# Complications of diabetes mellitus

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# Complications of diabetes mellitus

* **Acute complications:**
  * Ketoacidosis
  * Hyperglycemic hyperosmolar nonketotic syndrome
  * Hypoglycemia
* **Chronic complications:**
  * Disorders of the microcirculation
    * Neuropathies
    * Nephropathies
    * Retinopathies
  * Macrovascular complications
  * Foot ulcers

# Diabetic ketoacidosis (DKA)

* Ketone production by the liver exceeds cellular use and renal excretion.
* Most commonly occurs in type 1 diabetes, lack of insulin leads to mobilization of fatty acids from adipose tissue, increase in fatty acid levels leads to ketone production by the liver.
* Stress increases the release of gluconeogenic hormones.
* DKA often is preceded by physical or emotional stress, such as infection, pregnancy, or extreme anxiety.
* In clinical practice, ketoacidosis also occurs with the omission or inadequate use of insulin.

# Diabetic ketoacidosis (DKA)

* The three major metabolic derangements in DKA are:
  * **Hyperglycemia**
  * **Ketosis**
  * **Metabolic acidosis**

# Diabetic ketoacidosis (DKA)

* The definitive diagnosis consists of
  * hyperglycemia (blood glucose levels >250 mg/dL)
  * low bicarbonate (<15 mEq/L) and low pH (<7.3)
  * ketonemia (positive at 1:2 dilution) and moderate ketonuria.
* Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes.
* Hyperosmolality → Extracellular sodium concentration frequently is low or normal despite enteric water losses because of the intracellular-extracellular fluid shift. This dilutional effect is referred to as *pseudohyponatremia*.
* Serum potassium levels may be normal or elevated.
* Metabolic acidosis is caused by the excess ketoacids.

# Manifestations

* Typically history of 1 or 2 days of polyuria, polydipsia, nausea, vomiting, and marked fatigue→stupor →coma.
* Abdominal pain and tenderness may be present without abdominal disease. (glucose waste product)
* The breath has a characteristic smell because of the presence of the volatile ketoacids. The rate and depth of respiration increase (*i.e.*, Kussmaul's respiration) as the body attempts to prevent further decreases in pH
* Hypotension may be present because of a decrease in blood volume.

# Treatment

* The goals in treating DKA are:
  * To improve circulatory volume and tissue perfusion
  * To decrease serum glucose
  * To correct the acidosis and electrolyte imbalances
* Accomplished through the administration of insulin and intravenous fluid and electrolyte replacement solutions.
* Identification and treatment of the underlying cause.

# The hyperglycemic hyperosmolar nonketotic (HHNK) syndrome

* HHNK is characterized by
  * Hyperglycemia (blood glucose >600 mg/dL),
  * Hyperosmolarity (plasma osmolarity >310 mOsm/L) and dehydration
  * Absence of ketoacidosis
  * Depression of the sensorium.
* It is seen most frequently in people with type 2 diabetes.
* Two factors appear to contribute to the hyperglycemia that precipitates the condition:
  * An increased resistance to the effects of insulin
  * An excessive carbohydrate intake.

# The hyperglycemic hyperosmolar nonketotic (HHNK) syndrome

* The most prominent **manifestations** are dehydration:
  * Neurologic signs and symptoms:
    * Generalized seizures
    * Hemiparesis
    * Aphasia
    * Muscle fasciculations
    * Hyperthermia
    * Visual field loss
    * Nystagmus
    * Visual hallucinations
  * Excessive thirst
* The onset of HHNK syndrome often is insidious, and because it occurs most frequently in older people, it may be mistaken for a stroke.

# Treatment

* The goals of treatment are same as DKA but need more intensive circulatory volume.
* Judicious medical observation and care because water moves →brain cells during treatment → cerebral edema.
* Extensive K+ losses occurred during the diuretic phase of the disorder require correction.

# Hypoglycemia

* Hypoglycemia

→ relative excess of insulin in the blood and is characterized by below-normal blood glucose levels.

* It occurs most commonly with insulin injections and some oral hypoglycemic agents (*i.e.*, beta cell stimulators).
* Many factors precipitate an insulin reaction in a person with type 1 diabetes, including:
  * Error in insulin dose
  * Failure to eat
  * Increased exercise
  * Decreased insulin need after removal of a stress situation
  * Medication changes and a change in insulin site
* Alcohol decreases liver gluconeogenesis, and people with diabetes need to be cautioned about its potential for causing hypoglycemia.

# Hypoglycemia

* Brain function relies on blood glucose (energy source)
* Hypoglycemia produces behaviors related to altered cerebral function:
  * Headache
  * Difficulty in problem solving
  * Disturbed or altered behavior
  * Coma
  * Seizures
* At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger → if not corrected → parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (*i.e.*, the skin is cool and clammy).

