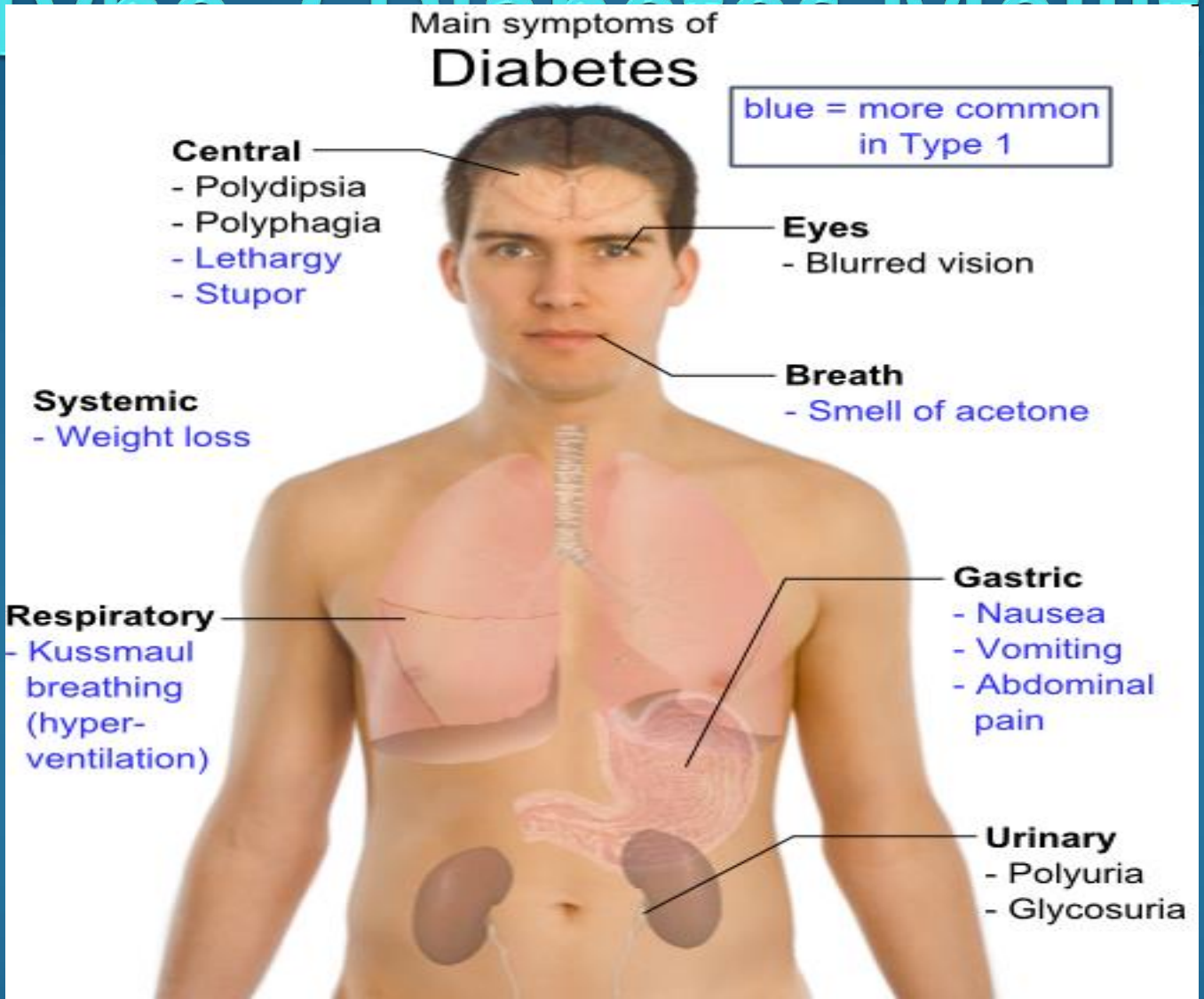
Type 2 Diabetes Mellitus



Background

- Type 2 diabetes mellitus comprises an array of dysfunctions resulting from the combination of resistance to insulin action and inadequate insulin secretion. It is disorders are characterized by hyperglycemia and associated with microvascular (ie, retinal, renal, possibly neuropathic), macrovascular (ie, coronary, peripheral vascular), and neuropathic (ie, autonomic, peripheral) complications

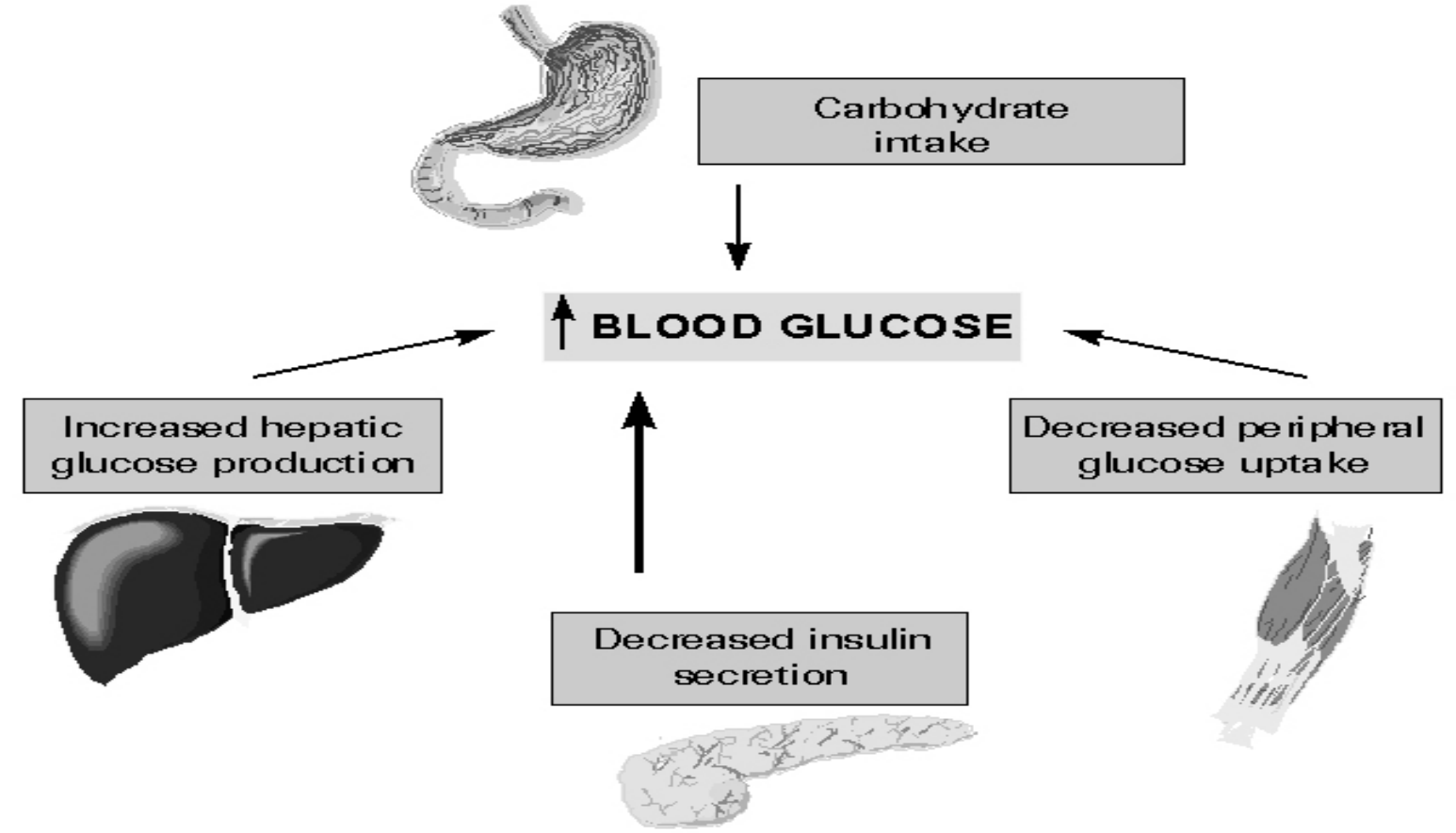
- Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent upon insulin for life.
- This distinction was the basis for the older terms for types 1 and 2, insulin dependent and non–insulin dependent diabetes.
- However, many patients with type 2 diabetes are ultimately treated with insulin.
- Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin.

- Another older term for type 2 diabetes mellitus was adult-onset diabetes.
- Currently, because of the epidemic of obesity and inactivity in children, type 2 diabetes mellitus is occurring at younger and younger ages.
- Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes.

- Diabetes mellitus is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur.
- It is a disproportionately expensive disease; in the United States in 2002, the per-capita cost of health care was $13,243 for people with diabetes, while it was $2560 for those without diabetes.
- The emergency department utilization rate by people with diabetes is twice that of the unaffected population

Diagnosis of Diabetes Mellitus

- Classic symptoms of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss and random plasma glucose ≥200 mg/dL
- Fasting plasma glucose ≥126 mg/dL
- Two hour post glucose load (75 g) plasma glucose ≥200 mg/dL, and confirmed by repeat test


Carbohydrate intake
BLOOD GLUCOSE
Increased hepatic glucose production
Decreased peripheral glucose uptake
Decreased insulin secretion

Treatment of Type 2 Diabetes Mellitus

	*monotherapy**	*add*	*add*
obese	metformin	sulfonylurea	exenatide or insulin or glitazone
non-obese	sulfonylurea or metformin	metformin or sulfonylurea	exenatide or insulin or glitazone
elderly	low dose secretagogue	switch to simple insulin regimen	----
Asians	glitazone	metformin	sulfonylurea or insulin or exenatide**

*for symptomatic patients, may initially use secretagogue or insulin to rapidly decrease glucose
**exenatide not approved for use with glitazone

Etiology

- Presumably, type 2 diabetes mellitus develops when a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed upon a susceptible genotype.
- The body mass index at which excess weight increases risk for diabetes varies with different racial groups.
- For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight.

- Hypertension and prehypertension are associated with greater risk of developing diabetes in whites compared with African Americans.
- In addition, an in utero environment resulting in low birth weight may predispose some individuals to develop type 2 diabetes mellitus

- About 90% of patients who develop type 2 diabetes mellitus are obese.
- However, a large, population-based, prospective study has shown that an energy-dense diet may be a risk factor for the development of diabetes that is independent of baseline obesity.

- Diabetes mellitus may be caused by other conditions. Secondary diabetes may occur in patients taking glucocorticoids or when patients have conditions that antagonize the actions of insulin (eg, Cushing syndrome, acromegaly, pheochromocytoma).

The major risk factors for type 2 diabetes mellitus are the following:

- Age greater than 45 years (though, as noted above, type 2 diabetes mellitus is occurring with increasing frequency in young individuals)
- Weight greater than 120% of desirable body weight
- Family history of type 2 diabetes in a first-degree relative (eg, parent or sibling)
- Hispanic, Native American, African American, Asian American, or Pacific Islander descent
- History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Hypertension (>140/90 mm Hg) or dyslipidemia (high-density lipoprotein [HDL] cholesterol level < 40 mg/dL or triglyceride level >150 mg/dL)
- History of gestational diabetes mellitus or of delivering a baby with a birth weight of >9 lb
- Polycystic ovarian syndrome (which results in insulin resistance)

- The genetics of type 2 diabetes are complex and not completely understood.
- Evidence supports the involvement of multiple genes in pancreatic beta-cell failure and insulin resistance.

- Some forms of diabetes, however, have a clear association with genetic defects. The syndrome previously known as maturity onset diabetes of youth (MODY) has now been reclassified as a variety of defects in beta-cell function. These defects account for 2-5% of individuals with type 2 diabetes who present at a young age and have mild disease. The trait is autosomal dominant and can be screened for through commercial laboratories. To date, 6 mutations have been identified:
- HNF-4-alpha
- Glucokinase gene
- HNF-1-alpha
- IPF-1
- HNF-1-beta
- NEUROD1

- In addition, the SURI-1 gene causes hyperglycemia in infancy, which is often misdiagnosed as type 1 diabetes.
- Variants in mitochondrial DNA have been proposed as an etiologic factor.
- A specific mitochondrial point mutation has been identified as a rare cause of maternally inherited type 2 diabetes and sensorineural hearing loss.

Pathophysiology

- Type 2 diabetes is characterized by the combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells.
- Insulin resistance, which has been attributed to elevated levels of free fatty acids in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

Pathophysiology

- For type 2 diabetes mellitus to occur, both defects must exist.
- For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance.
- Their insulin concentrations may be high, yet inappropriately low for the level of glycemia.

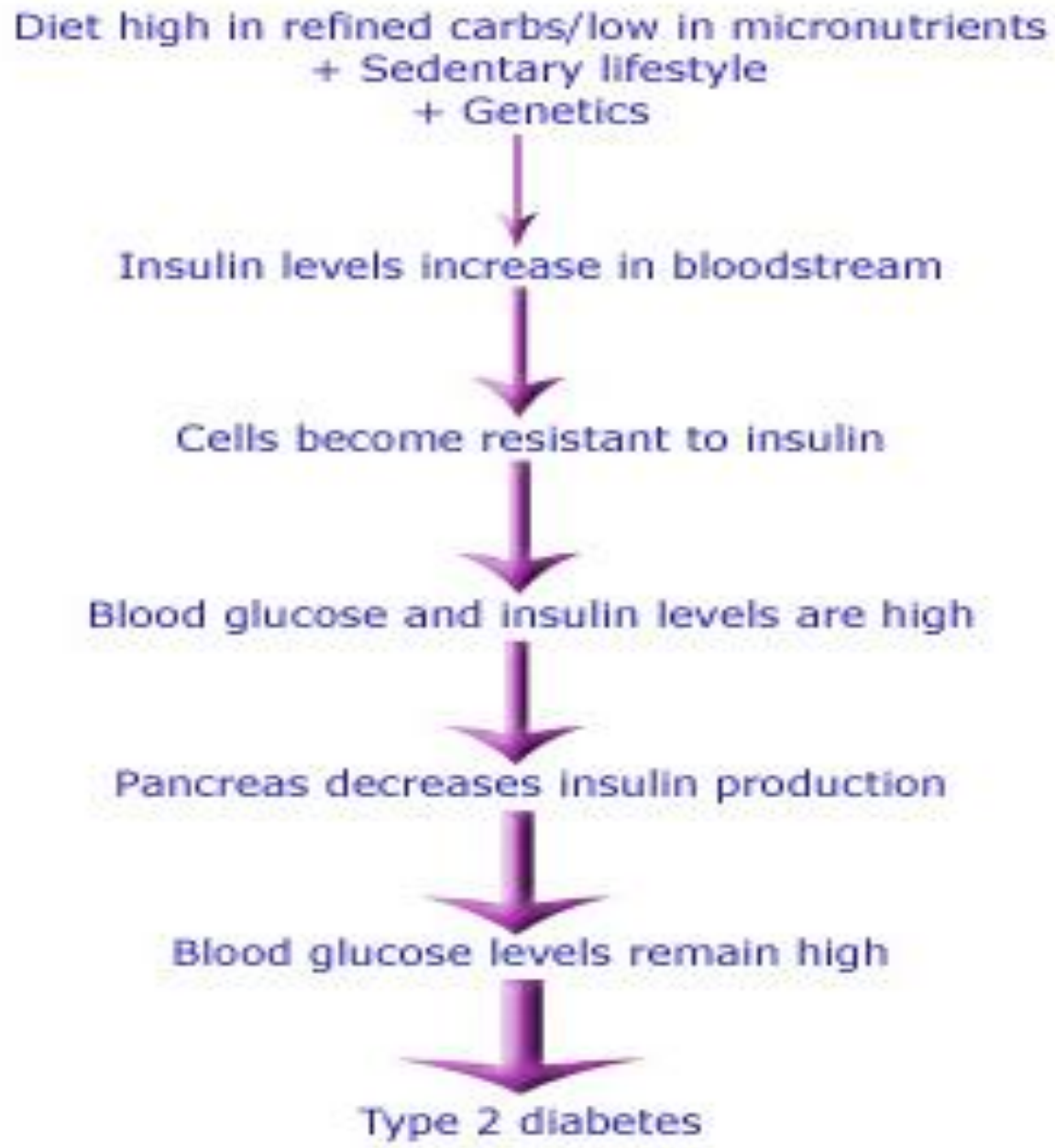
Pathophysiology

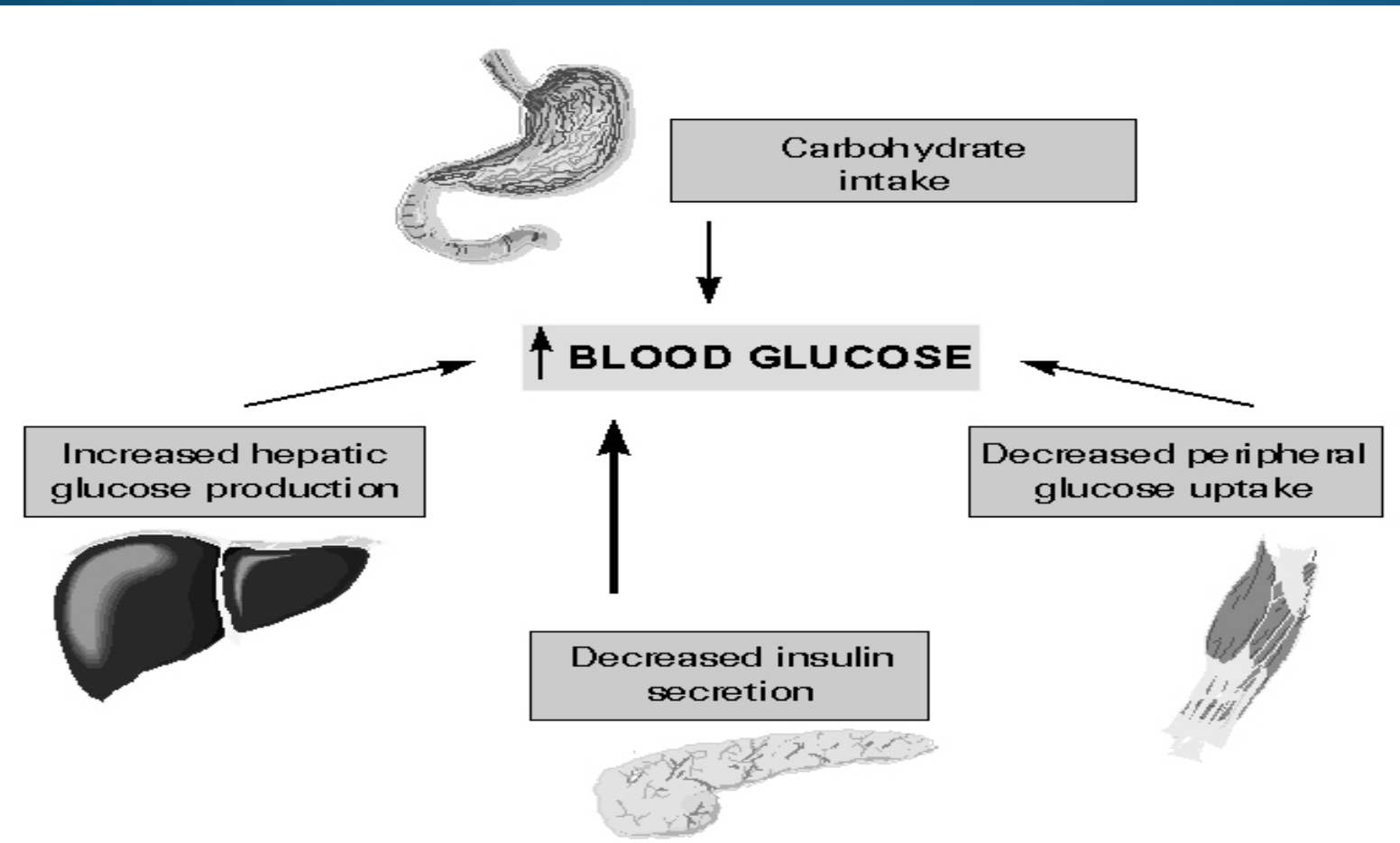
- Beta cell dysfunction is a major factor across the spectrum of pre-diabetes to diabetes.
- A study of obese adolescents by Bacha et al confirms what is increasingly being stressed in adults as well: Beta cell function happens early in the pathological process and does not necessarily follow stage of insulin resistance.
- Singular focus on insulin resistance as the "be all and end all" is gradually shifting, and hopefully better treatment options that focus on the beta cell pathology will emerge to treat the disorder early.

