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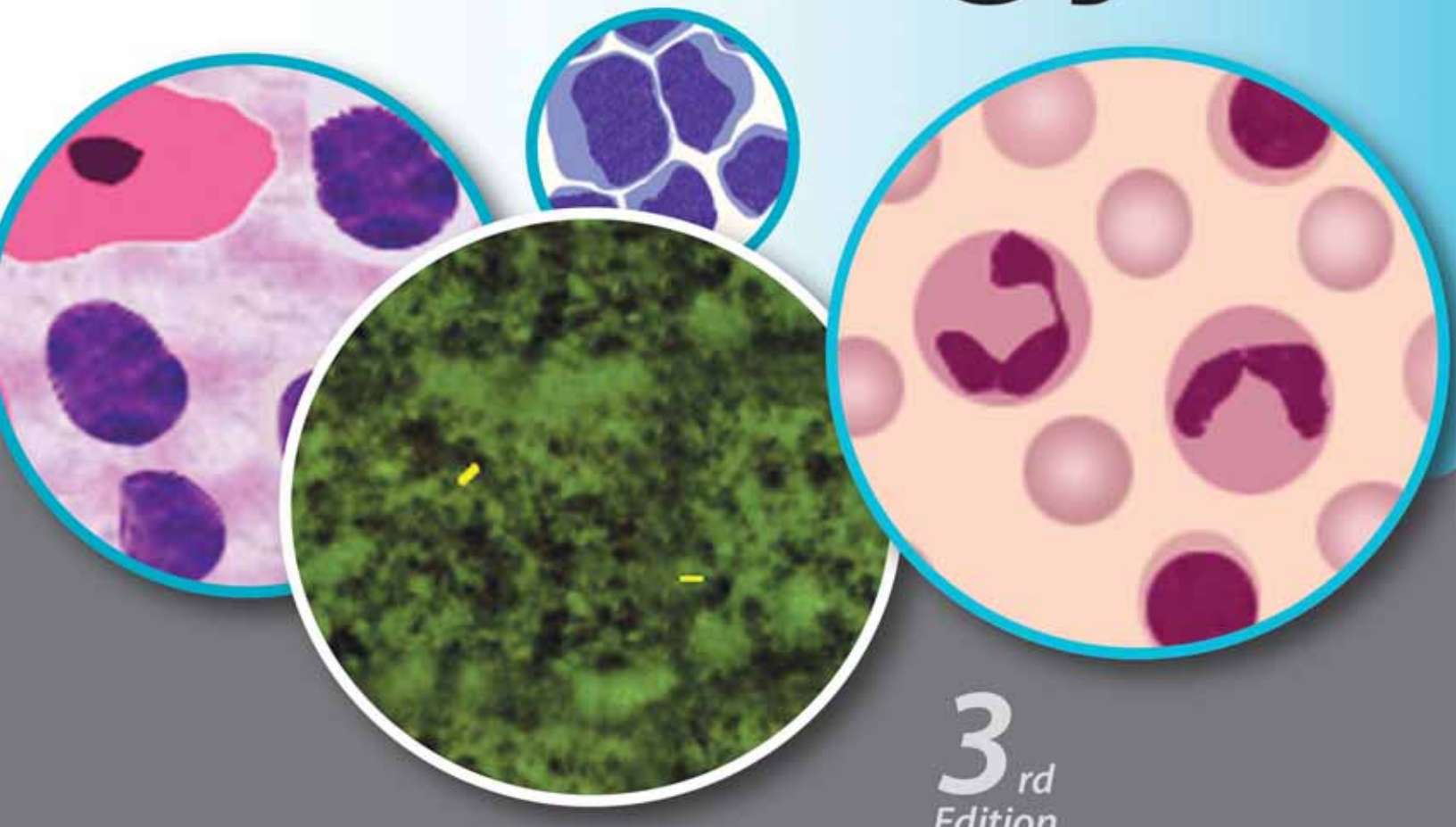

3rd Edition

Shirish M Kawthalkar

JAYPEE

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4 CHAPTER

Laboratory Tests in Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic group of disorders characterized by persistent hyperglycemia due to deficiency and/or diminished effectiveness of insulin. There are derangements of carbohydrate, protein and fat metabolism due to failure of insulin action on target cells. Typical features of DM are as follows:

- Fasting hyperglycemia
- Glycosuria
- Symptoms due to marked hyperglycemia: Polyuria, polydipsia, weight loss, weakness, polyphagia, and blurred vision
- Long-term complications like atherosclerosis (leading to ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) and microangiopathy (which can cause nephropathy with risk of renal failure; retinopathy with potential loss of vision; and peripheral neuropathy with risk of foot ulcers, amputations, or Charcot joints).
- Acute metabolic complications (hyperosmolar hyperglycemic state, diabetic ketoacidosis).
- Susceptibility to infections especially of skin, respiratory tract and urinary tract.

