MINISTRY OF HEALTH OF THE REPUBLIC
OF BELARUS
ESTABLISHMENT OF EDUCATION
VITEBSK STATE MEDICAL UNIVERSITY

V.Yanholenka

ENDOCRINOLOGY

Vitebsk
Publishing house VSMU
2011

УДК: 616.43(075)
ББК 54.151 я7
Я60

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Я60 Эндокринология. пособие/Янголенко В.В. -Витебск: ВГМУ, 2011-221 с.;

ISBN 978-985-466-320-3

„Пособие по эндокринологии" содержит подробное изложение курса эндокринологии, соответствующего программе обучения студентов 4 и 6 курсов лечебного факультета медицинских ВУЗов. Учебник следует междисциплинарному подходу и содержит аналитический обзор современных представлений о структуре, функции, методах диагностики и лечения наиболее распространенных заболеваний эндокринных желез. Книга учитывает базовые материалы и программные требования квалификационных экзаменов, требующихся для верификации медицинского диплома за рубежом.

Утверждено и рекомендовано к изданию: Центральным учебно-научно-методическим Советом непрерывного медицинского и фармацевтического образования Витебского государственного медицинского университета 25.02. 09 , протокол № 2 для внутреннего пользования.

УДК: 616.43(075)
ББК 54.151я7
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ISBN 978-985-466-320-3

CONTENS

List of Abbreviations Used:

ABP – androgen binding protein
ADA – American Diabetes Association
AIA – antiiflamatory agents
ADH =AVP – antidiuretic hormone
ALT – alanine amino-transferase
ACTH – adrenocorticotropin hormone
AM – morning
AMI – acute myocardial infarction
ANA – antinuclear antibody
BP – blood pressure
BMI – body mass index
Ca – calcium
CNS – central nervous system
CRF – corticotrophin releasing factor
CT – computerized tomography
CSII – continuous subcutneous infusion
CVD – cardiovascular disorder
D - dopamine
GDM – gestational diabetes
GDT –gastrodigestive tract
GLP-1 – glucagon-like peptide -1
GLUT – glucose transporter
GnRF – gonadotrophin releasing factor
DKA – diabetic ketoacidosis
DM – diabetes mellitus
DCCT – The Diabetes Control and Complications Trial
ESRD – end-stage renal disease
ECG – electrocardiogram
FPG – fasting plasma glucose
ER – endoplasmic reticulum
GAD – glutamic acid decarboxylase
GIP – glucose-dependent insulinotropic peptide
GH – growth hormone
Gm – gram
HbA1c – glycozylated hemoglobin
HDL –high-density lipoproteins
Hg – mercury
hr's - hour
IAPP – islet amyloid polypeptide
ICA – ilet cell antibodies
ICP – intracranial pressure

IGT- impaired glucose tolerance
IGH -1 - inhibitor growth hormone -1
IFG - impaired fasting glucose
IRI –immunoreactive insulin
IRG –immunoreactive glucagons
IP3 – inositol phosphate 3
IV – intravenous
K – potassium
L – liter
mL – milliliter
mm – millimeter
LADA – latent autoimmune diabetes of adulthood
Lb = pounds (1kg = 2,2 lb)
LDL – low -density lipoproteins
LH – leutenizing hormone
M - male
MEN – multiple endocrine neoplasia
MODY – maturity-onset diabetes of the young
MRI – magnetic resonance imaging
Na – sodium
NPH – neutral protamine Hagedorn
OGTT – oral glucose tolerance test
PAI-1 - plasminogen activator inhibitor type 1
PCOD – polycystic ovarian disease
PTH - parathhormone
PRL – prolactin
PPG – postprandial glacemia
PM - afternoon
PVD - pulmonary vascular disease
TSI – thyroid stimulating immunoglobulin
TSAb –thyroid stimulating antibodies
Tg – triglycerides
T4 – thyroxine level
T3 – treiodothyronine level
TB – tuberculosis
TSI – thyroid stimulating immunoglobulin
TSab - thyroid stimulating antibodies
TPH – thyrotrophin realizing hormone
TSH – thyroid-stimulating hormone
TSH –R - thyroid-stimulating hormone receptor
TZDs –thiazolidindiones
F- female
FFA – free fatty acids

FNA – fine needle aspiration
FSH – follicle stimulating hormone
URTI – urgent respiratory tract infection
UKPDS – The United Kingdom Prospective Diabetes Study
TFT – thyroid function test
VLDL – very-low density lipoprotein
WHR – waist:hip circumference ratio
WHO – World Helth Organisation
URTI – upper respiratory tract infection
V - volume
u - units

Chapter I. Disorders of Glucose Metabolism.

Diabetes Mellitus (DM).

General consideration

Glucose is a simple sugar found in food. Glucose is an essential nutrient that provides energy for the proper functioning of the body cells. Carbohydrates are broken down in the small intestine and the glucose is digested food is then absorbed by the intestinal cells into the bloodstream, and is carried by the bloodstream to all the cells in the body where it is utilized. Glucose cannot enter the cells alone and needs insulin to aid in its transport into the cells. In addition to helping glucose enter the cells, insulin is also important in tightly regulating the level of glucose in the blood. After a meal, the blood glucose level rises. In response to the increased glucose level, the pancreas normally releases more insulin into the bloodstream to help glucose enter the cells and lower blood glucose levels after a meal. When the blood glucose levels are lowered, the insulin release from the pancreas is turned down. It is important to note that even in the fasting state there is a low steady release of insulin than fluctuates a bit and helps to maintain a steady blood glucose level during fasting. Without insulin, the cells become starved of glucose energy despite the presence of abundant glucose in bloodstream. The cells' inability to utilize glucose gives rise to the ironic situation of "starvation in the midst of plenty". The abundant, utilized glucose is wastefully excreted in the urine.

There are two types of mutually antagonistic metabolic hormones affecting blood glucose levels:

- catabolic hormones (such as glucagon, growth hormone,catecholamines), which increase blood glucose - termed contrinsular hormones
- and one anabolic hormone (insulin), which decreases blood glucose

Anatomy of the pancreatic gland.

The pancreas located behind the stomach. It is deep-seated organ in the abdomen. Weight 70-80g, 15x7x3 cm. The pancreas consists of three parts: head (caput), body (corpus), and tail (cauda). The external secretory apparatus occupies the greater part of the pancreatic parenchyma and secretes different component of the pancreatic juice. The pancreas is innervated by branches of the vagus and sympathetic nerves, and is supplied with blood by the pancreatic-duodenal artery and by branches of the splenic artery.

Endocrine tissue making up **the Langerhans islets** (contains approximately 1 -1, 5 million islets).

