatic ß cells.[9]
IRS-3 and IRS-4 play central role in insulin signaling IRS-1 defect has been demonstrated in type 2 diabetes mellitus.[7]

Table A:Actions of insulin and glucagon on carbohydrate, fat and protein metabolism.

Carbohydrate metabolism (glucose):

Parameters	Insulin	Glucagon
Glucose transport	Insulin enhances glucose transport to skeletal muscle and adipose tissue	-
Glycogen synthesis	Increased glycogen synthesis Decreases gluconeogenesis	Enhances glycogen breakdown Increases gluconeogenesis

Fat metabolism:

Parameters	Insulin	Glucagon
Fatty acids and triglycerides synthesis	Promotes fatty acid and triglycerides by the liver	-
Fat storage in adipose tissue	Increases fatty acid into adipose tissue Increases the conversion of fatty acids into triglycerides by increasing availability of a-glycerol phosphate through increased transport of glucose in adipose tissue Maintains fat storage by inhibiting breakdown of stored triglycerides by adipose cell lipase	Activates adipose cell lipase, making increased amounts of fatty acids available to the body for use as energy

Proteins metabolism:

Parameters	Insulin	Glucagon
Amino acids transport	Increases active transport of amino acids into the cells	Increases amino acids uptake by liver cells and their conversion to glucose by gluconeogenesis
Protein synthesis	Increases protein synthesis by increasing transcription of messenger RNA and accele- rating protein synthesis by ribosomal RNA Decreases protein breakdown by increasing the use of glucose and fatty acids as fuel	

Table B:C-peptide revati in lype 1 and type 2 diabetes melitus

Parameters	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Beta Cell mass	Beta cell mass is reduced	Beta cell mass is normal
Endogenous insulin synthesis	It is absent or reduced	There is normal synthesis of insulin. But peripheral tissue shows resistance to insulin
Binod C-peptide level	Absent or low level	Increased level

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- Diabetes mellitus is a metabolic disease of carbohydrate, fat and protein brought about by impaired ß cell synthesis or release of insulin, or the inability of tissues to utilize insulin leading to hyperglycemia.[18][16]
- Uncontrolled diabetes mellitus is associated with increased risk of life-threatening complications, ie. Macrovascular diseases (atherosclerosis) like coronary artery disease, cerebral vascular disease, peripheral vascular disease (gangrene) and microvascular diseases like retinopathy, nephropathy and neuropathy.[15][12]

V. DIAGNOSTIC CRITERIA OF DIABETES MELLITUS:

[Full Overview Book]

Euglycemic individual (normal person): Fasting blood glucose <100 mg/dl is considered as normal and <140 mg/dl is considered as normal after oral glucose tolerance test (OGTI) (Table C). Diagnostic criteria of diabetes mellitus is any one of the following:

• Fasting blood glucose level ≥ 126 mg/dl (7 mmol/L): Fast- ing is defined as no caloric intake for at least 8 hours.[1]

• Randomblood glucose level ≥200 mg/dl (11.1 mmol/ Patient has classical signs and symptoms of diabetes mellitus.[4]

• Abnormal blond sugar level after oral glucose tolerance (OGTT): Two-hour plasma glucose level is estimated after a glucose challenge of 1.75g/kg (maximum doseof 75 g) is ≥200 mg/dl (11.1 mmol/L).[9]

• Impaired oral glucose tolerance test (OGTT): Individuals with fasting blood glucose between 100 and 126 and OGTT between 140 and 200 mg/dl are considered pre-diabetics. There is increased risk of development of diabetes mellitus in 5-10% of cases.[2]

• HbAlc (Glycated hemoglobin): Hemoglobin Alc is 26.5% is accepted additional criteria for diagnosing diabetes mellitus. Glycosylated HbAlc is formed by non-enzymatic combination of glucose with globin of hemoglobin.[13] Its estimation is used for diagnosis and monitoring diabetes mellitus (Table D)

Table C:Diagnostic criteria of diabetes mellitus (any one of these criteria) adapted from the American Diabetes Association.

Test		Normoglycemic state	Diabetes mellitus
Fasting blood sugar	<100 mg/dl (5.6 mmol/L)	≥126 mg/dl (7 mmol/L)	
Two-hour OGTTS	<140 mg/dl (7.8 mmol/L)	2200 mg/dl (11.1 mmol/L)	
HbA1c (glycated hemoglobin)	-	≥ 6.5%	
Classic symptoms of hyperglycemia or hyperglycemic crisis and blood sugar level	-	≥200 mg/dl (11.1 mmol/L)	

Metabolic derangements in diabetes mellitus:

• Insulin deficiency prevents tissueMetabolism of glucose and liver storage of glucose as glycogen, hyperglycemia is the result.

• Instead of glucose, tissue burn fat,Which produces a large amount of acid.

• Excess glucose spills into urine and carries water with it; dehydration is the result.

Table D:Glycosylated HbAlc levels interpretation.

Parameters	Level	Percentage
Normal glucose tolerance test	HbA1c	<5.6%
Pre-diabetes mellitus	HbA1c	5.7-6.4%
Diabetes mellitus	HbA1c	≥ 6.5 %

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VI. CLASSIFICATION OF DIABETES MELLITUS:

Diabetes mellitus is classified as diabetes mellitus.[18][11]

Primary or Based on pathogeneses, it may be type 1 immune mediated) or type-2 (non-immune mediated) (Table E to G)

Table E:Classification of diabetes melitus.

