

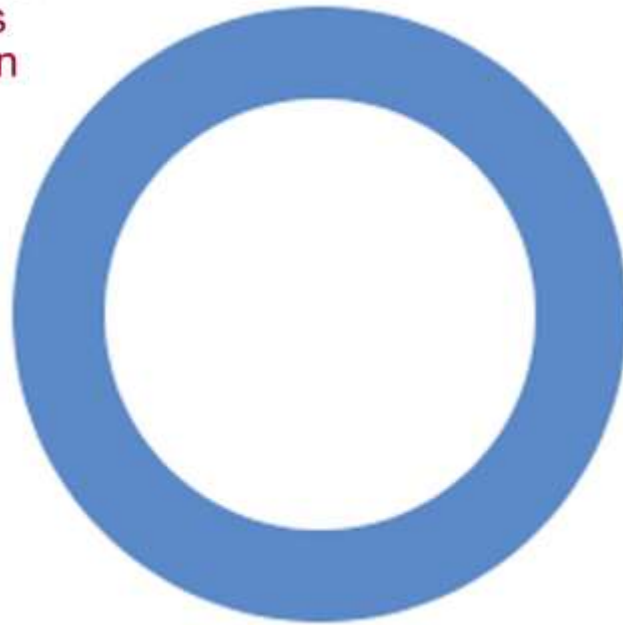
Supportive module 1: “Essentials of diagnosis, treatment and prevention of major endocrine diseases”			
1.	Diabetes. The current classification, etiology, symptoms, diagnosis. Current question of angio-and neuropathy	2	06/09
2.	New methods of treatment for patients with diabetes. Oral hypoglycemic agents, modern insulin and its analogues.	2	13/09
3.	Diseases of the thyroid gland. Goiter: diagnosis, differential diagnosis, prevention and treatment.	2	20/09
4.	Diseases of the adrenal glands. Chronic adrenal insufficiency. Hormonally active tumors.	2	27/09
5.	Diseases of the hypothalamic-pituitary system. Its part in correction of the functional activity of the endocrine glands.	2	04/10

Essentials of Diagnosis, Treatment and Prevention of Major Endocrine Diseases: Diabetes Mellitus

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

M. Yabluchansky, L. Bogun, L. Martymianova, O. Bychkova, N. Lysenko, N. Makienko
V.N. Karazin National University Medical School' Internal Medicine Dept.

Plan of the Lecture



- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

Definition

Diabetes mellitus (DM) or diabetes is a group of a chronic, often debilitating and sometimes fatal, incurable, costly, and increasing but largely preventable non-communicable metabolic diseases that causes high blood sugar (glucose) levels when the body is unable to produce or effectively use insulin with unique multisystem complications of microvascular endpoints, including retinopathy, nephropathy, neuropathy, and macrovascular endpoints in forms of ischaemic heart disease, stroke and peripheral vascular disease).

There are three main types of DM:

- Type 1 (insulin-dependent DM or juvenile DM) results from the pancreas's failure to produce enough insulin,
- Type 2 (non insulin-dependent DM or adult-onset DM) begins with insulin resistance, when body cells fail to respond to insulin properly,
- Gestational occurs when pregnant women without a previous history of DM develop high blood-sugar levels.

Epidemiology 1

- DM is one of the most common endocrine disorders affecting almost 6% of the world's population.
- The number of patients will reach 300 million in 2025 (International Diabetes Federation, 2001).
- More than 97% of these patients will have type II DM.

Epidemiology 2

Prevalence estimates of diabetes, 2025

>300 million diabetics worldwide



Risk Factors

Type 1 DM

- Family history
- Environmental factors (exposure to a viral illness)
- The presence of damaging immune system cells (autoantibodies)
- Dietary factors (low vitamin D consumption, early exposure to cow's milk formula, and exposure to cereals before 4 months of age)
- Geography (Finland, Sweden, etc.).

Type 2 DM

- Family history
- Race (Blacks, Hispanics, American Indians, Asian-Americans)
- Age (risk increases with age)
- Gestational diabetes
- Polycystic ovary syndrome (women)
- High blood pressure
- Abnormal cholesterol and triglyceride levels.

Gestational DM

- Family or personal history
- Race (Black, Hispanic, American Indian or Asian are more likely to develop gestational diabetes)
- Age (women older 25 are at increased risk)
- Weight (being overweight before pregnancy increases risk).

Etiology

Type 1 DM

- Type 1 DM is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency
- The majority of type 1 DM is of the immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin
- Sensitivity and responsiveness to insulin are usually normal, especially in the early stages
- Type 1 DM can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children
- Type 1 DM can be accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis, and sometimes with serious low blood sugar levels
- Type 1 DM is partly inherited, with multiple genes, including certain HLA genotypes, and can be triggered by one or more environmental factors, such as a viral infection or diet (gliadin (a protein present in gluten)).

Etiology

Type 2 DM

- Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.
- The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor.
- In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity.
- Type 2 DM is due primarily to lifestyle factors and genetics (obesity, lack of physical activity, poor diet, stress, urbanization)
- Dietary factors also influence the risk of developing type 2 DM (sugar-sweetened drinks, saturated fats, trans fatty acids, white rice).

Etiology

Gestational DM

- Gestational diabetes mellitus (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness and occurs in 2–10% of all pregnancies)
- After pregnancy approximately 5–10% of women with gestational DM found to have most commonly type 2 DM
- Gestational DM is fully treatable, but requires careful medical supervision throughout the pregnancy
- Gestational DM can damage the health of the fetus or mother, and risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, skeletal muscle malformations, respiratory distress syndrome, and red blood cell destruction.

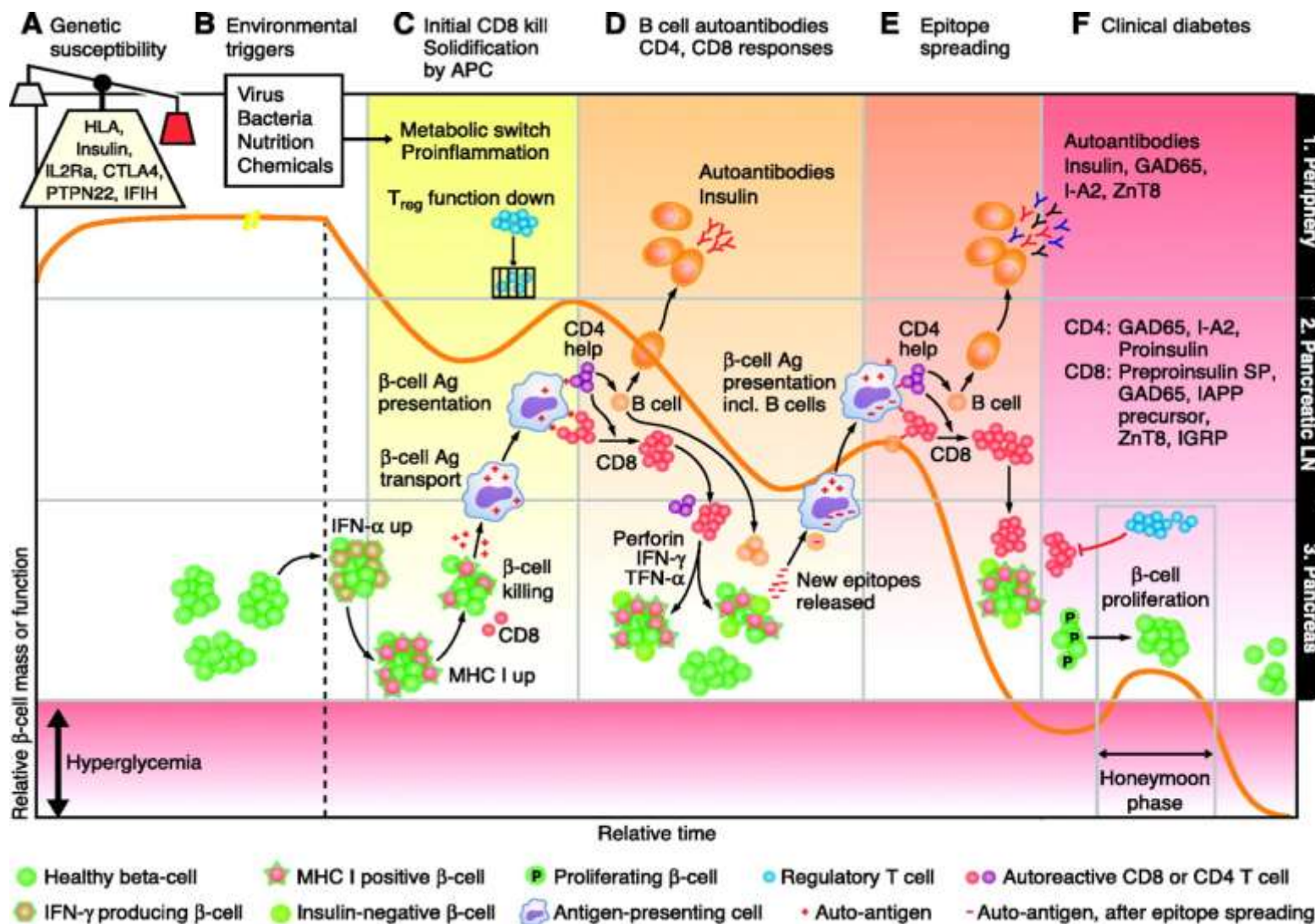
Mechanisms

Type 1 DM: 1

- Type 1 DM is the culmination of autoimmune inflammatory lymphocytic infiltration with destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas
- As beta-cell mass declines, 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
- Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM.

