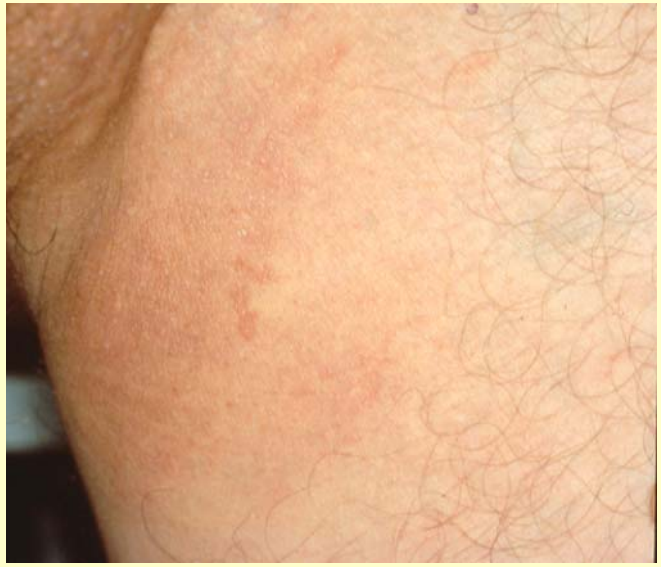
# Case Report - Endocrinology

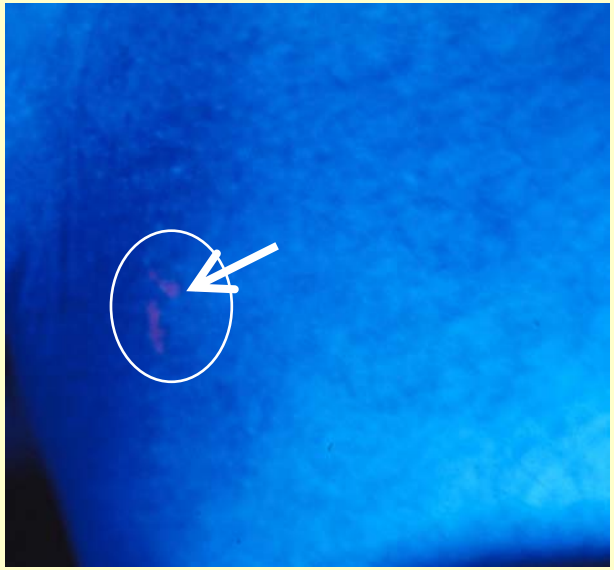
Jan Živný
Department of Pathophysiology
jzivny@LF1.cuni.cz

- M 38 y
- loosing weight (6 kg in last 4 mo) with polyuria and dysuria
- His father has been treated for last few years with insulin (DM)
- High BP was detected 1 yr. ago so far w/o pharmacotherapy
- Drinking: 5 beers/d., occasionally shots

# Clinical examinations

- BP 135/70 mmHg, HR 76/min
- Differences from normal findings:
  - obesity (height 176 cm, weight 88 kg)
  - erythrasma: light brown spots on inner parts of thighs caused by bacterial infection (*Corynebacterium minutissimum*)





porphyrins produced by the bacteria fluoresce with a coral pink color under UV (~ 365 nm)

# ECG:

- HR 76/min.
- PQ 152 ms (120 – 200)
- QRS 90 ms (< 100)
- ST-T normal

# Laboratory examinations

- ESR 3/8
- Blood count: within normal range
- Biochemical examination of blood:

| | |
|---|---|
| Na+ 142 mmol/l (135-145) | Cl- 98 mmol/l (98-106) |
| K+ 4.7 mmol/l (3.5-5.0) | **BUN** 9.2 mmol/l (2.9-8.9) |
| creatinine 114 µmol/l (53-110) | **uric acid** 458 µmol/l (200–420) |
| **ALT** 0.86 µkat/l (0-0.67) | AST 0.58 µkat/l (0-0.58) |
| ALP 1.53 µkat/l (0.25-1.67) | GMT 0.99 µkat/l (up to 1.77) |
| CK 2.4 µkat/l (0.42-2.86) | bilirubin 12 µmol/l (5.1-17) |

# Urine laboratory tests

- glucose +++
- bacteria
- Leu ++, Ery +
- cultivation: E. coli $10^5$ / ml
- proteinuria: 0.66 g/l ~ 0.86 g/24 hod