Anatono-Physiological Data

Langerhars islets cells and effects of hormons

- **A-cell: produces glucagons**(12 -18 all of its, located nearer to the periphery of the island)

Glucagon effects

- antagonist of insulin
- stimulate glycogenolysis
- lipolysis
- gluconeogenesis
- biosynthesis glucose from amino acids

Slow down

- glycogen synthesis

- **B-cell: produces insulin** (60 -70% all of its, located nearer to the centre of the island) and **amylin**, which similar to insulin

Insulin is a peptide hormone composed of 51 amino acid residues and has a molecular weight of 5808 Da. Iinsulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes, known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications of proinsulin remove the center portion of the molecule, or C-peptide, from the C- and N- terminal ends of the proinsulin. The remaining polypeptides (51 amino acids in total), the B- and A- chains, are bound together by disulfide bonds. Both C-peptide and mature insulin are biologically active. Insulin binds to its receptor which in turn starts many protein activation cascades. These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose glycogen synthesis ,glycolysis and fatty acid synthesis .

Insulin effects

Stimulate

- entering glucose the cells
- reabsorbtion H2O, Na+ in the kidney
- regulation the level of glucose in the blood
- lypogenesis
- glycogenesis
- DNA replication and protein synthesis and via control of amino acid uptake.
- potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption

- arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.

Slow down

- Glyconeogenesis
- Ketogenesis
- Glycogenolysis
- Lipolisis
- Proteolisis

Amylin, or Islet Amyloid Polypeptide (IAPP): is a 37-residue peptide hormone secreted by pancreatic B-cells at the same time as insulin (in a roughly 100:1 ratio). Complete function may not yet be known. , and therein

Amylin effects

- glucose control during the postprandial period
- reduce the total insulin demand
- to slow gastric emptying
- promote satiety
- inhibit secretion of glucagon during hyperglycemia

- **D-cell: produces somatostatin** (2-8% all of its, regulator of insulin secretion)

Mechanism for release of insulin and regulation

Beta cells in the islets of Langerhans are sensitive to variations in blood glucose levels through the following mechanism (see figure to the right):

- Glucose enters the B-cells through the **glucose transporter GLUT2**
- Glucose goes into the glycolysis and the respiratory cycle where multiple high-energy ATP molecules are produced by oxidation
- Dependent on ATP levels, and hence blood glucose levels, the ATP-controlled potassium channels (K^+) close and the cell membranes depolarize
- On depolarisation, voltage controlled calcium channels (Ca^{2+}) open and calcium flows into the cells
- An increased calcium level causes activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate into inositol 1,4,5-triphosphate and diacylglycerol.
- Inositol 1,4,5-triphosphate (IP3) binds to receptor proteins in the membrane of endoplasmic reticulum (ER). This allows the release of Ca^{2+} from the ER via IP3 gated channels, and further raises the cell concentration of calcium.

- Significantly increased amounts of calcium in the cells causes release of previously synthesised insulin, which has been stored in secretory vesicles

This is the main mechanism for release of insulin and regulation of insulin synthesis. In addition some insulin synthesis and release takes place generally at food intake, not just glucose or carbohydrate intake, and the B-cells are also somewhat influenced by the autonomic nervous system. The signalling mechanisms controlling this are not fully understood.

Other substances known which stimulate insulin release are acetylcholine, released from vagus nerve endings (parasympathetic nervous system), cholecystokinin, released by enteroendocrine cells of intestinal mucosa and glucose-dependent insulinotropic peptide (GIP). The first of these acts similarly to glucose through phospholipase C, while the last acts through the mechanism of adenylate cyclase.

The sympathetic nervous system (via α_2-adrenergic agonists such as norepinephrine) inhibits the release of insulin.

When the glucose level comes down to the usual physiologic value, insulin release from the B- cells slows or stops. If blood glucose levels drop lower than this, especially to dangerously low levels, release of hyperglycemic hormones (most prominently glucagon from Islet of Langerhans' A- cells) forces release of glucose into the blood from cellular stores, primarily liver cell stores of glycogen. By increasing blood glucose, the hyperglycemic hormones correct life-threatening hypoglycemia. Release of insulin is strongly inhibited by the stress hormone norepinephrine (noradrenaline), which leads to increased blood glucose levels during stress.

Classification of the diseases of the islet apparatus of the pancreas

- **Diabetes mellitus** –absence or insufficient production of insulin
- **Insulinoma**- hypersecretion of insulin by hormon active tumor
- **Glucagonoma**- hypersecretion of glucagon by hormon active tumor
- **Terminology and classification of the Disorders of Glucose metabolism**

Difenition

Diabetes mellitus is a common refer accumulated a group of the disorders of glucose metabolism which differ by etiology, pathogenesis and complications but with one common manifestation: hyperglycemia . Chronic hyperglycemia causes damage to the eyes, kidneys, nerves, and blood vessels.

- Is a group of metabolic diseases characterized by fasting hyperglycemia
- Which result from defects in insulin secretion, or action, or both
- Is chronic diseases

- It lasts a lifetime
- Is characterized as a consequence by disorders of all kinds of metabolism
- Is characterized as a micro-and macro veselpathy and neuropathy
- Patients with DM1 was1994 – 11,5millions and by the year 2010 it will reach 23,7 millions
- Patients with DM2 was 1994 – 99 millions and by the year 2010 it will reach 216 millions
- over time, DM lead to blindness, kidney failure, nerve damage
- 3% of the patients have DM1 and 97% have DM2

Two variants of disorders of Glucose metabolism

1. **Diabetes mellitus.**
2. **Pre-diabetes or Other Categories of Hyperglycemia** .

In 1997, the ADA issued new diagnostic and classification criteria ; in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (IFG). This etiologic classification indentifies four types of a diabetes mellitus : type 1, type 2, "other specific types" and gestational diabetes. Arabic numerals used to minimize the occasional confusion of type "II" as the number "11". Each of the types of DM identified extends across a clinical continuum of hyperglycemia and insulin requirements.

Classification of Diabetes Mellitus (DM). ADA, 2003

1. Type 1 Diabetes (results from ß-cell destruction, usually leading to absolute insulin deficiency):

A - idiopathic

B - auto-immune.

2. Type 2 Diabetes (results from a progressive insulin secretory defect on the background of insulin resistance).

3. Other Specific types of Diabetes Mellitus

Genetic defects of pancreatic B cell function:

MODY1 (HNF-4alfa); rare

MODY2 (glucokinase); less rare

MODY3 (HNF-1 alfa); accounts for two-thirds of all MODY

MODY4 (IPF -1); very rare

MODY5 (HNF-1beta): very rare

MODY 6 (neuroD1); very rare

Mitochondrial DNA

Genetic defects in insulin action

Type A insulin resistance

Leprechaunism

Rabson-Mendenhall syndrome
Lipoatrophic diabetes
Diseases of the exocrine pancreas
Endocrinopathies
Drug- or chemical-induced diabetes
Other genetic syndromes (Down's, Klinefelter's, Turner's, others) sometimes associated with diabetes.