Pathophysiology

- In the progression from normal glucose tolerance to abnormal glucose tolerance, postprandial blood glucose levels increase first; eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

How insulin resistance progresses toward type 2 diabetes




Carbohydrate intake
BLOOD GLUCOSE
Increased hepatic glucose production
Decreased peripheral glucose uptake
Decreased insulin secretion

Pathophysiology

- During the induction of insulin resistance, such as is seen after high-calorie diet, steroid administration, or physical inactivity, increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance; however, postprandial glucagonlikepeptide-1 (GLP-1) response is unaltered.

Pathophysiology

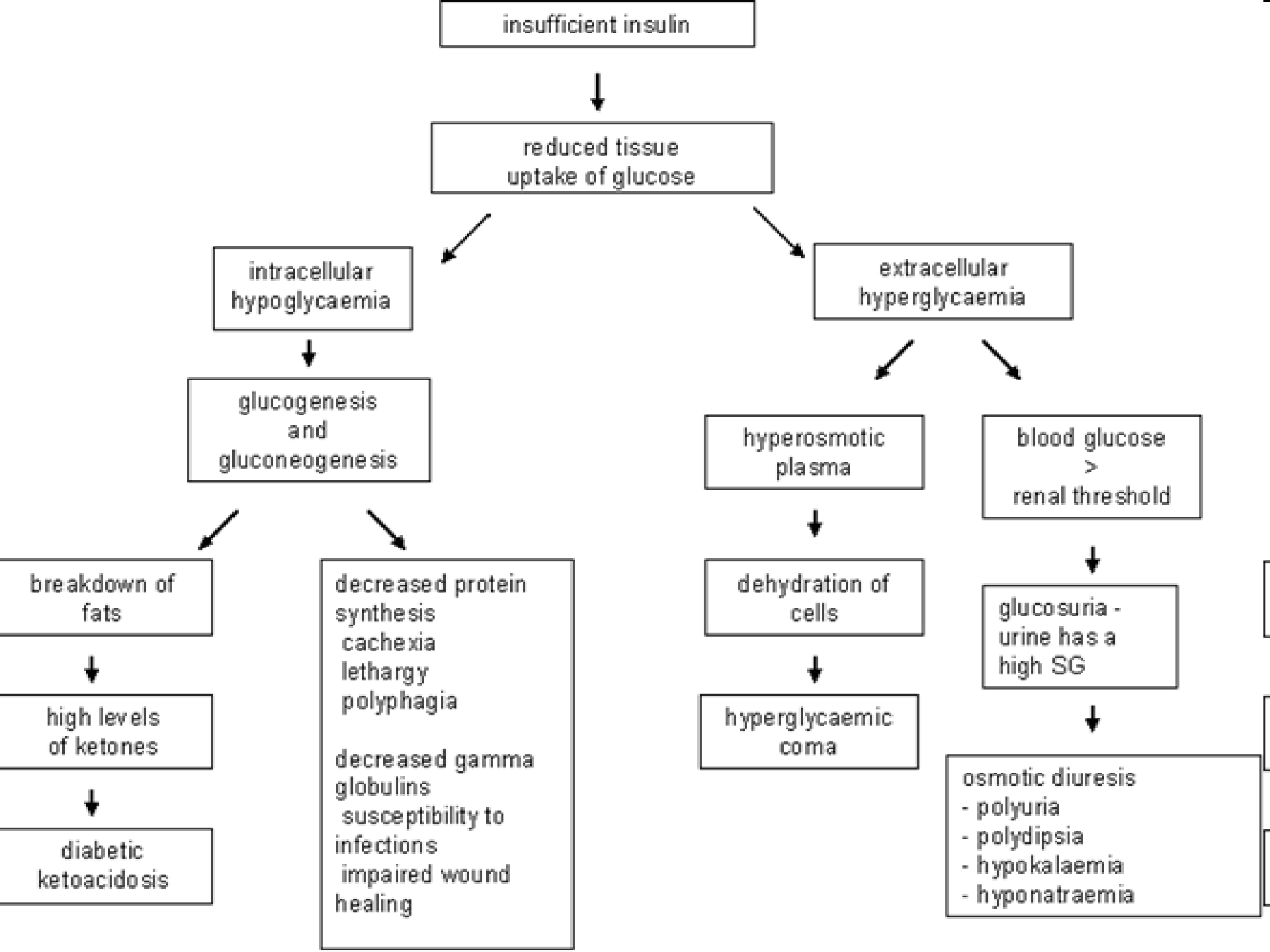
- Hyperglycemia appears to be the determinant of microvascular and metabolic complications. Macrovascular disease, however, is much less related to glycemia.
- Insulin resistance with concomitant lipid abnormalities (ie, elevated levels of small dense low-density lipoprotein cholesterol [LDL-C] particles, low levels of high-density lipoprotein cholesterol [HDL-C], elevated levels of triglyceride-rich remnant lipoproteins) and thrombotic abnormalities (ie, elevated type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen), as well as conventional atherosclerotic risk factors (eg, family history, smoking, hypertension, elevated LDL-C, low HDL-C), determine cardiovascular risk.

Pathophysiology

- Increased cardiovascular risk appears to begin prior to the development of frank hyperglycemia, presumably because of the effects of insulin resistance.
- Stern in 1996 and Haffner and D'Agostino in 1999 developed the "ticking clock" hypothesis of complications, asserting that the clock starts ticking for microvascular risk at the onset of hyperglycemia, while the clock starts ticking for macrovascular risk at some antecedent point, presumably with the onset of insulin resistance.

Pathophysiology

- Various other types of diabetes, previously called secondary diabetes, are caused by other illnesses or medications. Depending on the primary process involved (eg, destruction of pancreatic beta cells or development of peripheral insulin resistance), these types of diabetes behave similarly to type 1 or type 2 diabetes. The most common are diseases of the pancreas that destroy the pancreatic beta cells (eg, hemochromatosis, pancreatitis, cystic fibrosis, pancreatic cancer), hormonal syndromes that interfere with insulin secretion (eg, pheochromocytoma) or cause peripheral insulin resistance (eg, acromegaly, Cushing syndrome, pheochromocytoma), and diabetes induced by drugs (eg, phenytoin, glucocorticoids, estrogens).


insufficient insulin
reduced tissue uptake of glucose
intracellular hypoglycaemia
extracellular hyperglycaemia
glucogenesis and gluconeogenesis
hyperosmotic plasma
blood glucose > renal threshold
breakdown of fats
decreased protein synthesis
cachexia
lethargy
polyphagia
decreased gamma globulins
susceptibility to infections
impaired wound healing
dehydration of cells
glucosuria - urine has a high SG
high levels of ketones
hyperglycaemic coma
osmotic diuresis
- polyuria
- polydipsia
- hypokalaemia
- hyponatraemia
diabetic ketoacidosis

Pathophysiology

- Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Gestational diabetes mellitus is a complication of approximately 4% of all pregnancies in the United States.

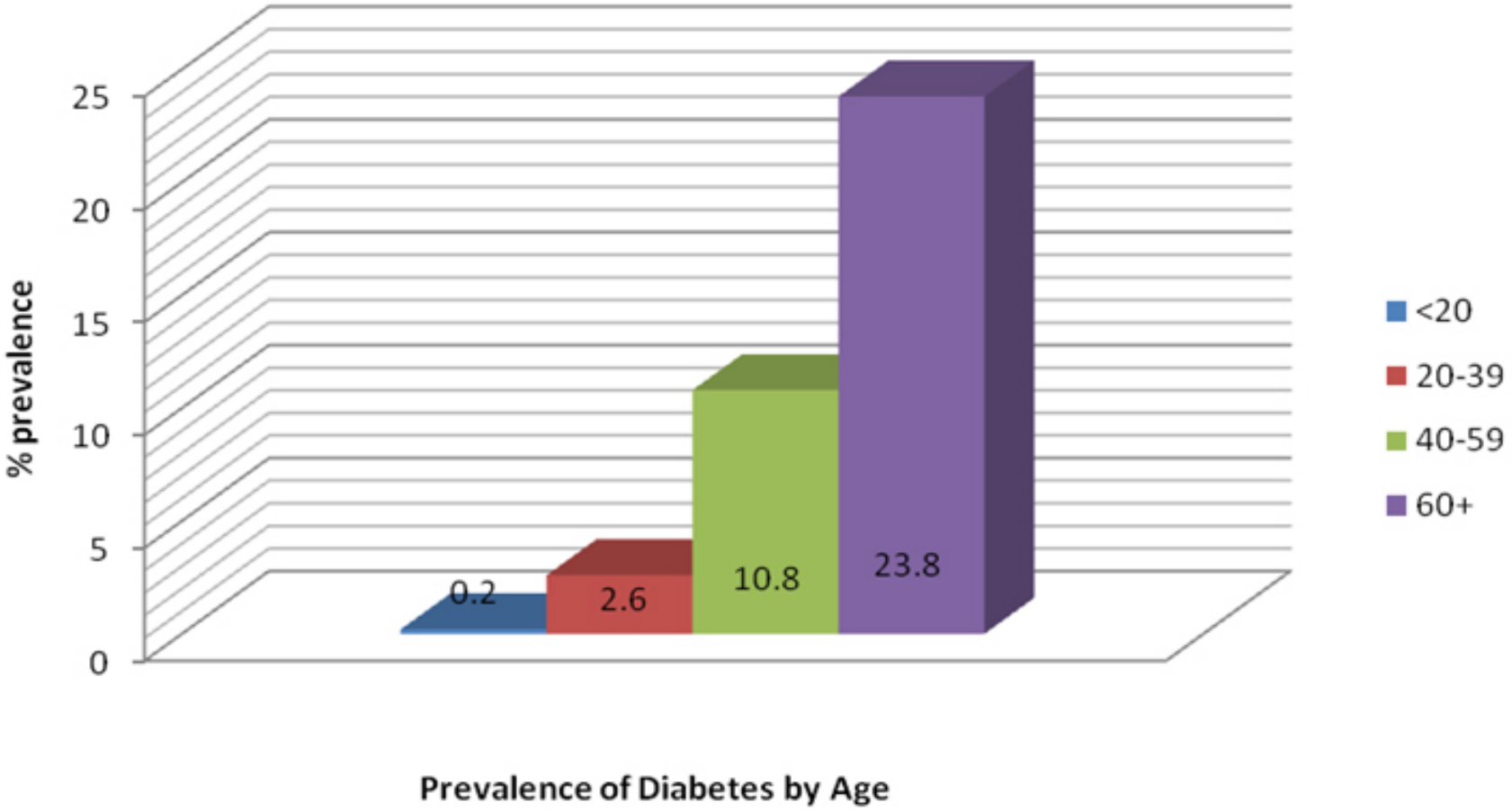
- Untreated gestational diabetes mellitus can lead to fetal macrosomia, hypoglycemia, hypocalcemia, and hyperbilirubinemia. In addition, mothers with gestational diabetes mellitus have increased rates of cesarean delivery and chronic hypertension.

Epidemiology

- International statistics
- Type 2 diabetes mellitus is less common in non-Western countries where the diet contains fewer calories and daily caloric expenditure is higher. However, as people in these countries adopt Western lifestyles, weight gain and type 2 diabetes mellitus are becoming virtually epidemic.
- Rates of diabetes are increasing worldwide. At least 171 million people currently have diabetes, and this figure is likely to more than double to 366 million by 2030. The top 10 countries, in numbers of people with diabetes, are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh. The greatest percentage increase in rates of diabetes will occur in Africa over the next 20 years. However, at least 80% of people in Africa with diabetes are undiagnosed, and many in their 30s to 60s will die from diabetes there.

- Type 2 diabetes mellitus occurs most commonly in adults aged 40 years or older, and the prevalence of the disease increases with advancing age.
- Indeed, the aging of the population is one reason that type 2 diabetes mellitus is becoming increasingly common. Virtually all cases of diabetes mellitus in older individuals are type 2.

- n addition, however, the incidence of type 2 diabetes is increasing more rapidly in adolescents and young adults than in other age groups.
- The disease is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese.
- In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults.


% prevalence
25
20
15
10
5
0
0.2
2.6
10.8
23.8
<20
20-39
40-59
60+
Prevalence of Diabetes by Age

- The risk for coronary heart disease is 2-4 times greater in patients with diabetes than in individuals without diabetes.
- Cardiovascular disease is the major source of mortality in patients with type 2 diabetes mellitus.
- Approximately two thirds of people with diabetes die of heart disease or stroke.
- Men with diabetes face a 2-fold increased risk for coronary heart disease, and women have a 3-fold to 4-fold increased risk. Although type 2 diabetes mellitus, both early onset (< 60 y) and late onset (>60 y), is associated with an increased risk of major coronary heart disease and mortality, only the early onset type (duration >10 y) appears to be a coronary heat disease risk equivalent.

- In patients with type 2 diabetes mellitus, a fasting glucose level of more than 100 mg/dL significantly contributes to the risk for cardiovascular disease and death, independent of other known risk factors.

- Adolescents with obesity and obesity-related type 2 diabetes mellitus demonstrate a decrease in diastolic dysfunction.
- This suggests that they may be at increased risk of progressing to early heart failure compared with adolescents who are either lean or obese but do not have type 2 diabetes mellitus.

- Women with depression have a relative higher risk for diabetes. Women with diabetes have higher risk for depression, particularly in those receiving insulin, which might reflect a complicated and poor glycemic state.
- The prognosis in patients with diabetes mellitus is strongly influenced by the degree of control of their disease. Chronic hyperglycemia is associated with an increased risk of microvascular complications

History

- The diagnosis of diabetes mellitus is readily entertained when a patient presents with classic symptoms (ie, polyuria, polydipsia, polyphagia, weight loss).
- Other symptoms that might suggest hyperglycemia include blurred vision, lower extremity paresthesias, or yeast infections, particularly balanitis in men.
- However, many patients with type 2 diabetes are asymptomatic, and their disease remains undiagnosed for many years.

- Studies suggest that at the time of diagnosis, the typical patient with type 2 diabetes has had diabetes for at least 4-7 years.
- Among patients with type 2 diabetes, 25% are believed to have retinopathy; 9%, neuropathy; and 8%, nephropathy at the time of diagnosis.

Patients with established diabetes

- In patients with known type 2 diabetes, inquire about the duration of the patient's diabetes and about the care the patient is currently receiving for diabetes.

- The duration of diabetes is significant because the chronic complications of diabetes are related to the length of time the patient has had the disease.

A focused diabetes history should also include the following questions:

- Is the patient's diabetes generally well controlled (with near-normal blood glucose levels)? Patients with poorly controlled blood glucose levels heal more slowly and are at increased risk for infection and other complications.
- Does the patient have severe hypoglycemic reactions? If the patient has episodes of severe hypoglycemia and therefore is at risk for losing consciousness, this possibility must be addressed, especially if the patient drives.
- Does the patient have diabetic nephropathy that might alter the use of medications or intravenous radiographic contrast material?
- Does the patient have macrovascular disease, such as coronary artery disease (CAD) that should be considered as a source of acute symptoms?
- Does the patient self-monitor his or her blood glucose levels? Note the frequency and range of values at each time of day.
- When was the patient's hemoglobin A1C (HbA1C) value (an indicator of long-term glucose control) last measured? What was it?

As circumstances dictate, additional questions may be warranted, as follows

- Does the patient give a history of recent polyuria, polydipsia, nocturia, or weight loss? These are symptoms of hyperglycemia.
- Has the patient had episodes of unexplained hypoglycemia? If so, when, how often, and how does the patient treat these episodes?
- Does the patient have hypoglycemia unawareness (ie, does the patient lack the adrenergic warning signs of hypoglycemia)? Hypoglycemia unawareness indicates an increased risk of subsequent episodes of hypoglycemia.

- Regarding retinopathy, when was the patient's last dilated eye examination? What were the results?
- Regarding nephropathy, does the patient have known kidney disease? What were the dates and results of the last measurements of urine protein and serum creatinine levels?
- Does the patient have hypertension (defined as a blood pressure of >130/80)? What medications are taken?
- Does the patient have CAD?

- Regarding peripheral vascular disease, does the patient have claudication or a history of vascular bypass?
- Has the patient had a stroke or transient ischemic attack?
- What are the patient's most recent lipid levels? Is the patient taking lipid-lowering medication?
- Does the patient have a history of neuropathy or are symptoms of peripheral neuropathy or autonomic neuropathy present (including impotence if the patient is male)?
- Does the patient have a history of foot ulcers or amputations? Are any foot ulcers present?
- Are frequent infections a problem? At what site?

Physical Examination

- Early in the course of diabetes mellitus, the physical examination findings are likely to be unrevealing.
- However, ultimately, end-organ damage may be observed.

Possible Physical Findings in Patients with Type 2 Diabetes Mellitus

- Obesity, particularly central
- Hypertension
- Eye-hemorrhages, exudates, neovascularization
- Skin-acanthosis nigricans (particularly in dark skinned ethnic and racial groups); candida infections
- Neurologic-decreased or absent light touch, temperature sensation, and proprioception; loss of deep tendon reflexes in ankles
- Feet-dry, muscle atrophy, claw toes, ulcers

- A diabetes-focused examination includes vital signs, funduscopic examination, limited vascular and neurologic examinations, and a foot assessment.
- Other organ systems should be examined as indicated by the patient's clinical situation.