Primary diabetes mellitus	**Secondary diabetes mellitus**
Juvenile onsetinsulin -dependent diabetes mellitus (5-10%)	Pancreatic diseases Hereditary hemochromatosis acute pancreatitis, cystic fibrosis diabetes mellitus, parec carcinoma of alpha cells, amyloidosis pancreas
Adult onset non-insulin-dependent diabetes mellitus	Adrenal gland diseases: Cushing syndrome and pheochromocytoma
Maturity onset diabetes mellitus of the young: MODI, MOD2, MOD3, MODI, MOD5, neonatal diabetes mellitus and maternal inherited diabetes mellitus and deafness (MIDD)	Thyroid gland disorders: Hyperthyroidism Gestational diabetes mellitus
Gestational diabetes mellitus	Therapeutic agents administration: Glucocorticoids. Thiazide Drugs, cyclosporine Infectious agents: Mumps, cytomegalovirus, HIV infections

Table F:Differences between type 1 and type 2 diabetes mellitus

Parameters	**Type 1 diabetes mellitus**	**Type 2 diabetes mellitus**
Prevalence	5 to 10%	90 to 95%
Age on onset	Children and adolescents <20 years	Adults >30 years
Type of onset	Rapid (abrupt), symptomatic polyuria, polydipsia, polyphagia often with severe ketoacidosis (fruity odor to breath)	Gradual often symptomatic
Body habitus	Normal, recent loss of weight (usually thin)	Usually obese (80%)
Family history	Uncommon (<20%)	Common (>60%)
Monozygotic twins	50% concordant	90% concordant
HLA association	Present	Absent
Insulin gene VNTR (variable number of tandem repeats)	Present	Absent
Diabetogenic and obesity related candidate genes	Present	Absent
Islet lesions	Early inflammation, late fibrosis and atrophy	Late fibrosis and atropby
Islet cell autoantibodies	Present	Absent
Beta-cells mass	Markedly reduced	Normal to slightly reduced
Circulating insulin status	Lack of insulin	Peripheral resistance to insulin
Insulin in blood	Decreased	Normal or increased
C-peptide in blood	Decreased	Increased
Hyperglycemia	Common	Uncommon

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6.1Juvenile Oonset NSET insulin dependent type 1 diabetes mellitus:Juvenile onset insulin-dependent type 1 diabetes mellitus is less common than type 2 disease. It is the most common form of diabetes in children. It often begins before 30 years of age (juvenile or ketosis-prone diabetes mellitus).[18]

6.2Pathogenesis:

In genetically susceptible persons, a triggering eventPossibly a viral infection causes production of auto- antibodies against ß cells of pancreas.[11]Incidence is increased with a specific point mutation in the HLA-DQ gene with HLA-DR3- and HLA-DR4 Positive persons. Destruction of ß cells (>90%) leads to absolute defi- diency of insulin. These patients require insulin for their survival.

Light Microscopy

- The islets of Langerhans are small with decrease in number or absence of cells.
- There is heavy lymphocytic infiltrates in and around islets.

Etiology

- Pancreatic cells of the islets of Langerhans synthesize very little or no insulin at all (absolute deficiency).

Unless insulin is replaced in type 1 diabetes mellitus, Patient develops marked carbohydrate intolerance with hyperglycemia, resulting in polyuria, polydipsia, and weight loss despite increased appetite, ketoacidosis, coma, and death. Ketoacidosis results from increased catabolism B-hydroxybutyric acid, acetoacetic acid along with small of fat, with production of ketone bodies (principally quantities of acetone) by liver. It is worth mentioning that ketoacidosis is not limited to type 1 diabetes mellitus. Ketoacidosis may also seen in starvation.[9]

6.3Non-insulin-dependent type 2 diabetes mellitus:

Non-insulin-dependent diabetes mellitus (NIDDM), is also known adult-onset, or ketosis-resistant diabetes mellitus. It is much more common than type 1 disease. It begins later in life, most often in middle age. Obesity and sedentary lifestyle accelerate the onset. It is characterized by decreased response of peripheral tissues to insulin and ß cells dysfunctional.[7]

6.4Pathogenesis:[Overview Article]

•Less insulin is replaced in type 1 diabetes mellitus, Patient develops marked carbohydrate intolerance withNIDDM2 occurs due to increased insulin resistance mediated by decreased peripheral cell membrane insulin receptors or post-receptor dysfunction (insulin-resistant).[3]

•It may be associated with impaired processing of pro- insulin to insulin by ß cells, decreased sensing of glucose by ß cells, or impaired function of intracellular carrier proteins.[18]

•The plasma insulin concentration is normal and often increased. Central obesity (abdominal fat deposition) is strongly related with insulin resistance.[13]

•Peripheral tissue resistance to insulin by NEFAS:Accumulation of non-esterified fatty acids (NEFAs): These are increased in liver and muscle in obese persons.

These are correlated with peripheral tissue resistance to insulin. Toxic intermediates of NEFAs such as ceramide and diacylglycerol decrease signaling response and adversely affect insulin receptors. These toxic intermediates compete with glucose for substrate oxidation and cause feedback inhibition of glycolysis.[9][4][1]

6.5Role of alipokines synthesized by adipose tissue:These include retinol binding protein 4 and resistin. Anti glycemic adipokines are leptin and adiponectin. These increase tissue sensitivity by activating AMP and AMPK (protein kinase) and enhance fatty acid oxidation.[18][16][2]

6.5.1Role of pro-inflammatory cytokines:IL-6 and tumor necrosis factor-a may also reduce insulin sensitivity.[12][11][6][1]

6.5.2Role of ß cells dysfunction: TCF7L2 gene and other genes cause ß cells of pancreas dysfunctional.[16] These ß cells synthesize more insulin to maintain blood sugar in type 2 DM with increased peripheral resistance to insulin. Amyloid deposition may be directly toxic to ß cells of pancreas.[17]

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Light Microscopy

The islets of Langerhans show focal fibrosis and hyalinization due to deposition of amylin also known as islet amyloid polypeptide (IAPP)

Therapeutic Correlation

These patients are managed by diet and oral antidiabetic agents. Insulin therapy is not usually required. Patterns may do reasonably well on diet, exercise and oral hypoglycemic agents for years before they need insulin

VII. MONOGENIC FORM OF DIABETES MELLITUS:

[Handbook]