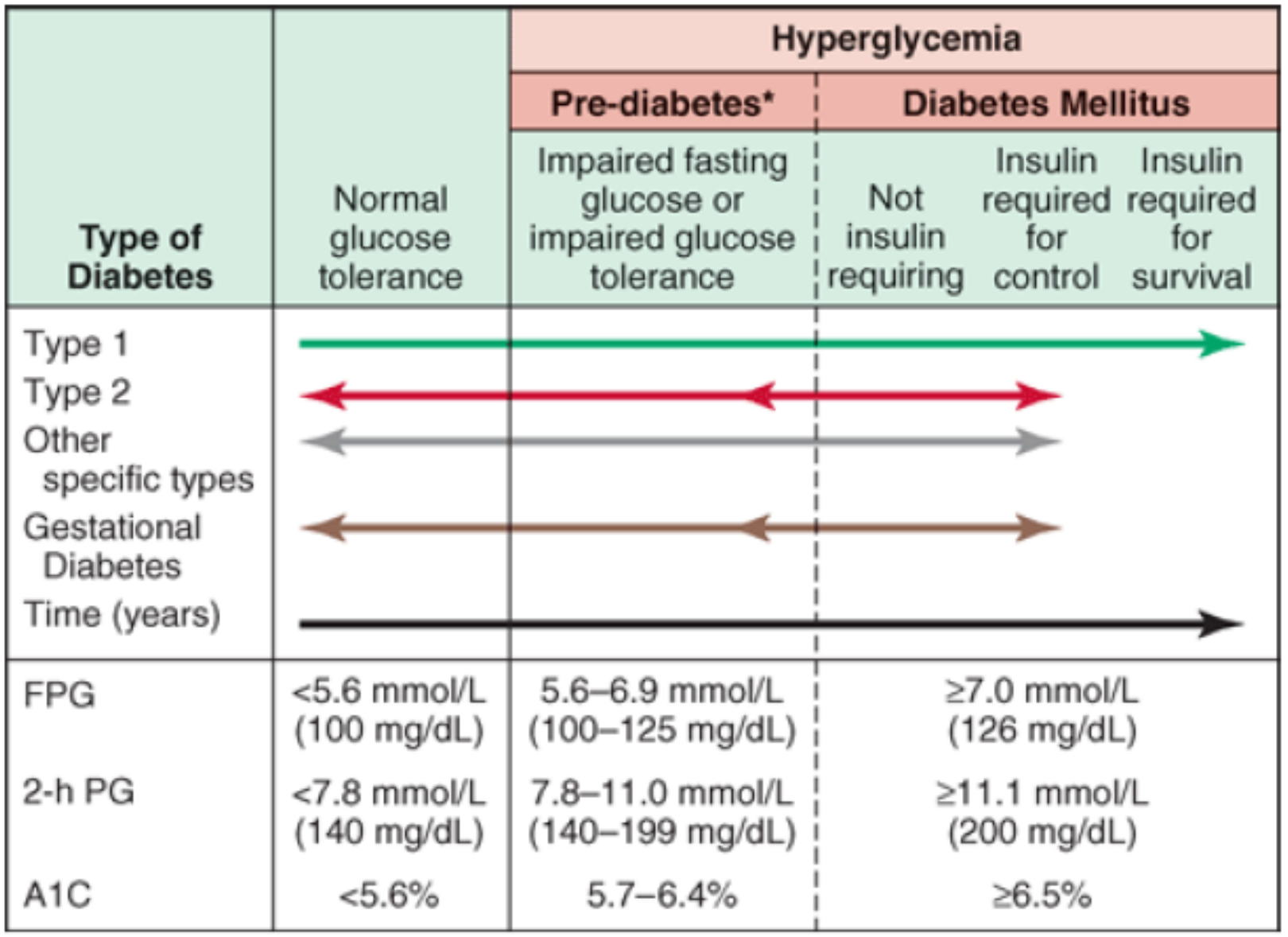
# Diabetologic evaluation

- glycemia:
  - at admission: 25.4 mmol/L (3.9-5.6 mmol/L)
- glycosuria:
  - at admission: 55 mmol/L

Diabetes mellitus ?

Diagnostic criteria?

# Etiopathogenic classification of major glucose tolerance disorders



# Diagnostic Criteria of DM

- Casual plasma glucose level $\geq$ 11.1 mmol/L (200 mg/dL)
- Fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dL)
- oGTT with 75 g of glucose p.o.: Two hour plasma glucose level $\geq$ 11.1 mmol/L (200 mg/dL)

Casual = any time of the day w/o regard to time since last meal

Adapted from American Diabetic Association: Diabetes Care 22 (Suppl. 1) 5-S19, 1999

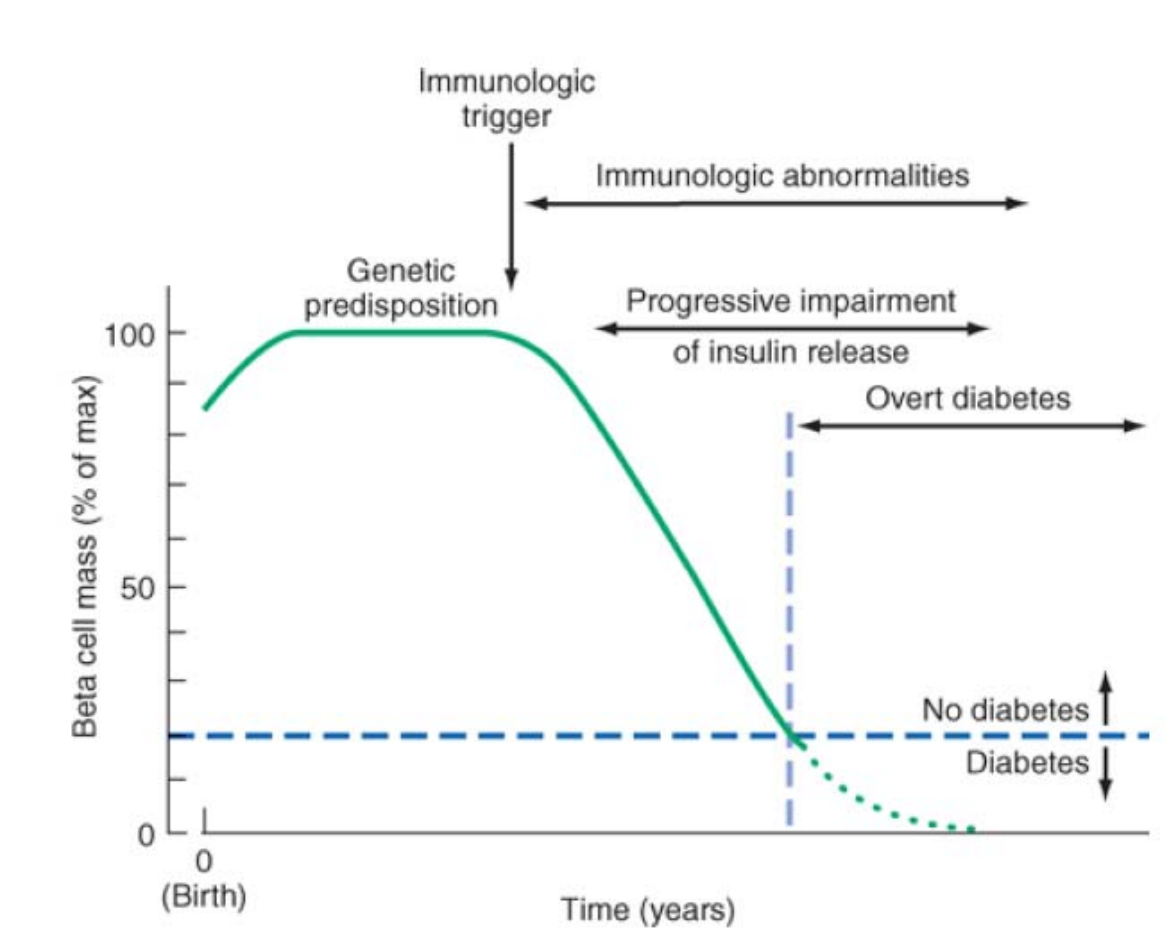
# Type 1 diabetes mellitus

Characterized by absolute insulin deficiency.