# Treatment

* The most effective treatment
  * Immediate ingestion of a concentrated carbohydrate source, such as sugar, honey, candy, or orange juice. (Rule of 15)
* Alternative methods when the person having the reaction is unconscious or unable to swallow:
  * Glucagon may be given intramuscularly or subcutaneously.
  * In situations of severe or life-threatening hypoglycemia, it may be necessary to administer glucose intravenously.

# Chronic complications

* These disorders occur in the insulin-independent tissues of the body tissues that do not require insulin for glucose entry into the cell→ intracellular glucose concentrations in many of these tissues approach or equal those in the blood.
* Chronic complications can be reduced by intensive diabetic treatment.

# Peripheral neuropathies

* Two types of pathologic changes with diabetic peripheral neuropathies.
  * The first is a thickening of the walls of the nutrient vessels that supply the nerve, leading to the assumption that vessel ischemia plays a major role in the development of these neural changes.
  * The second finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.
* The clinical manifestations of the diabetic peripheral neuropathies vary with the location of the lesion.

# Classification of diabetic peripheral neuropathies

* **Somatic:**
  * Polyneuropathies (bilateral sensory)
    * Paresthesias, including numbness and tingling
    * Impaired pain, temperature, light touch, two-point discrimination, and vibratory sensation
    * Decreased ankle and knee-jerk reflexes
  * Mononeuropathies
    * Involvement of a mixed nerve trunk that includes loss of sensation, pain, and motor weakness.
  * Amyotrophy
    * Associated with muscle weakness, wasting, and severe pain of muscles in the pelvic girdle and thigh.
* **Autonomic:**
  * Impaired vasomotor function
    * Postural hypotension
  * Impaired gastrointestinal function
    * Gastric atony
    * Diarrhea, often postprandial and nocturnal
  * Impaired genitourinary function
    * Paralytic bladder
    * Incomplete voiding
    * Impotence
    * Retrograde ejaculation
  * Cranial nerve involvement
    * Extraocular nerve paralysis
    * Impaired pupillary responses
    * Impaired special senses

# Diabetic nephropathy

* Diabetic nephropathy
  * Cause of end-stage renal disease, accounting for 40%-50% of new cases.
* The term *diabetic nephropathy* is used to describe the combination of lesions that often occur concurrently in the diabetic kidney → Glomerular changes may occur, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis.
* Among the suggested risk factors for diabetic nephropathy are:
  * Genetic and familial predisposition
  * Elevated blood pressure
  * Poor glycemic control
  * Smoking
  * Hyperlipidemia
  * Microalbuminuria