4. Gestational diabetes (GDM): diagnosed during pregnancy.

1.Type 1 Diabetes Mellitus:

- 3% of general DM
- formerly called type I, insulin-dependent diabetes mellitus, juvenile diabetes.

Type 1 DM is due to the pancreatic islet B-cell destruction predominantly by an autoimmune process, and these patients are prone to ketoacidosis. This form of diabetes is immune-mediated in over 90% of case and idiopathic in less than 10%.

Epidemiology DM 1 type

Type 1 DM incidence tends to increase to the north from equator – a northern-southern latitude gradient phenomenon. Almost simultaneously the seasonal fluctuations were revealed, manifesting with the grouse of DM1 incidence in a cold season in different countries of the world sharp peaks of DM1 new cases not meeting to natural variability of the incidence are registered periodically.

Etiology and Pathogenesis of Immune-mediated type 1 diabetes mellitus

Genetics

- associated with HLA II classis: DR3, DR4, DQ allelea
- concordance in monozygotic twins (40%)
- genes located in the short shoulder of VI chromosomas which (*diabetigenic lokus)*. Nowadays known 10 diabetigenic loki.

Risk factors (diabetogenic factors) DM 1 type

- Personal history of autoimmune diseases increases likelihood of developing DM (e.g. Grave's disease, myasthenia gravis, Addison's disease, pernicious anemia)
- B - cytotropic viruses: coxsackie, parotitis, rubella, reovirus
- Toxins (alloxan, streptozotocin)
- Vaccination
- Dietary factors

Immune-mediated type 1 diabetes mellitus is a result from an infectious (mumps, coxsackie B4 virus) or toxic insult to persons whose immune system is genetically predisposed to develop a vigorous autoimmune response either againt altrered pancreatic B cell antigens or against molecules of the B cell resembling the viral protein (*molecular mimicry*). Most islet cell antibodies (ICA) are directed against glutamic acid decarboxylase (anti –GAD - marker of type 1 DM). This action released from *sensitized immunocytes*. Specific HLA immune response genes are believed to predispose patients to a destructive autoimmune response against their own cells (autoaggression) which is *mediated primarily by cytotoxic T cells.* Autoimmune destroyed B-cell is referring as **insilitis** is a complex multitude processes.

6 stages of pathogenesis DM type 1

DM type 1 appears when more than 90% of B-cells of pancreas are destroyed by an autoimmune process.

1. Genetic predisposition:

- About 95% of patient with DM type 1 have either HLA DR3 and /or DR4.
- genetics markers only;
- prolonged 1-2 months to 1-3 years;
- glucose metabolism normal.

2. Triggering/initiation of autoimmune processes:

- infection or toxic insult in neonatal life period:;
- very short time;
- clinically unrecognized.

3. Third step in the sequence is an inflammatory response in the pancreas called "insilitis". There is infiltration of the islets with activated T lymphocytes.

- ICA, anti –GAD present but glucose metabolism normal;
- prolonged 2-3 months to 2-3 years.

4. Active immunological processes:

- Involving both cellular and humoral components of immune system.
- Alteration of the surface of the B-cells such that it is no longer recognized as "self", but is seen by the immune system as a foreign cell or "nonself".
- Clinically – "latent diabetes".
- OGTT +.
- Clinical symptoms and sign absent.
- Prolonged 2-4 years.

5. Development of an immune response and progressive reduction of insulin secretion:

- Activated T lymphocytes present in the islets release cytokines (tumor necrosis factor @,interferon & and interleukin 1) which destroy B-cells. CD8+

cell-induced cytotoxicity and apoptosis are also involved. This results in an immune attack on B-cells, which resultant destruction of B-cells.

- clinic and laboratory manifested diabetes;
- B-cell mass diminishes progressive; A-cells remain intact.
- - Prolonged 2 months – 1,5 years.

6. Clinically manifested diabetes:

- Destruction > 95% B-cells;
- Occur during stress, infection or puberty
- During the early "honeymoon phase", they may not require insulin for control, but are still ketosis prone, need and most need insulin acutely and long time;
- Prolonged from 4 years for very long time;
- Long-term complication of DM.

Pathogenesis of DM typel - summary

1. Genetic predisposition.
2. Environmental event
3. Insulitis
4. Activation of autoimmunity
5. Immune attack on B-cells
6. Diabetes mellitus

CLINICS DM Type 1

An absolute deficiency of insulin results in accumulation of circulating glucose and fatty acids, with consequent hyperosmolality and hyperketonemia.

- **Polyuria** (abundant urination) is a consequence of osmotic diuresis secondary to sustained hyperglycemia. This results in a loss of glucose as well as free water and electrolytes in the urine.
- **Polydipsia** (thirst) is a consequence of the hyperosmolar state.
- **Dryness in the mouth.**
- **Weight loss and weakness** is due to depletion of water, glycogen,and triglycerides; thereafter, redused muscle mass occurs as amino acids are diverted to form glucose and ketone bodies.
- **Blurry vission** is a consequence of the hyperosmolar state when the lenses are exposed to hyperosmolar fluids.
- **Skin itching** is a consequence of ketoacidosis.

Ceneral Characterictic of DM Type 1

- Onset usually before age 30
- Acute or subacute onset
- Body habitus typically normal to wasted

- Genetics: associated with HLA DR3, DR4 and DQ alleles
- Absolute insulin deficiency
- Circulating Islet cell antibodies 50%-85%: IAA, ICA, GAD, IA2- IA2 B
- Prone to ketoacidosis
- Pharmacological therapy – insulin required

2. Type 2 Diabetes Mellitus:

- 97% of general DM
- formerly called non-insulin-dependent diabetes mellitus, type II or adult-onset.

Definition

Type 2 DM is the more prevalent form of relative insulin deficiency and results from insulin resistance. This represents a heterogeneous group comprising milder forms of diabetes that occur predominatly in adults but occasionally in juveniles.

Circulating insulin is sufficient to prevent ketoacidosis but is inadequate to prevent hyperglycemia in the face of increased needs owing to tissue insensitivity. In most cases of this type of DM, the cause is unknown. Two subgroups of patients are currently distinguished by the absence or presence of obesity.