The term "Diabetes mellitus" is derived from the (1) Greek word "diabainein" which means "siphon," because affected people excreted excessive amounts of urine, and (2) Latin word "mellitus" meaning sweet.

METABOLIC ACTIONS OF INSULIN

Insulin is the major hormone regulating blood glucose level. Insulin is synthesized by β cells of pancreas as preproinsulin, which is rapidly converted to proinsulin. Proinsulin is a single chain polypeptide with 86 amino acids. In the Golgi apparatus, proinsulin is broken down into 2 units—insulin (51 amino acids) and C (connecting)-polypeptide (31 amino acids) **(Fig. 4.1)**. Both insulin and C peptide are stored in membrane-bound granules in the cytoplasm of β cells. Upon stimulation (mainly by blood glucose), both insulin and C peptide are released in circulation. C peptide is often measured as a marker of activity of β cells. C peptide has no known function.

Insulin acts on various cells (especially those of liver, muscle, and adipose tissue) through receptors.

Important actions of insulin are shown in **Box 4.1**.

"Stress hormones" like glucagons, glucocorticoids, growth hormone and adrenaline oppose action of insulin **(Box 4.2)**.

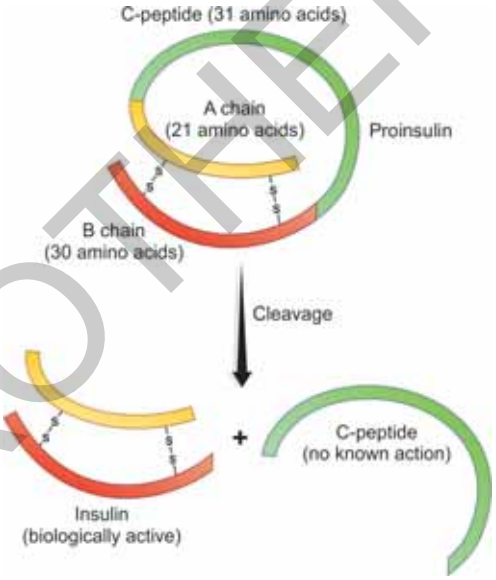

Fig. 4.1: Proinsulin, insulin and C-peptide. The biochemical cleavage of proinsulin to insulin and C-peptide occurs in Golgi apparatus of β cell. Secretion of insulin is stimulated by glucose, mannose, amino acids and sulfonylureas.

BOX 4.1

Major actions of insulin

- *Increases:*
  - Uptake of glucose in skeletal muscle and adipose tissue
  - Glycogenesis in liver and muscle
  - Fatty acid and triglycerides in liver and adipose tissue
  - Protein synthesis in liver and muscle
- *Decreases:*
  - Gluconeogenesis in liver
  - Glycogenolysis in liver and muscle
  - Lipolysis in adipose tissue
  - Ketogenesis in liver

CLASSIFICATION OF DIABETES MELLITUS

According to American Diabetes Association (1997), DM is classified into following types:

- *Type 1* (Absolute deficiency of insulin due to destruction of cells of pancreas)
- *Type 2* (Insulin resistance along with progressive loss of adequate insulin secretion)

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BOX 4.2

Hormones regulating glucose

Hormones decreasing glucose level

- Insulin:
  - » Increases glucose uptake by cells (skeletal muscle, adipose tissue)
  - » Increases glycogen synthesis
  - » Decreases gluconeogenesis and glycogenolysis in liver

Hormones increasing glucose level

- *Glucagon:*
  - » Increases glycogenolysis and gluconeogenesis in liver
- *Adrenaline (Epinephrine):*
  - » Increases glycogenolysis in liver and skeletal muscle
- *Growth hormone:*
  - » Increases glycogenolysis in liver
- *Cortisol:*
  - » Increases gluconeogenesis in liver
  - » Decreases glucose utilization by tissues
- *Thyroxine:*
  - » Increases glycogenolysis
  - » Increases intestinal glucose absorption

Note: The two most important hormones in glucose regulation are insulin and glucagon.

- ❖ *Other specific types*
- ❖ *Gestational DM* (onset or first recognition of glucose intolerance during pregnancy).

Type 1 Diabetes Mellitus

It accounts for 5–10% of all cases of DM. This was previously called as insulin-dependent DM or IDDM (because insulin therapy is essential to prevent ketosis), juvenile-onset DM (because it commonly presents during childhood or adolescence), brittle DM, or ketosis-prone DM. It is characterized by **absolute deficiency of insulin secretion.**

Type 1 DM is an autoimmune disease characterized by absolute insulin deficiency due to destruction of β cells of pancreas. It results from genetic predisposition (e.g., inheritance of HLA haplotypes DR3 or DR4-DQ8) with a superimposed precipitating event (like viral infection, alteration of intestinal microbiome).