Mechanisms

Type 1 DM: 2



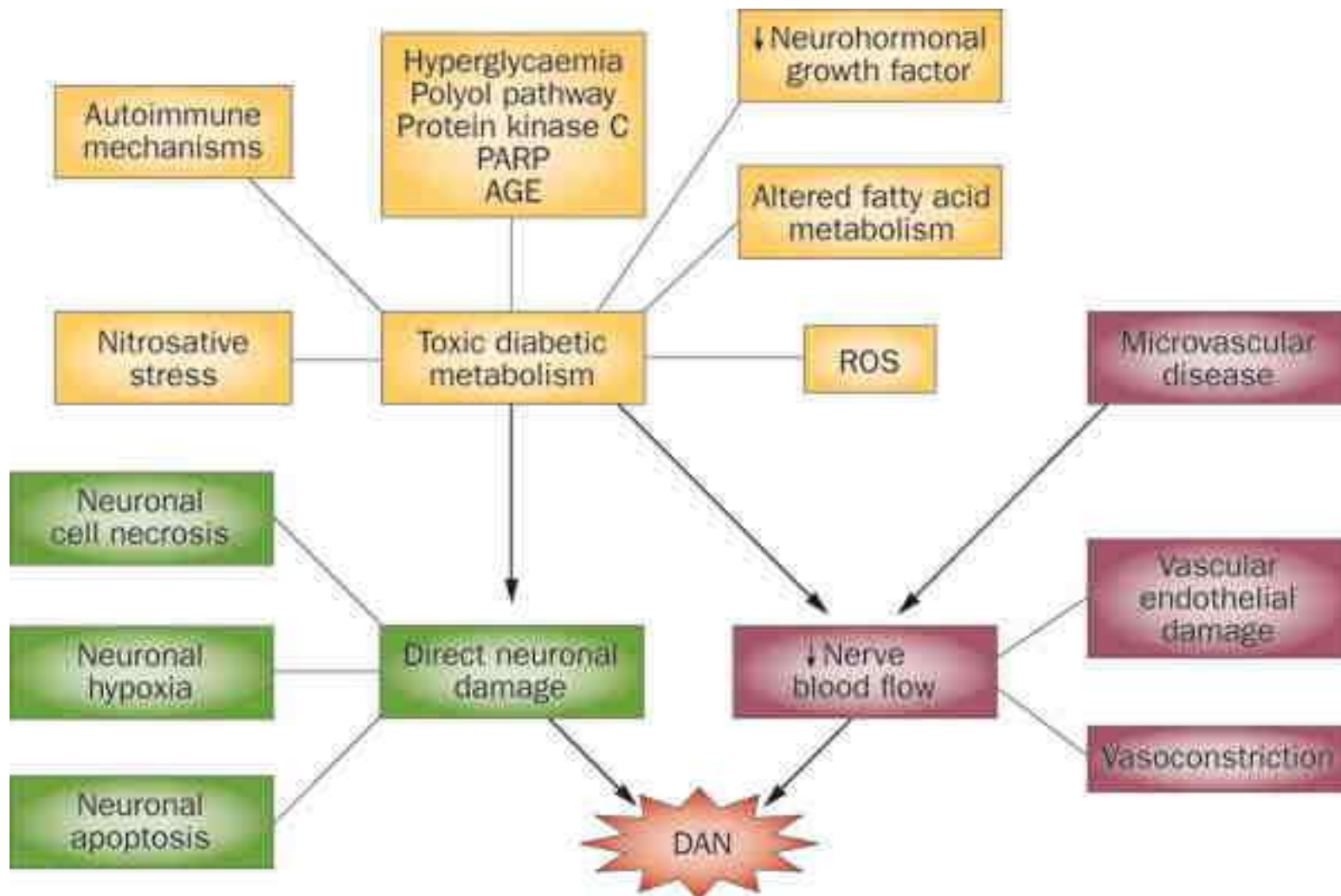
Mechanisms

Type 1 DM and Neuropathy: 1

- Sensory and autonomic neuropathy in people with DM are caused by axonal degeneration and segmental demyelination
- Many factors are involved, including the accumulation of sorbitol in peripheral sensory nerves from sustained hyperglycemia
- Motor neuropathy and cranial mononeuropathy result from vascular disease in blood vessels supplying nerves.

Mechanisms

Type 1 DM and Neuropathy: 2



Mechanisms

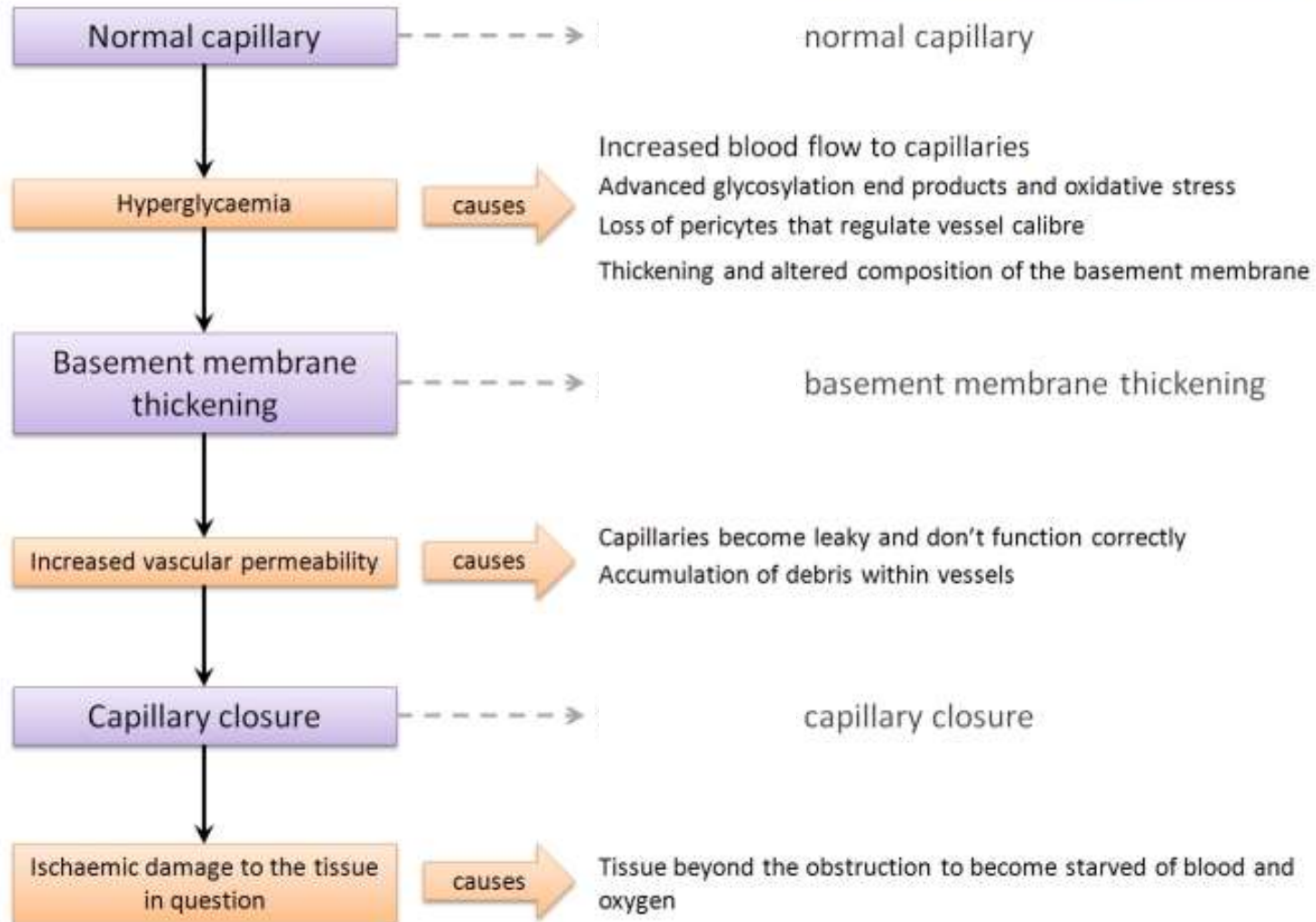
Type 1 DM and Angiopathy: 1

- Microvascular disease causes multiple pathologic complications in people with DM
- Hyaline arteriosclerosis, a characteristic pattern of wall thickening of small arterioles and capillaries, is widespread and is responsible for ischemic changes in the kidney, retina, brain, and peripheral nerves
- Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia
- Vitamin D deficiency is an important independent predictor of development of coronary artery calcification in individuals with type 1 DM.