Ethiology

Genetic marker is unknown. Likelyhood in all:
- monozygotic twins over 40 years of age
- gene on chromosome 2 encoding a cysteine protease *calpain-10*
- monogenes form (MODY, see below)
-polygenes form

Pathogenesis

- No HLA relationship has been iudentified, and autoimmune mechanism are not operative
- Genetics influence is much more powerfull in type 2 DM, in contrast to the situation with DM type 1
- A-cells population is increased
- Associated with increased hepatic prodaction of glucose, resistance to the action of insulin and impaired insulin secretion
- Insulin resistance may be due to any one of the three general causes: an abnormal insulin molecule, an excessive amout of circulating antagonists, and target defect.
- Defects in the receptors in the receptors present in target tissues is generally at the post-receptor level
- Reduced utilization of glucose by peripheral tissues results in postprandial hyperglycaemia

- In the early stages, glucose tolerance remains normal despite insulin resistance. This is due to compensatory increase in insulin secretion by B-cells. As insulin resistance and compensatory hyperinsulinemia progress, the B-cells become unable to sustain this hypercecretion.This results in impaired glucose tolerance and later frank DM. Ultimately, B-cell failure develops.
- Over-eating, especially when combined with obesity and underactivity, is asssosiated with the development of DM type 2.
- In women who are genetically predisposed, pregnancy may be associated with the development of hyperglycaemia. It may or may not disappear following pregnancy. Repeated pregnancies may increase the likelihood of developing permanent diabetes, particually in obese women.
- Deposition of amyloid in pancreatic islets which is accompanied by atrophy of islet epithelial cells

Risk factors (diabetogenic) of DM Type 2 and Etiology

- age
- Obesity, especially abdominal–visceral obesity; standardized tables of waist-to-hip ratio indicate that ratios of "greater then 0.9 in M and "greater then 0,8" in women
- Family history
- Sedentary lifestyle
- >BP
- Women, who have delivered large babies >4,1 kg, have had polyhydramnions, preeclampsia or unexplained fetal losses

Exogenous factors

Prevalence depends on:

- Age –increasing
- Residence (urban/rural) - urbanization increasing
- Obesity –increasing wordwide
- Food composition –high fat content –fast food
- Physical activity –industrialization reduces physical activity

Tree Main Mechanisms of the pathogenesis of DM type 2:

1. **Linkage reduction of pancreatic B-cells.**

Hyperplasia of pancreatic B cell is often present and probably accounts for the fasting hyperinsulinism and exaggerated insulin and proinsulin responses to glucose and other stimuli seen early in the disease. After several years' duration of DM, chronic deposition of *amyloid* in the islets may combine with inherited genetic abnormality to progressively impair B cell function.

2. **Insulin resistance**

Deficiency caused by:

- genetic factors
- overweigh
- sedéntary lifestyle.

Increased insulin resistance in target tissues, likely due to:

- receptor abnormality
- post-receptor abnormality.

The mechanisms underlying the insulin resistance are poorly understood. Insulin resistance deficiency caused by: genetic factors, overweigh, sedentary lifestyle. Obesity is generally associated with abdominal distribution of fat, producing an abnormally high waist-to-hip-ratio. The abdominal-visceral obesity, due to accumulation of fat in the omental and mesenteric regions, correlates with insulin resistance; subcutaneous abdominal fat seems to have less of an association with insulin insensitivity. Several *adipokines (leptin, adiponectin, tumor necrosis factor-@, resistin),*secreted by fat cells, can affect insulin action in obesity.Leptin and adiponectin ,seem to increase sensitivity to insulin,presumably by increasing hepatic responsiveness. FNO-@ and resistin interfere with insulin action on glucose metabolism and have been reported to be elevated in obese animal models. Mutation or abnormal levels of this adipokines may contribute to the development of insulin resistance. Correction of the lifestyle and overweight can prevent or revers hyperglycemia.

3. Acquired glucose toxicity.

Hyperglycemia per se can impair insulin action by causing accumulation of hexosamines in muscle and fat tissue and inhibits glucose transport. Correction of hyperglycemia revers this acquired insulin resistance.

CLINICS of DM Type 2

- asymptomatic initially
- polyuria
- thirst
- weekness
- chronic skin infection
- generalised pruritus and chronic candidal vulvovaginitis in women
- occult disease: CVD, neuropathy, poor vision

Ceneral Characterictic of DM Type 2

- Onset usually after age 40 years
- Genetically-linked
- Non-HLA-associated
- Greater heritability than Type1
- Typically overweigh
- Relative insulin deficiency
- Abnormal insulin secretion
- Insulin resistance
- Increased hepatic gluconeogenesis
- Pharmacological therapy: combination of oral hypoglycemic agents
- Not prone to ketoacidosis but prone to hyperosmolar coma

Patients with type 2 DM may or may not preset with characteristic features.

Among subgroup of patients with nonobese type 2 DM< the majority are idiopathic. A variety of etiologic genetic abnormalities have been documented in a subset of this patients who have recently been reclassified within a group designated "other specific types".

3. Laboratory Findings of the Disorders of Glucose et abolism

Pre-diabetes: Impaired Fasting Glucose (IFG) and **Impaired Glucose Tolerance** (IGT)

IFG and IGT have been officially termed "pre-diabetes." Both categories are associated with an increased risk of developing type 2 DM and cardiovascular disease.

Terminology and Diagnosis

Blood testing procedures

a) Normoglycemia. *A normal fasting plasma glucose level is less than 6,1 mmol/L (110 mg/DL)* and normal 2hr PPG levels are less than 7,75 mmol/L (140 mg/dL).

b) Blood glucose levels above the normal level but below the criterion established for DM indicate impaired glucose homeostasis. Persons with fasting plasma glucose levels ranging from 6.1 to 7.0 mmol/L (110 -126 mg/dL) are said to have impaired fasting glucose, while those with a 2hrs PPG level between 7,75 to 11,1 mmol/l (140 -200mg/dL) are said impaired glucose tolerance. Diagnosis based on:

c) Impaired Glucose Tolerance (IGT).

- Fasting (preprandial) glucose 6.1-6,9mmol/l and after 2 hrs OGTT >7,8 but<11,1mmol/l .
- 1-5% per year developing DM
- 50-80% revert to normal (IGT)
- Weight loss may improve glucose tolerance
- Associated with progressive greater risk of developing macrovascular complications.

d) **Impaired Fasting Glycemia (IFG)**

Fasting – glucose>5.6 mmol/l and after 2 hrs < 7,8mmol/l.

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either IFG or impaired glucose tolerance (IGT), depending on whether it is identified through a FPG or an OGTT:

- **IFG** = FPG 5.6 mmol/l (100 mg/dl) to 6.9 mmol/l (125 mg/dl)
- **IGT** = 2hrs plasma glucose 7.8 mmol/l (140 mg/dl) to 11.0 mmol/l (199 mg/dl).

-2 hrs.OGTT 75gr glucose < 7.8 mmol/l.