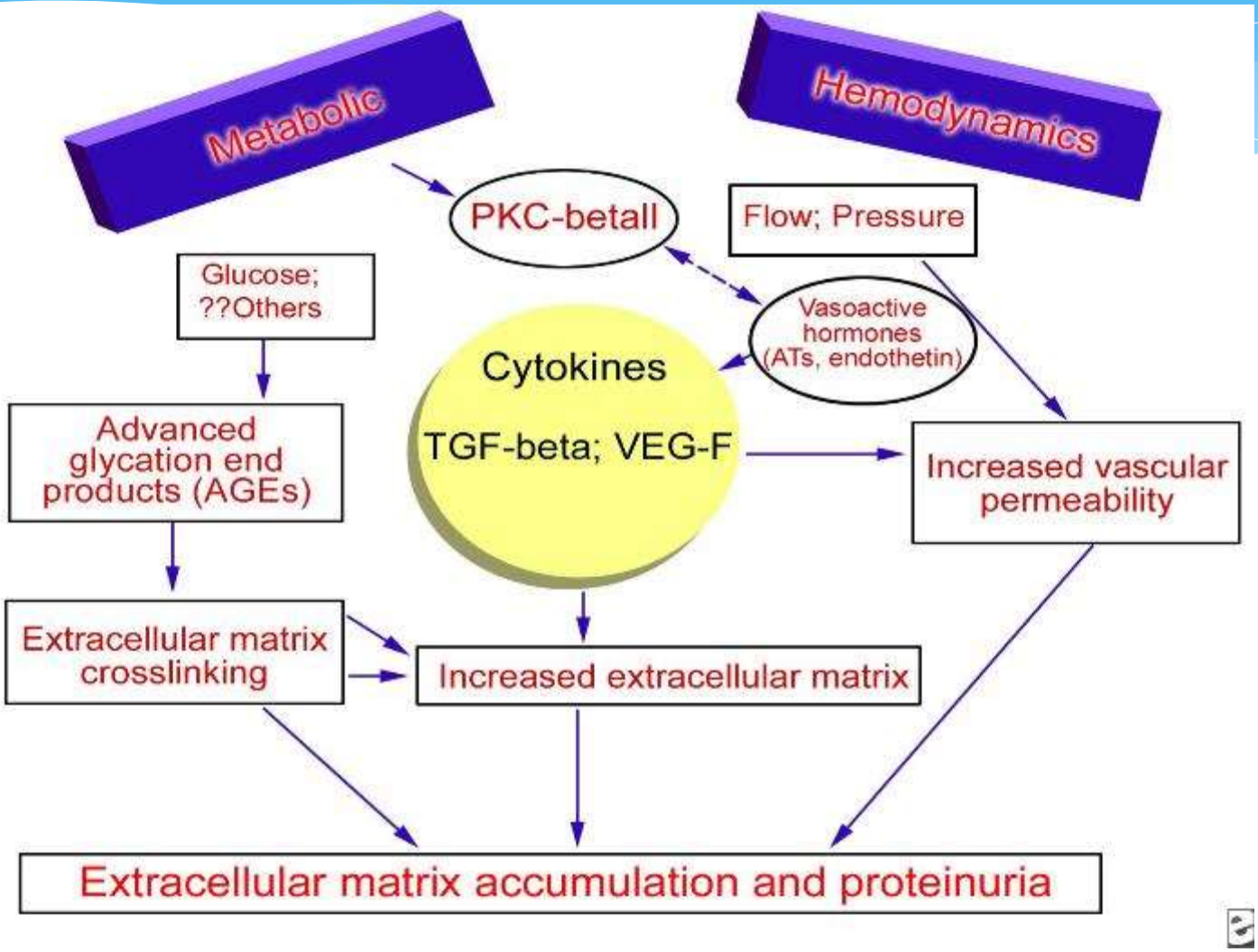
# Pathogenesis

* Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) in the glomeruli and of matrix proteins specifically stimulated by this cytokine. TGF-beta may contribute to the cellular hypertrophy and enhanced collagen synthesis observed in persons with diabetic nephropathy→ renal hemodynamic alterations, patients with overt diabetic nephropathy (dipstick-positive proteinuria and decreasing GFR) generally develop systemic hypertension.
* Hypertension is an adverse factor in all progressive renal diseases and seems especially so in diabetic nephropathy. The deleterious effects of hypertension are likely directed at the vasculature and microvasculature.
* Familial or perhaps even genetic factors also play a role.
  * Certain ethnic groups, particularly African Americans, persons of Hispanic origin, and American Indians, may be particularly disposed to renal disease as a complication of diabetes.

# Pathogenesis

* The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are:
  * Hyperglycemia (causing hyperfiltration and renal injury)
  * Advanced glycosylation products
  * Activation of cytokines

# Pathogenesis



# Retinopathies

* Retinopathy is the most common pattern of eye disease.
* Diabetic retinopathy is characterized by
  * abnormal retinal vascular permeability
  * microaneurysm formation
  * neovascularization
  * hemorrhage, scarring, and retinal detachment.
* Risk factors associated with diabetic retinopathy are poor glycemic control, elevated blood pressure, and hyperlipidemia.
* Diabetes is important for regular dilated eye examinations.
* Another condition called macular edema → damaged blood vessels leak fluid and lipids onto the macula, the part of the retina. The fluid makes the macula swell, which blurs vision.

# Pathogenesis

* Diabetic retinopathy → microvascular retinal changes.
* These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels become more permeable.
* The lack of oxygen in the retina causes fragile, new, blood vessels to grow along the retina and in the clear, gel-like vitreous humour that fills the inside of the eye.
* Without timely treatment, these new blood vessels can bleed, cloud vision, and destroy the retina. Fibrovascular proliferation can also cause tractional retinal detachment.
* The new blood vessels can also grow into the angle of the anterior chamber of the eye and cause neovascular glaucoma.

# Macrovascular complications

* Diabetes mellitus is a major risk factor for coronary artery disease, cerebrovascular disease, and peripheral vascular disease.

* Multiple risk factors for vascular disease
  * obesity, hypertension, hyperglycemia, hyperlipidemia, altered platelet function, and elevated fibrinogen levels.
* In people with type 2 diabetes, macrovascular disease may be present at the time of diagnosis.

* In type 1 diabetes, the attained age and the duration of diabetes appear to correlate with the degree of macrovascular disease.

# Diabetic foot ulcers

* Approximately
  * 60% to 70% of people with diabetic foot ulcers have neuropathy without vascular disease,
  * 15% to 20% have vascular disease,
  * 15% to 20% have neuropathy and vascular disease.
* Distal symmetric neuropathy is a major risk factor for foot ulcers.
* Unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing or infections.
* Motor neuropathy with weakness of the intrinsic muscles of the foot may result in foot deformities, which lead to focal areas of high pressure → a foot ulcer.
* Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking.

# Infections

* Certain types of infections occur with increased frequency in people with diabetes:
  * Soft tissue infections of the extremities
  * Osteomyelitis
  * Urinary tract infections and pyelonephritis
  * Candidal infections of the skin and mucous surfaces
  * Dental caries and infections
  * Tuberculosis
* Suboptimal response to infection in a person with diabetes is caused by the presence of chronic complications, such as vascular disease and neuropathies, and by the presence of hyperglycemia and altered neutrophil function.
* Hyperglycemia and glycosuria may influence the growth of microorganisms and increase the severity of the infection.