Mechanisms

Type 1 DM and Angiopathy: 2

Mechanisms leading to microvascular damage



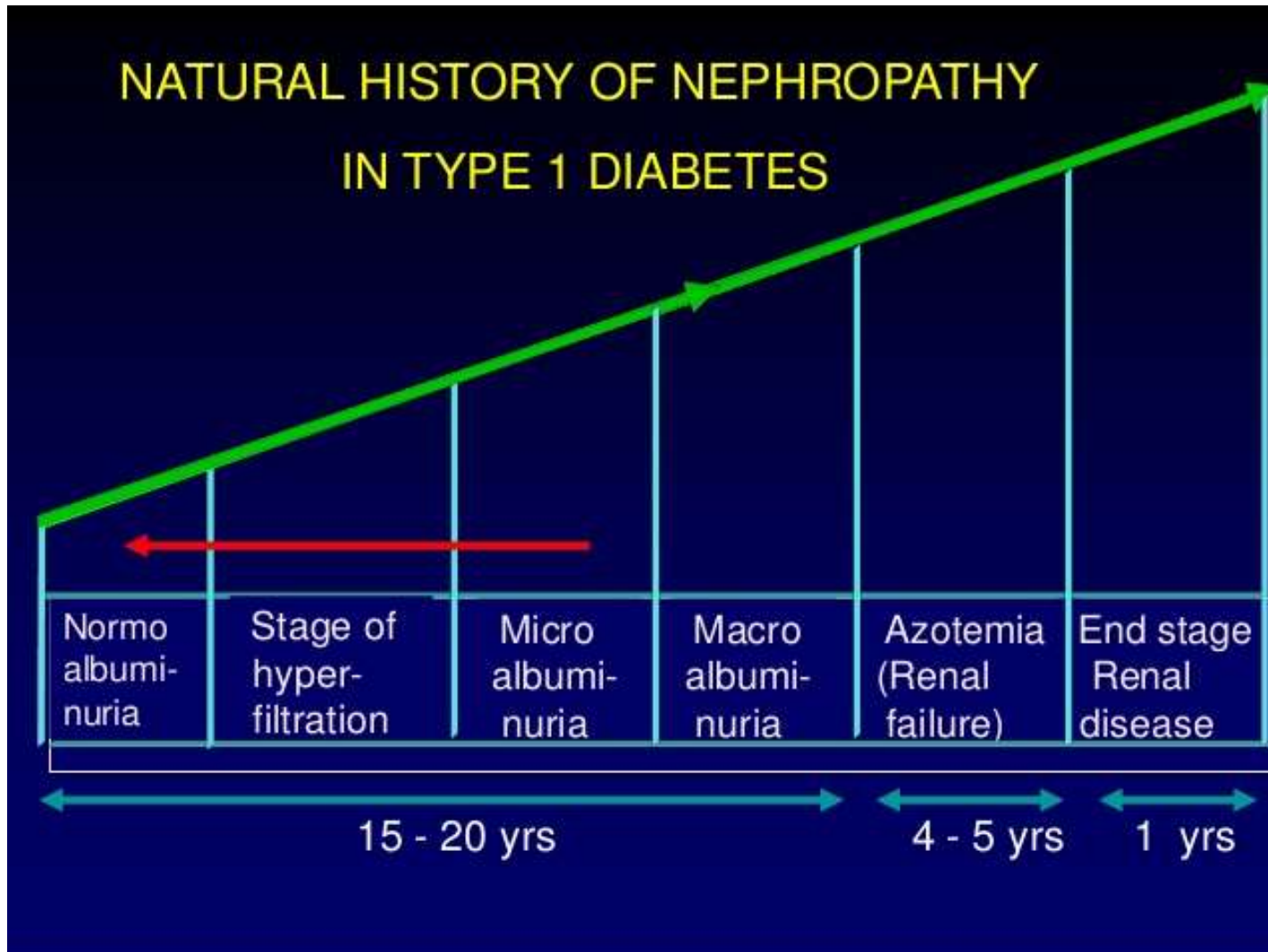
Mechanisms

Type 1 DM and Nephropathy: 1

- In the kidneys, the characteristic wall thickening of small arterioles and capillaries leads to diabetic nephropathy, which is characterized by proteinuria, glomerular hyalinization (Kimmelstiel-Wilson), and chronic renal failure
- Exacerbated expression of cytokines such as tumor growth factor beta 1 is part of the pathophysiology of glomerulosclerosis, which begins early in the course of diabetic nephropathy
- Single-nucleotide polymorphisms affecting the factors involved in its pathogenesis appear to influence the risk for diabetic nephropathy in different people with type 1 DM.

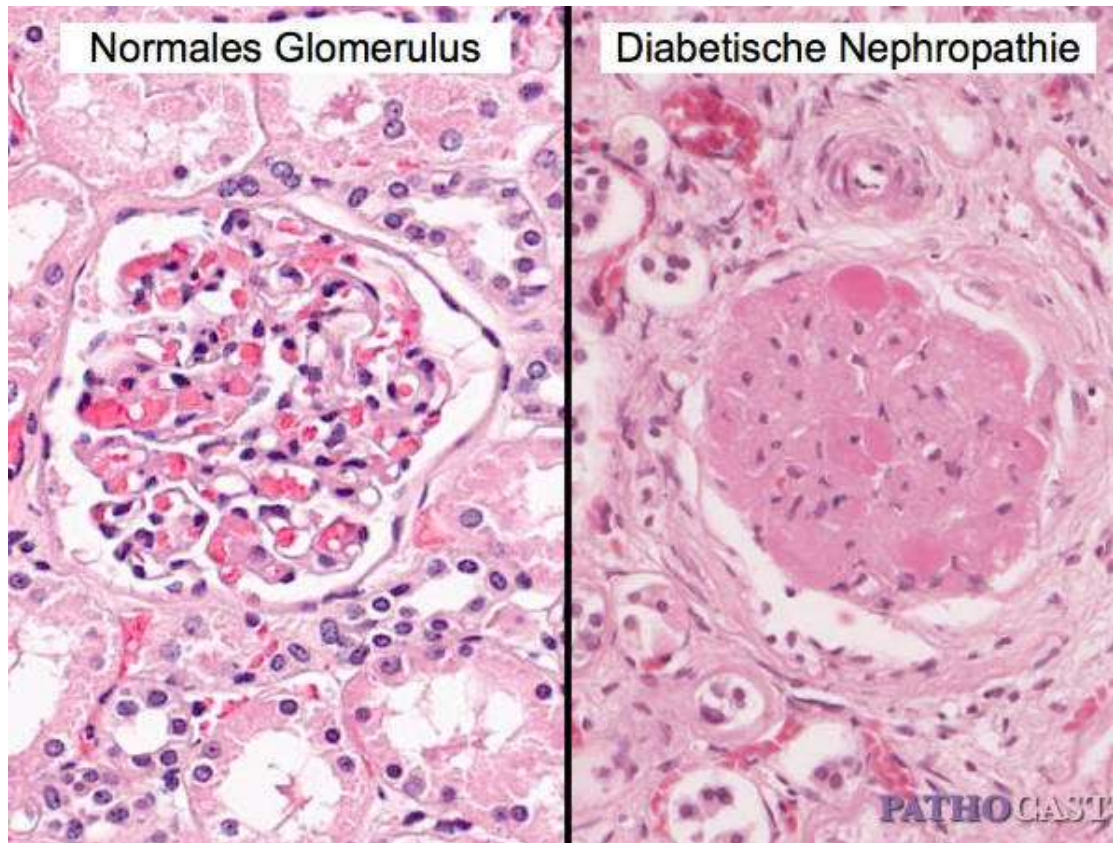
Mechanisms

Type 1 DM and Nephropathy: 2



Mechanisms

Type 1 DM and Nephropathy: 3



- Histological comparison of a healthy glomerulus and a glomerulus in diabetic nephropathy
- One can notice an augmentation of the mesangial matrix
- The matrix appears in light pink and has a nodular structure, the capillary lumen is obstructed
- This condition is called complete glomerular sclerosis.

Mechanisms

Type 1 DM: Double diabetes

DOUBLE DIABETES

Symptoms of Both Diseases

- Increased Thirst
- Frequent Urination
- Blurred Vision
- Slow Healing Sores
- Frequent Infections

In areas where rates of type 2 DM and obesity are high, individuals with type 1 DM may share genetic and environmental factors that lead to their exhibiting type 2 DM features such as reduced insulin sensitivity (double diabetes).

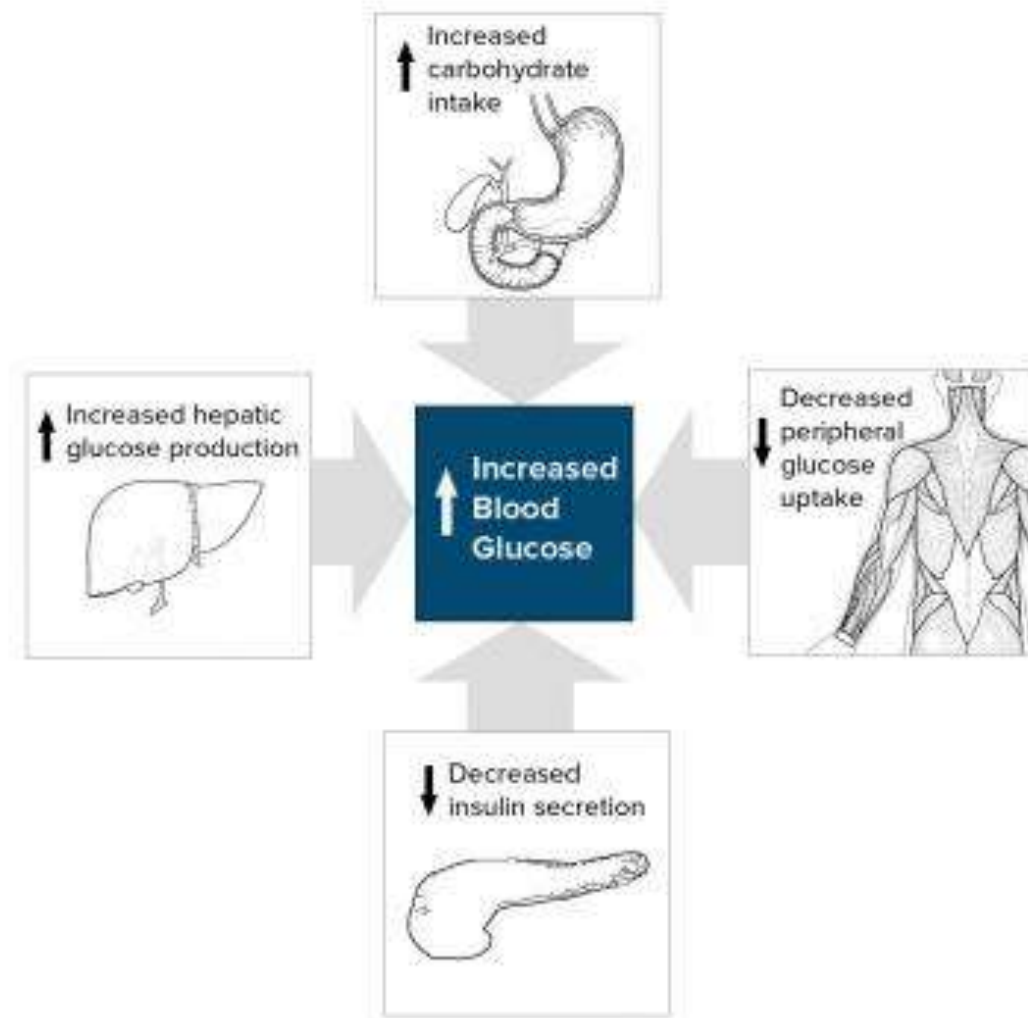
Mechanisms

Type 2 DM

- Type 2 DM is characterized by a 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 and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat
- A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia
- With prolonged diabetes, atrophy of the pancreas may occur.