These are uncommon causes of diabetes mellitus due to genetic defects in function and action of ß celis. It is autosomal dominant disorder. Early onset of diabetes mellitus may occur in non-obese young age group <25 years of age and even neonates. Autoantibodies are not demonstrated in these patients (Table H)

Table G : Genetic defects of maturity onset diabetes mellitus

Maturity onset diabetes mellitus	Genetic defects
MODY-1	Hepatocyte nuclear factor-4alpha (HNF-4alpha)
MODY-2	Glucokinase (CCK)
MODY-3	Hepatocyte nuclear factor-la (HNF-1alpha): it is most common type of MODY in 60% cases
MODY-4	Pancreas and duodenal homebox-1 (PDX-1)
MODY-5	Hepatocyte necrotic factor-18 (HNF-18)
Neonatal diabetes mellitus	KCNJ11 and ABCC8 gene mutations
Maternally inherited diabetes mellitus and deafness (MIDD)	Mitochondrial DNA mutations in 3243A-G
MODY denotes maturity onset diabetes mellitus of the young.	

Table H : Monogenic forms of diabetes mellitus: mechanisms.

Genetic defects of ß cells of pancreas

- Maturity onset diabetes mellitus of the young: It is the largest subgroup in this category.
- Maternally inherited diabetes mellitus with deafness: It occurs due to mutations of mitochondrial DNA. It leads to decreased ATP production resulting in diminished insulin release. These develop diabetes mellitus with sensorineural deafness.

Genetic defects of action of insulin

- Mutations of several genes adversely affect synthesis of receptors on tissues, insulin binding and intracellular signaling these persons are associated with acanthosis nigricans, polycystic ovaries and increased androgens levels
- Lipoatrophic diabetes mellitus is accompanied by loss of subcutaneous adipose due to mutation of OPAR-gamma.

VIII. GESTATIONAL DIABETES MELLITUS:[ARTICLE]

Pregnancy associated transient diabetes mellitus is known as gestational diabetes mellitus, Gestational diabetes mellitus is usually identified in the 24-28 weeks of gestation. Woman, who develops gestational diabetes mellitus, has high risk

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for development of type 2diabetes mellitus later in life.[16][12][10][9][2][1]

8.1Ellopathogenesis:

During pregnancy, anti-insulin hormones are synthe- sized by placenta such as estrogen, prolactin, human Chorionic somatomamototropin, cortisol and progesterone. Human chorionic somatomamototropin regulates carbohydrate and protein metabolism of the mother toensure delivery of glucose and protein for fetal growth.It is also know as chorionic growth hormone prolactinor placental lactogen.[14][11][9][2][1]

8.2Complications:

Maternal complication: Due to increased fetal birth weight, there is increased indication of cesarean section.[14][11][2][1]

8.3Neonatal complications:

There is increased fetal birth weight, brachial plexus injuries, and neonatal respiratory distress syndrome (hyaline membrane disease).[18]

During intrauterine life in diabetic mothers, fetus develops islet ß cells hyperplasia in response to hyperglycemia and increased demand of insulin during early gestation. Pancreatic B cells, which may secrete insulin autonomously and cause hypo- glycemia at birth of newborn.[14]

8.4Diagnostic Approach:Gestational diabetes mellitus is diagnosed by oral glucose tolerance test, in which the woman drinks 75 gm glucose. Blood glucose level after an hour >140 mg/dl is considered significant.[18]

The confirmatory test is a 3-hour, 100 gm glucose tolerance test in which the blood glucose values are set at highest sensitivity. Urine analysis is done for sugar.[13][12][2]

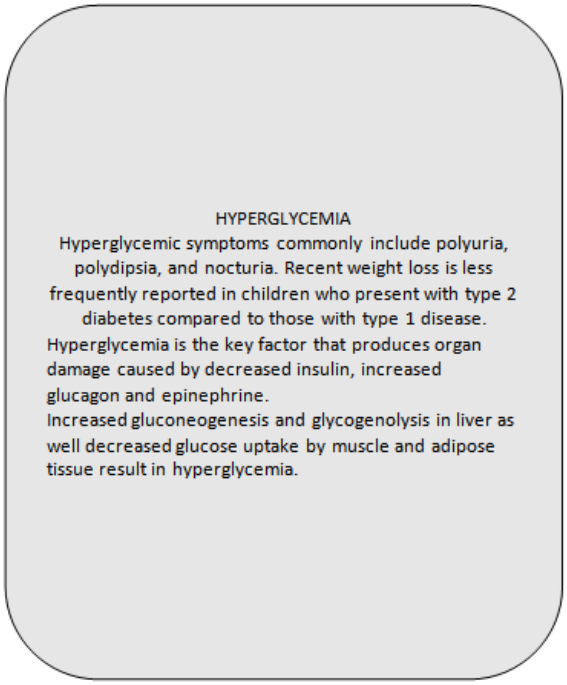
IX. PATHOPHYSIOLOGY OF DIABETES MELLITUS:

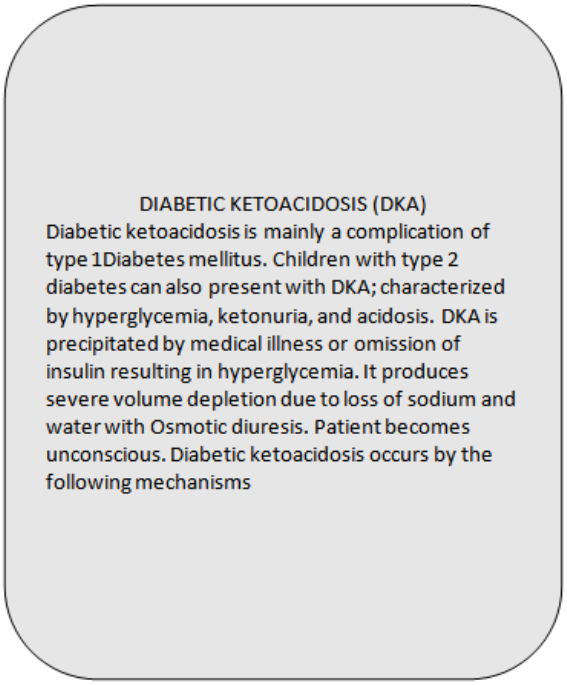
9.1Mechanism:

Lipolysis: Unchecked hormone-sensitive lipase increases lipolysis with release of fatty acids (Fig. 26.4).[18]

B-oxidation of fatty acids: It results in increased production of acetyl CoA.