Cell-mediated autoimmune destruction of β cells of pancreas is responsible for majority of cases of type 1 DM (type 1A or immune-mediated type 1 DM), leading to inability of pancreas to synthesize insulin. There is infiltration by cytotoxic CD8+ T-lymphocytes in and around islets. It is thought that many cases follow a viral infection that has damaged the β islet cells of pancreas **(Fig. 4.2)**. Markers of immune destruction of β cells, which can be detected in peripheral blood, are islet cell antibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD_{65}), and autoantibodies to tyrosine phosphatases (IA-2 and IA-2β). The disease has strong association with HLA DR3 and HLA DR4 haplotypes **(Fig. 4.3)**. Stages of type 1 DM are shown in **Figure 4.4**. This type occurs mainly in children and adolescents, but can occur at any age. These patients are also at risk of other autoimmune disorders like Graves' disease, Hashimoto's thyroiditis, vitiligo, Addison's disease, pernicious anemia, etc.

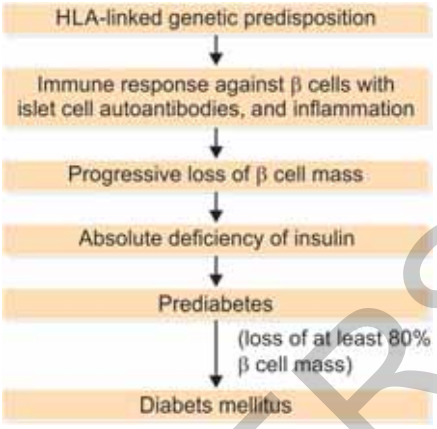

Fig. 4.2: Pathogenesis of type 1 diabetes mellitus.

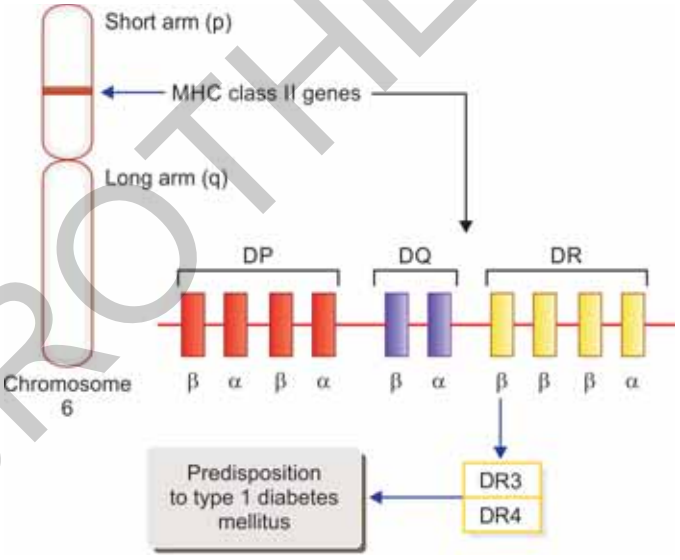

Fig. 4.3: HLA-linked genetic predisposition to type 1 diabetes mellitus.

Some cases of type 1 DM do not have any known etiologies or evidence of autoimmunity. These individuals are of Asian or African origin and their disease is strongly inherited. This form of type 1 DM is called as **idiopathic DM (type 1B)**.

Type 2 Diabetes Mellitus

This is the **most common form of DM** comprising about 90–95% of all patients of DM. This was previously called as non-insulin-dependent DM (NIDDM), maturity-onset DM (because onset usually occurs during adult life), stable DM, or ketosis-resistant DM. **It is characterized by insulin resistance along with relative deficiency of insulin secretion** (i.e., inadequate insulin secretory response to overcome peripheral insulin resistance) **(Fig. 4.5)**. Type 2 DM is not HLA-linked and there is no role of autoimmunity in its pathogenesis. It has a strong genetic predisposition. Risk factors for type 2 DM (American Diabetes Association) are given in **Box 4.3**.

Type 2 DM is polygenic and is associated with a stronger genetic predisposition than type 1 DM; however, the high-risk genes have not been clearly identified. Type 2 DM develops when acquired factors (like central or visceral obesity, sedentary lifestyle, stress, sleep disorders like obstructive sleep

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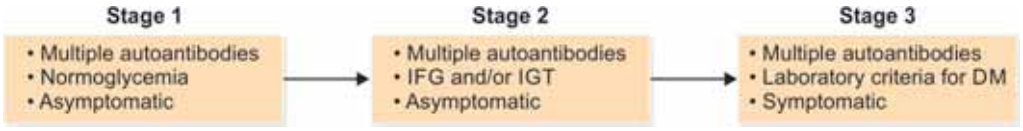

Fig. 4.4: Stages of type 1 diabetes mellitus.
(IFG: impaired fasting glucose; IGT: impaired glucose tolerance)

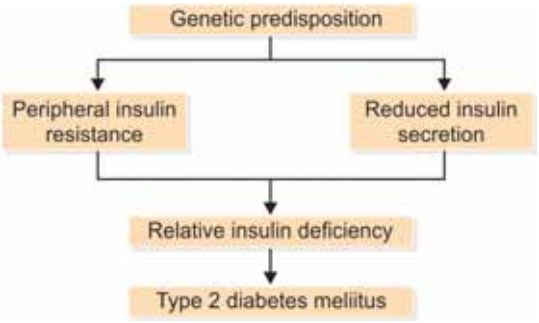

Fig. 4.5: Pathogenesis of type 2 diabetes mellitus.