Mechanisms

Type 2 DM: Scheme of abnormal glucose metabolism



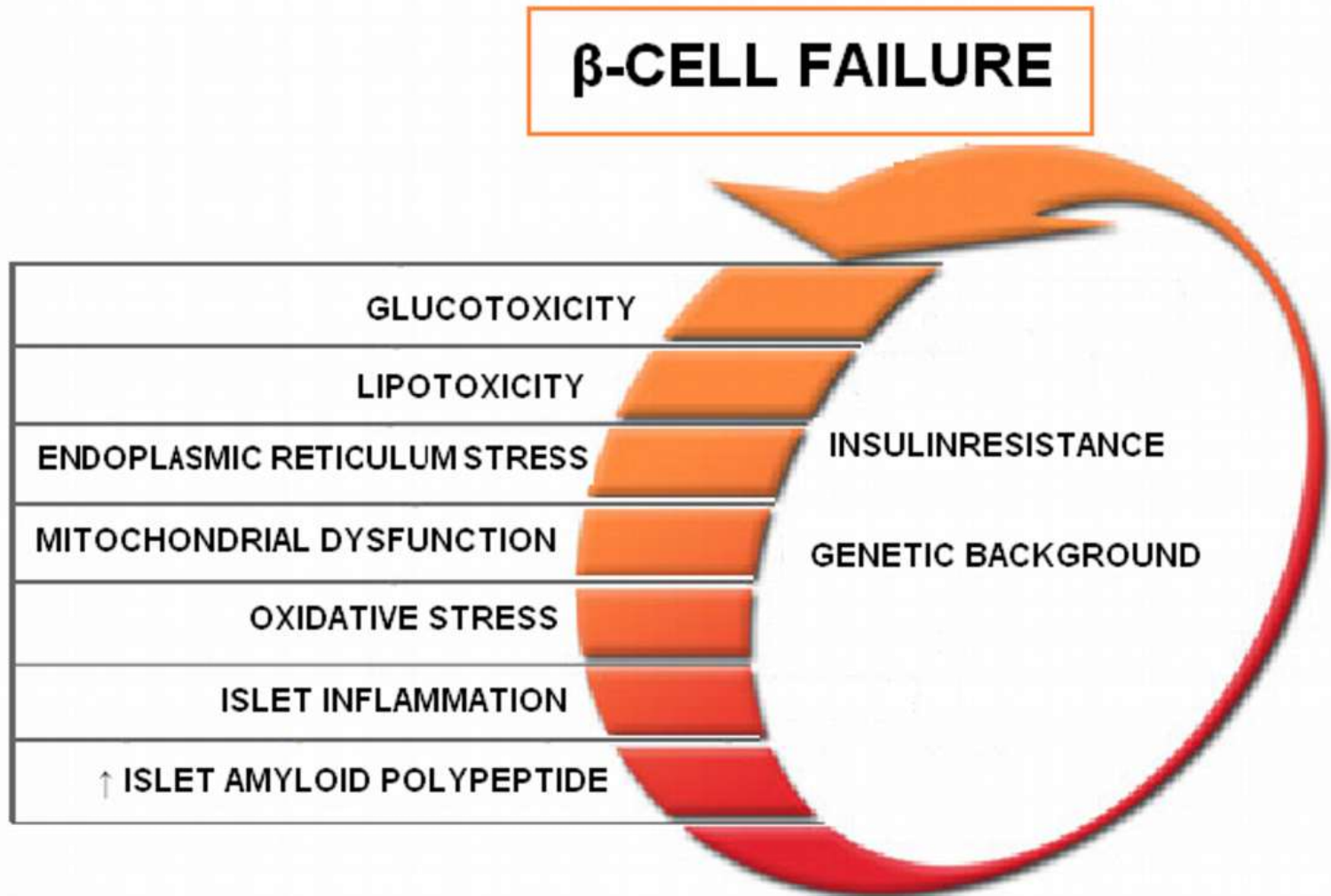
Mechanisms

Type 2 DM and Beta-cell Dysfunction: 1

- Beta-cell dysfunction is a major factor across the spectrum of prediabetes to DM
- Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the 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 address the beta-cell pathology will emerge for early therapy.

Mechanisms

Type 2 DM and Beta-cell Dysfunction: 2



Mechanisms

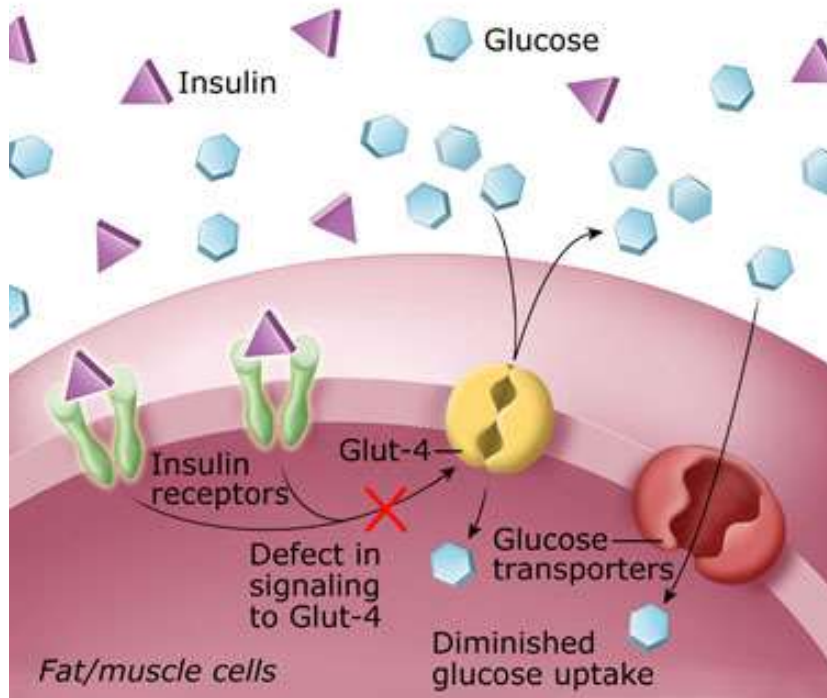
Type 2 DM and Insulin Resistance: 1

- In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first
- Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails
- During the induction of insulin resistance (such as occurs with a high-calorie diet, steroid administration, or physical inactivity), increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance
- The postprandial glucagonlike peptide-1 (GLP-1) response is unaltered.

Mechanisms

Type 2 DM and Insulin Resistance: 2

Type 2 Diabetes: Insulin Resistance



- Insulin resistance means the signal insulin gives to a cell is weakened
- This results in less glucose uptake by muscle and fat cells and a reduction in insulin mediated activities inside cells
- Compounding this problem of resistance, there is additional defect in insulin production and secretion by the insulin producing beta cells in the pancreas.

Mechanisms

Type 2 DM: Genomic factors

- Genome-wide association studies of single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants that are associated with beta-cell function and insulin resistance
- Some of these SNPs appear to increase the risk for type 2 diabetes
- Over 40 independent loci demonstrating an association with an increased risk for type 2 diabetes have been shown.

Mechanisms

Gestational DM: 1

- If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results, that are the most significant source of the accelerated growth exhibited by the fetus
- Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia
- Fetal hyperinsulinemia promotes excess nutrient storage, resulting in macrosomia. The energy expenditure associated with the conversion of excess glucose into fat causes depletion in fetal oxygen levels that are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red cell hyperplasia, and increased hematocrit.

Mechanisms

Gestational DM: 2



Classification

(American Diabetes Association)

- Type 1 DM (β -cell destruction, usually leading to absolute insulin deficiency): immune-mediated, idiopathic
- Type 2 DM (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)
- Gestational DM (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt DM)
- Other specific types of DM: genetic defects of the β -cell, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced DM, infections, uncommon forms of immune-mediated DM, other genetic syndromes sometimes associated with DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).

Classification

(International Classification of Diseases (ICD))

IV Endocrine, nutritional and metabolic diseases

(E10-E14) Diabetes mellitus

E10 Type 1 diabetes mellitus

E11 Type 2 diabetes mellitus

E12 Malnutrition-related diabetes mellitus

E13 Other specified diabetes mellitus

E14 Unspecified diabetes mellitus

XV Pregnancy, childbirth and the puerperium

O20-O29 Other maternal disorders predominantly
related to pregnancy

O24 Diabetes mellitus in pregnancy

Clinical Investigation

(Signs and Symptoms: 1)

- The classic symptoms of untreated DM are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger) that may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM
- Several other signs and symptoms are not specific to DM and include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin
- Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes
- A number of skin rashes are collectively known as diabetic dermatomes.

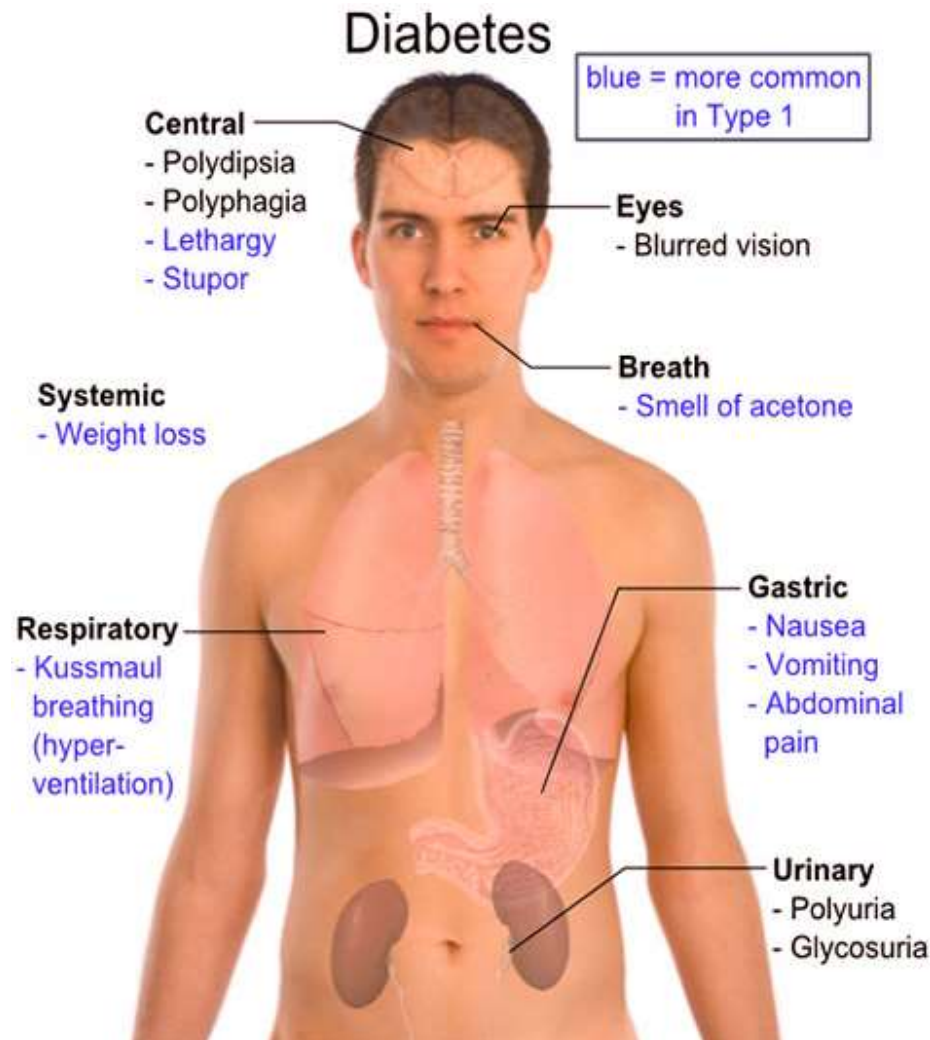
Clinical Investigation

(Signs and Symptoms: 2)