Conversion of acetyl CoA into ketone bodies: It results in increased production of ketone bodies, i.e. acetoacetic acid, B-hydroxybutyric acid and acetone in liver, giving a fruity odor to the breath.[1]





HYPEROSMOLAR HYPERGLYCEMIA STATE

Hyperosmolar hyperglycemia state (HHS) was earlier known as hyperosmolar nonketotic coma. It is a condition similar to DKA, characterized by marked hyperglycemia (plasma glucose>600 mg/dl) and severe dehydration but little or no ketonuria,

It Is usually seen in adult patients with poorly con- trolled type 2 diabetes mellitus, but has been reported in adolescents

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Recognition of HHS is important because it is characterized by more severe dehydration than DKA, with high morbidity and mortality (20 to 50%) if not adequately treated.

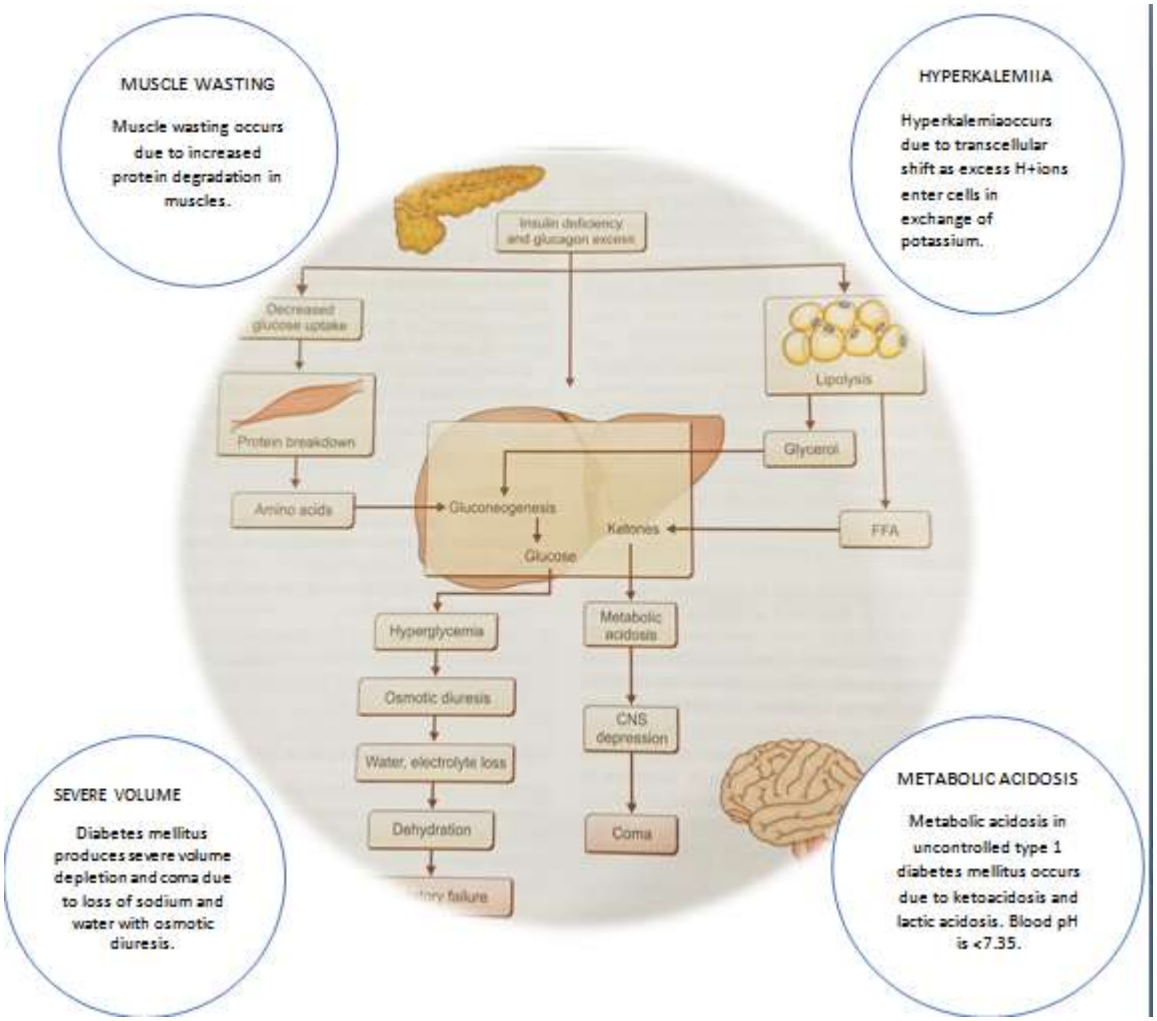

Fig. 26.4: Mechanisms of diabetic ketoacidosis (DKA). DKA is associated with very low Insulin levels and extremely high leves of glucagon, catecholamines, and other counter-regulatory hormones increased levels of glucagon and catecholamines lead to mobilization of substrates for gluconeogenesis and ketogenesis by the liver, Gluconeogenesis in excess of that needed to supply glucose for the brain and other glucose dependent fissues produces a rise in blood glucose levels, Mobilization of free fatty acids (FFA) from triglyceride stores in adipose tissue leads to accelerated ketone production and ketosis (CNS: central nervous system)

DILUTIONAL HYPONATREMIA

Serum sodium is decreased in diabetes mellitus. Glucose overrides sodium in controlling the osmotic gradient.Hence, water shifts out of the intracellular fluid compartment into the extracellular compartment resulting in dilutional hyponatremia.[15][12][11][4][2]