BOX 4.3

Major risk factors for type 2 diabetes mellitus in asymptomatic adults that should prompt screening (American Diabetes Association 2018)

- Overweight or obese adults (body mass index ≥25 kg/m^2) with one or more of the following risk factors:
  - First degree relative having diabetes
  - High-risk ethnicity or race (African American, Latino, Native American, Asian American, Pacific islander)
  - History of cardiovascular disease
  - Hypertension
  - Lipid disorder: HDL-C <35 mg/dL and/or triglyceride level >250 mg/dL
  - Women with polycystic ovarian syndrome
  - Physical inactivity
  - Clinical evidence of insulin resistance: severe obesity, acanthosis nigricans
- Patients with prediabetes (yearly testing)
- History of gestational diabetes mellitus (testing every 3 years)
- All individuals other than above: Testing should begin at 45 years with repeat testing every 3 years.

apnea, circadian disruption, pregnancy, glucocorticoid use) are superimposed on genetic predisposition.

Pathogenesis of type 2 DM is complex. It involves two key abnormalities: (1) insulin resistance in skeletal muscle (causing failure of glucose uptake and glycogen synthesis), adipose tissue (causing excess triglyceride breakdown and high free fatty acids in circulation), and liver (causing failure to inhibit endogenous glucose production or gluconeogenesis), and (2) progressive failure of β cells to produce insulin (relative insulin deficiency) in the face of insulin resistance and hyperglycemia.

Type 2 diabetes is more common in certain racial groups like South Asians and Africans. Rising trend of type 2 DM is due to increasing tendency towards obesity in urban populations coupled with high-calorie diet.

Differences between type 1 and type 2 DM are listed in **Table 4.1**.

Other Specific Types

There are several forms of DM associated with underlying conditions:

- *Genetic defects of β cell function*: In these disorders, insulin secretion from β cells is impaired. These are called as maturity onset diabetes of the young (MODY). They are inherited in an autosomal dominant manner and they are caused by mutations in genetic loci such as hepatic nuclear factor, glucokinase, etc.
- *Genetic defects in insulin action*: These result from mutations in insulin receptor gene.
- *Diseases of exocrine pancreas*: Diseases causing generalized pancreatic damage can result in DM. These include cystic fibrosis, hemochromatosis, chronic pancreatitis, trauma, pancreatectomy and pancreatic cancer.
- *Endocrine disorders*: Several hormones inhibit the action of insulin. Excessive secretion of these hormones will cause DM. Hyperglycemia is corrected following resolution of the primary endocrinopathy. Endocrine disorders associated with hyperglycemia are:
  - *Acromegaly:* Excess growth hormone
  - *Cushing's syndrome:* Excess cortisol
  - *Glucagonoma:* Excess glucagon
  - *Pheochromocytoma:* Excess epinephrine
  - *Hyperthyroidism:* Excess thyroxine
- *Drug- or chemical-induced DM:* Drugs or chemicals can impair insulin secretion or insulin action. Destruction of β cells and formation of islet cell antibodies have also been reported with some drugs. Examples include thiazide diuretics, α-interferon, and glucocorticoids.
- *Infections:* Certain viral infections (such as Coxsackie virus B, congenital rubella, cytomegalovirus) can cause destruction of β cells.
- *Other genetic syndromes sometimes associated with DM:* Many genetic syndromes (e.g., Down's syndrome, Klinefelter's syndrome, Turner's syndrome) are associated with increased risk of developing DM.

Gestational Diabetes Mellitus (GDM)

This refers to the onset or first recognition of glucose intolerance during pregnancy. GDM occurs in 2–3% of all pregnant women. It is associated with increased risk of **high birth weight of the newborn (fetal macrosomia due to hyperinsulinemia), cardiac defects, polyhydramnios, intrauterine fetal loss (due to placental insufficiency), premature birth, hypertension during pregnancy, pre-eclampsia, higher rate of cesarian section and metabolic derangements at birth (hypoglycemia, hypocalcemia). In contrast to pregestational DM, fetal anomalies are not increased in gestational DM.** Pregnancy is associated with

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Table 4.1: Differences between type 1 and type 2 diabetes mellitus.