Clinical Investigation

(Signs and Symptoms: 3)



Clinical Investigation

(Diabetic emergencies: 1)

- Low blood sugar is common in patients with DM, but most cases are mild and are not considered medical emergencies
- Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases
- Moderate hypoglycemia may easily be mistaken for drunkenness
- People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep (Kussmaul) breathing, and a decreased level of consciousness
- A rare possibility is hyperosmolar nonketotic state, which is more common in type 2 DM and is mainly the result of dehydration

Clinical Investigation

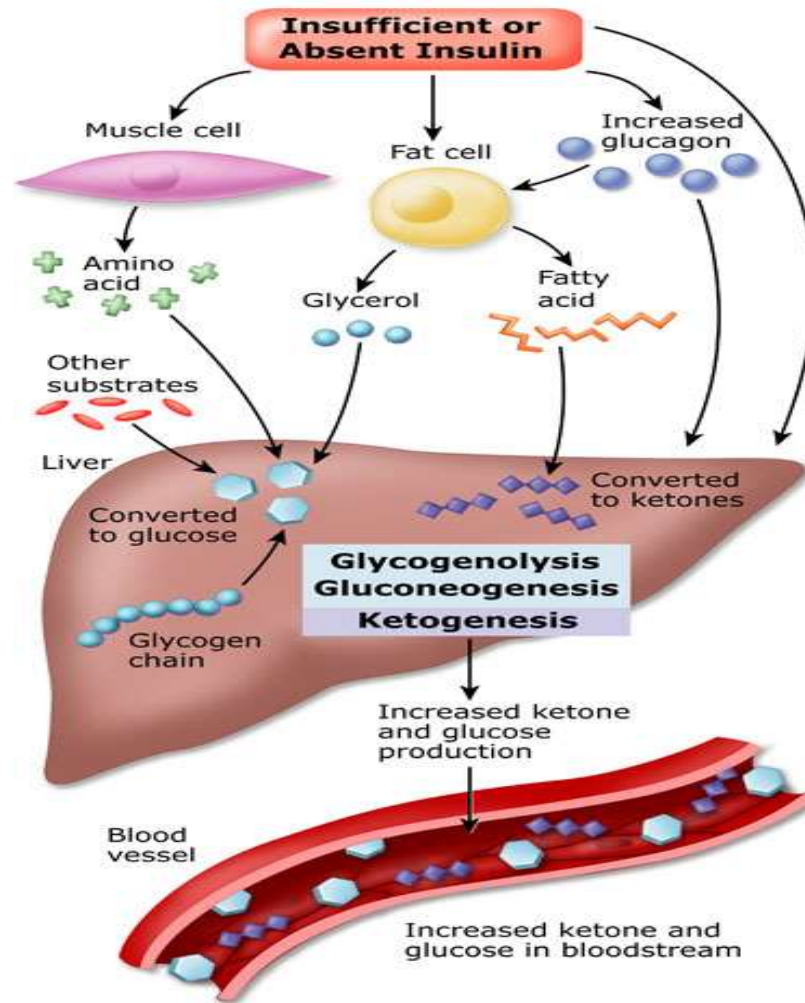
(Diabetic emergencies: 2)

Low Blood Sugar Symptoms



Clinical Investigation

(Diabetic emergencies: 3)



Diabetic ketoacidosis (DKA)

Clinical Investigation

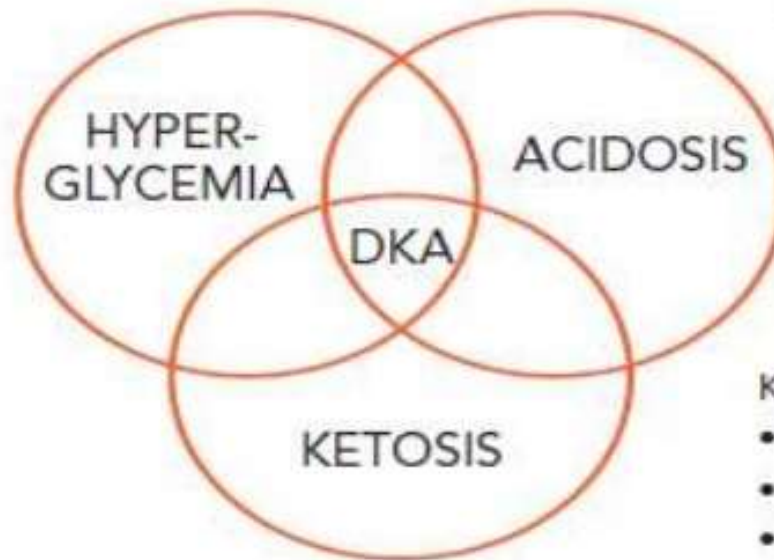
(Diabetic emergencies: 4)

HYPERGLYCEMIC STATES

- Diabetes Mellitus
- Hyperosmolar Hyperglycemic State
- Impaired Glucose Tolerance
- Stress Hyperglycemia

METABOLIC ACIDOTIC STATES

- Lactic Acidosis
- Hyperchloremic Acidosis
- Uremic Acidosis
- Drug-Induced Acidosis
(eg, salicylates, methanol,
ethylene glycol)



KETOTIC STATES

- Ketotic Hypoglycemia
- Alcoholic Ketosis
- Starvation Ketosis

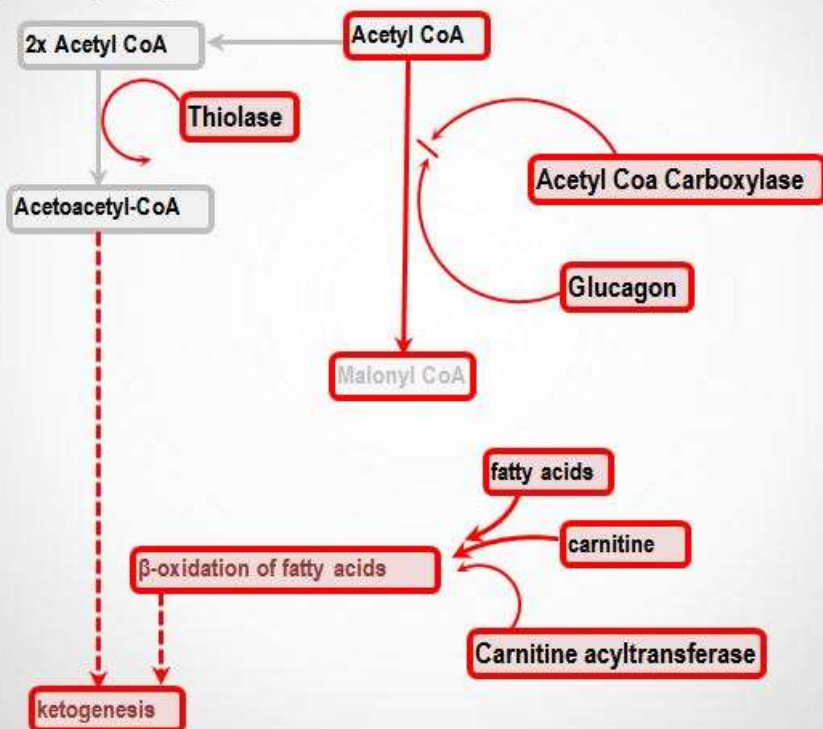
Diagnostic triad of diabetic ketoacidosis (DKA)

Clinical Investigation

(Diabetic emergencies: 5)

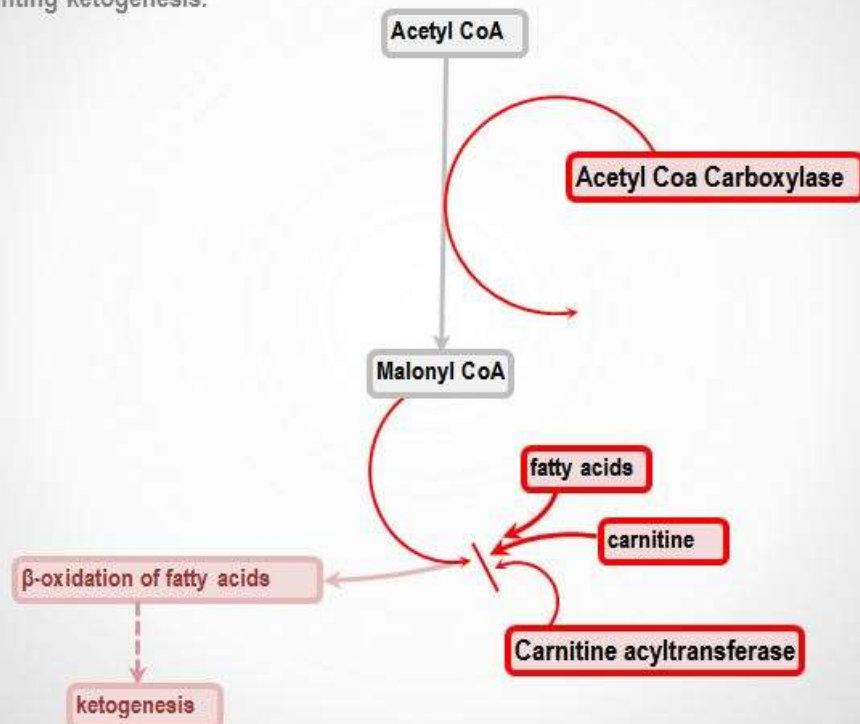
In DKA:

In the absence of insulin, glucagon inhibits the synthesis of malonyl CoA, resulting in an unregulated entry of fatty acids into the β -oxidation pathway, promoting ketogenesis.