- Type 1A
  - cellular-mediated autoimmune destruction of beta cells of the pancreas
- Type 1B
  - Idiopathic form of type 1 diabetes without evidence of autoimmunity or HLA association

- Amylin
  - co-secreted with insulin in response to meals, is also completely deficient in persons with type 1 diabetes mellitus.
  - glucoregulatory effects that complement those of insulin in postprandial glucose regulation

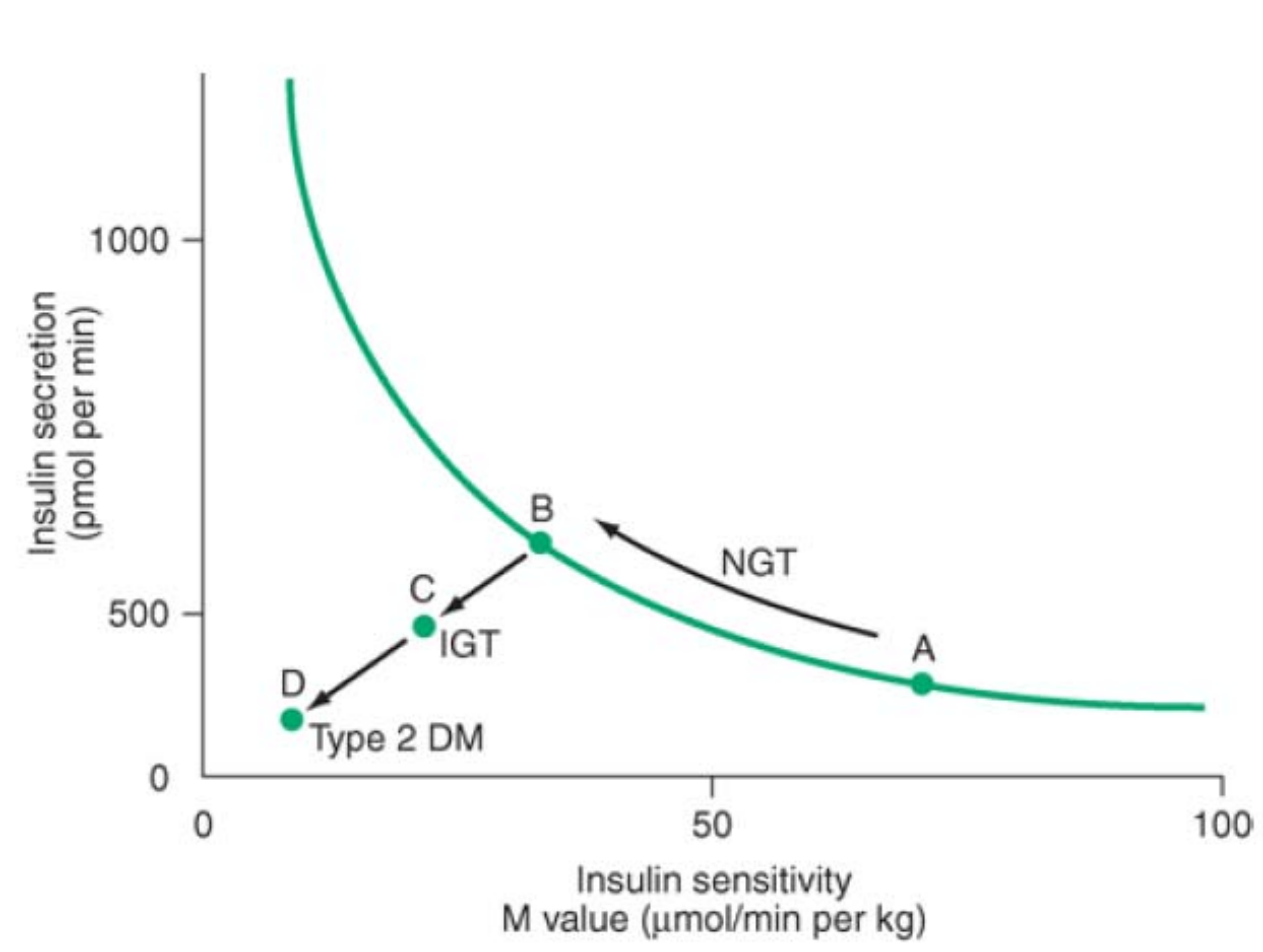
# Model for development of type 1 diabetes



# Type 2 diabetes mellitus

- Relative insulin deficiency
- Results from a defect in insulin secretion and an impairment of insulin action
- Genetic input is much stronger in type 2 diabetes than in the type 1 form
- Impaired glucose tolerance is a transitional state from normoglycemia to frank diabetes
- Development of glucose intolerance or diabetes is initiated by insulin resistance and worsened by the compensatory hyperinsulinemia

# Metabolic changes during the development of type 2 diabetes mellitus




Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

# Diabetologic evaluation

- glycemia:
  - at admission: 25.4 mmol/L (3.9-5.6 mmol/L)
- glycosuria:
  - at admission: 55 mmol/L

**Diabetes mellitus**

- Acute or chronic condition?
- Type I or Type II?