Parameter	*Type 1 DM*	*Type 2 DM*
Previous names	Type I, IDDM, juvenile-onset, ketosis-prone, brittle	Type II, NIDDM, maturity-onset, ketosis-resistant, stable
% of all DM cases	5–10%	90–95%
Age of onset	<35 years	>35 years
Body habitus	Usually thin	Usually obese
Presentation	Acute; symptoms (classical) since few weeks	Insidious; symptoms since few months or years
Genetic predisposition	Low	Strong
Family history of diabetes	Less common	Common
Glucose intolerance	Marked	Mild
Ketoacidosis	Common	Uncommon
Hyperosmolar hyperglycemic state	Uncommon	Common
Serum insulin	Undetectable	Normal or high
Autoimmunity (Islet cell antibodies)	Majority of cases	No
Associations	Other autoimmune diseases like Addison disease, celiac disease, pernicious anemia, thyroiditis, Graves' disease	No association with autoimmune diseases
HLA-linkage	Yes (DR3, DR4)	No
Pathogenesis	Absolute insulin deficiency due to destruction of pancreatic β cells	Insulin resistance with relative insulin deficiency
Serum C-peptide level	Very low to absent	Normal or high
Predisposing factors	Genetic, autoimmune, environmental	Genetic, obesity, lack of physical activity, race, hypertension, polycystic ovarian syndrome, lipid disorder
Insulin requirement for treatment	Always	In some situations

BOX 4.4

Risk factors for gestational DM

- Past history of GDM
- Previous high-birth-weight baby (>4000 g or 8¾ lb)
- Obesity (body mass index ≥30 kg/m^2)
- Family history of diabetes mellitus
- High-risk ethnic group: South Asian or African
- History of stillbirth or child with cardiac defects

increased peripheral resistance to insulin. Early diagnosis and treatment of GDM are essential to prevent perinatal morbidity and mortality. After delivery, GDM can have following course:

- Return to normal glucose tolerance (however, many of these patients are likely to develop DM during subsequent years), or
- Persistence of DM or impaired glucose tolerance. Patient should be reassessed 6 weeks or later following delivery.

Risk factors for GDM are shown in **Box 4.4**.

PREDIABETES

Prediabetes is a state in which plasma glucose level is higher than normal but not high enough for diagnosis of DM. It is also referred to as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on which test is used for its detection. Studies have shown that majority of individuals with prediabetes develop type 2 DM within 10 years. Prediabetic persons do not develop acute complications of DM and microangiopathy, but are at increased risk of cardiovascular disease (1.5 times normal individuals). Development of DM can be delayed or prevented through modest amount of weight loss, diet modification and regular moderate exercise in patients with prediabetes.

Metabolic Syndrome (Insulin Resistance Syndrome, Reaven's Syndrome, Syndrome X)

The metabolic syndrome refers to a constellation of lipid and non-lipid risk factors that are of metabolic origin and associated with risk of cardiovascular disease. The Adult Treatment Panel III (ATP III) 1 of the National Cholesterol Education Program in 2001 proposed criteria for diagnosing the metabolic syndrome. The metabolic syndrome is diagnosed when three out of following five criteria are present.

1. Abdominal obesity
   - *Men:* Waist circumference >40 inches (102 cm)
   - *Women:* Waist circumference >35 inches (88 cm)
2. Fasting glucose ≥110 to <126 mg/dL (As these criteria were proposed in 2001, the fasting plasma glucose value should be reduced to 100 mg/dL according to revised criteria proposed by American Diabetes Association in 2004).
3. Blood pressure ≥130/85 mm Hg
4. Triglycerides ≥150 mg/dL (≥1.7 mmol/L)
5. Plasma high density lipoprotein (HDL)-cholesterol
   - *Men:* <40 mg/dL (<1 mmol/L)
   - *Women:* <50 mg/dL (<1.3 mmol/L)

Metabolic syndrome is common in Asian Indians in Britain and in Africa. It is said that insulin resistance is common to all

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above risk factors and plays an etiological role. These persons have increased risk of developing type 2 DM.

METABOLIC ALTERATIONS IN DIABETES MELLITUS

In DM, there are abnormalities of carbohydrate metabolism (hyperglycemia, glycosuria, impaired glucose tolerance), protein metabolism (increased protein catabolism with muscle wasting, gluconeogenesis), and fat metabolism (increased fatty acid synthesis, ketosis) **(Fig. 4.6)**. Metabolic alterations in type 2 DM are less severe than in type 1 DM.