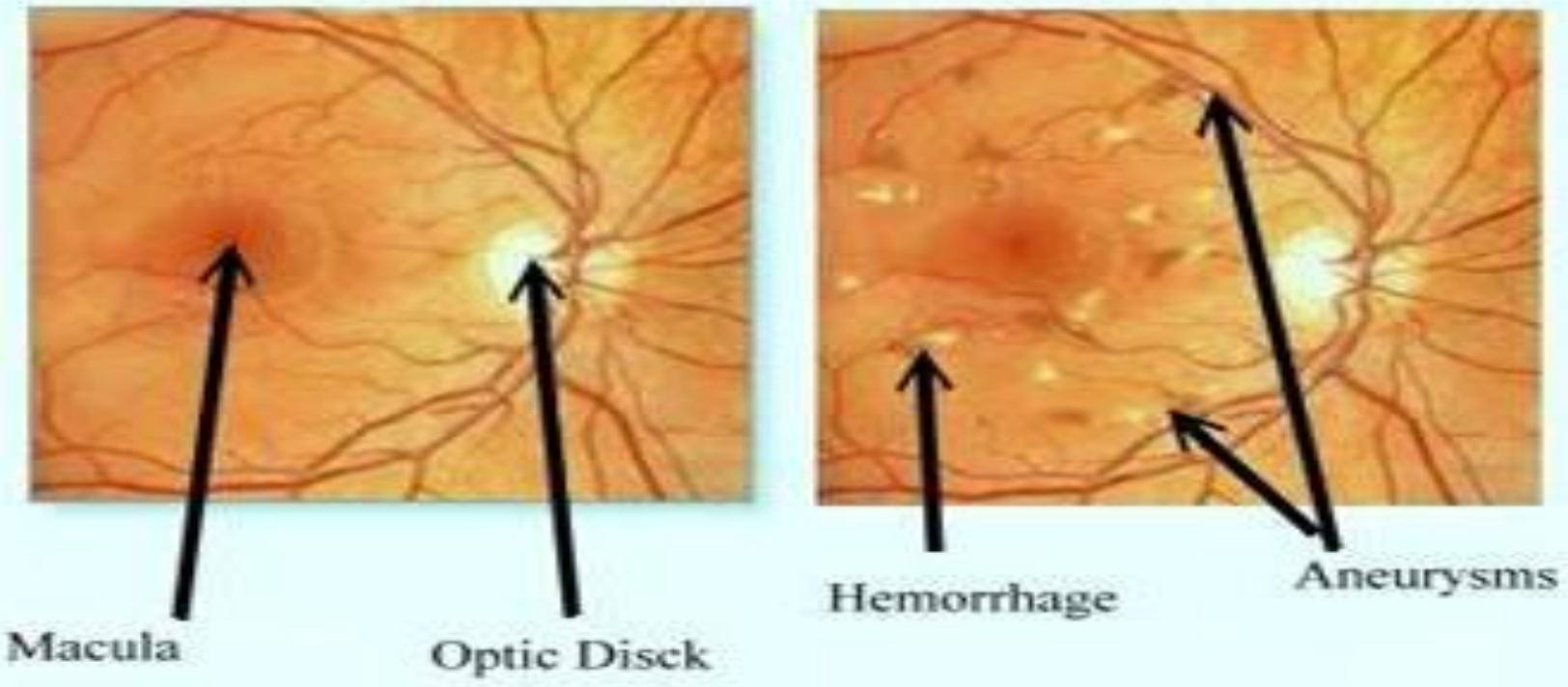
Assessment of vital signs

- Is the patient hypertensive or hypotensive? Orthostatic vital signs may be useful in assessing volume status and in suggesting the presence of an autonomic neuropathy.
- If the respiratory rate and pattern suggest Kussmaul respiration, DKA must be considered immediately, and appropriate tests ordered.

Funduscopic examination

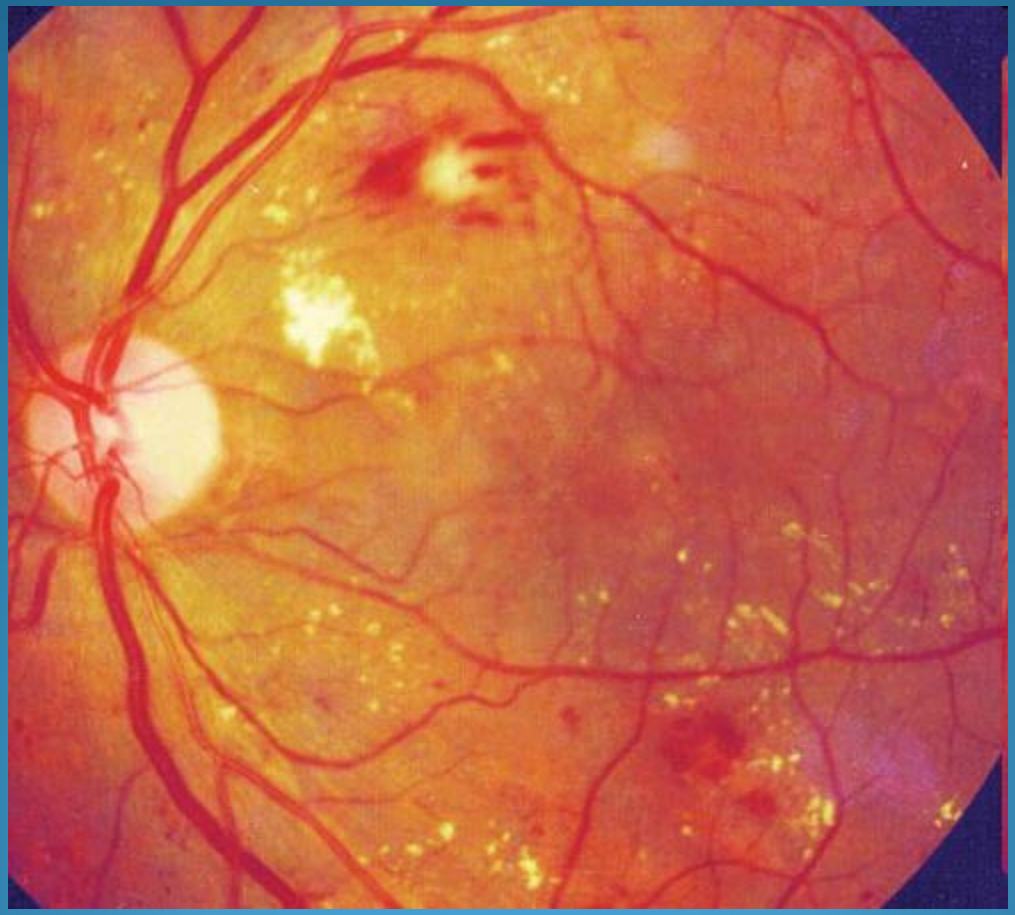
- The funduscopic examination should include a careful view of the retina, including both the optic disc and the macula.
- If hemorrhages or exudates are seen, the patient should be referred to an ophthalmologist as soon as possible. Examiners who are not ophthalmologists tend to underestimate the severity of retinopathy, especially if the patients' pupils are not dilated.

Diabetic Retinopathy



Normal Retina **Ratinopathy**

Diabetic rethinopathy

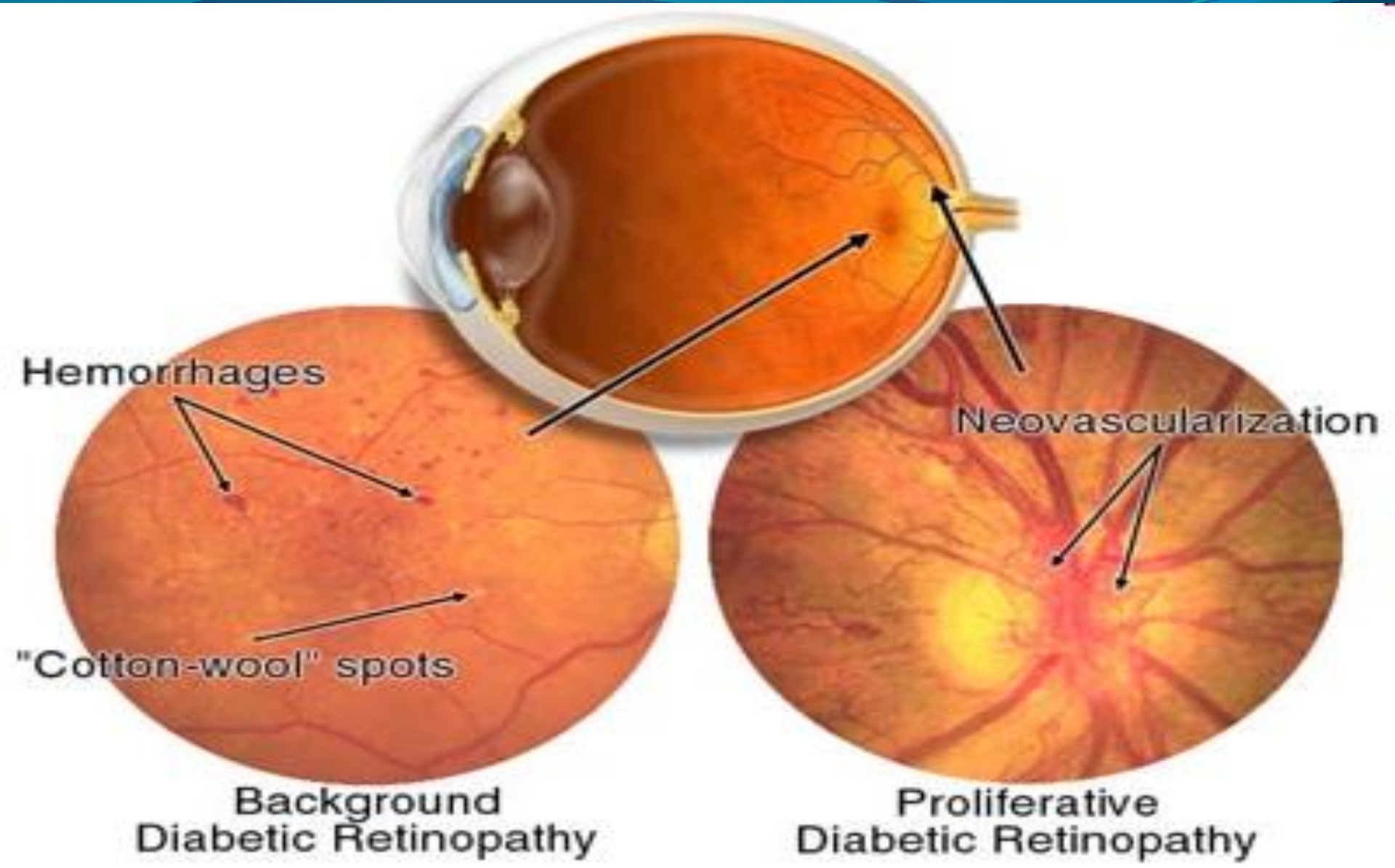


- Stages of diabetic retinopathy
- Diabetic retinopathy has four stages:
- Mild nonproliferative retinopathy. At this earliest stage, microaneurysms occur (see aneurysm. They are small areas of balloon-like swelling in the retina's tiny blood vessels.

- Moderate nonproliferative retinopathy. As the disease progresses, some blood vessels that nourish the retina are blocked.

- Severe nonproliferative retinopathy. Many more blood vessels are blocked, depriving several areas of the retina with their blood supply. These areas of the retina send signals to the body to grow new blood vessels for nourishment.

- Proliferative retinopathy. At this advanced stage, the signals sent by the retina for nourishment trigger the growth of new blood vessels. This condition is called proliferative retinopathy. These new blood vessels are abnormal and fragile. They grow along the retina and along the surface of the clear, vitreous gel that fills the inside of the eye. By themselves, these blood vessels do not cause symptoms or vision loss. However, they have thin, fragile walls. If they leak blood, severe vision loss and even blindness can result

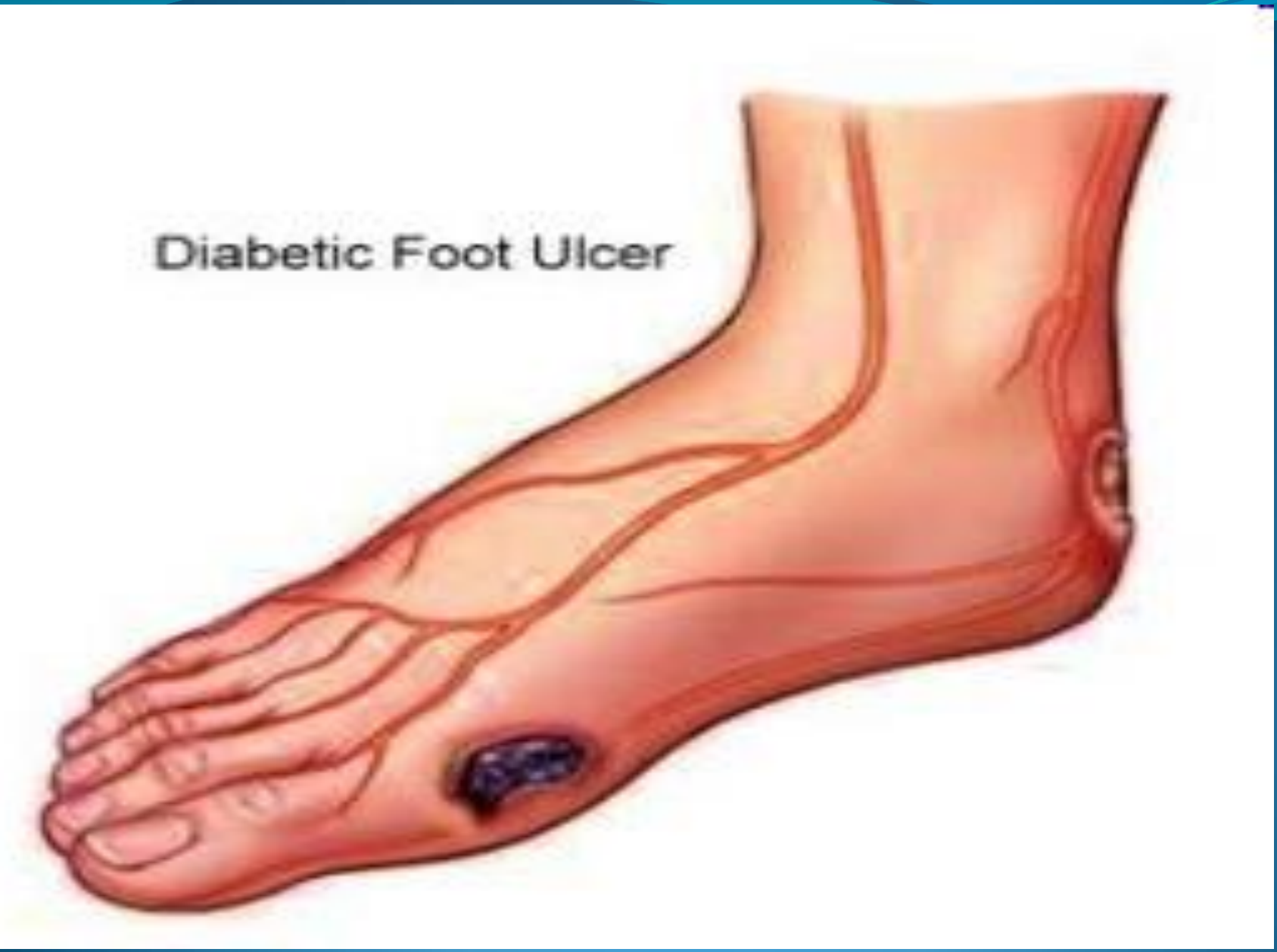

Hemorrhages
"Cotton-wool" spots
Neovascularization
Background
Diabetic Retinopathy
Proliferative
Diabetic Retinopathy

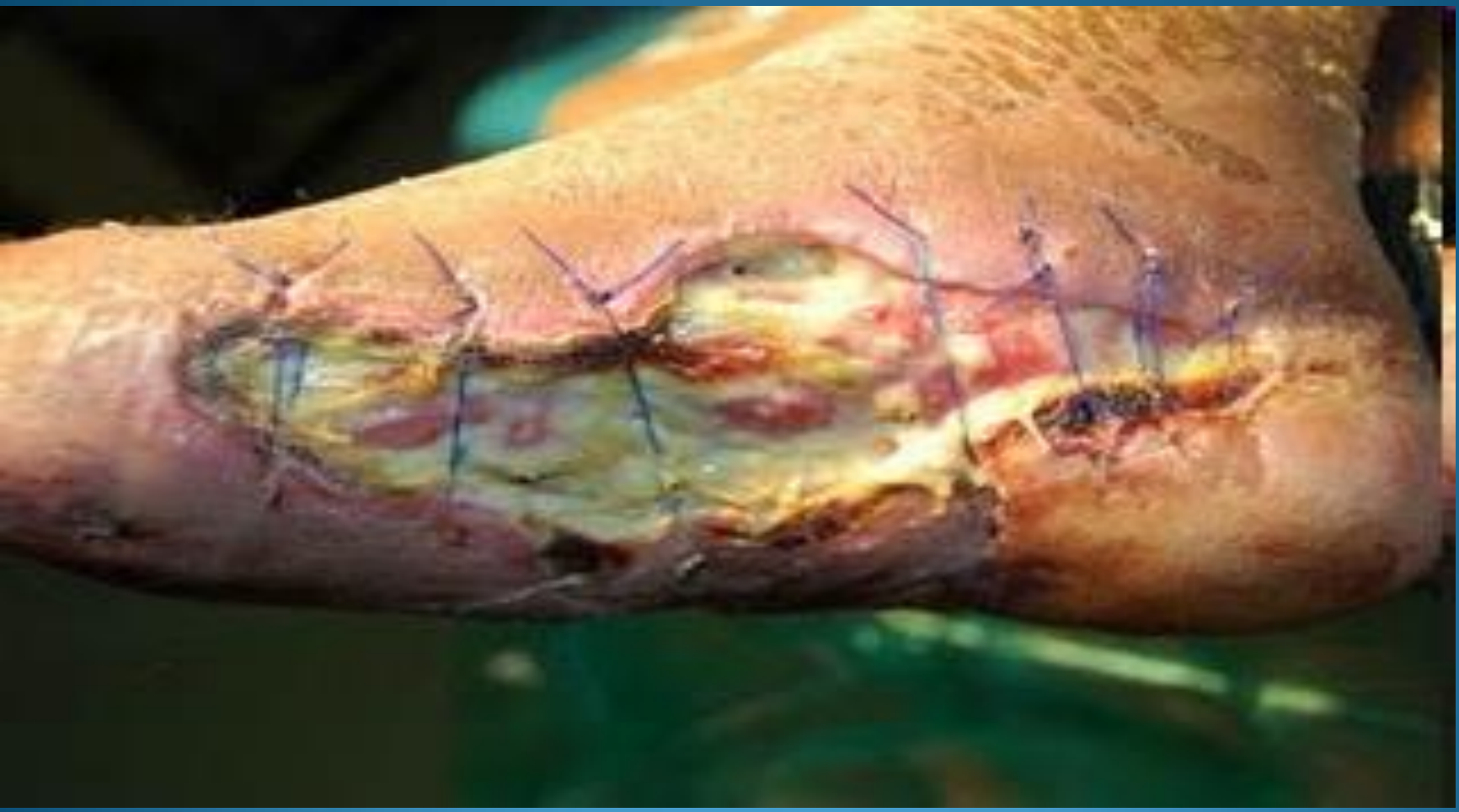
Foot examination

- The dorsalis pedis and posterior tibialis pulses should be palpated and their presence or absence noted. This is particularly important in patients who have foot infections, because poor lower-extremity blood flow can delay healing and increase the risk of amputation.