In HONK:

Under the regulatory influence of insulin, malonyl CoA exerts a normal inhibitory effect on the entrance of fatty acids into the β -oxidation pathway, thus limiting ketogenesis.



Differences in diabetic ketoacidosis (DKA) and hyperosmolar nonketotic state (HONK)

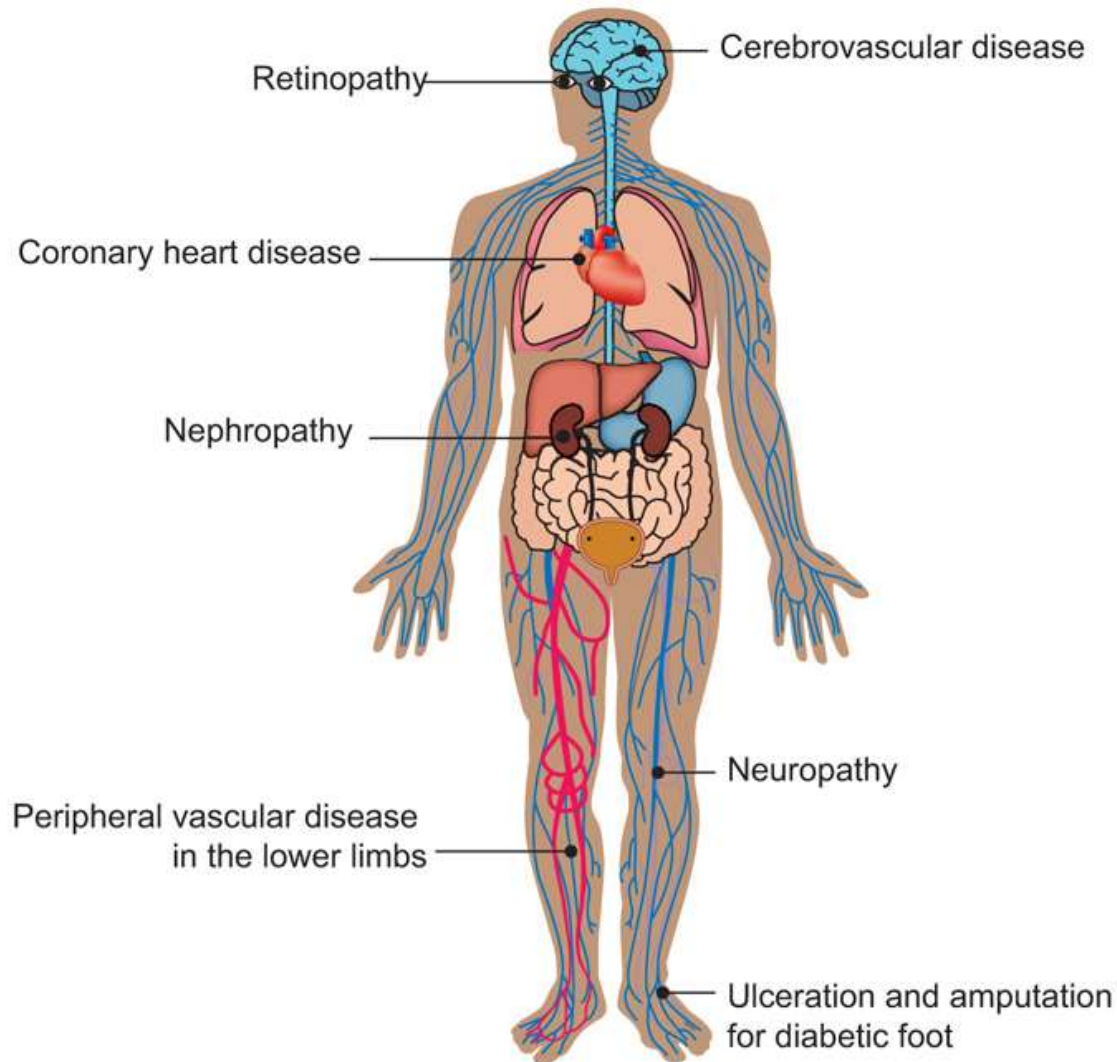
Clinical Investigation

(Complications: 1)

- The major long-term complications relate to damage to blood vessels with the risk of "macrovascular" diseases development (coronary artery disease, stroke, peripheral vascular disease)
- The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves (diabetic retinopathy that result in gradual vision loss and blindness, diabetic nephropathy that leads to chronic kidney disease, diabetic neuropathy, diabetes-related foot problems (diabetic foot ulcers, occasionally requiring amputation), proximal diabetic neuropathy that causes painful muscle wasting and weakness, cognitive deficit .

Clinical Investigation

(Complications: 2)



Clinical Investigation

(Complications: Peripheral Neuropathy)

- Numbness or reduced ability to feel pain or temperature changes
- A tingling or burning sensation
- Sharp pains or cramps
- Increased sensitivity to touch — for some people, even the weight of a bed sheet can be agonizing
- Muscle weakness
- Loss of reflexes, especially in the ankle
- Loss of balance and coordination
- Serious foot problems, such as ulcers, infections, deformities, and bone and joint pain

Clinical Investigation

(Complications: Autonomic Neuropathy)

- A lack of awareness that blood sugar levels are low (hypoglycemia unawareness)
- Bladder problems (urinary tract infections, urinary retention or incontinence)
- Constipation and/or uncontrolled diarrhea
- Slow stomach emptying (gastroparesis), leading to nausea, vomiting, bloating and loss of appetite
- Difficulty swallowing
- Erectile dysfunction in men
- Vaginal dryness and other sexual difficulties in women
- Increased or decreased sweating
- Inability of patient's body to adjust blood pressure and heart rate, leading to sharp drops in blood pressure after sitting or standing that may cause him to faint or feel lightheaded
- Problems regulating body temperature
- Changes in the way eyes adjust from light to dark
- Increased heart rate at rest

Clinical Investigation

(Complications: Radiculoplexus Neuropathy)

- Radiculoplexus neuropathy (diabetic amyotrophy, femoral neuropathy, proximal neuropathy) affects nerves in the thighs, hips, buttocks or legs more common in older adults with type 2 DM
- Symptoms are usually on one side of the body, though in some cases symptoms may spread to the other side
- Most people improve at least partially over time, though symptoms may worsen before they get better
- This condition is often marked by:
 - Sudden, severe pain in hip and thigh or buttock
 - Eventual weak and atrophied thigh muscles
 - Difficulty rising from a sitting position
 - Abdominal swelling, if the abdomen is affected
 - Weight loss

Clinical Investigation

(Complications: Mononeuropathy)

- Mononeuropathy (focal neuropathy) involves damage to a specific nerve and it's most common in older adults
- Mononeuropathy can cause severe pain, it usually doesn't cause any long-term problems
- Signs and symptoms depend on which nerve is involved and may include: difficulty focusing eyes, double vision or aching behind one eye; paralysis on one side of the face (Bell's palsy); pain in a shin or foot; pain in a lower back or pelvis; pain in the front of a thigh, pain in the chest or abdomen
- Sometimes mononeuropathy occurs when a nerve is compressed, e.g. carpal tunnel syndrome (numbness or tingling in fingers or hand, especially in thumb, index finger, middle finger and ring finger, etc.).

Clinical Investigation

(Complications: Diabetic Foot Ulcers)



- Diabetic foot ulcers occur in 15% of people with DM and precedes 84% of all diabetes-related lower-leg amputations
- Risk factors are diabetic neuropathy, peripheral vascular disease, cigarette smoking, poor glycemic control, previous foot ulcerations or amputations, diabetic nephropathy, and ischemia of small and large blood vessels
- Diabetic foot lesions are responsible for more hospitalizations than any other complication of diabetes

Diagnosis

World Health Organization (WHO) Criteria

Methods and criteria for diagnosing diabetes

- Diabetes symptoms (e.g. polyuria, polydipsia and unexplained weight loss for Type 1) plus:
 - a random venous plasma glucose concentration ≥ 11.1 mmol/l or
 - a fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or
 - two hour plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).
- With no symptoms diagnosis should not be based on a single glucose determination but requires confirmatory plasma venous determination.

Diagnosis

World Health Organization (WHO) Criteria

Gestational diabetes

The criteria for diagnosing gestational diabetes is different.

Gestational diabetes should be diagnosed if the woman has either:

- a fasting plasma glucose level of 5.6mmol/l or above or
- a 2-hour plasma glucose level of 7.8mmol/l or above.

Diagnosis

World Health Organization (WHO) Criteria

Glycated Hemoglobin A1c (HbA1c) testing to diagnose diabetes

- An HbA1c of 48mmol/mol (6.5%) is recommended as the cut off point for diagnosing diabetes
- Finger-prick HbA1c should not be used unless the methodology and the healthcare staff and facility using it can demonstrate within the national quality assurance scheme that they match the quality assurance results found in laboratories
- In patients without symptoms of diabetes the laboratory venous HbA1c should be repeated, and if the second sample is <48mmol/mol (6.5%) the person should be treated as at high risk of diabetes and the test should be repeated in 6 months or sooner if symptoms develop.

Diagnosis

Glycated hemoglobin (Hb A1C) test

- Glycated hemoglobin (Hb A1C) test indicates average blood sugar level for the past two to three months
- Glycated hemoglobin (Hb A1C) test measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells
- The higher blood sugar levels, the more hemoglobin patient will have with sugar attached
- An Hb A1C level of 6.5 percent or higher on two separate tests indicates that patient have diabetes
- An Hb A1C between 5.7 and 6.4 percent indicates prediabetes
- Below 5.7 is considered normal.