- *Hyperglycemia:* Hyperglycemia is due to deficient uptake of glucose by muscle and fat cells (due to insulin deficiency). In reaction to this, there are compensatory glycogenolysis (breakdown of glycogen to glucose) and gluconeogenesis (formation of glucose from noncarbohydrates like proteins), which contribute to hyperglycemia. Typical clinical features of hyperglycemia are polyuria, polydipsia, polyphagia, weakness, weight loss and blurring of vision.
- *Glycosuria:* Glycosuria results when blood glucose level exceeds renal threshold (180 mg/dL or 10 mmol/L in most individuals). Excess glucose increases osmolality of glomerular filtrate with resultant osmotic diuresis and polyuria. This causes depletion of water and electrolytes, cellular dehydration, and intense thirst (polydipsia). Insulin deficiency leads to catabolism of proteins, and released amino acids are used for formation of glucose (gluconeogenesis). Breakdown of lipids also occurs and coupled with proteolysis, lead to negative energy balance and weight loss. This in turn induces polyphagia (increased appetite).
- *Ketosis:* Insulin deficiency leads to increased degradation of lipids (lipolysis), resulting in increased levels of free fatty acids in circulation. These are converted to acetoacetyl CoA in the liver. Acetoacetyl CoA, in turn, is converted to ketone bodies. If muscles or other tissues do not utilize ketone bodies equal to the rate of their formation, they accumulate in blood. With the rise in blood levels of ketone bodies (ketonemia), they are excreted in urine (ketonuria). Ketone bodies are strong acids, which dissociate and release H^+ ions. Bicarbonate removes these H^+ ions in plasma and the level of bicarbonate falls. This produces metabolic acidosis. Symptoms of metabolic acidosis are nausea, vomiting, and hyperpnea (air hunger). Diabetic ketoacidosis (DKA) is a typical feature of type 1 DM. It usually does not occur in type 2 diabetes mellitus because endogenous insulin prevents lipolysis.
- *Hyperosmolar hyperglycemic state (HHS):* This occurs in type 2 patients due to combination of severe dehydration (secondary to sustained osmotic diuresis coupled with inadequate fluid intake) and hyperglycemia. It occurs usually in elderly with unrecognized DM or DM of recent onset.

LONG-TERM COMPLICATIONS OF DIABETES MELLITUS

In long standing DM of both types, a wide variety of lesions develop in many organs, which are important causes of morbidity and mortality.

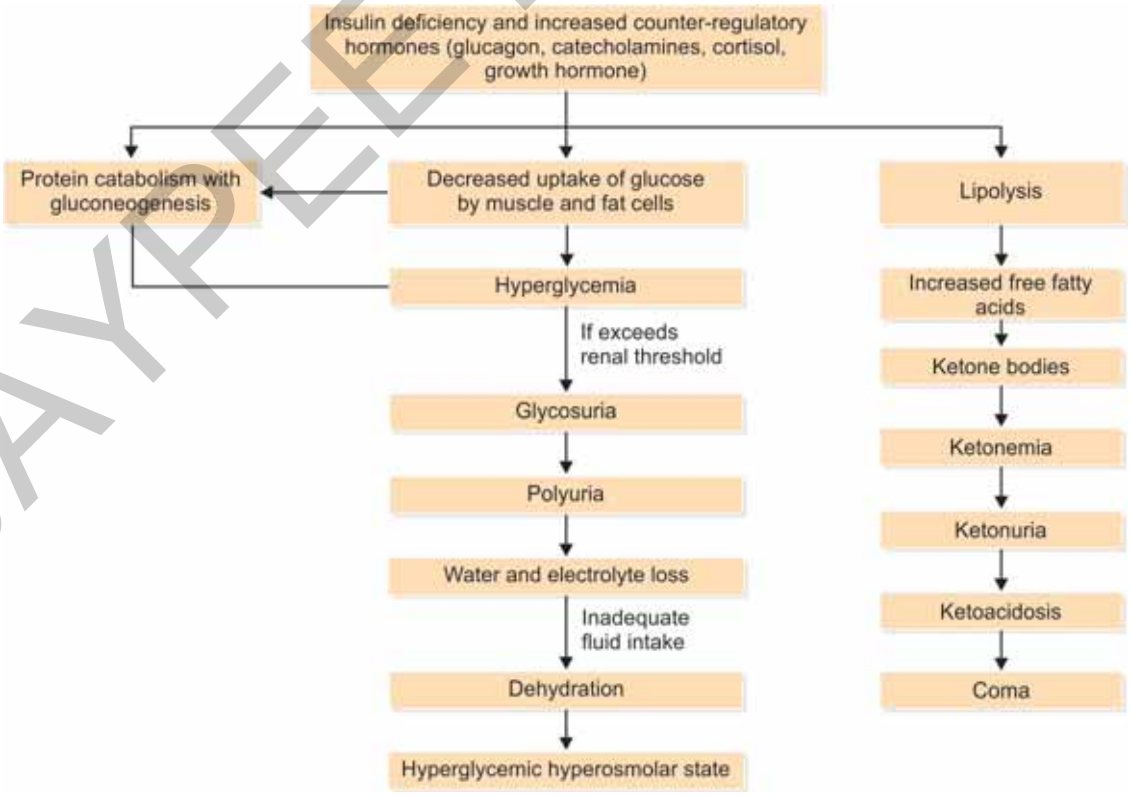

Fig. 4.6: Metabolic alterations in diabetes mellitus.