# Diabetologic evaluation

- Glycated hemoglobin (HbA1c):
  - 7.4 % (normal 3 - 4.7 %)
  - glycohemoglobin measurement reflects average glycemic control over 3-4 months
  - For DM patients:
    - The International Diabetes Federation and American College of Endocrinology recommend HbA1c values below 6.5%,
    - American Diabetes Association recommends that the HbA1c be below 7.0%

# Diabetologic evaluation

- Glycated proteins:
  - Fructosamine 2.5 mmol/L
  - Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins, predominantly albumin
  - Normal values vary in relation to the serum albumin concentration and are 200-285 µmol/L, when the serum albumin concentration level is 50 g/L
  - level of blood glucose control over the past 2-3 weeks
  - HbA1c = 0.017 X fructosamine level (µmol/L) + 1.61

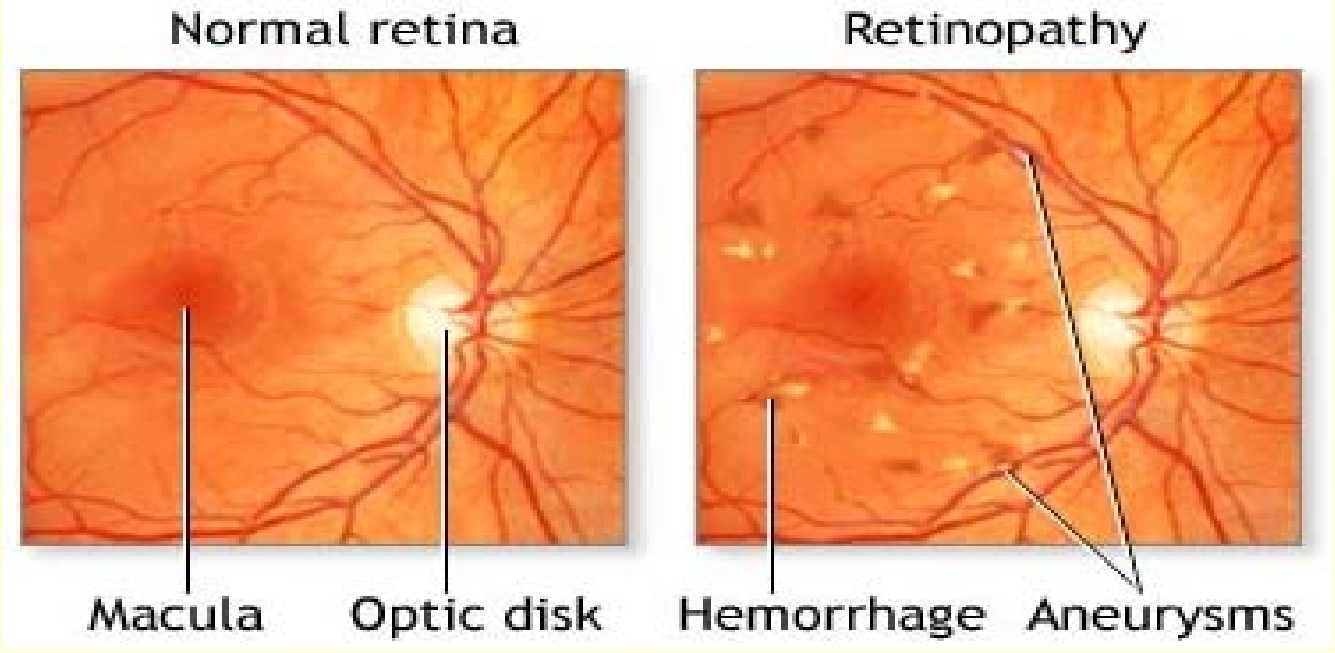
# Complications of DM ?

# What DM complications are present?

- Diabetic retinopathy
  - suggest microangiopathy in other tissues

# Imaging methods

- *Eye examination: Dilated fundus examination*
  - diabetic retinopathy



# What DM complications are present?

- Diabetic retinopathy
  - suggest microangiopathy in other tissues
- Glomerulosclerosis (renal mikroangiopathy)
  - proteinuria (can be also caused by urinary infection)
  - BUN and creatinin levels are borderline (can be also caused by renal defect ond/or dehydratation caused by polyuria)

# What DM complications are present?

- Defect of lipid metabolism
  - often associated with DM especially when in combination with  obesity (metabolic sy)

# Lipidologic evaluations

- Cholesterol **7.2** mmol/l (3.1- 5.2)
- HDL-cholesterol **0.8** mmol/l (1.1-1.4)
- LDL-cholesterol **5.4** mmol/l (2.2 - 4.5)
- Triglycerides **2.7** mmol/l (0.68 – 1.69)

# What DM complications are present?

- Defect of lipid metabolism
  - often associated with DM especially when in combination with  obesity (metabolic sy)
- Erythrasma
  - is present more frequently in patients with DM (?)

# Clinical diagnosis?

- Diabetes mellitus (DM) poorly controlled:
  - hyperglycemia
  - glykosuria
  - high glycation products
  - diabetic retinopathy
  - Proteinuria (bacteriuria or diabetic nephropathy?)
  - Combined hyperlipidemia (hypercholesterolemia with low HDL a high LDL cholesterol and hypertriglyceridemia)