Diagnosis

World Health Organization (WHO) Criteria

Condition	2 hour glucose	Fasting glucose	Hb A1C	
	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) & <7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

Management

(Organization of DM Care)

- All people with DM should be receiving continuing preventative care through education and medical interventions
- All people with DM need annual surveillance to detect early on the development of late tissue damage, and where this is detected access to protocols and resources for its management
- All people with DM should have continuing access to DM team, for help in management and social difficulties arising from DM
- All people with DM have a role in the development and organization of the service of which they are a part
- All DM management teams should have an active policy of quality improvement
- Appropriate special care should be offered to those with special needs, including pregnant women.

Management (Diet and Activity)

- All patients on insulin should have a comprehensive diet plan, created with the help of a professional dietitian, that includes the following:
- A daily caloric intake prescription
- Recommendations for amounts of dietary carbohydrate, fat, and protein
- Instructions on how to divide calories between meals and snacks
- Exercise is also an important aspect of diabetes management. Patients should be encouraged to exercise regularly.

Management

(Self-Monitoring in Glycemic Control)

- Benefits of tight glycemic control include not only continued reductions in the rates of DM complications but also in overall mortality
- Optimal DM control requires frequent self-monitoring of blood glucose levels, which allows rational adjustments in hypoglycemic medications
- All patients should learn how to self-monitor and record their blood glucose levels with home analyzers and adjust their hypoglycemic medications doses accordingly
- Real-time continuous monitoring of glucose—using continuous glucose monitors (CGMs)—can help patients improve glycemic control.

Management (Continuous Glucose Monitors (CGMs))



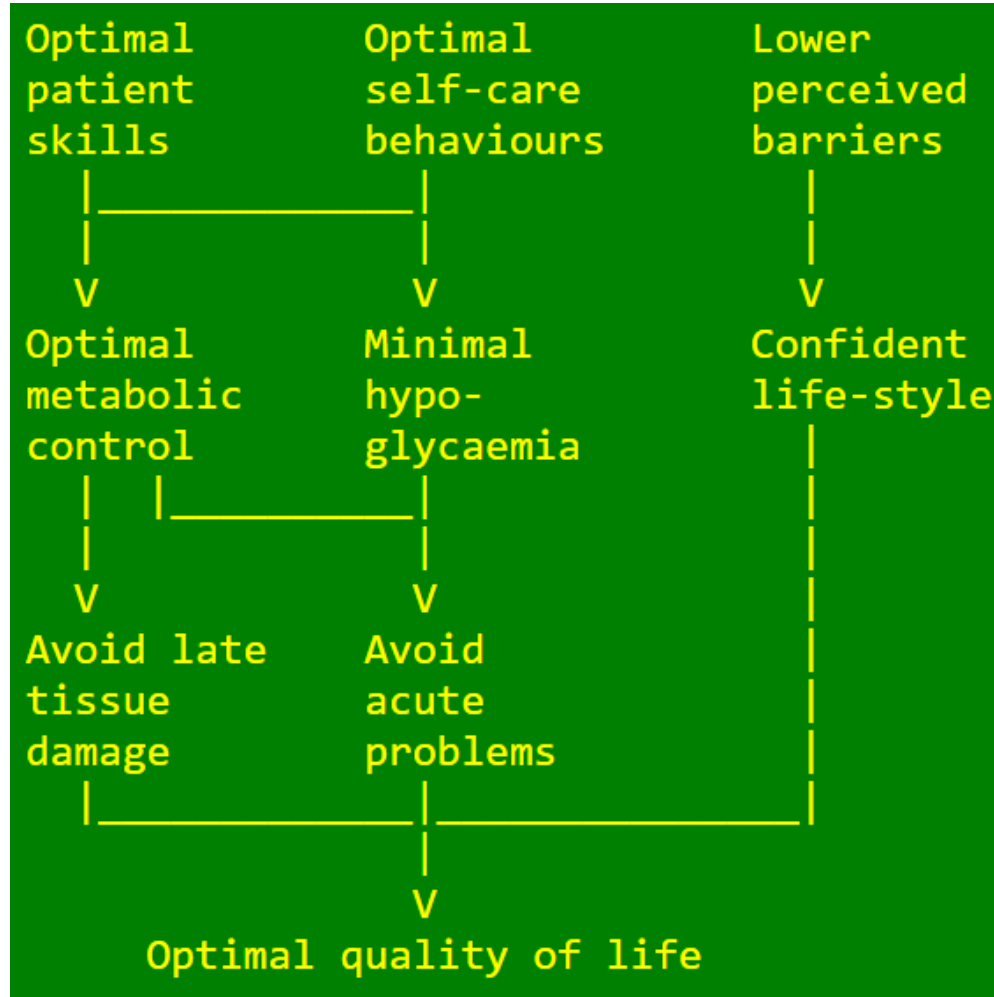
Continuous glucose monitors (CGMs) contain subcutaneous sensors that measure interstitial glucose levels every 1-5 minutes, providing alarms when glucose levels are too high or too low or are rapidly rising or falling.

Management (Glucose Meters)



Management

(Objectives of DM Management)



Management

(Insulin: Therapy)

- Patients with type 1 DM require lifelong insulin therapy
- Most require 2 or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels
- Insulin replacement is accomplished by giving a basal insulin and a preprandial (premeal) insulin
- The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (NPH)
- The preprandial insulin is either rapid-acting (lispro, aspart, insulin inhaled, or glulisine) or short-acting (regular).

Management

(Insulin: Types)

The commonly used types of insulin in DM patients are:

- i) fast-acting which begin to work within 5 to 15 minutes and are active for 3 to 4 hours
- ii) short-acting which begins working within 30 minutes and is active about 5 to 8 hours
- iii) intermediate-acting, includes NPH insulin which begins working in 1 to 3 hours and is active 16 to 24 hours; long acting, which begins working within 1 to 2 hours and continue to be active, without major peaks or dips, for about 24 hours, although this varies in many individuals
- iv) ultra-long acting, which begins working within 30–90 minutes, and continues to be active for greater than 24 hours
- v) combination insulin products, which include a combinations of either fast-acting or short-acting insulin with a longer acting insulin and begin to work with the shorter acting insulin (5–15 minutes for fast-acting, and 30 minutes for short acting), and remain active for 16 to 24 hours.

Management

(Insulin: Methods of Administration)

- Insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump, by repeated-use insulin pens with needles, or by use an injection port in conjunction with syringes
- Administration schedules often attempt to mimic the physiologic secretion of insulin by the pancreas
- Insulin pumps are a reasonable solution for some, and advantages are better control over background or 'basal' insulin dosage, bolus doses calculated to fractions of a unit, and calculators in the pump that may help with determining 'bolus' infusion dosages
- Insulin pumps may be like 'electrical injectors' attached to a temporarily implanted catheter or cannula.

Management (Insulin: Insulin Pump)



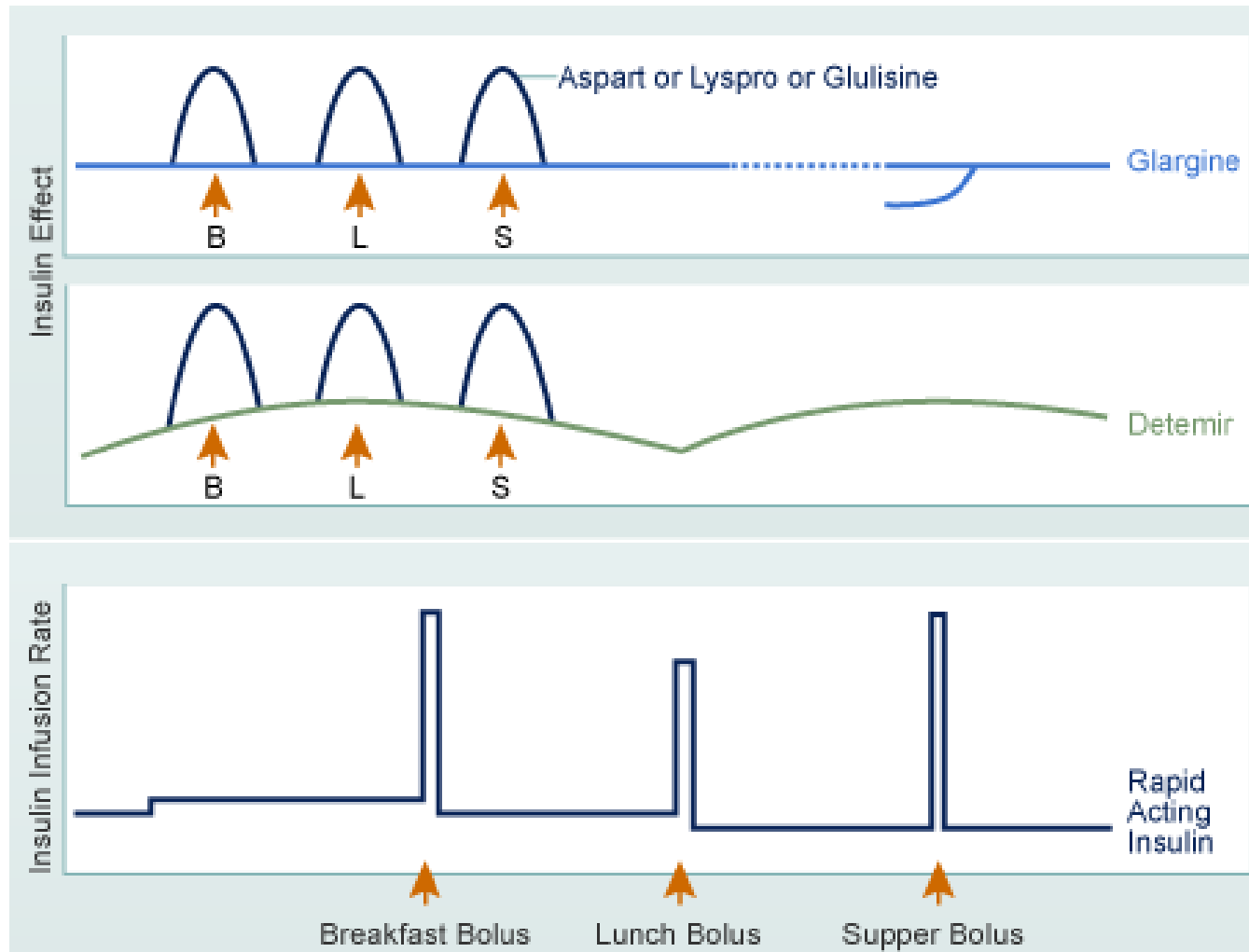
Management

(Insulin: Dosage and Timing)

- One international unit of insulin (1 IU) is defined as the "biological equivalent" of 34.7 μg pure crystalline insulin
- The unit of measurement used in insulin therapy is not part of the International System of Units (abbreviated SI) which is the modern form of the metric system
- Instead the pharmacological international unit (IU) is defined by the WHO Expert Committee on Biological Standardization.