X. HYPERLIPIDEMIA:

[Overview]

Lack of insulin decreases capillary lipoprotein lipase activity in peripheral blood resulting in accumulation of chylomicrons and VLDL in blood. It may precipitate acute pancreatitis and eruptive xanthoma in the skin (called the hyperchylomicronemia syndrome).[18][11]

Hyperlipidemia in diabetes mellitus (insulin- dependent or non-insulin-dependent) accelerates atherosclerosis at an early age.[18]The risk of cerebrovascular disease is high and frequency to develop gangrene of foot is about 100 times increased.[10]

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XI. PRERENAL AZOTEMIA:

Prerenal azotemia in diabetes mellitus occurs due to volume depletion resulting in accumulation of waste products in the body.[8]

12.Mechanism of organs damage:[Mechanism]The pathological abnormalities associated with diabetes mellitus.[6][2]

XII. NON-ENZYMATIC GLYCOSYLATION MECHANISM:

- Glycosylation refers to glucose attaching to amino acids of the basement membrane of vessels rendering them permeable to proteins.
- Glycosylated end products: Glucose combines with proteins and forms Schiff's base. It leads to formation of early glycosylated end products (amadori product) and then advanced glycosylated end products (irreversible change), which resist enzymatic degradation.
- Mechanism of damage by glycosylated end products: Advanced glycosylated end products cause increased permeability of glomerular basement membrane, hyaline arteriosclerosis of small vessels in kidney; and atherosclerosis of large elastic and medium-sized arteries.
- Blood vessels involved:Arteries affected include abdominal aorta, coronary, cerebral, anterior tibial, posterior tibial and popliteal vessels. Atheromatous plaques are formed in these blood vessels resulting in decreased blood supply to the organs.

12.2Enzymatic glycosylation mechanism:

•Osmotic damage occurs due to conversion of glucose to sorbitol and fructose by aldose reductase and sorbitol dehydrogenase respectively.[18]Both sorbitol and fructose are osmotically active, and draw water into tissue leading to permanent damage.

•Complications associated with osmotic damage include peripheral neuropathy (damage to Schwann cells leading to demyelization), cataracts, and microaneurysms in retina (damage to pericytes weakens the vessel wall).[18][12][9][2]

12.3Macrovascular Disorders: Advanced glycosylated end (AGE) products bind to collagen of blood vessels in uncontrolled diabetes mellitus. These also trap LDL resulting in atherosclerosis of aorta, coronary, cerebral and popliteal arteries.Macrovascular disorders such as coronary artery disease, cerebral stroke and peripheral vascular disease reflect the combined effects of unregulated blood glucose levels, elevated blood pressure and hyperlipidemia. The most common cause of death with diabetes mellitus is myocardial infarction.Microvascular disorders include nephropathy, neuro- pathy and retinopathy.[11]

12.4Angina pectorisand acute myocardial infarction: Atheromatous plaque in coronary arteries may cause Angina, acute myocardial infarction and cardiac failure. Patients become symptomatic if vessels consisting of atherosclerotic plaque involve >75% of lumen. Treatment of acute myocardial infarction includes angioplasty, stents and coronary bypass surgery.[18][1]

12.5Cerebral vascular disease: Cerebral vascular disease refers to diseased arteries in the brain. Partial blockage may result in temporary reduction of blood supply to a part of the brain (transient ischemic attacks).A complete loss of blood supply to an area of the brain due to clogging or breaking of a blood vessel results in cerebral vascular stroke.[18][14][12][11][2]

XIII. PERIPHERAL VASCULAR DISEASE:

Popliteal arteries, anterior and posterior tibial arteries Diabetic patients develop atheromatous plaque in rest resulting in peripheral vascular disease. In arteriosclerosis,atheromatous plaques buildup in a vessel and limit the blood flow to the organs and limbs.Partial or complete blockage adversely affects the circulation to lower extremities.[13]

XIV. DIABETIC NEPHROPATHY:

[Overview]Diabetes mellitus adversely affects glomeruli, tubules, blood vessels and interstitial tissue Uncontrolled kidneys. Renal lesions include diabetic glomeru Mosclerosis, Kimmelsteil-Wilson disease (nodulas of sclerosis), hyaline arteriosclerosis, acute or glomerulosc chronic pyelonephritis, papillary necrosis, capsular drops and fibrin cap.[18][14]Advanced glycosylated end (AGE) products bind to collagen fibers of glomerular basement membrane. It leads to impairment of interaction of laminin, thus resulting to increased capillary permeability. Increased width of glomerular basement membrane is the earliest and most common renal manifestation.[12]

14.1Glomeruli:Diffuse and nodular glomerulosclerosis occur due to increased synthesis of type IV collagen in glomerular basement membrane and mesangium resulting in massive proteinuria and ultimately chronic renal failure.[12] Exudative lesion, i.e. capsular drop due to deposition of plasma proteins especially fibrin is also seen. Glomeruli show increased synthesis of

type IV collagen in glomerular basement membrane and mesangial region. If the glomeruli in the kidneys become "full," it may indicate a problem with their filtration capacity. Normally, glomeruli filter the blood to remove waste products and excess substances, which then become part of urine. If the glomeruli are overwhelmed or damaged, they may not filter efficiently, leading to conditions like proteinuria (protein in the urine) or hematuria (blood in the urine). This could be a sign of kidney disease or another underlying health issue, and it should be evaluated by a healthcare professional.Glomeruli are small, ball-shaped clusters of blood vessels in the kidneys.[16]They play a crucial role in the filtration of blood to remove waste products and excess substances, ultimately forming urine. Dysfunction of the glomeruli can lead to kidney problems, such as glomerulonephritis or kidney failure.Dysfunction of the glomeruli, which are the tiny filtering units in the kidneys, can lead to various kidney-related problems. Some common issues associated with glomerular dysfunction include:

1. Glomerulonephritis: This is a group of kidney diseases where the glomeruli become inflamed. It can be acute or chronic and may result from infections, autoimmune disorders, or other causes. Symptoms can include blood or protein in the urine, high blood pressure, and swelling.
2. Nephrotic Syndrome: This condition involves the leakage of large amounts of protein into the urine due to glomerular damage. It often leads to edema (swelling), high cholesterol levels, and a susceptibility to infections.
3. Decreased GFR (Glomerular Filtration Rate): Glomerular dysfunction can lead to a decreased GFR, which is an important measure of kidney function. A reduced GFR indicates that the kidneys are not filtering blood as effectively as they should.[12]

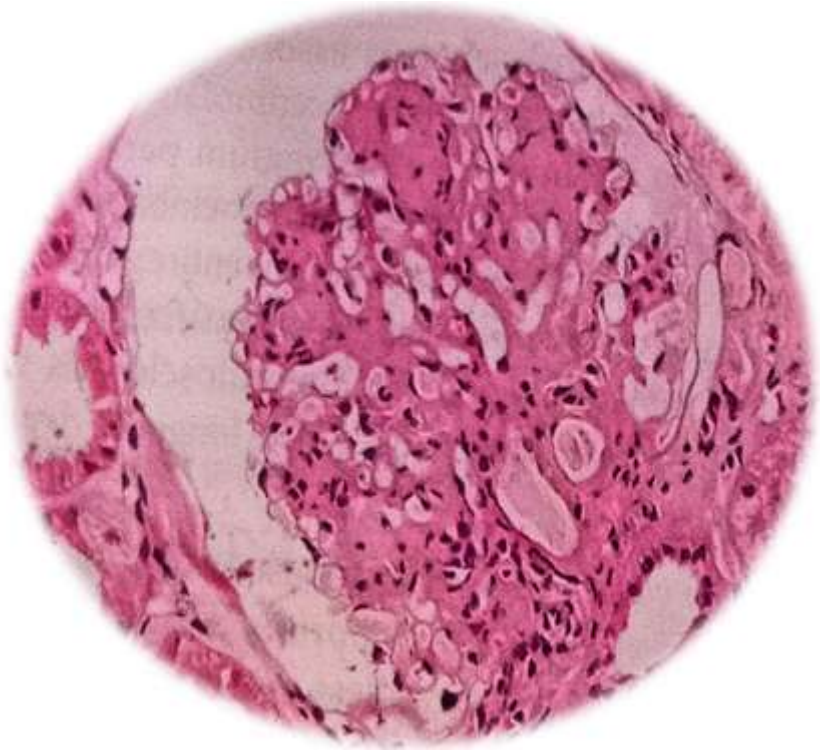

Fig. 26.7: Nodular glomerulosclerosis (Kimmelsteil-Wilson disease) in diabetic nephropathy. It shows sclerotic nodules in the peripheral region of intercapillary region of glomeruli. These nodules are formed due to accumulation of trapped proteins and synthesis of type IV collagen in mesangial matrix (400X)

Glomerulosclerosis is a medical term referring to the scarring or hardening of the glomeruli in the kidneys. Glomeruli are tiny structures in the kidneys responsible for filtering blood and removing waste products. Glomerulosclerosis can lead to kidney dysfunction and is often associated with conditions like diabetes or hypertension. Treatment options vary depending on the underlying cause and severity of the condition, and they may include medications, lifestyle changes, or in some cases, dialysis or kidney transplantation. If you have concerns about glomerulosclerosis, it's important to consult a

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healthcare professional for proper evaluation and guidance.[14][2]

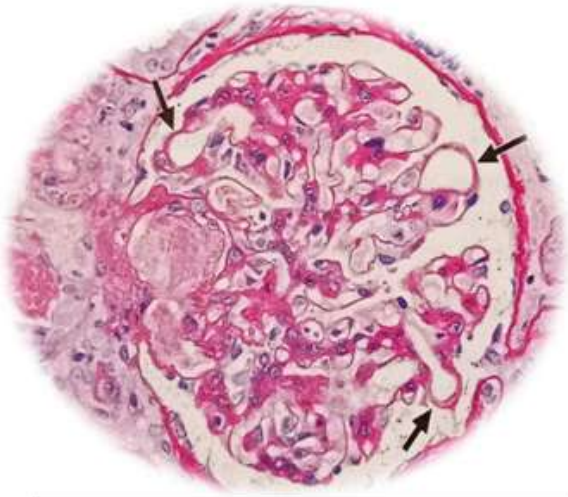
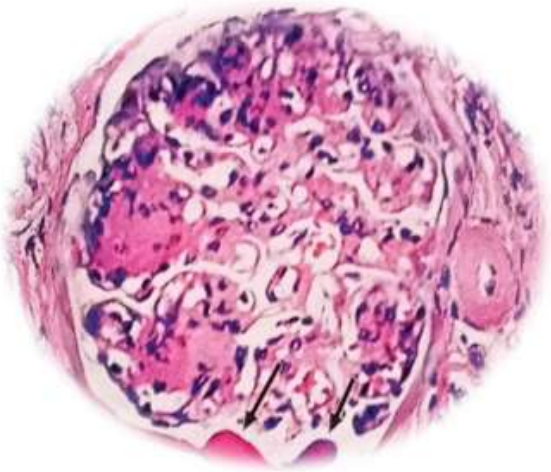


Fig. 26.8: Micro aneurysm (arrows)

14.2Blood Vessels:Hyaline arteriosclerosis of renal arterioles is the main cause of renal microangiopathy in diabetic patients (Fig. 26.8).