- Documenting lower-extremity sensory neuropathy is useful in patients who present with foot ulcers because decreased sensation limits the patient's ability to protect the feet and ankles. This can be assessed with a monofilament, or more readily by assessment of reflexes, position, and vibration sensation.

- If peripheral neuropathy is found, the patient should be made aware that foot care (including daily foot examination) is very important for the prevention of foot ulcers and lower-extremity amputation.


Diabetic Foot Ulcer




Date:
Site:
Client:
I.D.#:
L x W x D cm
cm 0 1 2 3 4 5

Patient #: 4XXX
Age: 60 M
Diagnosis: Diabetes – Infection w/imminent gangrene

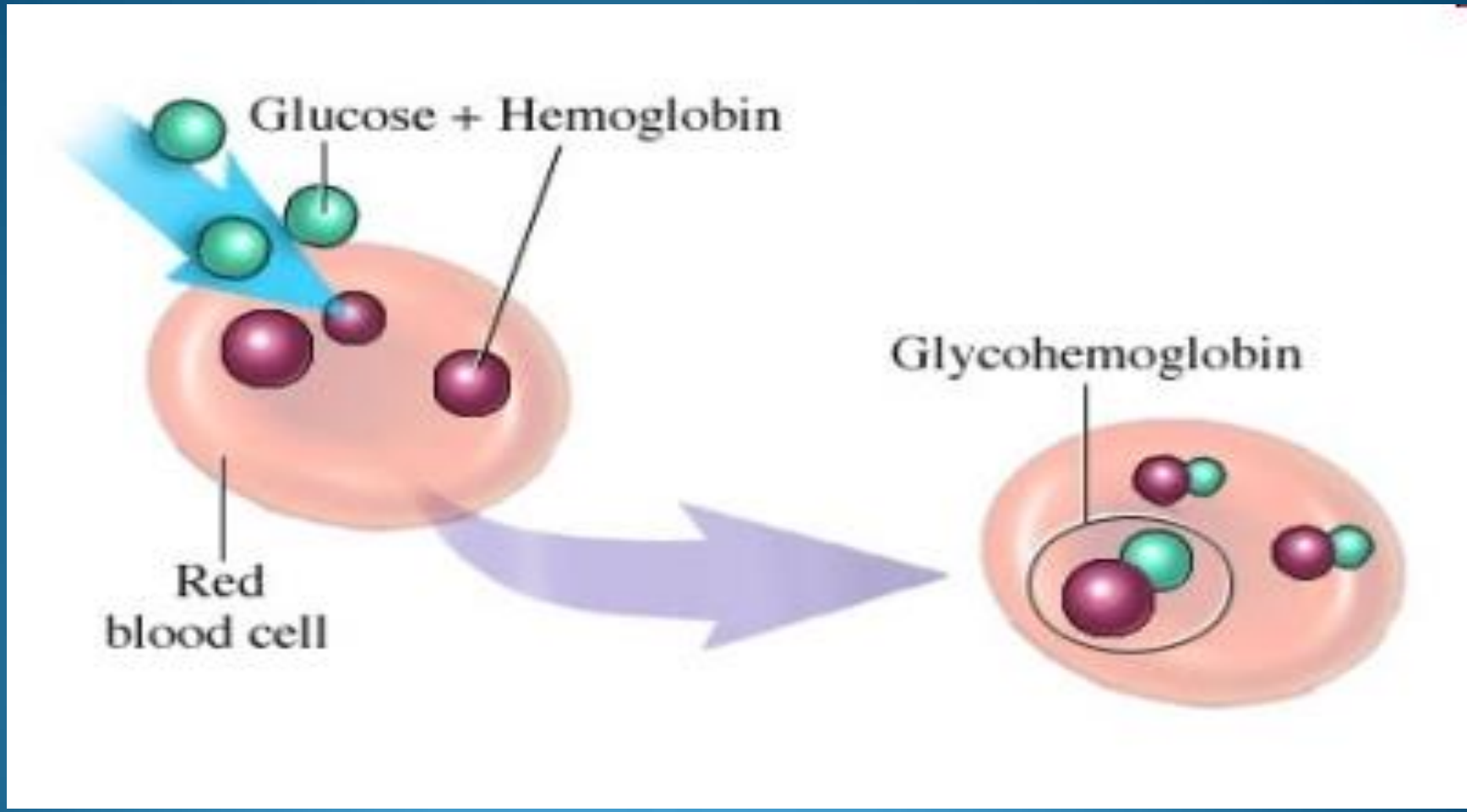
The American Diabetes Association criteria for the diagnosis of diabetes

Diagnosis of Diabetes Mellitus

- Classic symptoms of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss and random plasma glucose ≥200 mg/dL
- Fasting plasma glucose ≥126 mg/dL
- Two hour post glucose load (75 g) plasma glucose ≥200 mg/dL, and confirmed by repeat test

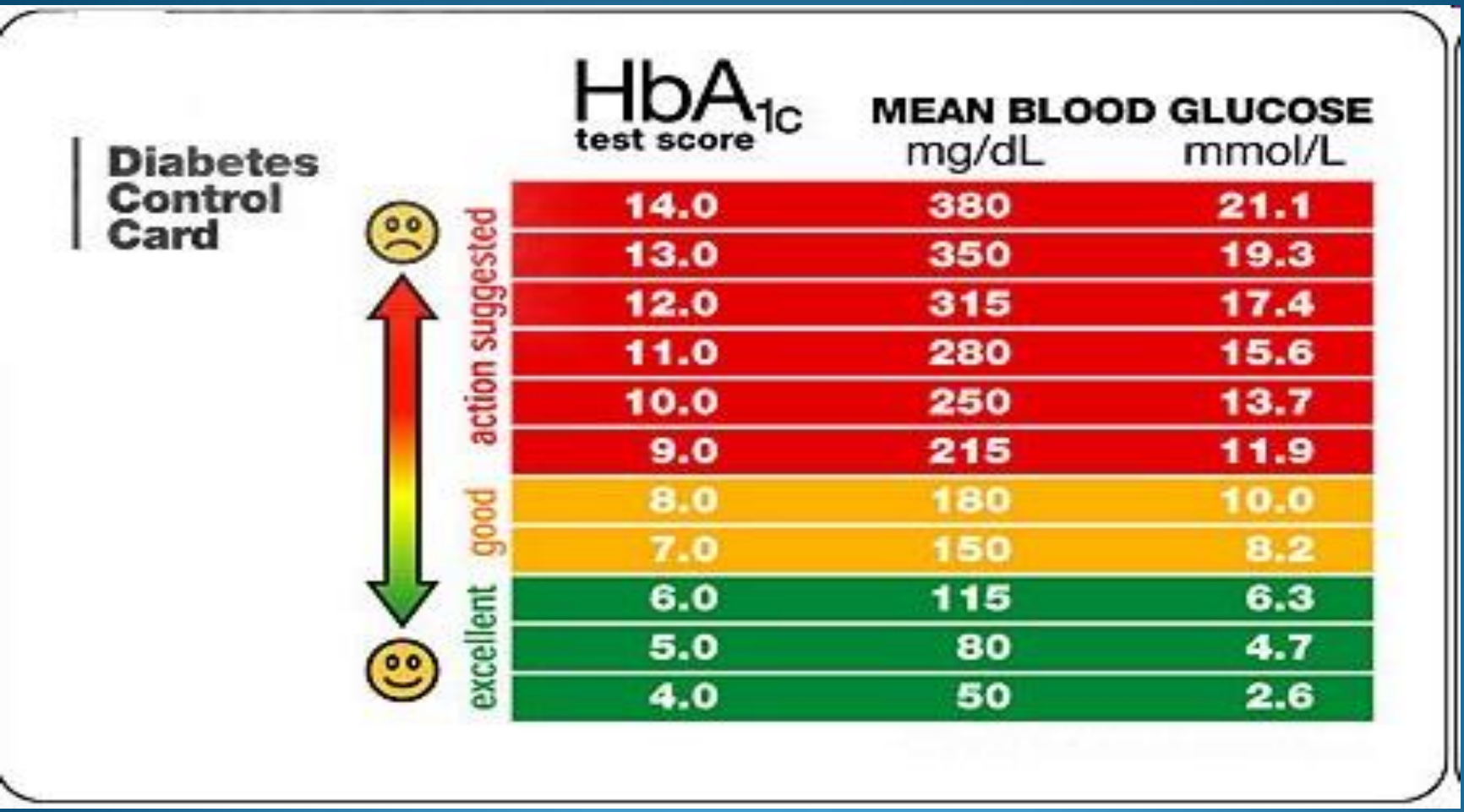
fasting: no caloric intake for at least 8 hr
plasma glucose obtained in a sodium fluoride (gray top) tube

- In asymptomatic patients whose random serum glucose level suggests diabetes (>140 mg/dL), an FPG concentration or a hemoglobin A1c (HbA1c) level should be measured.
- An FPG level of 100-125 mg/dL is considered impaired fasting glucose (IFG), and an FPG level of less than 100 mg/dL is considered normal glucose tolerance.


Glucose + Hemoglobin
Red
blood cell
Glycohemoglobin

Glycosylated hemoglobin (HbA1c)

- The concept of the test is to measure how good or bad a diabetic patient controls his or her disease.
- This is done by measuring how much glycated hemoglobin is in the blood.
- Glycated hemoglobin is a molecule formed when blood sugar (glucose) attaches or combines with hemoglobin.
- It is used to identify the blood sugar concentration over long periods of time thus HbA1c is directly related to the average concentration of glucose / sugar in the blood.


Diabetes Control Card
HbA1c test score
MEAN BLOOD GLUCOSE
mg/dL
mmol/L
14.0 380 21.1
13.0 350 19.3
12.0 315 17.4
11.0 280 15.6
10.0 250 13.7
9.0 215 11.9
8.0 180 10.0
7.0 150 8.2
6.0 115 6.3
5.0 80 4.7
4.0 50 2.6
action suggested
good
excellent

- An HbA1C level of 6.5% or greater is diabetes. An HbA1c below 6% is considered normal glucose tolerance
- However, an HbA1C of 6-6.4% is neither normal glucose tolerance nor diabetes.
- Hyperglycemia exists across a continuum in an individual, generally gradually increasing over time.

- A 2-hour oral glucose tolerance test (OGTT) value of 200 mg/dL or higher is diagnostic of diabetes.
- However, the OGTT is no longer recommended for the routine diagnosis of diabetes. It is used to diagnose gestational diabetes mellitus or impaired glucose tolerance (IGT).

Glucose Studies

- Plasma glucose is determined using blood drawn into a gray-top (sodium fluoride) tube, which inhibits red blood cell glycolysis immediately.
- A serum glucose measurement (commonly obtained on chemistry panels, using a red- or speckled-top tube) may be significantly lower than a plasma glucose measurement.
- Capillary whole blood measurements are not recommended for the diagnosis of diabetes mellitus, but they are valuable for assessment of patients in acute care situations.

- The World Health Organization criteria for IGare as follows:

- FPG < 140 mg/dL at 2 hours after a 75-g glucose loadPlasma glucose ≥ 140 mg/dL to < 200 mg/dL with 1 intervening plasma glucose value ≥ 200 mg/dL

Glycated Hemoglobin Studies

- HbA1c measurements are the criterion standard for monitoring long-term glycemic control and reflect glycemia for the previous 3 months.
- HbA1c measurements have previously not been considered useful for the diagnosis of diabetes mellitus because of a lack of international standardization and insensitivity for the detection of milder forms of glucose intolerance.
- Changes in standardization that could affect the actual values that individual laboratories generate have also been a concern.

- American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Association recommended the HbA1c assay for diagnosing type 1 and type 2 diabetes mellitus

The committee cited the following advantages of HbA1c testing over glucose measurement:

- Captures long-term glucose exposure
- Has less biologic variability
- Does not require fasting or timed samples
- Is currently used to guide management decisions

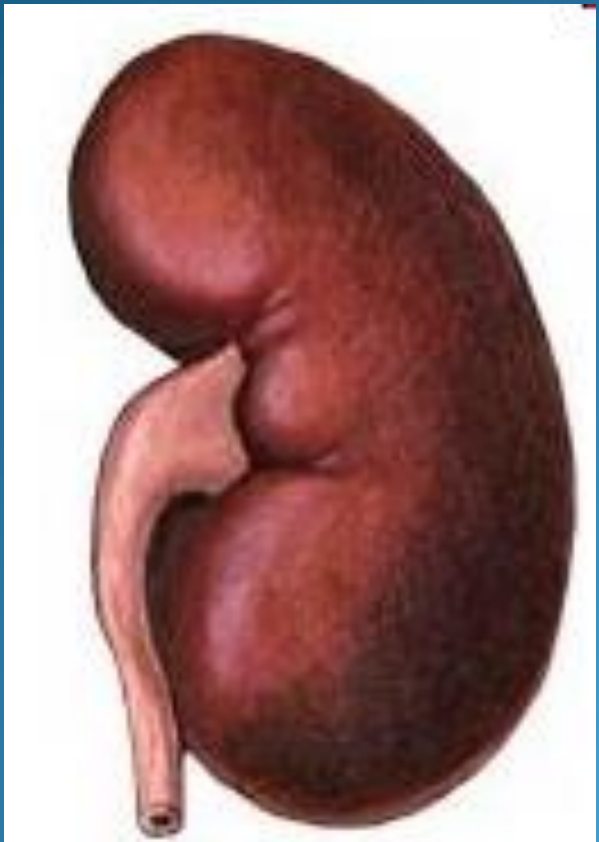
Hemoglobin A1c versus glycated hemoglobin

- Whether HbA1c or glycated hemoglobin (GHb) assays are superior for measuring glycemic control is debatable. Hemoglobinopathies can affect both measurements.

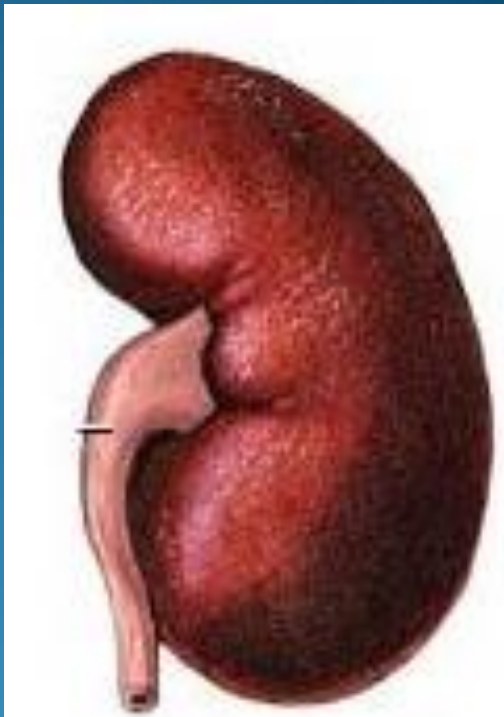
Urinary Microalbumin Studies

- Annual screening for microalbuminuria is recommended in all patients with diabetes. Measuring the albumin-to-creatinine ratio in a spot urine sample is probably the easiest method; the ratio, expressed in mg/g, is equivalent to albumin excretion in mg/day.
- A result greater than 30 mg/g indicates albuminuria, in which case a quantitation on a timed urine specimen (ie, overnight, 10 hours, or 24 hours) should be performed.
- Normal urine albumin excretion is defined as less than 30 mg/d. Microalbuminuria is defined as 30-300 mg/d (20-200 mcg/min).
- Because of wide variability among patients, confirm persistent microalbuminuria on at least 2 of 3 samples over 3-6 months. Greater values can be detected by standard protein dipstick screening and are considered macroproteinuria.

- Unlike type 1 diabetes mellitus, in which microalbuminuria is a good indicator of early kidney damage, microalbuminuria is a common finding (even at diagnosis) in type 2 diabetes mellitus and is a risk factor for macrovascular (especially coronary heart) disease.
- It is a weaker predictor for future kidney disease in type 2 diabetes mellitus.



Normal Kidney



Diabetic Kidney Nephropathy

- The U.S. Preventive Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg (grade B recommendation).

- The ADA recommends considering testing for pre-diabetes and diabetes in asymptomatic adults who are overweight (body mass index [BMI] ≥25 kg/m2; may be lower in at-risk ethnic groups) and one or more of the following additional risk factors :

- Physical inactivity
- First-degree relative with diabetes
- Members of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing >9 lb or were diagnosed with gestational diabetes mellitus
- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein (HDL) cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
- Women with polycystic ovary disease
- Impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
- Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
- History of cardiovascular disease

- In the absence of the above criteria, the ADA recommends testing for pre-diabetes and diabetes beginning at age 45 years. If results are normal, testing should be repeated at least every 3 years. More frequent testing may be considered, depending on initial results and risk status.

Tests to Differentiate Type 2 and Type 1 Diabetes

- Measuring concentrations of insulin or C-peptide (a fragment of proinsulin that serves as a marker for insulin secretion) rarely is necessary to diagnose type 2 diabetes mellitus or differentiate type 2 diabetes from type 1 diabetes mellitus. Insulin levels generally are high early in the course of type 2 diabetes mellitus and gradually wane over time.

- A fasting C-peptide level more than 1 ng/dL in a patient who has had diabetes for more than 1-2 years is suggestive of type 2 diabetes (ie, residual beta-cell function).
- Stimulated C-peptide concentrations (after a standard meal challenge such as Sustacal or after glucagon) are somewhat preserved until late in the course of type 2 diabetes mellitus.
- Absence of a C-peptide response to carbohydrate ingestion may indicate total beta-cell failure.

- Antibodies to insulin, islet cells, or glutamic acid decarboxylase (GAD) are absent in type 2 diabetes mellitus.

- Latent autoimmune diabetes of adults (LADA) is a form of slow-onset type 1 diabetes that occurs in middle-aged (usually white) adults.
- It can be differentiated from type 2 diabetes by measuring anti-GAD65 antibodies.
- Such patients may respond to insulin secretagogues for a brief period (months).