Management

(Insulin: Multiple Daily Injections)

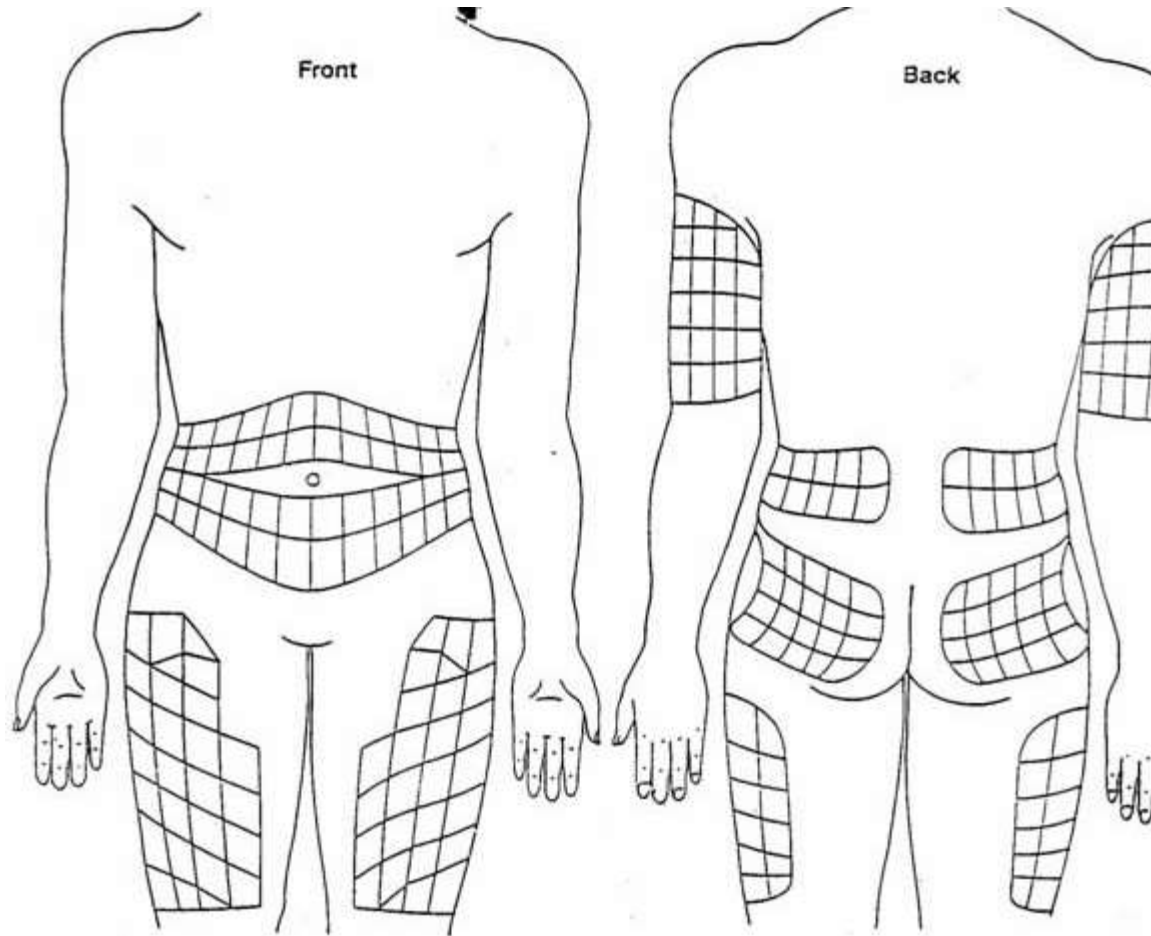


Management

(Insulin: Sample regimen using insulin NPH and regular insulin)

		before breakfast	before lunch	before dinner	at bedtime
NPH dose		12 units		6 units	
regular insulin dose if fingerstick glucose is (mg/dl) [mmol/L]:					
70-100	[3.9-5.5]	4 units		4 units	
101-150	[5.6-8.3]	5 units		5 units	
151-200	[8.4-11.1]	6 units		6 units	
201-250	[11.2-13.9]	7 units		7 units	
251-300	[14.0-16.7]	8 units	1 unit	8 units	1 unit
>300	[>16.7]	9 units	2 units	9 units	2 units

Management (Insulin Administration)



Management

(Treatment of Type 2 DM)

- Individualized glycemic targets and glucose-lowering therapies
- Diet, exercise, and education as the foundation of the treatment program
- Use of metformin as the optimal first-line drug unless contraindicated
- After metformin, the use of 1 or 2 additional oral or injectable agents, with a goal of minimizing adverse effects if possible
- Ultimately, insulin therapy alone or with other agents if needed to maintain blood glucose control
- Where possible, all treatment decisions should involve the patient, with a focus on patient preferences, needs, and values
- A major focus on comprehensive cardiovascular risk reduction

Management

(Oral Antihyperglycemic Drugs: Biguanides)

- Biguanides decrease hepatic glucose production, decrease gastrointestinal glucose absorption, and increase target cell insulin sensitivity
- Example: Metformin
- Contraindications: Metabolic acidosis with or without coma, abnormal creatinine clearance from any cause including diabetic ketoacidosis, shock, acute myocardial infarction, septicemia, renal disease (serum creatinine level ≥ 1.5 mg/dL in males or ≥ 1.4 mg/dL in females), lactation, radiologic contrast study within 48 hours

Management

(Oral Antihyperglycemic Drugs: Sulfonylureas)

- Sulfonylureas increase beta-cell insulin secretion, decrease hepatic glucose output, and increase insulin receptor sensitivity at peripheral target tissues
- Examples: Glyburide, glipizide, glimepiride, tolazamide, tolbutamide
- Contraindications: Sulfa allergy, type 1 DM, diabetic ketoacidosis, concomitant use with bosentan

Management

(Oral Antihyperglycemic Drugs: Thiazolidinediones)

- Thiazolidinediones increase insulin receptor sensitivity and influence the production of gene products involved in lipid and glucose metabolism; their mechanism of action depends on the presence of insulin for activity
- Examples: Pioglitazone, rosiglitazone
- Contraindications: Hypersensitivity to product or components, established NYHA class III/IV heart failure

Management

(Oral Antihyperglycemic Drugs: Alpha-Glucosidase Inhibitors)

- Inhibit the upper gastrointestinal enzymes that convert dietary starch and other complex carbohydrates into simple sugars, which can be absorbed
- Examples: Acarbose (Precose) & Miglitol (Glycet)
- Contraindications: Diabetic ketoacidosis; cirrhosis; inflammatory bowel disease, colonic ulceration, partial intestinal obstruction,

Management (Peptide analogs)

- Injectable Incretin mimetics as insulin secretagogues: glucagon-like peptide-1 (GLP-1) analog and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP) analog
- Injectable Amylin analogues that slow gastric emptying and suppress glucagon have all the incretins actions except stimulation of insulin secretion
- Glycosurics (SGLT-2 inhibitors) block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine.

Management

(Treatment of Gestational DM)

- Diet: avoid single large meals and foods with a large percentage of simple carbohydrates
- Insulin: the goal of insulin therapy during pregnancy is to achieve glucose profiles similar to those of nondiabetic pregnant women
- Glyburide and metformin: trials have shown these 2 drugs to be effective, and no evidence of harm to the fetus has been found
- Management of the neonate: the employment of frequent blood glucose checks and early oral feeding (ideally from the breast) when possible, with infusion of intravenous glucose if oral measures prove insufficient.

Management (Surgery)

- A pancreas transplant is occasionally considered for people with type 1 DM who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation
- Weight loss surgery in those with obesity and type 2 DM is often an effective measure
- Many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased.

Prognosis

- The general statistical prognosis is that 15% of sufferers of type 1 DM will die before the age of 40, sensible blood sugar control and a healthy diet can lead to a long life for sufferers
- Contracting type 2 DM in 40's means five to 10 years off average life expectancy; however, as with the above, this is a vast improvement on recent years
- As Heart Disease is the leading cause of death in Type 2 DM sufferers, keeping to a regime that minimises the risk is very much recommended.

Prophylaxis

- There is no known preventive measure for type 1 DM
- Type 2 DM can often be prevented or delayed by maintaining a normal body weight, engaging in physical exercise, and consuming a healthful diet
- Higher levels of physical activity reduce the risk of diabetes by 28%
- Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish
- The relationship between type 2 DM and the main modifiable risk factors (excess weight, unhealthy diet, physical inactivity and tobacco use) is similar in all regions of the world.

Abbreviations

CGMs - continuous glucose monitors

DKA - diabetic ketoacidosis

DM - diabetes mellitus

GDM - Gestational diabetes mellitus

GIP - glucose-dependent
insulinotropic polypeptide

GLP-1 - the postprandial glucagonlike
peptide-1

HbA1c - Glycated Hemoglobin A1c

HLA - human leukocyte antigen

HONK - hyperosmolar nonketotic
state

IGT - impaired glucose tolerance

IFG - impaired fasting glucose

IU - international unit of insulin

NYHA - New York Heart Association

OGTT - oral glucose tolerance test

SGLT-2 - Sodium-glucose co-
transporter 2

SNPs - single-nucleotide
polymorphisms

WHO - World Health Organization

Diagnostic and treatment guidelines

- [IDF Clinical Practice Guidelines](#)
- [Type 2 diabetes in adults: management](#)
- [Diabetes in pregnancy: management from preconception to the postnatal period](#)
- [Guidelines on diabetes, pre-diabetes, and cardiovascular diseases](#)
- [Managing older people with type 2 diabetes: global guidelines\(external link\)](#)