Screen for pre-diabetes

- individuals ≥45 years of age, with a BMI ≥ 25 kg/m^2(repeat testing should be carried out at 3-year intervals).
- individuals <45 years of age and are overweight if they have another risk factor for diabetes (repeat testing should be carried out at 3-year intervals):
- hypertensive>=140/90mm Hg
- HDL cholesterol >0,9mmol/L and/or Tg >=2,83 mmol/L
- history of IGT or IFG on prior testing
- Screen for pre-diabetes and diabetes in high-risk, asymptomatic, undiagnosed adults and children within the health care setting.

To screen for diabetes/pre-diabetes, either an FPG test or 2-h OGTT (75-g glucose load) or both are appropriate. An OGTT may be considered in patients with IFG to better define the risk of diabetes.

Treatment for pre-diabetes

- Individuals at high risk for developing diabetes need to participating in regular physical activity.
- Patients with IGT should be given counseling on weight loss as well as instruction for increasing physical activity. In addition, some physicians advocate the use **Metformin (Glucophage)**, to prevent/delay the onset of overt DM.
- Patients with IFG should be given counseling on weight loss as well as instruction for increasing physical activity.
- Follow-up counseling appears important for success.
- Monitoring for the development of diabetes in those with pre-diabetes should be performed every 1–2 years.

Diagnoses of Diabetes Mellitus (WHO, 1999)

Glucose connection

* Fasting – whole blood > 6,1mmol/l (120mg/dl), plasma >7,0 mmol/l (140mg/dl)

* 2hr's. after consuming 75 gm glucose orally (OGTT) – whole blood >11,1mmol/l (180mg/dl), plasma>200(mg/dl)

For the occasional patient, measurement of islet cell, glutamic acid decarboxylase (GAD65), insulin antibodies, and ICA512 antibodies can help distinguish between DM type 1 and DM type 2 diabetes. At attempt should be made to characterize the diabetes as type 1 or type 2, based on the clinical features present and on whether or not ketonuria accompanies the glucosuria.

The fasting blood glucose test is the preferred way to diagnose DM.

- a plasma glucose levels < 6,1 mmol/L (110mg/dL) , in FPG and a 2hrs post-load value < 7,8mmol/L (140 mg/dL).

If the overnight FPG >11,1 mmol/l (126 mg/dL) on two or more tests on different days the diagnosis of DM is made. If the FPG is 11.1 mmol/L or higher on more than one occasion, further evaluation of the patient with a glucose challenge is unnecessary.

A random blood glucose test can also be used to diagnose DM.

Random blood samples (if taken shortly after eating or drinking) may be used to test for DM when symptoms are present: > 11,1mmol/l (200 mg/dl) or higher indicates DM, but it most be reconfirmed on another day with a FPG or an oral glucose tolerance test.

Oral Glucose Tolerance Test (OGTT).

OGTT is a gold standart for making the diagnosis of type 2 DM and GDM.

For proper evaluation of the test, the individuals should be normally active (not lying down) and free from acute illness. Medicaitions that may impair glucose tolerance include diuretics, contraceptive drugs, glucocorticoids, niacin, and penytoin. For 3 days before the test, the person should have eaten a diet high in carbohydrates (100 -200 grams per day). The morning of the test, the person should not smoke or drink coffee.

With an OGTT, the person fasts overnight (at least 8 but not more tan 16 hrs).Then first, the FPG is tested. After this test, the person receives 75 grams of glucose (100 grams for pregnant women) dissolved in 300 mL of waterBlood samples are taken at specific intervals to measure the blood glucose. The classic OGTT measures blood glucose levels 5 times over a period of 3 hrs. Nowadays, physicians simply get a baseline blood sample followed by a sample 2 hrs after drinking the glucose solution.

Evaluating the results of the OGTT

Glucose tolerance tests may lead to one of the following diagnosis:

*** Normal response:**
- FPG < 6.1 mmol/L (110mg/dL) ,
- 2hr's PPG < 7,8mmol/L (140 mg/dL)

*** Impaired fasting glucose:**
- FPG <6.1 to7.0 mmol/l (from 110mg/dL)

*** Impaired glucose tolerance:**
- 2hr'sPPG from 7,8 to<11,1mmol/l (from 140 to <200mg/dL)

*** Diabetes mellitus:**
- FPG>=7,0mmol/L (126mg/dL) or
- 2hr'sPPG>= 11,1mmol/l (200mg/dL) after a 75 grams glucose load

*** Gestational diabetes:**

- FPG 100g OGTT > 5,3mmol/L(95mg/dL), and 1hrs glucose level > 10,6 mmol/L(180 mgdL), 2hrs >=8,9mmol/L (160mg/dL) or a 3 hrs > 140 mg/dL (7,8mmol/L).

Urinanalysis

- Glucosuria.

A specific and convenient method to detect glucosuria is the paper strip impregnated with glucose oxidase and chromogen system (Clinistix, Diastix), which is sensitive to as little as 0.1% glucose in urine. Diagnostic paper strip applied to the urinary stream, and differing color responses of the indicator strip reflect glucose concentration. Estimation of glucosuria is used to monitor treatment in patient with DM, but is not recommended for routine diagnosis DM.

Differential diagnosis of glucosuria

1. When glucosuria is found, it shoud be determined whether it is secondary to hyperglycaemia or renal glucosuria. Glucosutia occurs when blood glucose level exceeds the renal glucose threshold of 10 mmol/l (180 mg/dL).

2. Renal glucosuria

Non-diabetic melituria occurs in a number of conditions, the most important being renal glucosuria and alimentary (lag storage) glucosuria.

Diagnosis of renal glucosuria is based on the Marble's criteria.

- Glucosuria is absence of hyperglycaemia.
- Constant glucosuria with little fluctuation related to diet.
- Normal oral glucose tolerance test.
- Identification of urinary reducing substance as glucose.
- Normal storage and utilization of carbohydrates.

3. Alimentary (lag storage) glucosuria

There is a transient abnormal rise in blood glucose level following a meal, and the concentration exceeds the normal renal threshold. During this time glucose spills into the urine. This may occur in the following conditions:

- Following gastric surgery with rapid gastric empting time.
- Some normal people.
- Hyperthyroidism
- Hepatic diseases

Ketonuria.

A specific method to detect of ketone bodies is the paper strip (Clinistix, Diastix) by nitroprusside tests. Ketostix can be directly applied to the urinary stream and estimate of ketonuria. Estimation of ketonuria is recommended for ketoasidosis presenting.

Glycated hemoglobin (also known as glycohemoglobin, glycosylated hemoglobin or HbA1c).