- Autoantibodies can be useful in differentiating between type 1 diabetes and type 2 diabetes. Islet-cell (IA2), anti-GAD65, and anti-insulin autoantibodies can be present in early type 1, but not type 2, diabetes.
- Measurements of islet-cell (IA2) autoantibodies within 6 months of diagnosis can help differentiate type 1 and type 2 diabetes.
- These titers decrease after 6 months. Anti-GAD65 antibodies are suggestive of type 1 diabetes.
- They can be present at diagnosis and are persistently positive over time.

Type 1 Diabetes Mellitus

Background

- Diabetes mellitus (DM) is a multisystem disease with both biochemical and anatomical/structural consequences. It is a chronic disease of carbohydrate, fat, and protein metabolism caused by the lack of insulin, which results from the marked and progressive inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells.

- Type 1 DM can occur at any age. It occurs most commonly in juveniles but can also occur in adults, especially in those in their late 30s and early 40s.

- Unlike people with type 2 DM, those with type 1 DM generally are not obese and may present initially with diabetic ketoacidosis (DKA). The distinguishing characteristic of a patient with type 1 diabetes is that if his or her insulin is withdrawn, ketosis and eventually ketoacidosis develop. Therefore, these patients are dependent on exogenous insulin.

- Treatment of type 1 DM requires a multidisciplinary approach by physician, nurse, and dietitian. In patients with new-onset type 1 diabetes, lifelong insulin therapy must be started.
- As a chronic disease, DM requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur.

Etiology

- The etiology of type 1 DM has a strong genetic component. Nevertheless, identical twins have a concordance rate for type 1 DM of less than 50%. In studies of identical twin pairs in which 1 twin has type 1 diabetes, antibodies to the islet cell and to insulin are positive for several years in the nondiabetic twin before overt diabetes develops.

Etiology

- Extragenetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, mumps, rubella, coxsackievirus B4), toxic chemicals, exposure to cow's milk in infancy, and cytotoxins.
- As beta-cell mass declines with ongoing immunologic destruction, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed.

Etiology

- A meta-analysis suggests a significant association between enterovirus infection and autoimmune/type 1 DM.
- The role of enterovirus in development of type 1 DM warrants investigation in larger prospective studies.

Pathophysiology

- 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 fail to respond to all insulin-secretory stimuli.
- The pancreas shows lymphocytic infiltration and destruction of insulin-secreting cells of the islets of Langerhans, causing insulin deficiency.
- Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism.

Pathophysiology

- One theory regarding the etiology of type 1 DM is that it results from damage to pancreatic beta cells from infectious or environmental agents. In a genetically susceptible individual, the immune system is thereby triggered to develop an autoimmune response against altered pancreatic beta cell antigens or molecules in beta cells that resemble a viral protein. Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also have detectable anti-insulin antibodies before receiving insulin therapy. Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) within pancreatic beta cells.

Pathophysiology

- Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM. Prevalence is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and Addison disease. Approximately 95% of patients with type 1 DM have either human leukocyte antigen (HLA)-DR3 or HLA-DR4. HLA-DQs are considered specific markers of type 1 DM susceptibility.

Pathophysiology

- Amino acid metabolism also plays a key role in the pathogenesis of diabetes. Amino acid profiles could help assess risk of developing diabetes. It might help elucidate further how diabetes evolves.

Pathophysiology

- Recent evidence suggests a role for vitamin D in the pathogenesis and prevention of diabetes mellitus. Vitamin D deficiency is also an important independent predictor of development of coronary artery calcification in individuals with type 1 DM.

International statistics

- Internationally, rates of type 1 diabetes are increasing. In Europe, the Middle East, and Australia, rates of type 1 diabetes are increasing by 2-5% per year.
- Scandinavia has the highest prevalence rates for type 1 DM (ie, approximately 20% of the total number of people with DM), while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes.
- Some of these differences may relate to definitional issues and the completeness of reporting.

Prevalence of diabetes by age

- Long called juvenile-onset diabetes, type 1 DM is typically diagnosed in childhood, adolescence, or early adulthood. Although the onset of type 1 DM often occurs early in life, 50% of patients with new-onset type 1 DM are older than 20 years of age.

- Type 1 DM usually starts in children aged 4 years or older, fairly abruptly, with the peak incidence of onset at age 11-13 years, coinciding with early adolescence and puberty.
- Also, a relatively high incidence exists in people in their late 30s and early 40s, when the disease tends to present in a less aggressive manner (ie, early hyperglycemia without ketoacidosis and gradual onset of ketosis).
- This slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (LADA).

Prevalence of diabetes by race

- Type 1 DM is more common among non-Hispanic whites, followed by African Americans and Hispanic Americans. It is comparatively uncommon among Asians.
- Whites seem to be affected more often than blacks, who have the lowest overall incidence of type 1 diabetes.

Sex distribution for diabetes

- Type 1 DM is more common in men than in women.
- The male-to-female ratio is approximately greater than 1.5:1 in populations of European origin.

Prognosis

- Type 1 DM is associated with a high morbidity and premature mortality.
- More than 60% of patients with type 1 DM fare reasonably well over the long term.
- Many of the rest develop blindness, end-stage renal disease, and, in some cases, early death.
- If a patient with type 1 DM survives the period 10-20 years after onset of disease without fulminant complications, he or she has a high probability of reasonably good health.
- Other factors affecting long-term outcomes are the patient's education, awareness, motivation, and intelligence level.

- The morbidity and mortality associated with diabetes are related to the short- and long-term complications. Such complications include hypoglycemia and hyperglycemia, increased risk of infections, microvascular complications (eg, retinopathy, nephropathy), neuropathic complications, and macrovascular disease. As a result of these complications, people with diabetes have an increased risk of developing ischemic heart disease, cerebral vascular disease, peripheral vascular disease with gangrene of lower limbs, chronic renal disease, reduced visual acuity and blindness, and autonomic and peripheral neuropathy. Diabetes is the major cause of blindness in adults aged 20-74 years, as well as the leading cause of nontraumatic lower-extremity amputation and end-stage renal disease (ESRD).

- Controlling blood glucose, hemoglobin A1c (HbA1c), lipids, blood pressure, and weight are important prognostic factors. Patients with diabetes have a lifelong challenge to achieve and maintain blood glucose levels as close to the normal range as possible. With appropriate glycemic control, the risk of both microvascular and neuropathic complications is decreased markedly. In addition, if hypertension and hyperlipidemia are treated aggressively, the risk of macrovascular complications decreases as well. The benefits of glycemic control and control of comorbidities are weighed against the risk of hypoglycemia and the short-term costs of providing high-quality preventive care. Studies have shown cost savings due to a reduction in acute diabetes-related complications within 1-3 years of starting effective preventive care.

History

- The most common symptoms of type 1 diabetes mellitus (DM) are polyuria, polydipsia, and polyphagia, along with lassitude, nausea, and blurred vision, all of which are due to the hyperglycemia itself.

History

- The disease onset may be sudden, with the presentation of an infection. It is not unusual for type 1 DM to present with diabetic ketoacidosis (DKA); it may occur de novo or develop with the stress of illness or surgery. An explosive onset of symptoms in a young lean patient with ketoacidosis always has been considered diagnostic of type 1 DM.

Symptoms

- Symptoms at the time of the first clinical presentation can usually be traced back several days to several weeks; however, beta cell destruction may have started months, or even years, before the onset of clinical symptoms.

The following symptoms may be noted with type 1 DM:

- Polyuria and thirst: Polyuria is due to osmotic diuresis secondary to hyperglycemia; thirst is due to the hyperosmolar state and dehydration.
- Polyphagia with weight loss: The weight loss with a normal or increased appetite is due to depletion of water and a catabolic state with reduced glycogen, proteins, and triglycerides.

- Fatigue and weakness may be due to muscle wasting from the catabolic state of insulin deficiency, hypovolemia, and hypokalemia.
- Muscle cramps are due to electrolyte imbalance.
- Nocturnal enuresis: Severe enuresis secondary to polyuria can be an indication of onset of diabetes in young children.

- Blurred vision is due to the effect of the hyperosmolar state on the lens and vitreous humor; glucose and its metabolites cause dilation of the lens, altering its normal focal length.

- Gastrointestinal (GI) symptoms:
- Nausea, abdominal discomfort or pain, and change in bowel movements may accompany acute DKA;
- acute fatty liver may lead to distention of the hepatic capsule, causing right upper quadrant pain; persistent abdominal pain may indicate another serious abdominal cause of DKA (eg, pancreatitis); chronic GI symptoms in the later stage of DM are due to visceral autonomic neuropathy.

- Patients may maintain their normal weight or exhibit wasting, depending on the interval between the onset of the disease and initiation of treatment.

- Peripheral neuropathy presents as numbness and tingling in both hands and feet, in a glove and stocking pattern; it is bilateral, symmetric, and ascending neuropathy, which results from many factors, including the accumulation of sorbitol in peripheral sensory nerves due to sustained hyperglycemia.

Ask questions about type, duration, and care of diabetes

- It is important to inquire about the type and duration of the patient's diabetes and about the care the patient is receiving for diabetes. Determination of the type of diabetes is based on history, therapy, and clinical judgment. The chronic complications of diabetes are related to the length of time the patient has had the disease.

- Ask about the type of insulin being used, delivery system (pump vs injections), dose, and frequency.

- Also ask about oral antidiabetic agents, if any.

- Patients using a pump or a multiple-injection regimen have a basal insulin (taken through the pump or with the injection of a long-acting insulin analogue) and a premeal rapid-acting insulin, the dose of which is determined as a function of the carbohydrate count plus the correction (to adjust for how high the premeal glucose level is).

In these patients, ask about the following:

- Basal rates (eg, units per hour by pump, generally 0.4-1.5 units/h, may vary based on time of day); total daily dose as basal insulin is a helpful value to know.
- Carbohydrate ratio (ie, units of insulin per grams of carbohydrate, generally 1 unit of rapid-acting insulin per 10-15 g carbohydrate)
- Correction dose (ie, how far the blood glucose level is expected to decrease per unit of rapid-acting insulin, often 1 unit of insulin per 50-mg/dL decrease, but individuals with insulin resistance may need 1 per 25-mg/dL decrease)
- Some patients may be taking premeal pramlintide (amylin analog).

A focused diabetes history should also include the following questions:

- Is the patient's diabetes generally well controlled (with near-normal blood glucose levels)? (Patients with poorly controlled blood glucose levels heal more slowly and are at increased risk for infection and other complications.)
- Does the patient have severe hypoglycemic reactions? (If the patient has episodes of severe hypoglycemia and therefore is at risk for losing consciousness, this possibility must be addressed, especially if the patient drives.)

- Does the patient have diabetic nephropathy that might alter the use of medications or intravenous radiographic contrast material?

- Does the patient have macrovascular disease, such as coronary artery disease (CAD), that should be considered in the emergency department (ED)?

- Does the patient self-monitor his or her blood glucose levels? (Note the frequency and range of values at each time of day.
- An increasing number of patients monitor with continuous sensors.)
- When was the patient's hemoglobin A1c (HbA1c) value (an indicator of long-term glucose control) last measured? What was it?

Questions regarding hypoglycemia and hyperglycemia

- Hypoglycemia and hyperglycemia should be considered. Ask the following questions, as needed:
- Does the patient have a history of recent polyuria, polydipsia, nocturia, or weight loss?
- Has the patient had episodes of unexplained hypoglycemia? If so, when, how often, and how does the patient treat these episodes?
- Does the patient have hypoglycemia unawareness (ie, does the patient lack the adrenergic warning signs of hypoglycemia)? (Hypoglycemia unawareness indicates an increased risk of subsequent episodes of hypoglycemia.)

Questions regarding microvascular complications

- Microvascular complications, such as retinopathy and nephropathy, should be considered as well. Consider the following questions:
- When was the patient's last dilated eye examination? What were the results?
- Does the patient have known kidney disease?
- What were the dates and results of the last measurements of urine protein and serum creatinine levels?

Questions regarding macrovascular complications

- Macrovascular complications should be explored. Questions should include the following:
- Does the patient have hypertension? What medications are taken?
- Does the patient have symptoms of claudication or a history of vascular bypass?
- Has the patient had a stroke or transient ischemic attack?
- What are the patient's most recent lipid levels?
- Is the patient taking lipid-lowering medication?

Neuropathy questions

- Potential neuropathy should be taken into account. Ask whether the patient has a history of neuropathy or symptoms of peripheral neuropathy or whether autonomic neuropathy is present (including impotence if the patient is male).

Foot disease questions

- The possibility of foot disease should be addressed. Inquire as to whether the patient has a history of foot ulcers or amputations or whether any foot ulcers are present.

Question about Infections

- Infections should be considered. Be sure to inquire about whether frequent infections are a problem and, if so, at what sites.

Physical Examination

- In new cases of diabetes, physical examination findings are usually normal, except in DKA, wherein signs of Kussmaul respiration, dehydration, hypotension, and, in some cases, altered mental status are present.

- In established cases, patients should be examined every 3 months for macrovascular and microvascular complications. They should have funduscopic examination for retinopathy and monofilament testing for peripheral neuropathy.

- A diabetes-focused physical examination includes an assessment of vital signs, funduscopic examination, limited vascular and neurologic examinations, and a foot assessment. Other organ systems should be examined, as indicated by the patient's clinical situation.

Assessment of vital signs

- Is the patient hypertensive or hypotensive? Orthostatic vital signs may be useful in assessing the patient's volume status, as well as suggesting the presence of an autonomic neuropathy.

- If the respiratory rate and pattern suggest Kussmaul breathing, DKA must be considered immediately, and appropriate tests obtained.

Funduscopic examination

- Funduscopic examination should include a careful view of the retina, including both the optic disc and the macula. If hemorrhages or exudates are seen, the patient should be referred to an ophthalmologist as soon as possible. Examiners who are not ophthalmologists tend to underestimate the severity of retinopathy, especially if the patients' pupils are not dilated.

Foot examination

- The dorsalis pedis and posterior tibialis pulses should be palpated and their presence or absence noted. This is particularly important in patients who have foot infections, because poor lower-extremity blood flow can delay healing and increase the risk of amputation.
- Documenting lower-extremity sensory neuropathy is useful in patients who present with foot ulcers, because decreased sensation limits the patient's ability to protect the feet and ankles.
- If peripheral neuropathy is found, the patient should be made aware that foot care (including daily foot examination) is very important for the prevention of foot ulcers and lower-extremity amputation.

Infections Seen in Patients With Diabetes

- People with diabetes are susceptible to various types of infections. The most common sites affected are the skin and urinary tract system. Increased risk of staphylococcal follicular skin infections, superficial fungal infections, cellulitis, erysipelas, and oral or genital candidal infections exists. These patients develop frequent lower urinary tract infections and are at increased risk of acute pyelonephritis. A few infections, such as malignant otitis externa, rhinocerebral mucormycosis, and emphysematous pyelonephritis, occur almost exclusively in patients with diabetes. Infections such as staphylococcal sepsis occur more frequently and result in greater mortality rates in patients with diabetes than in others. Infections such as pneumococcal pneumonia affect patients with diabetes and others the same

- Diabetes-Related Ophthalmologic Complications
- Diabetic Nephropathy
- Diabetic Neuropathy
- Macrovascular Complications of Diabetes

Measurement of Blood Glucose levels

- In asymptomatic patients, physicians diagnose DM using the American Diabetes Association (ADA) recommendation of 2 different fasting plasma glucose levels of greater than 125 mg/dL (ie, >6.99 mmol/L). In symptomatic patients, a random glucose of 200 mg/dL suggests diabetes.

- A fingerstick glucose test is appropriate in the emergency department (ED) for virtually all patients with diabetes. All fingerstick capillary glucose levels must be confirmed in serum or plasma to make the diagnosis. All other laboratory studies should be individualized to the clinical situation.

- Intravenous glucose testing may be considered for possible early detection of subclinical diabetes.

- Individually measured glucose levels widely vary from estimated glucose averages calculated from measured HbA1c.

- Therefore, caution is urged when estimating rather than actually measuring glucose concentration as this may potentially impact decision making.

- Use of continuous glucose monitoring was effective in helping avoid significant glucose variability and reduction in HbA1c among patients receiving either multiple daily injection therapy or continuous insulin infusion therapy.
- However, continuous glucose monitoring did not offer any singular advantage. Additionally, continuous glucose monitoring is associated with reduced time spent in hypoglycemia and concomitant decrease in HbA1c levels.

Urinalysis

- Urine ketones are not reliable for diagnosing or monitoring DKA. Rather, the plasma acetone, and, specifically, the beta-hydroxybutyrate level, is a reliable indicator of DKA.

Measurement of Glycated Hemoglobin levels

- Hemoglobin A1c (HbA1c) is the stable product of nonenzymatic irreversible glycation of the beta chain of hemoglobin by plasma glucose and is formed at rates that increase with increasing plasma glucose levels. Glycated hemoglobin predicts the progression of diabetic microvascular complications.

- Most physicians periodically determine HbA1c to estimate plasma glucose control during the preceding 1-3 months. The reference range for nondiabetic people is 6% in most laboratories. Although elevated HbA1c often indicates existing diabetes, the determination of HbA1c levels has not been universally considered a specific diagnostic test for diabetes.

Measurement of Fructosamine Levels

- Fructosamine levels also test for glucose levels. Fructosamine is formed by a chemical reaction of glucose with plasma protein and reflects glucose control in the previous 1-3 weeks. This assay, therefore, may show a change in control before HbA1c and often is helpful when applying intensive treatment and in short-term clinical trials.