# Other complications

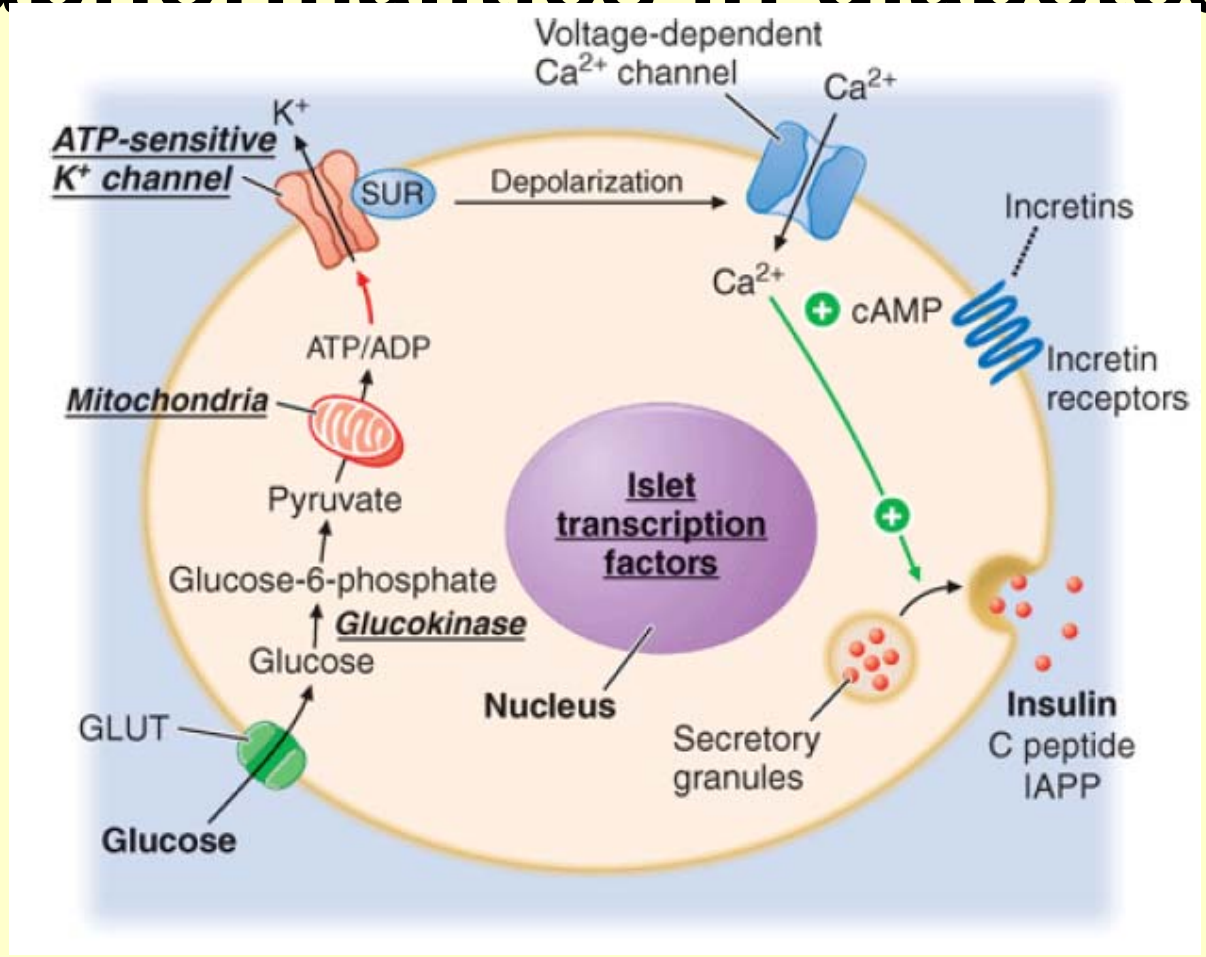
- *Chest X-rays*:
  - normal
- *Abdominal ultrasound*:
  - liver is of normal size
  - **increased echogenity** of liver tissue
  - pancreas cannot be evaluated
  - kidney and spleen w/o patological findings

# What type of DM is present? Diabetologic evaluation

- Immunoreactive insulin 32 µU/mL (normal < 20 µU/mL)
- C peptide 1.3 nmol/L (normal 0.3-0.9 nmol/L)

- DM type 2 associated with insulinoresistance

# Mechanisms of glucose-stimulated insulin secretion and abnormalities in diabetes

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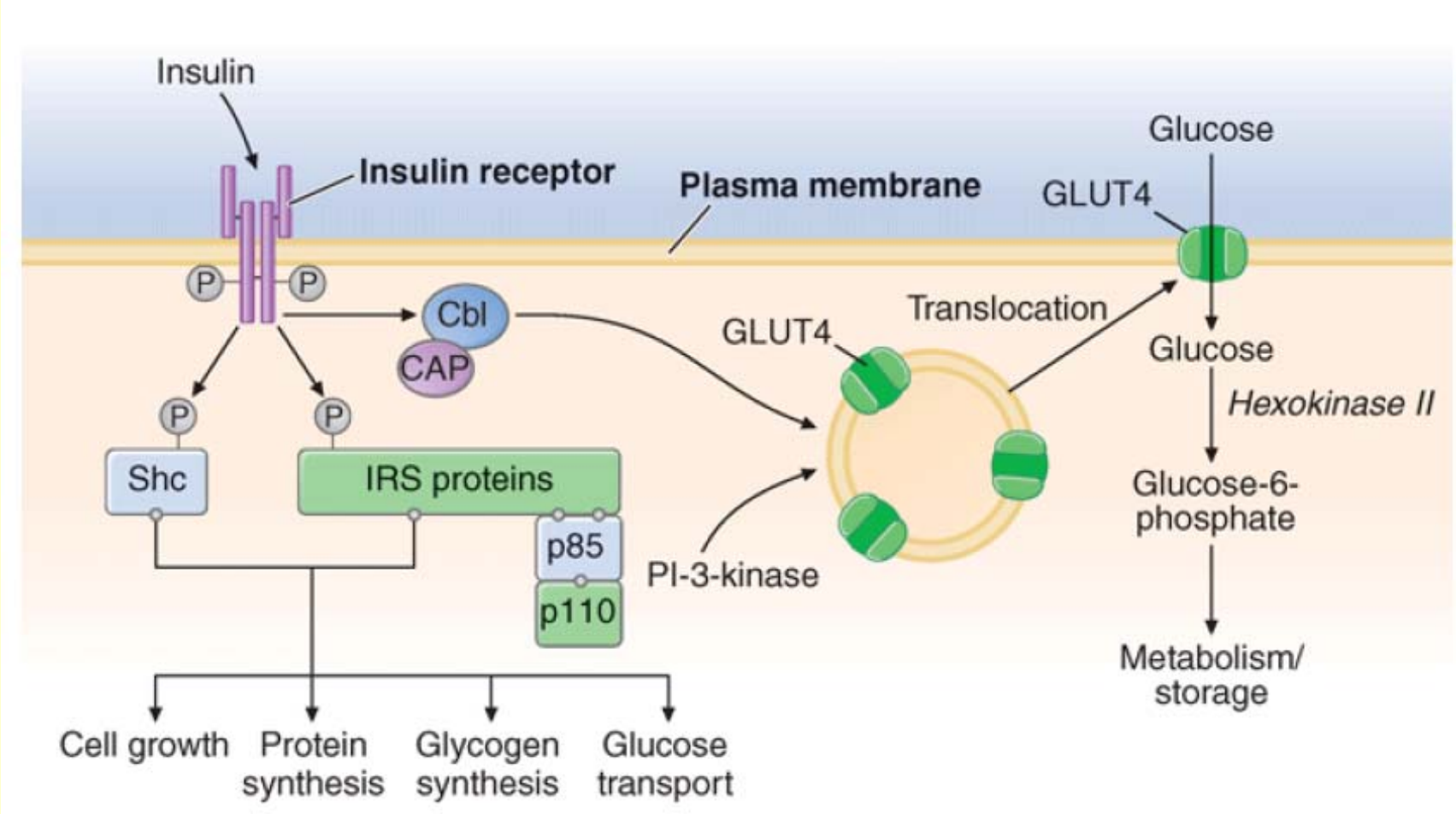
# Insulin signal transduction pathway in skeletal muscle