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BOX 4.5

Microangiopathy in diabetes mellitus

- Risk is directly related to presence of high glucose level for long duration
- Improved glycemic control significantly reduces the risk
- Consists of:
  - » *Retinopathy:* Visual loss can occur due to vitreous hemorrhage (from proliferating retinal vessels) and maculopathy
  - » *Nephropathy:* Early stage is characterized by increased glomerular filtration rate and microalbuminuria; with progressive renal damage, overt proteinuria and renal failure develop
  - » *Neuropathy:* Postural hypotension, impotence, sensory and motor neuropathy, foot ulcer.

Macroangiopathy (macrovascular disease): In DM, atherosclerosis of aorta and of medium size arteries (like coronary, cerebral and peripheral) occurs earlier in life and is more extensive than in nondiabetic patients. It can cause myocardial infarction, cerebrovascular accident, and gangrene of lower extremities. Pathogenesis of atherosclerosis in DM is related to hyperinsulinemia with peripheral insulin resistance and dyslipidemia (raised triglycerides, low high density lipoprotein or HDL, and raised low density lipoprotein or LDL).

Microangiopathy (microvascular disease): Microangiopathy is due to poor diabetes control **(Box 4.5)**. Microangiopathy (thickening of walls of small blood vessels with narrowing of lumina) is common in kidneys (leading to renal insufficiency), retina (visual impairment), and peripheral nerves (sensory, motor or autonomic neuropathy).

Infections: Diabetic patients are susceptible to infections of skin, respiratory tract (pneumonia, tuberculosis), and kidneys (pyelonephritis).

Average life expectancy of DM patients is reduced. Usual causes of death in DM include myocardial infarction, stroke, renal failure, infections and ketoacidotic or hyperosmolar hyperglycemic coma.

ROLE OF LABORATORY IN DIABETES MELLITUS

Applications of laboratory tests in diabetes mellitus are shown in **Box 4.6**.

Preclinical Screening

Aim of screening is to identify asymptomatic individuals who are likely to have DM. Since early detection and prompt institution of treatment can reduce subsequent complications of DM, screening may be an appropriate step in some situations.

Screening for type 2 DM: Type 2 DM is the most common type of DM and is usually asymptomatic in its initial stages. Its onset occurs about 5–7 years before clinical diagnosis. Evidence indicates that complications of type 2 DM begin many years before clinical diagnosis. American Diabetes Association recommends screening for type 2 DM in all asymptomatic individuals ≥45 years of age using fasting plasma glucose. If fasting plasma glucose is normal (i.e., <100 mg/dL), screening test should be repeated every three years.

BOX 4.6

Role of the laboratory in diabetes mellitus (DM)

- **Pre-clinical screening:** Serum autoantibodies, serum C-peptide, HLA markers, Blood glucose (fasting), Oral glucose tolerance test (OGTT), HbA1c
- **Diagnosis of DM:** Blood glucose, OGTT, HbA1c
- **Tests to distinguish between type 1 and type 2 DM:** Serum insulin, serum C-peptide, immune markers like GAD autoantibodies
- **Assessment of glycemic control:** HbA1c, 1,5-Anhydroglucitol (1,5-AG), fructosamine, Glycated albumin, self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM) systems
- **Assessment of long-term risks:** Urinary albumin excretion, lipid profile
- **Management of acute metabolic complications:** Blood and urine glucose, blood and urine ketone, arterial pH and blood gas analysis, serum electrolytes, Blood osmolality, lactate, serum creatinine and blood urea
- **Eligibility for insulin pump:** C-peptide
- **Monitoring pancreatic and islet cell transplant function:** C-peptide, Insulin.

Another approach is selective screening, i.e., screening all individuals at high-risk of developing type 2 DM **(Box 4.3)**. In such cases, screening is performed at an earlier age (30 years) and if normal, repeated more frequently.

Recommended screening test for type 2 DM is **fasting plasma glucose.** If ≥126 mg/dL, it should be repeated on a different day for confirmation of diagnosis. If <126 mg/dL, OGTT is indicated if clinical suspicion is strong. A 2-hour post-glucose load value in OGTT ≥200 mg/dL is indicative of DM and should be repeated on a different day for confirmation.

Screening for type 1 DM: Screening for type 1 asymptomatic low risk individuals is not recommended. However, some authorities suggest annual screening with anti-islet cell antibodies in high risk individuals, e.g., those who have first-degree relative with type 1 DM.

Screening for GDM: Given later under OGTT in gestational diabetes mellitus.

Laboratory Tests for Diagnosis of Diabetes Mellitus

Diagnosis of DM is based exclusively on demonstration of raised blood glucose level (hyperglycemia).

The current criteria (American Diabetes Association, 2020) for diagnosis of DM are shown in **Box 4.7**.