Measurements of HbA1c have commonly been used to monitor the glycemic control of persons already diagnosed with DM. Measurements of this hemoglobin aid in the evaluation of the stable linkage of glucose to minor hemog-

lobin components. It is produsedby nonenzymatic condensation of glucose molecules with free amino groups on the globin component of hemoglobin. The maior form of glycohemoglobin is termed hemoglobin A1c, which normally comprises 4-6% of the total hemoglobin.The remaining glycohemoglobin (2-4% of the total) consist of phosphorylated glucose or fructose and are termed hemoglobin A1a and hemoglobin A1b.Some laboratories measure the sum of these tree glycohemoglobin and report it as hemoglobin A1, but more laboratories are converting to the more intricate but highly specific HbA1c assay. There are now monoclonal innunoassays for measuring HbA1c.Machines based on this technology use capillary blood and give a result in about 10 minutes. Glycohemoglobins circulate within red blood cells whose life span lasts up to 120 days, they generally reflect the state of glycemia over the preceding 8 -12 weeks. Glycated hemoglobin reflects the state of glycemic control for the preceding 3-to-4 moths. Measurement should be made in patients with either type of DM at 3-to-4 month intervals.

ADA recommends an HbA1c <7%, other groups currently recommends an HbA1c < 6,5%.It shoul be mentioned here that there are a number of conditions in which an HbA1c is value may not be accurate, eg, anemia and hemoglobinpathies.

Studies have shown that there is about a 10% decrease in relative risk for microvascular disease for every 1% reduction in HbA1c.So, if a patient starts off with an HbA1c of 10.7 and drops to 8,2 , thought there not yet at goal, they have managed to decrease their risk of microvascular complications by about 20%.The closer to normal the HbA1c, the lower the absolute risk for microvascular complications.

HbA1 (%)	HbA1c (%)	Mean blood glucose (mmol/L)
6,0	5,0	4,4
7,2	6,0	6,3
8,4	7,0	8,2
9,0	7,5	9,1
10,2	8,5	11,0
11,4	9,5	12,8
12,0	10,0	13,7
13,2	11,0	15,6

Serum fructosamine.

Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins (predominantly albumin). Serum albumin has a much shorter half-life than hemoglobin. Serum fructosamine reflects the state of glycemic control for only the preceding 2 weeks. Normal valyes vary in relation to the serum albumin concentration and are 1.5 -2.4 mmol/L, when the serum albumin level is 5g/dL. Reduction in serum albumin will lower the srum fructosamine value, eg, hepatic disease or nephritic state.

4. Other Specific types of Diabetes Mellitus.

A. Maturity-onset diabetes of the young (MODY).

Six types of MODY have been described.

- autosomal dominant inheritance
- onset of 25 years or younger
- nonobese
- non-insulin-dependent diabetes
- hyperglycemia is due to impaired glucose-induced secretion of insulin
- need low doses of oral hypoglycemic agents or diet only.

B. Diabetes due to mutant insulins.

- Very rare
- nonobese
- heterozygous and possessed one normal insulin gene
- family history
- middle age.

C. Diabetes due to mutant insulin receptor

- extreme insulin resistance
- associated with acantosis nigricans
- leprechaun- like phenotype.

D. Diabetes associated with a mutation of mitochondrial DNA

- mutation of mitochondrial DNA that impairs the transfer of leucine or lysine into mitochondrial proteins
- 2/3 of patients hearing loss
- 2/3 of patients have a smaller proportion
- 1/3 have a syndrome of myopathy, encephalopathy, lactic acidosis, stroke-like episodes
- mild form of diabetes

J. Insulin Resistance Syndrome &Syndrome X & Metabolic Syndrome

25% of the general nondiabetic population have insulin resistance of a magnitude similar to that seen in type 2 DM. These individuals are at much higher risk of developing type 2 DM.

- Visceral obesity
- increase triglycerides (TG)
- lover high-density lipoproteins (HDL)
- small, dense, low-density lipoproteins (LDP)
- higher BP
- hyperuricemia
- protrombotic state with increased levels of plasminogen activator inhibitor type 1 (PAI-1)
- risk cerebrovascular and cardiac mortality and morbidity

- need of long-acting insulins ana sulfonylureas (promote sustained hyper-insilinism), insulin-sparing drugs (metformin or a thiazolidinedione]
- need not only correct hyperglycemia but also BP and dislipidemia (niacin)

Latent autoimmune diabetes of adulthood – LADA

Certain unrecognized patients with a milder expression of type 1 diabetes initially retain enough B cell function to avoid ketosis but later in life develop increasing dependency of insulin therapy as their B cell mass diminishes.

- indicate 15% patients "of type 2DM"
- age 35 -45 years
- no obesity
- insulin dependence manifested after 1 -6 years from onset DM
- first resistance to hypoglycemic drugs
- prone to ketoacidosis
- ICA, anti –GAD present
- low C-peptide

Idiopathic type 1 diabetes mellitus (type 1B)

- no evidence of pancreatic B cell autoimmunity to explain their hyperglycemia and ketoacidosis

5. Gestational Diabetes Mellitus (GDM).

DM can occur temporarily during pregnancy. Significant hormonal changes during pregnancy can lead to blood glucose elevation in genetically predisposed individuals.Women which have develop type 1 DM during pregnancy and women with undiagnosed asymptomatic type 2 DM that is discovered during pregnancy are classified with GDM. Women with DM before pregnancy are said to have "pregestational DM" and are not included in this group. However, most women classified with GDM have normal glucose homeostasis during the first half of the pregnancy and develop a relative insulin deficiency during the last half of the pregnancy, leading to hyperglycemia. The hyperglycemia resolves in most women after delivery but places them at increased risk of developing type 2 DM later in life. 25 -50% of women with GDM will eventually develop DM later in life.

Risk factors of GDM

- age>25
- glycosuria
- strong family history of diabetes
- obesity
- member of high-risk ethnic group
- previous GDM
- previous macrosomic baby >4 kg

Screening for GDM

- Screen for diabetes in pregnancy using risk factor analysis and, if appropriate, use of an OGTT.
- Women with GDM should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes.
- Any pregnant woman should be screened between 24 and 28 weeks
- *50g glucose challenge test*, measuring glucose 1 hrs later
- If abnormal (7,8mmol/L;140mg/dL), then 75g OGTT should be done

- if any two of the following tree values are met or exceeded, a diagnosis of GDM is established:

- FPG > 5,3mmol/L(95mg/dL), and 1hrs glucose level > 10,6 mmol/L(180 mgdL), 2hrs >=8,9mmol/L (160mg/dL) .

Testing should follow one of two approaches:

- One-step approach: perform a diagnostic 100-g OGTT
- Two-step approach: perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test) and perform a diagnostic 100-g OGTT on that subset of women exceeding the glucose threshold value on the glucose challenge test. When the two-step approach is used, a glucose threshold value ≥140 mg/dl identifies ~80% of women with GDM, and the yield is further increased to 90% by using a cutoff of ≥130 mg/dl.