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# Characteristics of the Major Clinical Types of DM

| Characteristic | Type I DM (Insulin-Dependent DM, Juvenile-Onset Diabetes) | Type II DM (Non–Insulin-Dependent DM) |
|---|---|---|
| Age at onset | Most commonly < 30 yr | Most commonly > 30 yr |
| Associated obesity | No | Very common |
| Propensity to ketoacidosis requiring insulin treatment for its control | Yes | No |
| Endogenous insulin secretion | Extremely low to undetectable plasma insulin and C-peptide levels | Significant but variable levels of insulin secretion that are low relative to plasma glucose levels and accompanied by insulin resistance |
| Islet cell antibodies at diagnosis | Yes | No |
| Islet pathology | Insulitis, selective loss of most β cells | Smaller, normal-appearing islets; amyloid (amylin) deposition is common |
| Associated risks for retinopathy, nephropathy, neuropathy, and atherosclerotic coronary and peripheral vascular disease in most Western populations | Yes | Yes |

# Patients symptoms

(polyuria, weight loss, dysuria)

- Polyuria
  - is caused by osmotic diuresis which is associated with glucosuria
- Weight loss
  - Insulinoresistance cause defective utilization of nutrients
  - Dehydration
- Dysuria
  - is caused by urinary infection often associated with DM (glycosuria and immunity defects)

# Interpret hyperuricemia?

## uric acid 458 µmol/l (200–420)

- Causes of hyperuricemia
  - **decreased excretion (underexcreation)** of uric acid
    - kidney disease, certain drugs (diuretics, salicylates, cytotoxic agents), and competition for excretion between uric acid and other molecules
  - increased production of uric acid
    - high levels of purine in the diet (adenine, hypoxantine) and increased purine metabolism
  - mixed type
    - high levels of alcohol and/or fructose in the diet and starvation

# Uric acid underexcretion

- Decreased glomerular filtration
  - can contribute to the hyperuricemia of renal insufficiency
- Decreased tubular secretion
  - in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis)
  - organic acids that accumulate in these conditions compete with urate for tubular secretion
- Enhanced tubular reabsorption
  - distal to the site of secretion is the mechanism thought to be responsible for diuretic therapy and diabetes insipidus

# Overproduction of uric acid

- exogenous:
  - diet rich in purines
- endogenous:
  - increased purine nucleotide breakdown
    - rapid cell proliferation and turnover (e.g. blast crisis of leukemia)
    - cell death (rhabdomyolysis, cytotoxic therapy
  - enzymatic defects
    - complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) (Lesch-Nyhan syndrome,
    - partial deficiency of HGPRT (Kelley-Seegmiller syndrome)
    - increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity
    - Glycogenoses types III, IV, and VII can result in hyperuricemia from excessive degradation of skeletal muscle ATP

# Combined mechanisms of hyperuricemia

- alcohol consumption
  - accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion
  - Enzymatic defects
    - glycogenoses type I and aldolase-B deficiency

# Increased liver enzyme plasma activity and increased echogenity of liver tissue ?

- suggest steatosis
  - may be caused by diabetes and/or obesity and/or alcohol consumption

# What disease/s is patient in increased risk of?

- Risk of progression of typical diabetic complications:
  - retinopathy
  - nefropathy
  - accelerated atherosclerosis

# What is insulin resistance?

- Decreased sensitivity of muscles, liver, and adipose tissue to insulin because of
  - low receptor levels
  - low affinity of insulin receptors (mutations)
  - postreceptor defect

- Various disease states make the body tissues resistant to the actions of insulin.
  - infection (mediated by the cytokine TNF$\alpha$)
  - acidosis
  - drugs (e.g., glucocorticoids)
  - obesity? (adipokines-the cytokines produced by adipose tissue)

# Insulin

- binds and acts through
  - insulin receptor (beta subunity is a tyrosine kinase)
  - insulinlike growth factor–1 (IGF-1) receptor

# Insulin resistance

- Insulin resistance in fat cells
  - elevated hydrolysis of stored triglycerides result in elevated free fatty acids in the blood plasma
- Insulin resistance in muscle cells
  - reduces glucose uptake (i.e. local storage of glucose as glycogen)
- Insulin resistance in liver cells
  - results in impaired glycogen synthesis and a failure to suppress glucose production (i.e. increased liver glucose production)

# (Dys)Metabolic syndrome / syndrome X

- Insulin resistance (type 2 diabetes or glucose intolerance)
- hyperinsulinemia
- obesity
- hypertension
- dyslipidemia

# Etiopathogenesis of type II DM

- genetic predispositions
  - about 15-20% of population
- environmental factors
  - diet, obesity, stress, age, physical activity