26.9: Capsular drop in glomerulus

14.3Papillary Necrosis:Diabetic glomerulosclerosis leads to ischemia of papillae (papillary necrosis). Necrotic papillae may detach and pass in the urine as tissue fragments. Undetached papillae may resolve by fibrosis. It may be noted that papillary necrosis can be seen as a complication of chronic analgesic abuse, diabetic nephropathy, infec- tious pyelonephritis and sickle cell anemia.[18][11][3]

14.4Capsular Drop:Accumulation of plasma proteins inside Bowman's capsule is known as capsular drop.[18][2][1]

XV. GLAUCOMAIN:

Severe retinopathy, neovascularization may lead to adhesions (synechiae) between iris and cornea or iris and lens. Neovascularization of the iris leads to secondary glaucoma resulting in blindness.[18][12][11][9][7]

15.1Cataracts:Cataracts are more common in diabetics. Hyperglycemia leads to accumulation of sorbitol that results in osmotic damage to the crystalline lens.[18][12]

15.2Bleeding into Vitreous:When massive bleeding into the vitreous has occurred, a vitrectomy may be performed. In this surgical proce- dure, the bloody vitreous is removed and replaced with clear, sterile fluids to restore vision.[18][13][9]

XVI. INFECTIOUS DISORDERS:

Increased glucose in tissues and body fluids provides favorable growth of conditions for bacteria and fungi. Diabetes mellitus impairs the function of neutrophils. Angiopathy caused by diabetes leads to tissue ischemia. Such ischemic tissues are more prone to infections.[18]

Patients develop vulvovaginitis (Candida), external otitis (Pseudomonas aeruginosa), cutaneous infections (Staphylococcus aureus), and rhinocerebral mucor- mycosis spreading to face, orbit, skull, and frontal lobe of brain.[13]

XVII. SKIN DISORDERS:

Patient develops well demarcated yellow plaques over anterior surface of the leg/dorsum of ankles known as necrobiosis lipoidica diabeticorum. It occurs due to increased synthesis of fat at insulin injection site. Patient may develop xanthomas due to collections of lipid-laden macrophages in the dermis.[14][11][9][8][1]

XVIII. MUCORMYCOSIS:

Diabetic ketoacidosis helps to potentiate the growth of mucormyosis. Most common site is typically naso- pharyngeal region, but the infection can spread to involve soft tissues and bone of the face, orbit, skull.[18]

FATTY LIVER

Fatty change refers to abnormal accumulation of triglycerides within parenchymal cells. It is commonly seen in liver, the major organ

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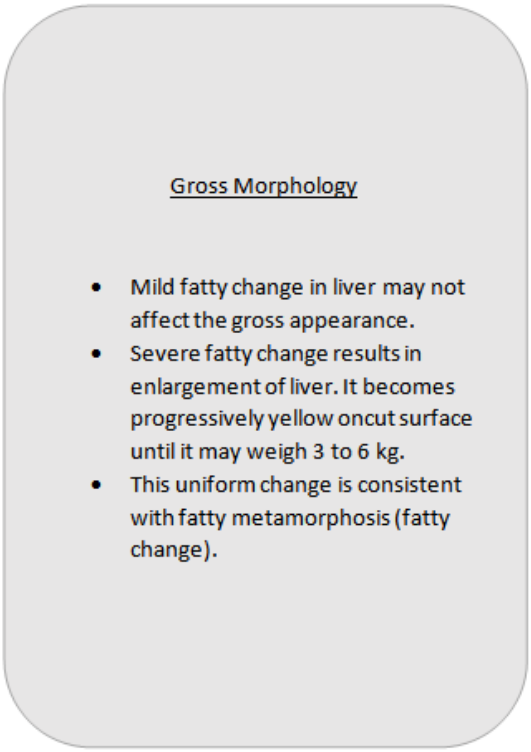
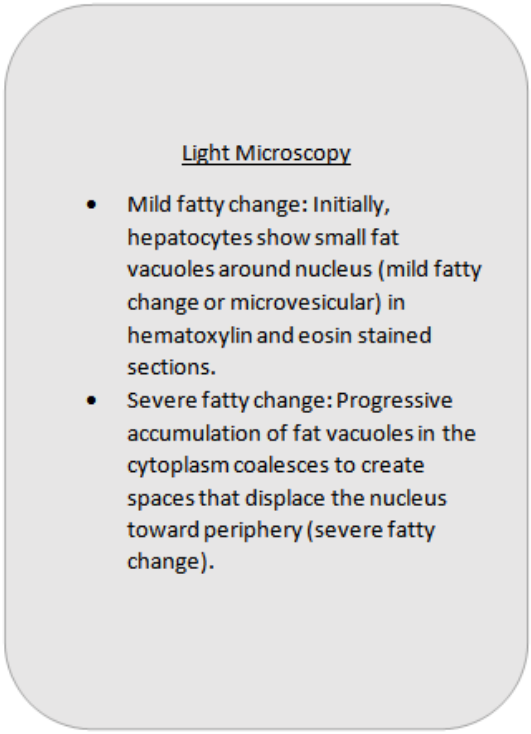
involved in fat metabolism The lipid accumulates when lipoprotein transport is disrupted.





XIX. LABORATORY DIAGNOSIS : BLOOD SUGAR:

[Principles]
Fasting≥126 mg/dl and random ≥200 mg/dl. Values are diagnostic estimated at different occasions.

XX. GLUCOSE TOLERANCE TEST:

Glucose tolerance is impaired in a patient, who does not fit in the established criteria of diabetes mellitus, but has increased risk of developing complications involving medium and large elastic arteries (eg. Atherosclerosis of aorta, coronary, cerebral and popliteal arteries) and neuropathy.[15]

20.1 Glycosylated hemoglobin (HbA1c):Serum hemoglobin Alc is an indicator of long-term blood glucose control in diabetes mellitus. In the normal individual, about 3-6% of adult hemoglobin is glycosylated, which accumulates in the RBCs. The percentage of glycosylated hemoglobin is increased depending upon the degree of hyperglycemia. A value >6.5 is diagnostic of diabetes. It is directly related to the average concentration of glucose in the blood. Its estimation evaluates long-term glycemic control.[18]

20.2 Lipid profile:Accumulation of chylomicrons and VLDL in blood leads to deranged lipid profile.

20.3Serum proteins:Total serum proteins are decreased with reversal of albumin/globulin ratio (normal 2:1).