Diagnostic criteria for the 100-g GOTT are as follows: ≥95 mg/dl fasting, ≥180 mg/dl at 1 hrs ≥155 mg/dl at 2 hrs and ≥140 mg/dl at 3 hrs. Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of 8–14 h. The diagnosis can be made using a 75-g glucose load, but that test is not as well validated for detection of at-risk infants or mothers as the 100-g GOTT.

Chapter II. Long term complications of Diabetes Mellitus.

Over time, DM can lead to the blindness, kidney failure, and nerve damage. Diabetes is also an important factor in accelerating atherosclerosis, leading to strokes, coronary heart disease and blood vessel diseases. Diabetes is the third cause of death after heart disease and cancer.

The majority of complications involve:

- the microvascular system: diabetic microangiopathy (retinopathy,nephropathy, neuropathy);
- the macrovascular system: diabetic macroangiopathy- accelerated atherosclerosis leading to coronary artery disease, stroke, pulmonary vascular disease;
- the nervus system: diabetic neuropathy;

- bone and joint disease: diabetic foot;
- skin disease: necrobiosis lipoidica diabeticorum
- can involve many other organs

Aggravating factors:

- poor glycemic control;
- inadequate control of hypertension and cholesterol;
- smoking;
- high fat diet.

1. Diabetic Retinopathy

Epidemiology

- present in 50% of patients after 10 years with DM,80% in 15 years, 25 yers and more risk of blindness
- one of the leading causes of blindness in adults 20 -74 years
- increased risk cataracts and open angle glaucoma

Risks

- poor glycemic control (persistent hyperglycemia)
- HLA-DR types
- hyperhomocysteinemia

Classification of Diabetic Retinopathy

1. Non-proliferative (background) Diabetic Rethynopathy
- generally no symptoms
- microaneurysms only
- milder degrees of venous loops, retinal hemorrhages
- hard exudates, (small) dot and blot hemorrhages

2. Pre-proliferative Diabetic Rethynopathy
- macula edema, venous shunts and beading
- cotton wool (soft)exudates :gray or white areas with soft, feathery edges indicate ischemia within retinal nerve fibers

3 . Proliferative Diabetic Rethynopathy
- great risk for loss of vision
- new vessels (neovascularization0 in the eye
- fibrous scarring, vitreous hemorrhages, retinal traction, tears

Prevention of Diabetic Retinopathy

- tight glycemic control
- activity limitation for proliferative diabetic rethynopathy;avoid all strenuous activities, valsalva, jarring, jogging, weight lifting, high impact aerobics, racquet sports
- frequent follow-up visits an ophthalmologist :after 5 years of type 1DM and immediate referral after diagnosis of type 2 DM

Managment of Diabetic Retinopathy

- Lazer Photocoagulation (eliminates neovascularization)

- - vitrectomy

Other abnormalities of the organ of vision

- Iritis and iridocyclitis
- Cataract
- Diseases of the uveal tract
- Glaucoma

2.Diabetic Nephropathy

The term diabetic nephropathy is a concept embracing all clinical manifestations of renal pathology due to diabetes mellitus, including intercapillary, intracapillary and intraarterial affectiona of the kidneys in the form of microangiopathy. Diabetes has become the most common single cause of end-stage renal disease (ESRD) in the world. A nodular intercapillary glomerulosclerosis know as the Kimmelstill-Wilson syndrome named after two authors who in 1936 described the pathological changes in the kidneys. The syndrome is characterized by retinopathy, arterial hypertension, proteinuria, hyperazotaemia and edema.

Eepidemiology

- may occur as early as 5 years after onset of DM
- 20-40% of patients with type 1DM and 4 -20% with type 2DM

Risks

- Genetics
- Hypertension
- Smoking
- Hyperlipidemia
- Poor glycemic control

Histology

Starts with nodular glomerulosclerosis, then diffuse, then exudative lesions of the glomeruli.

- In the *diffuse form* which is more common, there is widening of the glomerular basement membrane together with generalized mesangial thickening.
- In the *nodular form*, large accumulations of PAS-positive material are deposited at the periphery of glomerular tufts, the Kimmelsteil- Wilson lesion.
- In addition, there may be hyalinization of afferent and efferent arteriols, "dros" in Bowman's capsule, fibrin caps, and occlusion of glomeruli. Deposition of albumin and other proteins occurs in both glomeruli and tubules.

Classification of Diabetic Nephropathy and Clinical picture

Stage 1 (Preclinical).

- 0 -5 years with DM
- Renal hypertrophy (size >14 cm)
- Hyperfiltration . Clomerular filtration rate > 150ml/min

- With sustained microalbuminuria (microalbuminuria =30 -300mg protein/24 houres or 20 -200 ug/min timed collection, or 30 -300 ug/mg creatinine for spot collection).
- BP normal

Stage II

- Renal hypertrophy
- Clomerular filtration rate > 150 – 200 ml/min
- Albumin excretion < 30mg/d
- BP normal

Stage III (Incipient Nephropathy).

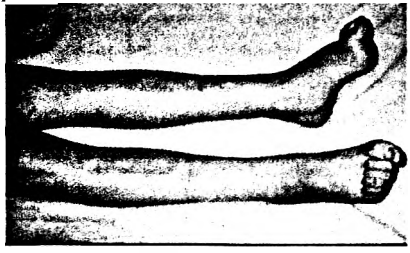
- 5 -20 years after onset of DM
- Loss of glomerular filtration rate 130- 150 ml/min
- normal kidneys size (12 cm)
- increased albumin 30 -300 mg/d, persistent proteinuria (macroalbuminuria)
- variable hypertension

Stage IV (Overt Nephropathy)

- Decrease renal size <10cm.
- Clomerular filtration rate< 120 ml/min
- Albumin excretion >3,5 g/l
- BP very high

Stages V (ESRD)

- atrophic kidneys , 8 cm
- Clomerular filtration rate < 20
- Albumin excretion > 3,5 3,5g/l
- BP very high
- Uremia if untreated, needs dialysis or transplant.



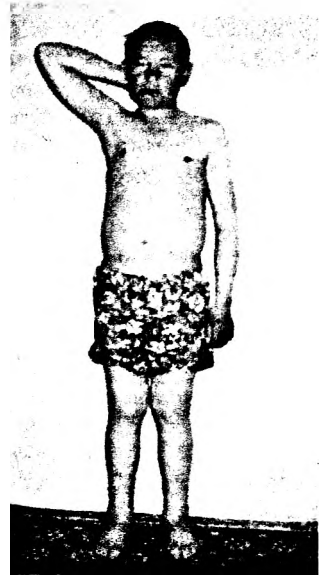


Fig.23 year-old patient with diabetes mellitus type 1: anasarka,edema at the lower extremities (right),hepatomegaly splenomegaly, hypogonadism (Diabetic nephropathy stages V, ESRD).