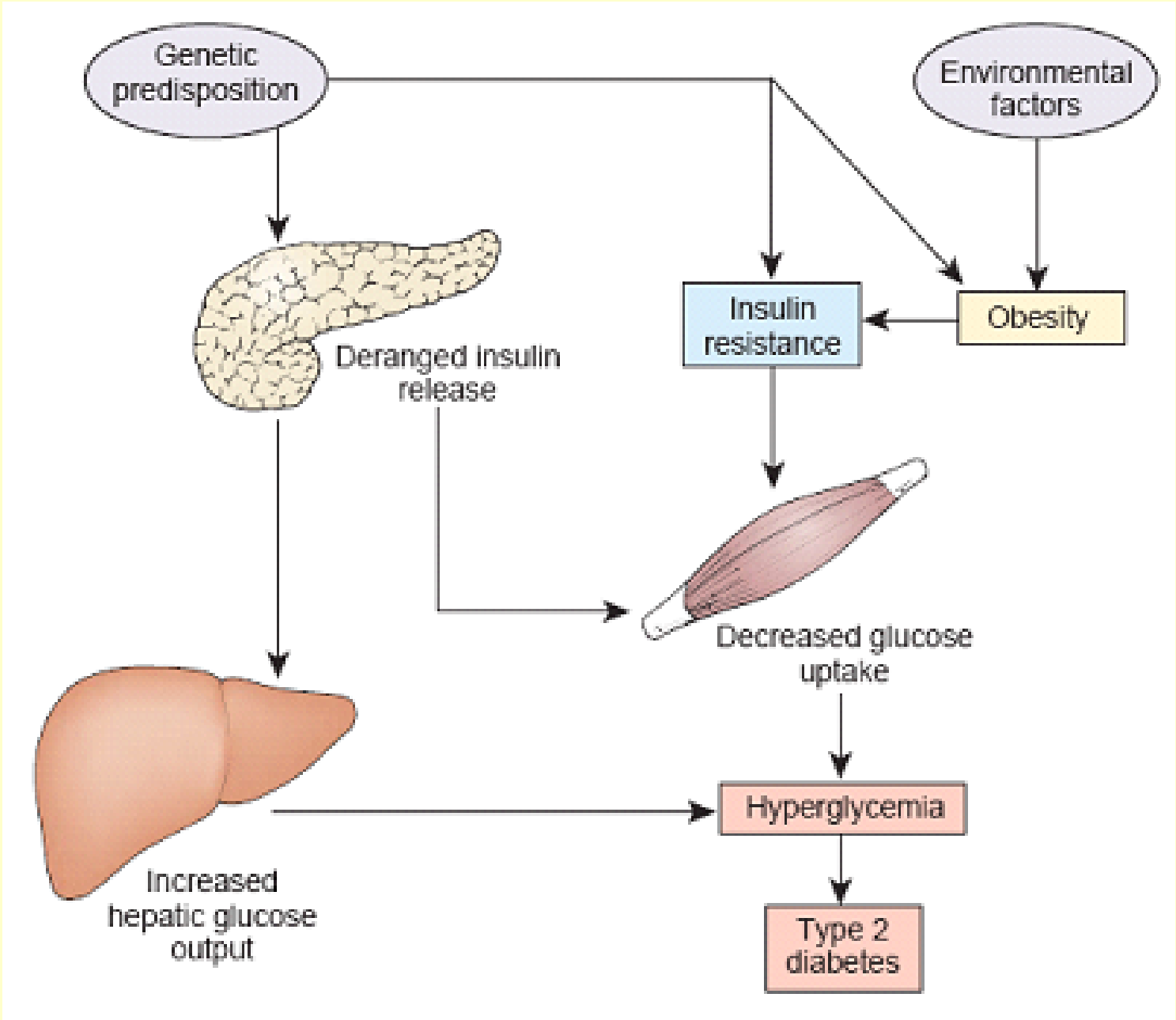
# Metabolic syndrome??

- Insulin resistance as unifying cause is uncertain
- Cardiovascular risk value is variable and dependent on specific risk factors present
- Treatment of syndrome is no different from treatment for each of its components
- Medical value of diagnosing the syndrome is unclear

# Type II DM

- Poorly controlled:
  - hyperglycemia
  - glykosuria
  - high glycation products
- Microangiopathy (retinopathy, ?glomerulonephritis?)
- Metabolic disease
  - Hyperlipidemia