White Blood Cell Count and Cultures

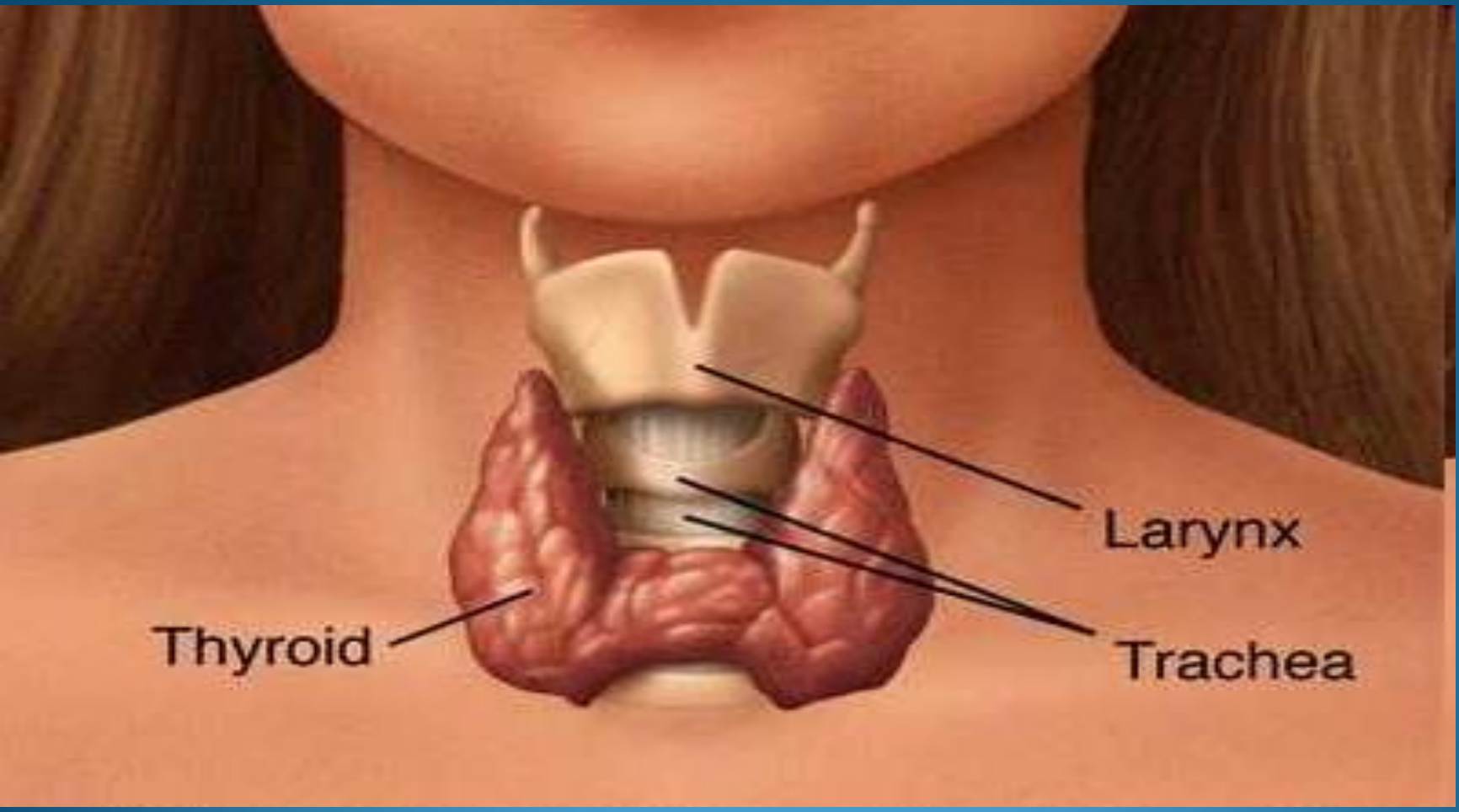
- White blood cell count and blood and urine cultures may be performed to rule out infection.

Human Leukocyte Antigen Typing

- Human leukocyte antigen (HLA) typing may be considered.

Hyperthyroidism

- Thyrotoxicosis is the hypermetabolic condition associated with elevated levels of free thyroxine (FT4) and/or free triiodothyronine (FT3).


Larynx
Thyroid
Trachea

- Hyperthyroidism includes diseases that are a subset of thyrotoxicosis, that are caused by excess synthesis and secretion of thyroid hormone by the thyroid; they are not associated with exogenous thyroid hormone intake and subacute thyroiditis.
- Most clinicians, exclusive of endocrinologists, use the terms hyperthyroidism and thyrotoxicosis interchangeably.

- The most common forms of hyperthyroidism include:
- *diffuse toxic goiter (Graves disease),*
- *toxic multinodular goiter (Plummer disease), and*
- *toxic adenoma.*
- Together with subacute thyroiditis, these conditions constitute 85-90% of all causes of thyrotoxicosis.

Common Forms (85-90% of cases)	Radioactive iodine uptake over neck
Diffuse toxic goiter (Graves disease)	Increased
Toxic multinodular goiter (Plummer disease)	Increased
Thyrotoxic phase of subacute thyroiditis	Decreased
Toxic adenoma	Increased
Less Common Forms	
Iodide-induced thyrotoxicosis	Variable
Thyrotoxicosis factitia	Decreased
Uncommon Forms	
Pituitary tumors producing thyroid-stimulating hormone	Increased
Excess human chorionic gonadotropin (molar pregnancy/choriocarcinoma)	Increased
Pituitary resistance to thyroid hormone	Increased

Causes

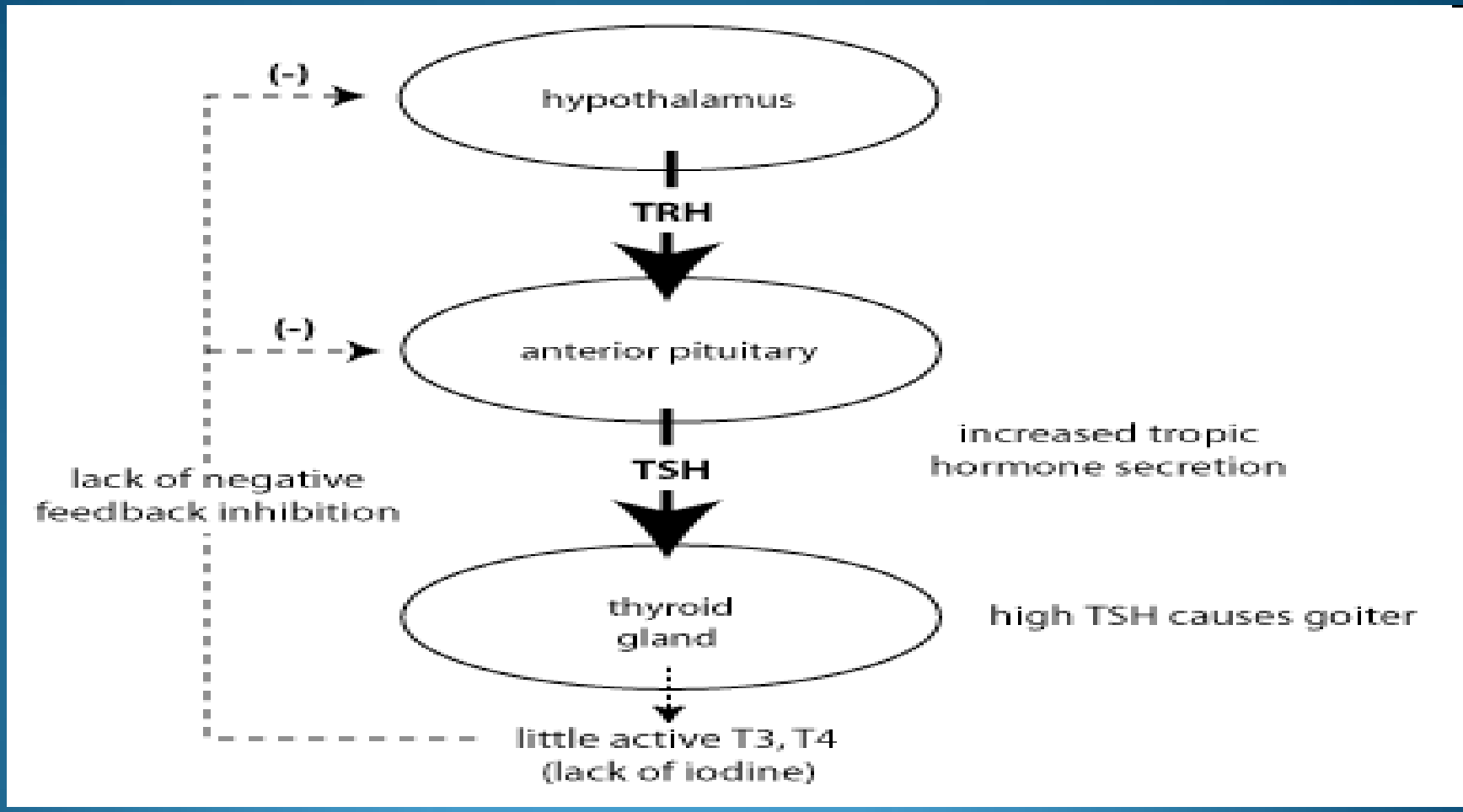
- Genetics and iodine intake appear to influence the incidence of thyrotoxicosis.
- Genetics - Autoimmune thyroid disease and Graves disease have a higher prevalence in patients with human leukocyte antigen (HLA)-DRw3 and HLA-B89.
- Graves disease is felt to be an HLA-related, organ-specific defect in suppressor T-lymphocyte function.

Causes

- Observing autoimmune thyroid disease, including Hashimoto hypothyroidism and Graves disease, in multiple members of a patient's family is common.
- Similarly, subacute painful or granulomatous thyroiditis occurs more frequently in patients with HLA-Bw35.
- Similar to other immune diseases, these thyroid conditions occur more frequently in women than in men.

Causes

- Iodine intake - Clearly, patients in borderline iodine-deficient areas of the world develop nodular goiter, often with areas of autonomy. When this population is moved to areas of sufficient iodine intake, thyrotoxicosis occurs. Evidence that iodine can act as an immune stimulator exists, precipitating autoimmune thyroid disease and acting as a substrate for additional thyroid hormone synthesis.


(-)
hypothalamus
TRH
(-)
anterior pituitary
increased tropic
hormone secretion
lack of negative
feedback inhibition
TSH
thyroid
gland
high TSH causes goiter
little active T3, T4
(lack of iodine)

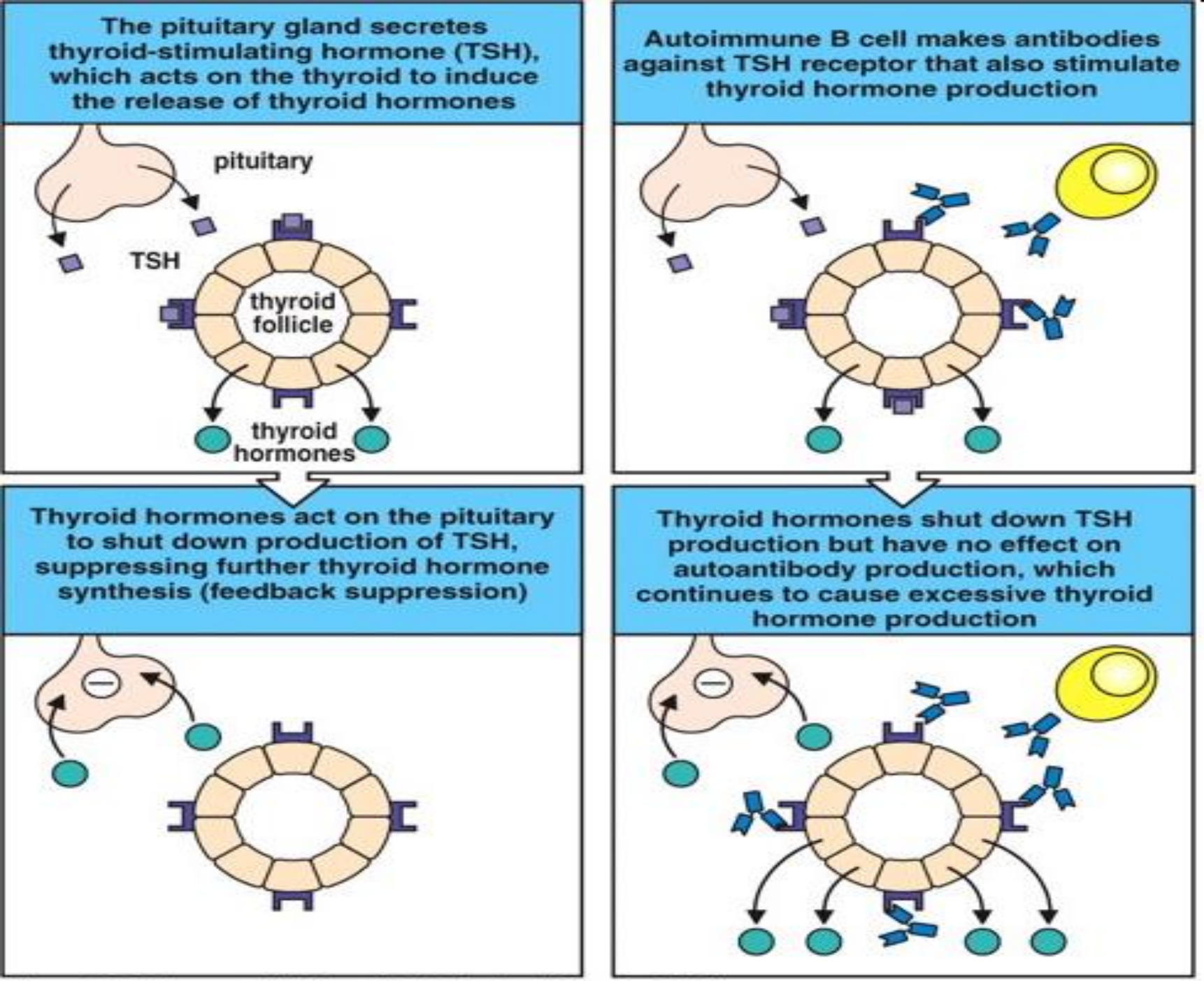
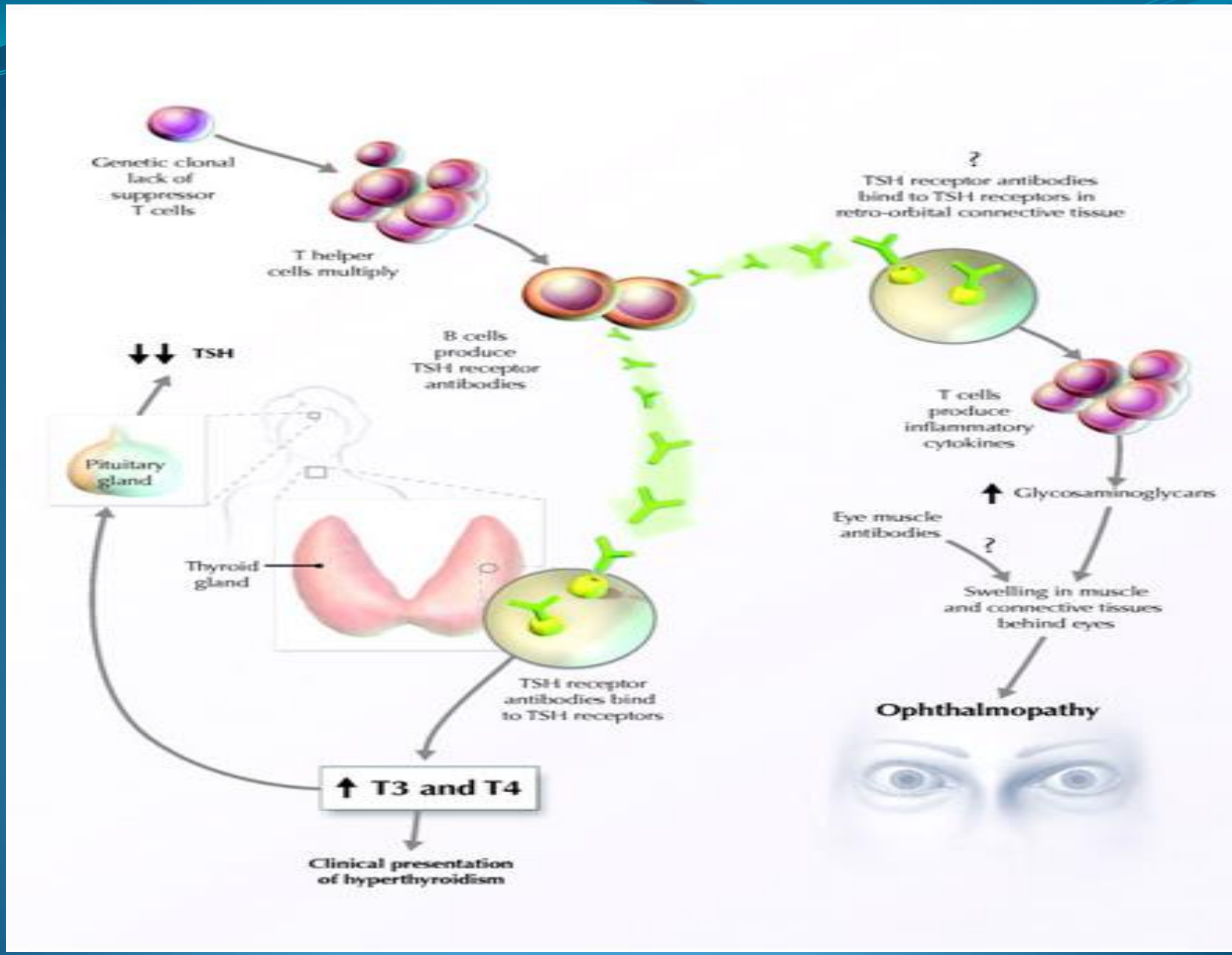


Figure 13-29 Immunobiology, 6/e. (© Garland Science 2005)


Genetic clonal lack of suppressor T cells
T helper cells multiply
B cells produce TSH receptor antibodies
↓↓ TSH
Pituitary gland
Thyroid gland
TSH receptor antibodies bind to TSH receptors
↑ T3 and T4
Clinical presentation of hyperthyroidism
?
TSH receptor antibodies bind to TSH receptors in retro-orbital connective tissue
T cells produce inflammatory cytokines
↑ Glycosaminoglycans
Eye muscle antibodies
?
Swelling in muscle and connective tissues behind eyes
Ophthalmopathy

- Iodine deficient goiter, (enlargement of the thyroid gland) results because iodine is a crucial component of active thyroid hormones.
- If there is a low level of iodine in the diet, then less active T3 and T4 can be synthesized.
- When there is less T3 and T4, there is reduced negative feedback inhibition on secretion of the tropic hormones, TRH (thyrotropin releasing hormone; released by the hypothalamus) and TSH (thyroid stimulating hormone or thyrotropin; released by the anterior pituitary).
- TSH stimulates all aspects of thyroid hormone synthesis; it also stimulates proliferation of follicle cells.
- When iodine in the diet is low but not too low, individuals may have goiter and yet be euthyroid, because the enlarged thyroid gland is better able to use the limited amount of iodine available.
- This is an example of hormonal homeostasis.