If any one of the four criteria is present, confirmation by repeat testing on a different day is necessary for establishing

BOX 4.7

Laboratory diagnosis of diabetes mellitus

- Fasting plasma glucose ≥126 mg/dL (≥7.0 mmol/L) **OR**
- 2-hour post glucose load (75 g) value during oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) **OR**
- Hemoglobin A1c ≥6.5% (48 mmol/mol) **OR**
- Typical symptoms of DM (polyuria, polydipsia, weight loss) or hyperglycemic crisis and random plasma glucose ≥200 mg/dL (≥11.1 mmol/L).

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Table 4.4: Categorization of cardiovascular risk in diabetes mellitus according to lipid levels (American Diabetes Association).

Category	*Low density lipoprotein*	*High density lipoprotein*	*Triglycerides*
High-risk	≥130	<35 (men) <45 (women)	≥400
Intermediate risk	100–129	35–45	200–399
Low-risk	< 100	>45 (men) >55 (women)	<200

- Low-density lipoprotein (LDL) cholesterol
- High-density lipoprotein (HDL) cholesterol.

The usual pattern of lipid abnormalities in type 2 DM is elevated triglycerides, decreased HDL cholesterol and higher proportion of small, dense LDL particles. Patients with DM are categorized into high, intermediate and low-risk categories depending on lipid levels in blood **(Table 4.4)**.

Annual lipid profile is indicated in all adult patients with DM.

Laboratory Tests in the Management of Acute Metabolic Complications of Diabetes Mellitus

The three most serious acute metabolic complications of DM are:

1. Diabetic ketoacidosis (DKA)
2. Hyperosmolar hyperglycemic state (HHS)
3. Hypoglycemia.

The typical features of DKA are hyperglycemia, ketosis, and acidosis. The common causes of DKA are infection, noncompliance with insulin therapy, alcohol abuse and myocardial infarction. Patients with DKA present with rapid onset of polyuria, polydipsia, polyphagia, weakness, vomiting, and sometimes abdominal pain. Signs include Kussmaul's respiration, odor of acetone on breath (fruity), mental clouding and dehydration. Classically, DKA occurs in type 1, while HHS is more typical of type 2 DM. However, both complications can occur in either types. If untreated, both events can lead to coma and death.

Hyperosmolar hyperglycemic state is characterized by very high blood glucose level (>600 mg/dL), hyperosmolality (>320 mOsmol/Kg of water), dehydration, lack of ketoacidosis and altered mental status. It usually occurs in elderly type 2 diabetics. Insulin secretion is adequate to prevent ketosis but not hyperglycemia. Causes of HHS are illness, dehydration, surgery, and glucocorticoid therapy.

Differences between DKA and HHS are presented in **Table 4.5**.

Laboratory evaluation consists of following investigations:

- Blood and urine glucose
- Blood and urine ketone
- Arterial pH, blood gases
- Serum electrolytes (sodium, potassium, chloride, bicarbonate)
- Blood osmolality
- Serum creatinine and blood urea.

Testing for ketone bodies: Ketone bodies are formed from metabolism of free fatty acids and include acetoacetic acid, acetone and β-hydroxybutyric acid. Indications for testing for ketone bodies in DM include:

- At diagnosis of diabetes mellitus
- At regular intervals in all known cases of diabetes, during pregnancy with pre-existing diabetes, and in gestational diabetes
- *In known diabetic patients:* during acute illness, persistent hyperglycemia (>300 mg/dL), pregnancy, and clinical evidence of diabetic acidosis (nausea, vomiting, abdominal pain).

An increased amount of ketone bodies in patients with DM indicate impending or established diabetic ketoacidosis and is a medical emergency. Method based on colorimetric reaction between ketone bodies and nitroprusside (by dipstick or tablet) is used for detection of both blood and urine ketones.

Table 4.5: Comparison of diabetic ketoacidosis and hyperosmolar hyperglycemic state.

Parameter	*Diabetic ketoacidosis*	*Hyperosmolar hyperglycemic state*
Type of DM in which more common	Type 1	Type 2
Age	Younger age	Older age
Prodromal clinical features	<24 hours	Several days
Abdominal pain, Kussmaul's respiration	Yes	No
Acidosis	Moderate/Severe	Absent
Plasma glucose	>250 mg/dL	Very high (>600 mg/dL)
Serum bicarbonate	<15 mEq/L	>15 mEq/L
Blood/urine ketones	++++	±
β-hydroxybutyrate	High	Normal or raised
Arterial blood pH	Low (<7.30)	Normal (>7.30)
Effective serum osmolality*	Variable	Increased (>320)
Anion gap**	>12	Variable

*Osmolality: Number of dissolved (solute) particles in solution; normal: 275–295 mOsmol/kg

**Anion gap: Difference between sodium and sum of chloride and bicarbonate in plasma; normal average value is 12.

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Test for urine ketones alone should not be used for diagnosis and monitoring of diabetic ketoacidosis. It is recommended to measure β-hydroxybutyric acid (which accounts for 75% of all ketones in ketoacidosis) for diagnosis and monitoring DKA.

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