# Pathogenesis of DM type II



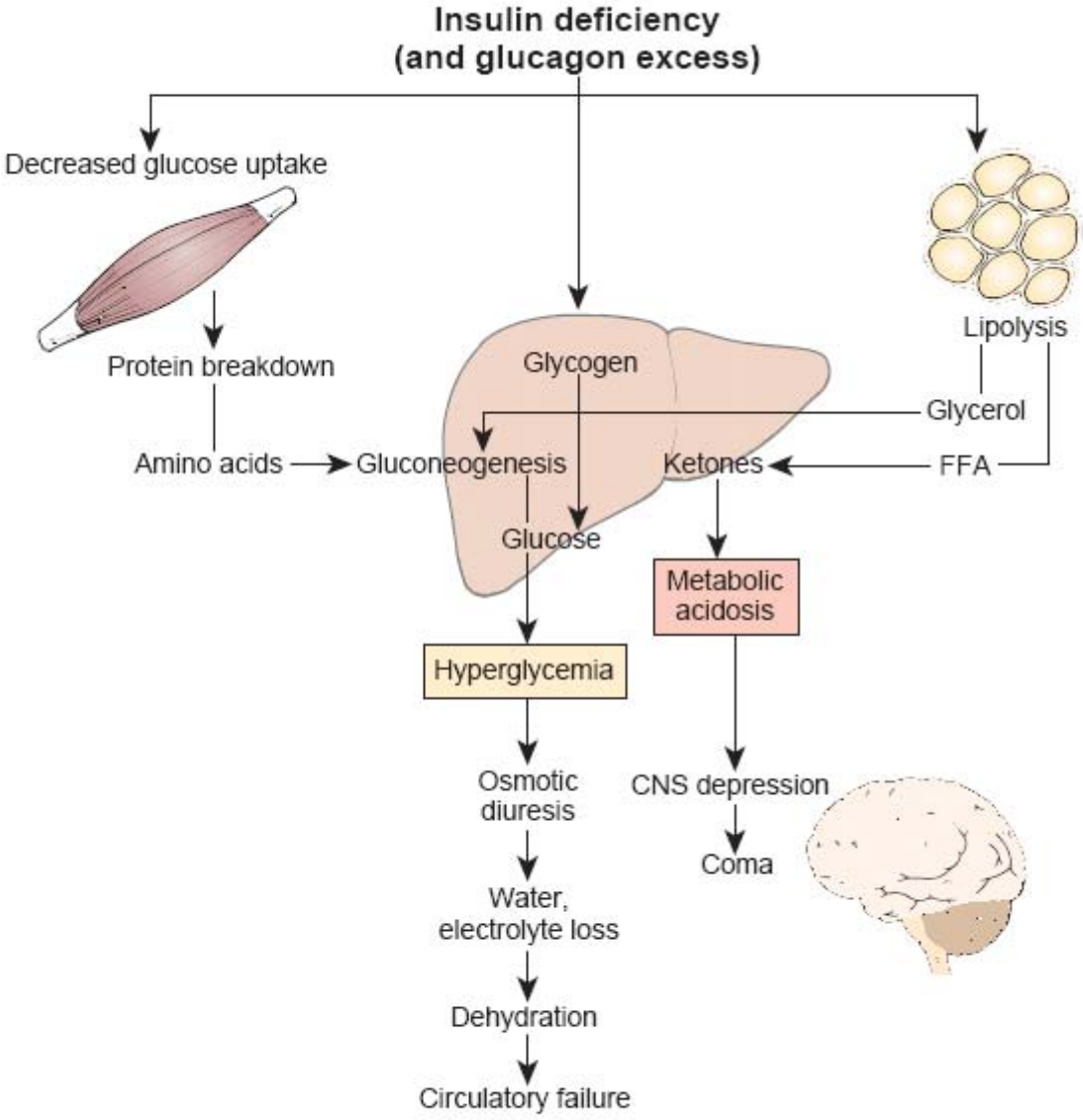



**FIGURE 43-10** Mechanisms of diabetic ketoacidosis. Diabetic ketoacidosis is associated with very low insulin levels and extremely high levels of glucagon, catecholamines, and other counterregulatory hormones. Increased levels of glucagon and the catecholamines (*red arrows*) lead to mobilization of substrates (*blue arrows*) for gluconeogenesis and ketogenesis by the liver (*green arrows*). Gluconeogenesis in excess of that needed to supply glucose for the brain and other glucose-dependent tissues produces a rise in blood glucose levels. Mobilization of free fatty acids (FFA) from triglyceride stores in adipose tissue leads to accelerated ketone production and ketosis.

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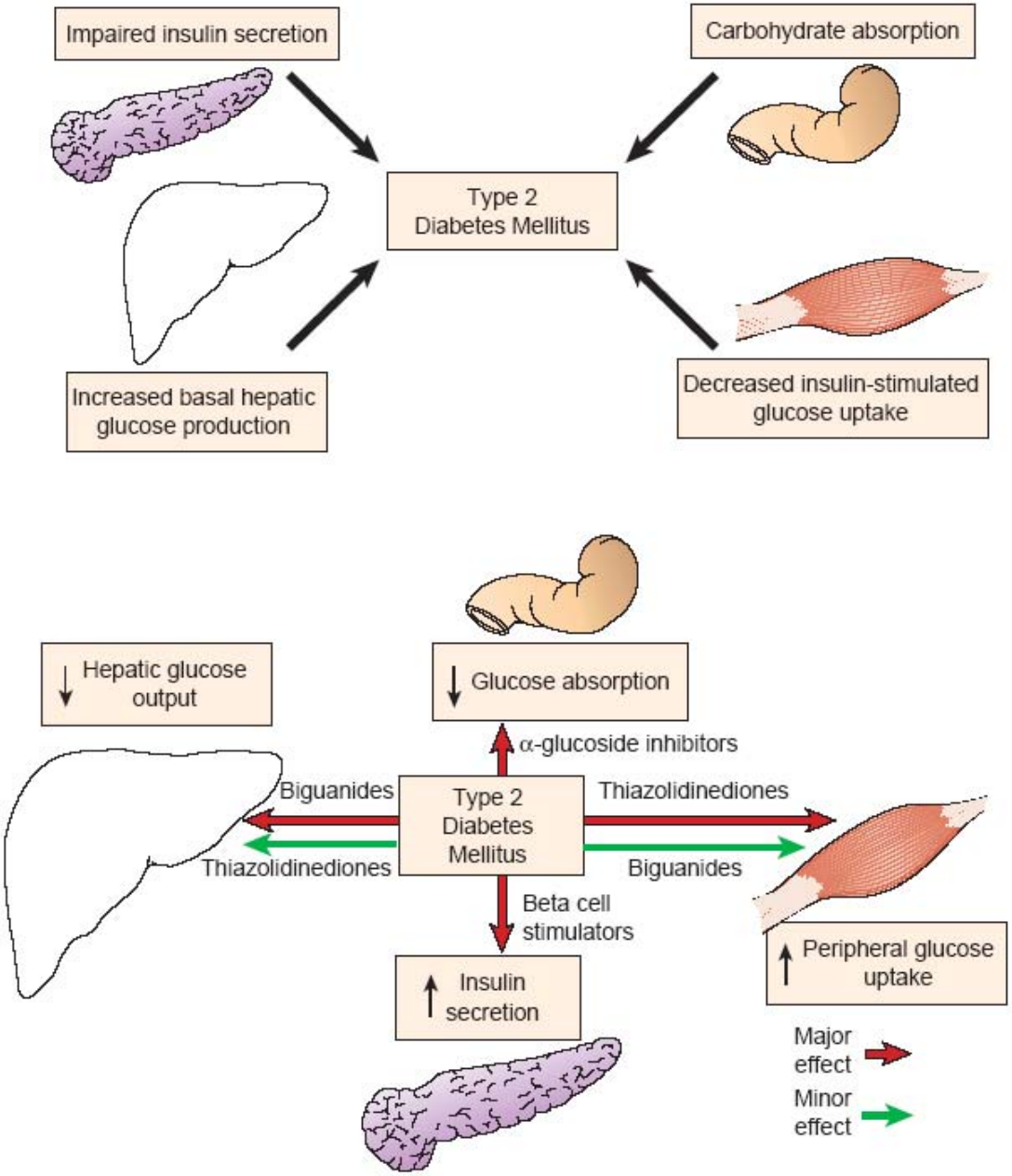


**FIGURE 43-8** (**Top**) Mechanisms of elevated blood glucose in type 2 diabetes. (**Bottom**) Action sites of oral hypoglycemic agents and mechanisms of lowering blood glucose in type 2 diabetes mellitus.