20.4Blood urea (20-40 mg/dl):It is increased in diabetic nephropathy. Never use antico- agulant containing ammonium salt as it increases urea concentration.

20.5Serum creatinine:(NORMAL 0.6-1.5 mg %)It is increased in diabetic nephropathy.

20.6SERUM Na+:The levels are decreased due to dilutional hyponatremia.

20.6.1SERUM K+ :The level of serum potassium is increased.

20.7Urine Analysis :

Diabetes nephropathy may show proteins, glucose, ketone bodies, pus cells, hyaline casts, fatty casts and oval fat bodies (lipid-containing renal tubular epithelial cells).Free fat droplets, fatty casts, and oval fat bodies; when examined by polarized light, the lipids in casts are seen as being

doubly refractile or birefringent and they display a symmetric ‘maltese-cross pattern[18][12][9][2]

20.8Renal Biopsy:
Renal biopsy should consist of at least five glomeruli to comment.[1]

XXI. CONCLUSION:

[National Diabetic Supply]Pancreas is a compound gland, i.e. exocrine and endocrine glands. Islets of Langerhans comprise three types of cells (a, β and y cells).India has around 101 million people living with diabetes and another 136 million people in pre-diabetes stages, found a recently published study by the Madras Diabetes Research Foundation and Indian Council of Medical Research.cells situated around capillaries within pancreatic bules synthesize insulin.High blood glucose level (hyperglycemia) stimulates eleas of insulin, Insulin acts on principal target tilates.The exact cause of most types of diabetes is unknown. In all cases, sugar builds up in the bloodstream. This is because the pancreas doesn’t produce enough insulin. Both type 1 and type 2 diabetes may be caused by a combination of genetic or environmental factors.Higher consumption of coffee, whole grains, fruits, and nuts is associated with lower risk of diabetes, whereas regular consumption of refined grains, red and processed meats, and sugar-sweetened beverages including fruits juices is associated with increased risk.Aug. 30, 2023 — Researchers have discovered a type of gut bacteria that might help improve insulin resistance, and thus protect against the development of obesity and type-2 diabetes.[Timing]

REFERENCE:

[1]. Association, A.D. Classification and diagnosis of diabetes: Standards of medical care in Diabetesd2018. Diabetes Care 2018, 41, 13–27.
[2]. Apovian, C.M. Obesity: Definition, comorbidities, causes, and burden. Am. J. Manag. Care 2016, 22, 176–185.
[3]. Asmar, M.; Tangaa, W.; Madsbad, S.; Hare, K.; Astrup, A.; Flint, A.; Bülow, J.; Holst, J.J. On the role of glucose-dependent insulintropic polypeptide in postprandial metabolism in humans. Am. J. Physiol. Endocrinol. Metab. 2010, 298, 614–621.
[4]. American Diabetes Association, Diagnosis and classification of diabetes mellitus, Diabetes Care, 2014.
[5]. Bhat, V.K.; Kerr, B.D.; Vasu, S.; Flatt, P.R.; Gault, V.A. A DPP-IV-resistant triple-acting agonist of GIP, GLP-1 and glucagon receptors with potent glucose-lowering and insulinotropic actions in high-fat-fed mice. Diabetologia 2013, 56, 1417–1424.
[6]. Busch, R.S.; Kane, M.P. Combination SGLT2 inhibitor and GLP-1 receptor agonist therapy: A complementary approach to the treatment of type 2 diabetes. Postgrad. Med. 2017, 129, 686–697.
[7]. Bertoni, A. G. et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care 27, 699–703 (2004).
[8]. Gregg, E. W., Sattar, N. & Ali, M. K. The changing face of diabetes complications. Lancet Diabetes Endocrinol. 4, 537–547 (2016).
[9]. Harding, J. L., Shaw, J. E., Peeters, A., Davidson, S. & Magliano, D. J. Age-specific trends from 2000–2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of more than one million people. Diabetes Care 39, 1018–1026 (2016).
[10]. Jiang, Y. et al. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur. J. Epidemiol. 26, 863–876 (2011).
[11]. Nishita singh et al, review on type2 diabetes Mellitus.
[12]. Pearson-Stuttard, J., Buckley, J., Cicek, M. & Gregg, E. W. The changing nature of mortality and morbidity in patients with diabetes. Endocrinol. Metab. Clin. North Am. 50, 357–368 (2021).
[13]. Pearson-Stuttard, J. et al. Trends in leading causes of hospitalisation of adults with diabetes in England from 2003 to 2018: an epidemiological analysis of linked primary care records. Lancet Diabetes Endocrinol. 10, 46–57 (2022).
[14]. Tolman, K. G., Fonseca, V., Dalpiaz, A. & Tan, M. H. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care 30, 734–743 (2007).
[15]. Tsilidis, K. K., Kasimis, J. C., Lopez, D. S., Ntzani, E. E. & Ioannidis, J. P. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 350, g7607 (2015).

[16]. Vinay Kamal Director Professor Of Pathology Maulana Azad Medical College Bahadur Shah Zafar Marg New Delhi (India) Editors-Anubhav MD Vigyat MD Illustrations By Ram Murti Senior Graphic Artist And Volume I Contains: General Pathology, Hematology Including Recent Diagnostic Techniques Volume II Contains: Systemic Pathology.

[17]. Vasen HF, Wasser M, Van Mil A, Et Al: Magnetic Resonance Imaging Surveillance Detects Early-Stage Pancreatic Cancer In Carriers Of A P16-Leiden Mutation. Gastroenterology 140:850-856, 2011.

[18]. Vinay Kamal Director Professor Of Pathology. Editors-Anubhav MD Vigyat MD Illustrations By Ram Murti Senior Graphic Artist And Volume II.