Pathophysiology

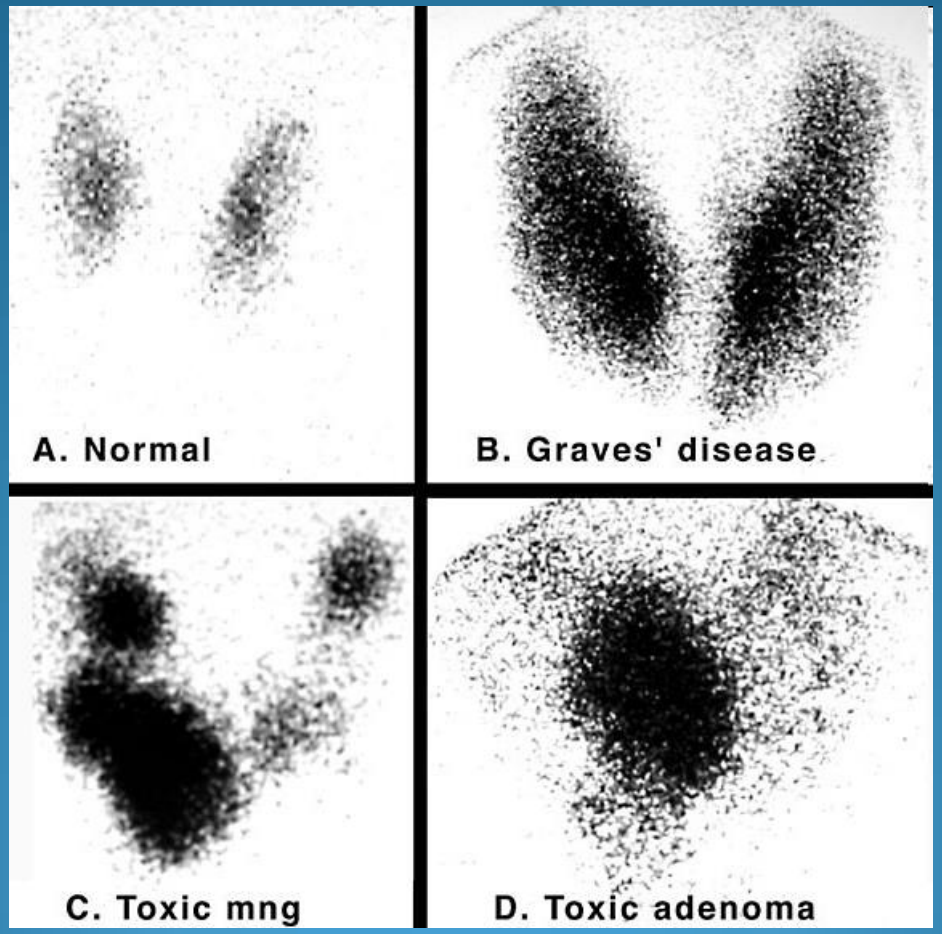
- The hypermetabolic effect of thyrotoxicosis affects every organ system.
- The pituitary gland stimulates the thyroid to make thyroid hormone, which is released into the circulation to reach every cell in the body.
- Thyroid hormone is necessary for normal growth and development, and it regulates cellular metabolism.
- Excess thyroid hormone causes an increase in the metabolic rate that is associated with increased total body heat production and cardiovascular activity (increased heart contractility, heart rate, vasodilation).

Graves disease

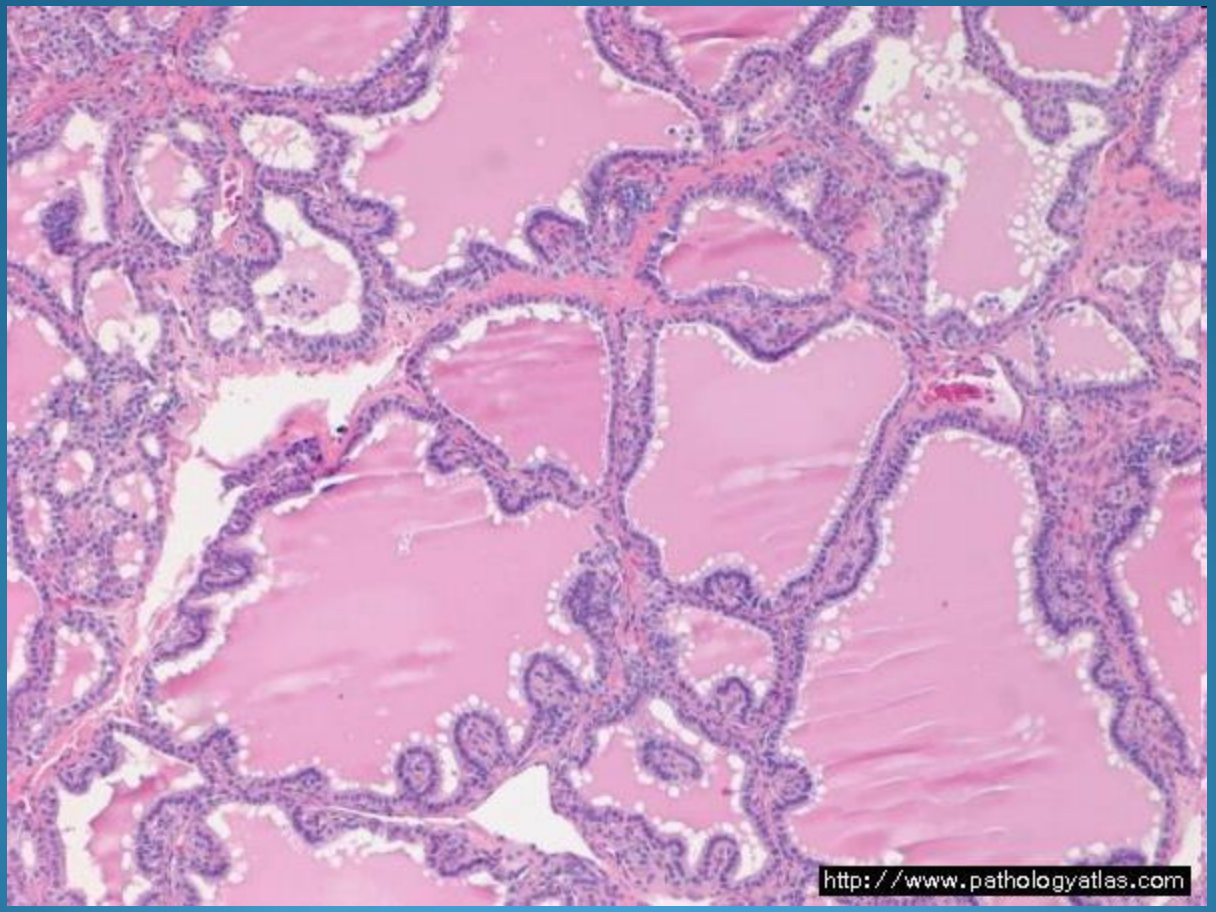
- The most common cause of thyrotoxicosis is Graves disease (50-60%). Graves disease is an organ-specific autoimmune disorder characterized by a variety of circulating antibodies, including common autoimmune antibodies, as well as anti-thyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) antibodies. The most important autoantibody is thyroid-stimulating immunoglobulin (TSI)
-

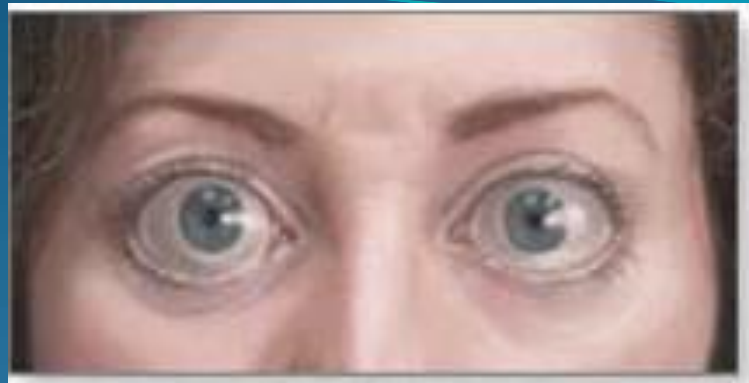
- TSI is directed toward epitopes of the thyroid-stimulating hormone (TSH) receptor and acts as a TSH-receptor agonist.
- Similar to TSH, TSI binds to the TSH receptor on the thyroid follicular cells to activate thyroid hormone synthesis and release and thyroid growth (hypertrophy).
- This results in the characteristic picture of Graves thyrotoxicosis, with a diffusely enlarged thyroid, very high radioactive iodine uptake, and excessive thyroid hormone levels compared with a healthy thyroid.

Iodine 123 (123I) nuclear scintigraphy: 123I scans of a normal thyroid gland (A) and common hyperthyroid conditions with elevated radioiodine uptake, including Graves disease (B), toxic multinodular goiter (C), and toxic adenoma (D).

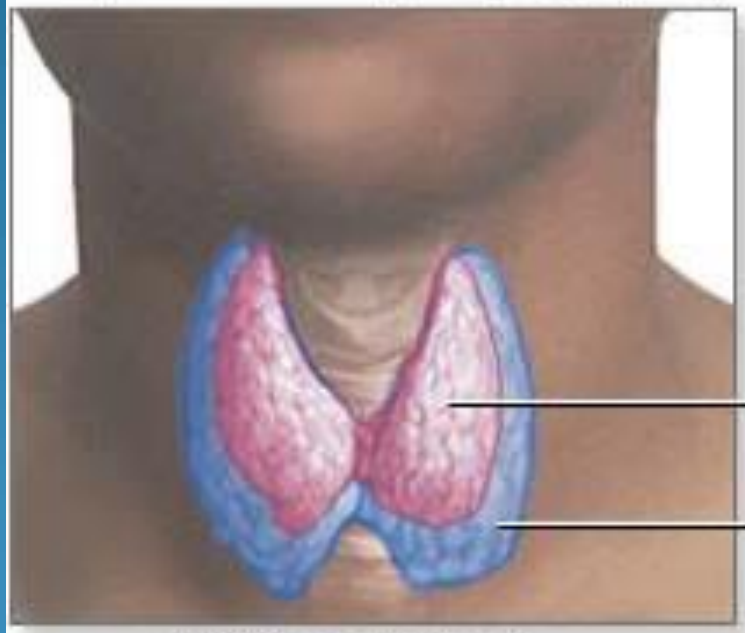


The essential lesion of Graves' disease is parenchymatous hypertrophy and hyperplasia, with tall cells, small follicles, scant and "scalloped" colloid, varying size and shape of the follicles, with columnar cells and reduced homogeneous colloid.





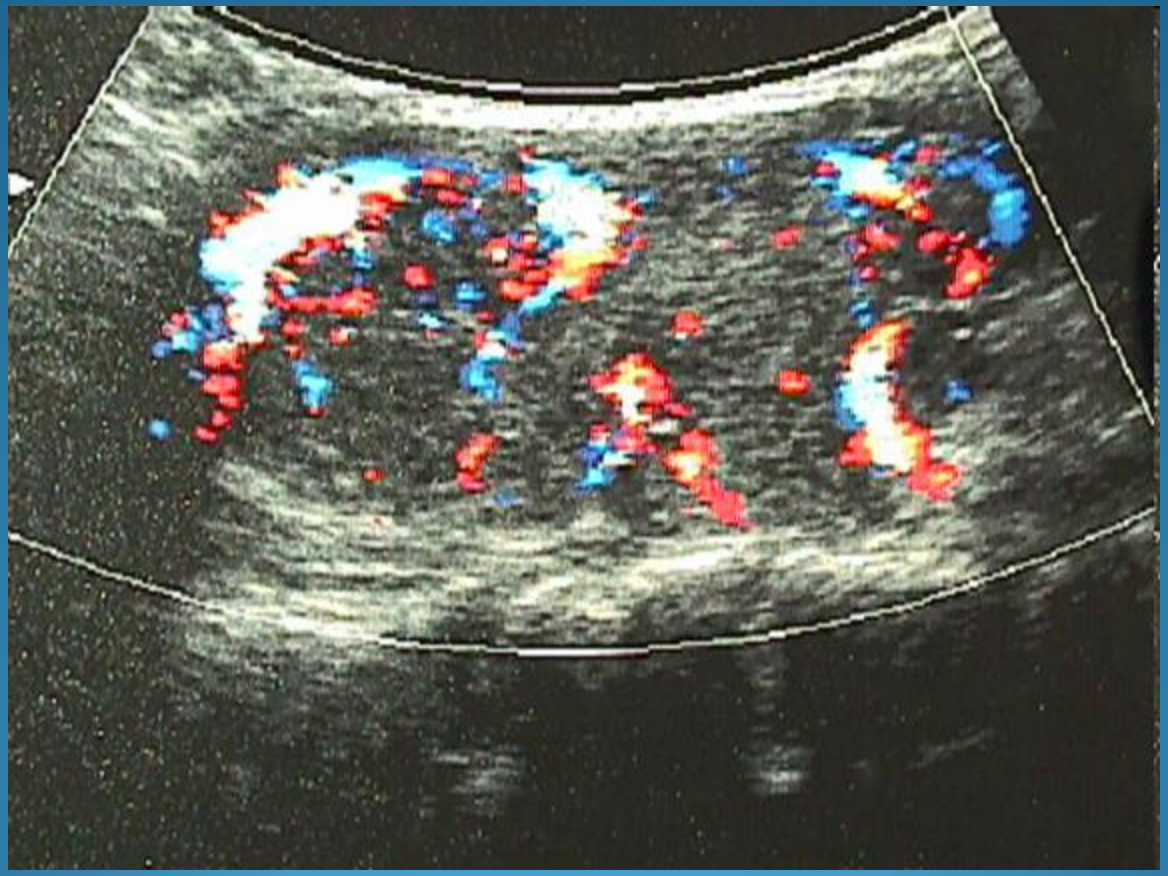
Exophthalmos (bulging eyes)



Diffuse goiter

Graves' disease is a common cause of hyperthyroidism, an over-production of thyroid hormone, which causes enlargement of the thyroid and other symptoms such as exophthalmos, heat intolerance and anxiety

Color flow ultrasonogram in a patient with Graves disease. Generalized hypervascularity is visible throughout the gland, which often can be heard as a hum or bruit with a stethoscope.



- Thyroid hormone levels can be extremely elevated in this condition.
- Clinical findings specific to Graves disease include thyroid ophthalmopathy (periorbital edema, chemosis [conjunctival edema], injection, proptosis) and, rarely, dermopathy over the lower extremities.
- This autoimmune condition may be associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, and type 1 diabetes mellitus.

Epidemiology

- International

- The incidences of Graves disease and toxic multinodular goiter change with iodine intake. Compared with regions of the world with less iodine intake, the United States has more cases of Graves disease and fewer cases of toxic multinodular goiters.

- Race

- Autoimmune thyroid disease occurs with the same frequency in Caucasians, Hispanics, and Asians, and it occurs less frequently in the black population.

- Sex
- All thyroid diseases occur more frequently in women than in men.
- Graves autoimmune disease occurs in a male-to-female ratio of 1:5-10.
- The male-to-female ratio for toxic multinodular goiter and toxic adenomas is 1:2-4.

- Age
- Autoimmune thyroid diseases have a peak incidence in people aged 20-40 years.
- Toxic multinodular goiters occur in patients who usually have a long history of nontoxic goiter and who therefore typically present when they are older than 50 years.
- Patients with toxic adenomas present at a younger age than do patients with toxic multinodular goiter.

History

- The presentation of thyrotoxicosis is variable among patients.
- Thyrotoxicosis leads to an apparent increase in sympathetic nervous system symptoms.
- Younger patients tend to exhibit symptoms of more sympathetic activation, such as anxiety, hyperactivity, and tremor, while older patients have more cardiovascular symptoms, including dyspnea and atrial fibrillation with unexplained weight loss.
- The clinical manifestations of thyrotoxicosis do not always correlate with the extent of the biochemical abnormality.

Common symptoms of thyrotoxicosis include the following:

- Nervousness
- Anxiety
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity
- Palpitations
- Weight loss despite increased appetite
- Reduction in menstrual flow or oligomenorrhea

Common signs of thyrotoxicosis include the following:

- Hyperactivity
- Tachycardia or atrial arrhythmia
- Systolic hypertension
- Warm, moist, and smooth skin
- Lid lag
- Stare
- Tremor
- Muscle weakness

- Generally, a constellation of information, including extent and duration of symptoms, past medical history, social and family history, and physical examination, help guide the clinician to the appropriate diagnosis.

- Subclinical hyperthyroidism is associated with no clinical symptoms of thyrotoxicosis.
- However, certain conditions, such as atrial fibrillation, osteoporosis, or hypercalcemia, may suggest the possibility of thyrotoxicosis.
- In fact, subclinical hyperthyroidism may be associated with a 3-fold increase in the risk of atrial fibrillation.
- The prevalence of subclinical hyperthyroidism may be as high as 12% in the general population.

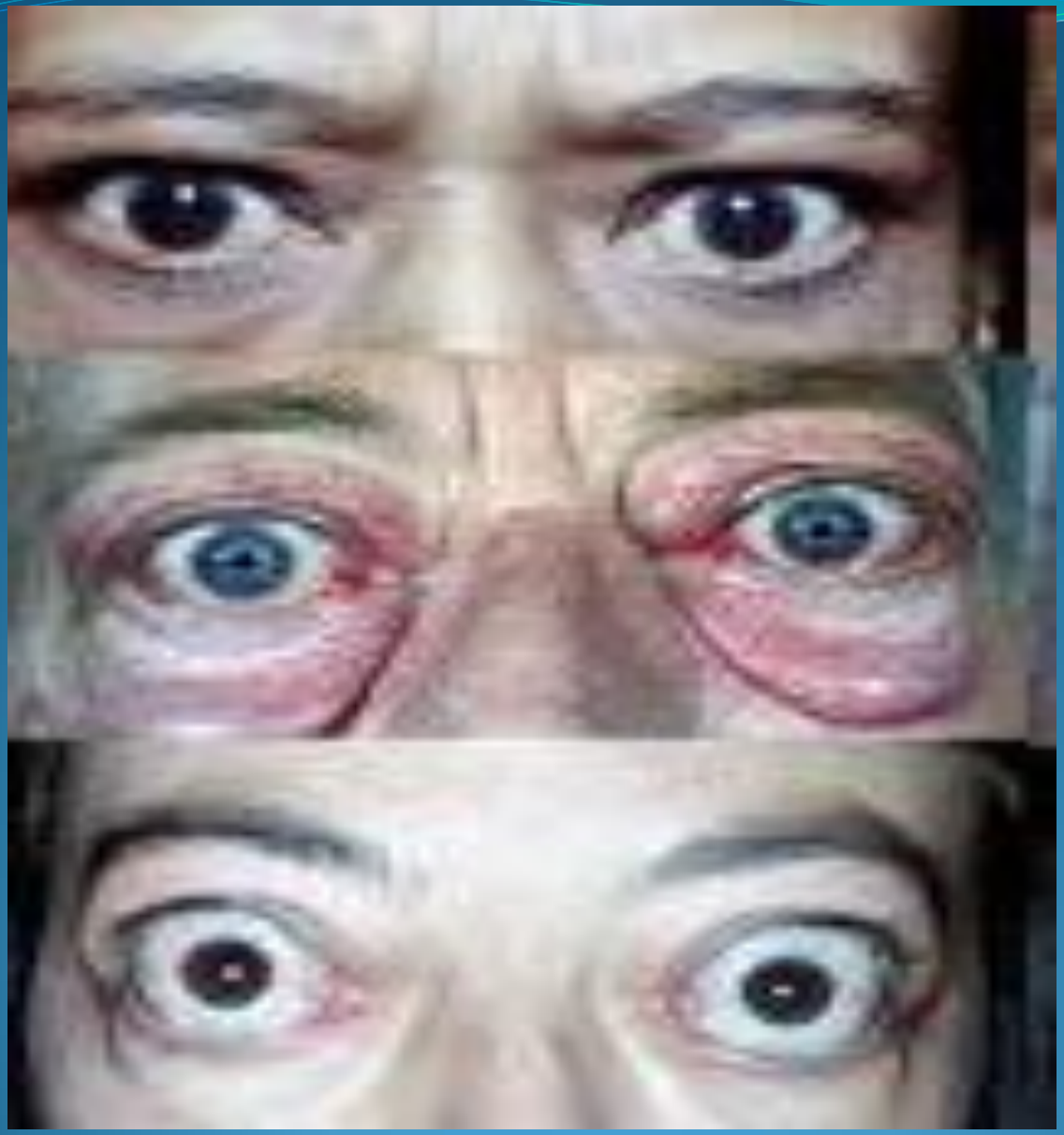
- Radiation exposure, whether due to radiation therapy or to lower-level radiographic therapy, increases the risk of benign and malignant nodular thyroid diseases, with an observed increase in the incidence of autoimmune hyperthyroidism.
- The frequency and severity of symptoms of thyrotoxicosis vary from person to person. Graves disease is an autoimmune disease, and often, a strong family history or past medical history exists with autoimmune diseases such as with rheumatoid arthritis, vitiligo, or pernicious anemia.

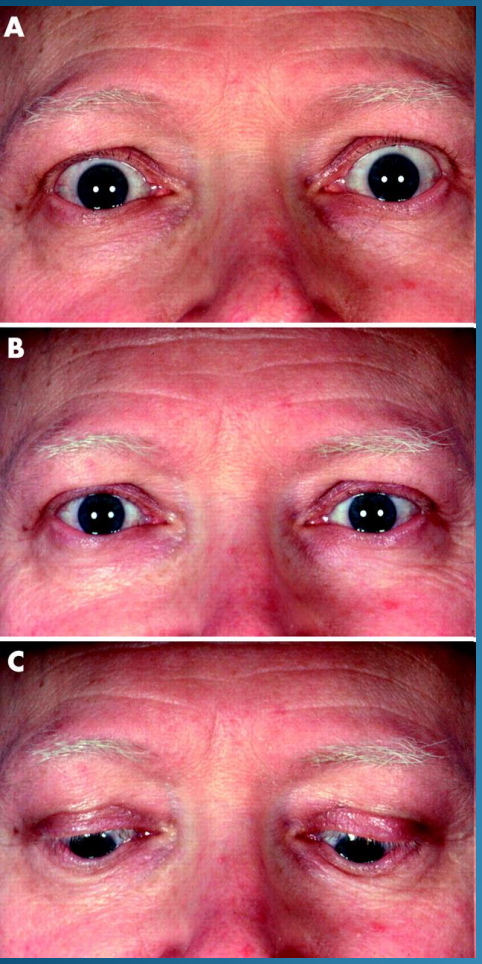
- The symptoms of Graves disease often are more marked, because thyroid hormone levels usually are the highest with this form of hyperthyroidism.
- Also consider the diagnosis of Graves disease if any evidence of thyroid eye disease exists, including periorbital edema, diplopia, or proptosis.
- Toxic multinodular goiters occur in patients who have had a known nontoxic goiter for many years or decades. Often, patients have emigrated from regions of the world with borderline low-iodine intake or have a strong family history of nontoxic goiter.

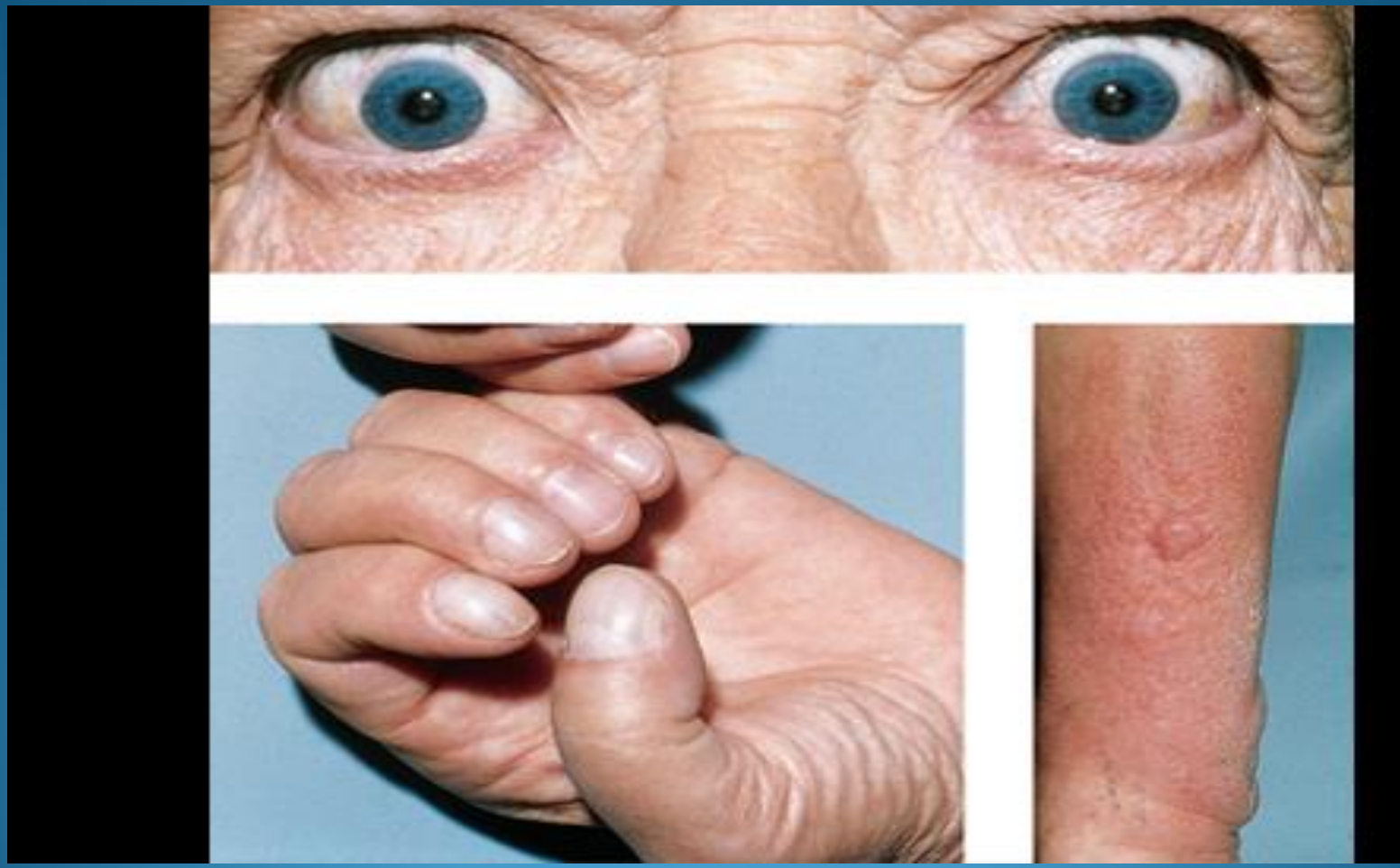
- Recording a careful family history of autoimmune disease, thyroid disease, and emigration from iodine-deficient areas is important.
- Review a complete list of medications. A number of compounds—including expectorants, amiodarone, health food supplements containing seaweed, and iodinated contrast dyes—contain large amounts of iodine that can induce thyrotoxicosis in a patient with thyroid autonomy. Rarely, iodine exposure can cause thyrotoxicosis in a patient with an apparently healthy thyroid.

Physical

- Thyroid examination - The thyroid is located in the lower anterior neck. The isthmus of the butterfly-shaped gland generally is located just below the cricoid cartilage of the trachea, with the wings of the gland wrapping around the trachea.




A
B
C



Graves' disease patient with exophthalmos and vitiligo.

Graves' dermopathy

An uncommon sign of Graves' disease is reddening and swelling of the skin, often on your shins and on the top of your feet, called Graves' dermopathy.

Physical

- Thyrotoxicosis due to Graves disease is associated with a diffusely enlarged and slightly firm thyroid gland. Sometimes, a thyroid bruit is audible using the bell of the stethoscope.
- Toxic multinodular goiters occur when goiters generally are enlarged to at least 2 to 3 times normal size. The gland often is soft, but individual nodules occasionally can be palpated.

Physical

- A toxic adenoma generally does not cause thyrotoxicosis in a patient until it is at least 2.5 cm in diameter.
- If the thyroid is enlarged and painful, the diagnosis is likely subacute painful or granulomatous thyroiditis, but consider degeneration or hemorrhage into a nodule or suppurative thyroiditis.

Thyroid-specific physical examination - Graves thyrotoxicosis can be associated with mild thyroid ophthalmopathy in 50% of patients.

- Often, it is manifested only by periorbital edema, but it also can include conjunctival edema (chemosis), injection, poor lid closure, extraocular muscle dysfunction (diplopia), and proptosis.
- Evidence of thyroid eye disease and high thyroid hormone levels confirms the diagnosis of autoimmune Graves disease.
- Graves disease rarely can affect the skin by deposition of glycosaminoglycans in the dermis of the lower leg. This causes nonpitting edema, usually associated with erythema and thickening of the skin, without pain or pruritus.

Physical

- Signs of thyrotoxicosis - Usually, signs upon physical examination include sinus tachycardia or atrial fibrillation, systolic hypertension, excessive perspiration, palmar erythema and sweating, lid lag, extension tremor, hyperkinesis, large-muscle weakness, and soft, smooth skin.

Laboratory Studies

- Laboratory evaluation of thyrotoxicosis: The most reliable screening measure of thyroid function is a TSH level. TSH levels usually are suppressed to immeasurable levels (< 0.05 µIU/mL) in thyrotoxicosis. Third-generation TSH assays are recommended for screening purposes.

Laboratory Studies

- The degree of thyrotoxicosis cannot be estimated easily by the TSH level and must be measured using an assay of thyroid hormone levels in the plasma. Thyroid hormone circulates as T3 and T4 with 99% bound to protein. Only the free unbound thyroid hormone is biologically active. T3 is 20-100 times more biologically active than T4. Of patients with thyrotoxicosis, 5% have only elevated T3 levels. Therefore, measuring free T4 (and T3 if T4 levels are normal) is recommended in patients with suspected thyrotoxicosis when TSH is low.

Laboratory Studies

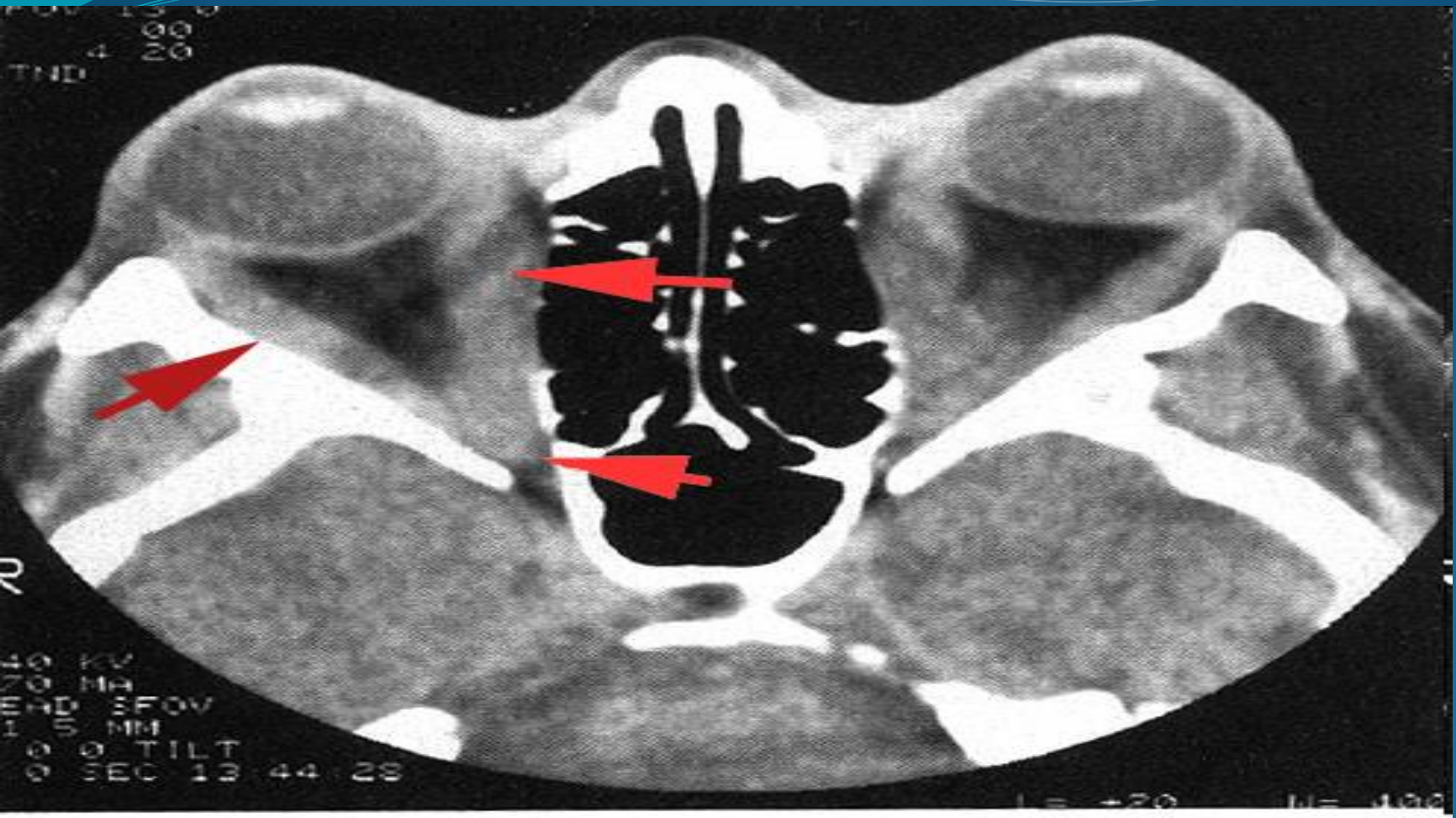
- Many laboratories do not measure free T4 directly and use a calculation to estimate the FT4 levels. The free thyroxine index (FTI) is equal to total T4 multiplied by the correction for thyroid hormone binding, such as thyroid hormone-binding ratio [THBR] or triiodothyronine resin uptake [T3 RU]). A similar calculation can be used with total T3.
- Subclinical hyperthyroidism is defined as a suppressed TSH level (< 0.5 μU/mL in many laboratories) in combination with serum concentrations of T3 and T4 that are within the reference range.

Laboratory Studies

- Thyroid autoantibodies - The most specific autoantibody for autoimmune thyroiditis is an enzyme-linked immunosorbent assay (ELISA) for anti-TPO antibody. The titers usually are significantly elevated in the most common type of hyperthyroidism, Graves thyrotoxicosis, and usually are low or absent in toxic multinodular goiter and toxic adenoma. A significant number of healthy people without active thyroid disease have mildly positive TPO antibodies; thus, the test should not be performed for screening purposes. TSI, if elevated, helps establish the diagnosis of Graves disease. A positive anti-TG antibody test does not predict the development of thyroid dysfunction and should not be measured.

Other Tests

- Hyperthyroidism in older patients often presents with atrial arrhythmias or CHF. ECG is recommended if an irregular heart rate or CHF is noted upon examination.



Computed tomogram of a patient showing enlargement of medial and lateral rectus muscles, which converge toward the orbital apex.

Table 12–4. Clinical findings in hyperthyroidism (thyrotoxicosis).

Symptoms

1. Alertness, emotional lability, nervousness, irritability
2. Poor concentration
3. Muscular weakness, fatigability
4. Palpitations
5. Voracious appetite, weight loss
6. Hyperdefecation (increased frequency of bowel movements)
7. Heat intolerance

Signs

1. Hyperkinesia, rapid speech
2. Proximal muscle (quadriceps) weakness, fine tremor
3. Fine, moist skin; fine, abundant hair; onycholysis
4. Lid lag, stare, chemosis, periorbital edema, proptosis
5. Accentuated first heart sound, tachycardia, atrial fibrillation (resistant to digitalis), widened pulse pressure, dyspnea

Laboratory findings

1. Elevated serum total T_4, elevated resin T_3 or T_4 uptake, elevated free thyroxine index
2. Suppressed serum TSH level
3. Increased radioiodine uptake by thyroid gland (some causes)
4. Increased basal metabolic rate (BMR)
5. Decreased serum cholesterol level

Rx Drugs Used to Treat Hyperthyroidism

Type	Drug	Selected Side Effects	Comments
Thionamides			
	Carbimazole Methimazole Propylthiouracil	Allergic reactions (usually skin rashes); nausea; loss of taste; infection (rare) due to a low white blood cell count; liver dysfunction	Decrease the produc- tion of thyroid hormone
Nonmetallic elements			
	Iodine	Skin rash	Decreases the production and release of thyroid hormone
Radioactive isotope			
	Radioactive iodine	Causes hypothyroidism	Destroys the thyroid gland
Beta-blockers			
	Atenolol Metoprolol Propranolol	In people with respiratory disease, may cause wheezing; can cause worsening of peripheral vascular disease and depression; may reduce blood pressure (hypotension)	Block many of the stimulating effects of excess thyroid hormone on other organs

STEDMANS

some autoimmune diseases in humans

disease	self-antigen	immune response
organ-specific autoimmune diseases		
Addison disease	adrenal cells	autoantibodies
autoimmune hemolytic anemia	red blood cell (RBC) membrane proteins	autoantibodies
Goodpasture syndrome	renal and lung basement membranes	autoantibodies
Graves disease	thyroid-stimulating hormone receptor	autoantibodies (stimulating)
Hashimoto thyroiditis	thyroid proteins and cells	T_{DTH} cells, autoantibodies
idiopathic thrombocytopenic purpura	platelet membrane proteins	autoantibodies
type 1 diabetes mellitus	pancreatic beta cells	T_{DTH} cells, autoantibodies
myasthenia gravis	acetylcholine receptors	autoantibody (blocking)
pernicious anemia	gastric parietal cells, intrinsic factor	autoantibody
poststreptococcal glomerulonephritis	kidney	antigen-antibody complexes
spontaneous infertility	sperm	autoantibodies
systemic autoimmune diseases		
ankylosing spondylitis	vertebrae	immune complexes
multiple sclerosis	white matter of brain and spinal cord	T_{DTH} cells and T_C cells, autoantibodies
rheumatoid arthritis	connective tissue, IgG	autoantibodies, immune complexes
scleroderma	nuclei, heart, lungs, gastrointestinal tract, kidney	autoantibodies
Sjögren syndrome	salivary gland, liver, kidney, thyroid	autoantibodies
systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC platelet membranes	autoantibodies, immune complexes