Prevention of Diabetic Nephropathy

- tight glucose control

Mamagment of Diabetic Nephropathy

- Meticulous control of diabetes can reverse microproteinuria in some patients
- In addition, angiotensin converting enzyme inhibitors can retard the progression of nephropathy at this stage.
- Aggressive control of hypertension is mandatory as high blood pressure can accelerate nephropathy.
- The BP should be decreased to less than 130/80 mm HG, with an optimal target of below 120/80 mm Hg espessially in patients with proteinuria or renal insufficiency.
- ACE inhibitors have proved beneficial in patients with diabetic renal disease and are considered preferred therapy in patient with hypertention and diabetes. These agent can be used if creatinine less than 3 mg/dL.
- Other agents which can be used include thiazide diuretics, calcium channel blokers, angiotensin II receptor blocers, beta-blockers and alfa-blockers.
- Low-protein diets may be beneficial, as there is some evidence suggesting that high-protein diets can accelerate glomerulosclerosis (0,8 g/kg/day in macroalbuminuria and 0,6g/kg/day in overt proteinuria).
- Once the azotaemic phase is reached, the management is similar to other forms of chronic renal failure.

Other urinary abnormalities

Persistent infection of has urinary tract has a latent course

- Fungal cystitis (also commonly see chronic/recurrent vaginitis
- Pyelitis
- Pyelonephritis for 10-30% of patients with DM
- Perinephric abscess

3. Diabetic Neuropathy

Epidemiology

- common in both type 1 and type 2DM
- due to protein glycation and polyol pathway(metabolic defect thouth to be due to increased sorbitol and/or decreased myoinositol

Risks

- Hypertension
- Increase LDL, decrease HDL

- Age
- Female
- Duration of DM

Classification of Diabetic neuropathy

1. Symmetric Distal Sensorimotor Polyneuropathy

Can be divided into 2 types:

A. A relatively asymptomatic form which is diffuse, distal, usually occurring in the lower extremities with a stocking type of distribution. There is numbness, tingling, or pins-and-needles sensation, often worse at night. This type is generally progressive and irreversible.

A painful form presenting with burning or dull aching sensation, or excruciating, lancinating pain. The pain is often worse at night ("restnessless foot"syndrome)and partially relieved by movement. Hyperasthesia may be marked.

The characteristic early finding in both forms are:

- Loss of ankle reflexes and distal vibration
- "Glow and stocking" polynuropathy - pain, pins-and-needle, burnining or cold
- Hyperthesia, eathesia, anesthesia can quantitate the sensory loss with successively rigid fleiible monofilament
- Worse at night -"restnessless foot"syndrome
- Decrease strength of intrinsic foot muscles
- Hammer/claw toe, bunion deformities, prominent metatarsal heads
- Muscle athrophy

2. Autonomic Neuropathy

a.Autonomic cardiopathy

- vagal denervation, lose the normal beat-beat variability in heart rhythms:

-o rtostatic hypotension with nocturnal hypertension
- resting tachycardia
- fixed heart rhythms
- painless ischemia
- sudden death.

b. Diabetic gastroparesis :

- impaired motility or increased secretory
- esophageal dysfunction.

c. Bowel disorders

- decreased gastrocolic reflex – constipation
- diarrhea at night – increased gastrocolic reflex.

d. Cutaneus disorders

- increased /decreased sudomotor (sweating) causes dry scaly skin and fissuring along with contracture and hammer toe it lead to ulcers

e. Genitourinary

- bladder-urgency
-vesicopathy
- incontinence
- impotence
- retrograde ejaculation

f. Secretomotor
- gustatory sweating
- nocturnal sweats without hypoglycaemia
- anhidrosis

g. Vasomotor
- dependent pedal oedema

h. Pupillary
- decreased pupil size
- resistance to mydriatics

3. Asymmetric neuropathy:

a. Cranial mononeuropathy and mononeuropathy multex
- Usually involve third, sixth, or fourth cranial nerve in order of frequency
- Third nerve involvement is characteristically pupil-sparing.

b. Peripheral mononeuropathy and mononeuropathy multiplex
- Manifest as carpal tunnel syndrome, foot drop or wrist drop

c. Radiculopathy is a sensory syndrome in which dysaesthesias and painful hyperaesthesia in the anatomic distribution of one or more spinal nerves.

d. Diabetic amyotrophy :
- athrophy and weakness of the muscles of thigh (especially quadriceps) and pelvic girdle.
- may associated with anorexia and depression

Treatment

1. Pain of diabetic neuropathy: non-steroidal anti-inflammatory drugs, codeine,phenytoin,carbamazepine,amitriptyline,imipramine or gabaptetine.
2. Mononeuropathies and radiculopathies are usually self-limiting and do not require any specific therapy.
3. Diabetic diarrhea: diphenoxylate, loperamide or tetracyclins.
4. Ortostatic hypotension: to sleeping with the head of the bed elevated, avoidance of sudden assumption of the upright position, and full-length elastic stocking.

Prevention and management of Diabetic neuropathy

- tight glucose control
- anti-depressants and anti-epileptics for painful neuropathic syndromes
- erythromycin and domperidone for gactroparesis
- foot care education

Chronic hyperglycaemia is associated with an increased risk of microvascular complications, as show in the Diabetes Control and Complication Trial (DCCT) of DM type 1 and the United Kingdom Prospective Diabetes Study (UKPDS) of DM type 2. In the DCCT, intensive therapy to maintain normal blood glucose levels greatly reduced the development and progression of retinopothy, microalbuminuria, proneinuria, and neuro pathy over 7 years. Intensive therapy was not associated with increased mortality or incidence of major macrovascular events and did not decrease the quality of life, though it did increase the likelihood of severe hypoglycemic episodes.

In the UKPDS, more than 5000 patient with DM type 2 were followed up for up to 15 years. Those in the intensely treated group had a significantly lower rate of progression of microvascular complication than that of those receiving standart care. Rates of macrovascular disease were not altered except in the metformin-monotherapy arm, in which the risk of IM was significantly decreased.Moreover, severe hypoglycaemia occurred less often than it did in patients with DM type 1 in the DCCT.

4. Other Complications.

Skin diseases Associated with DM.

No skin change is diagnostic of diabetes, but may changes are seen with diabetes.

1. Scleroderma.
2. Granuloma annulare – asymptomatic plaque over extensor joints that slowly heal from the center out.
3. Acanthus nigricans; skin tags (common as insulin is a growth factor).
4. Eruptive xantomas.
5. Diabetic bullae (bullosa diabeticorum).
6. Diabetic dermopathy: generalized thick skin, may have dark macululelar skin spots. Not of clinical sighificance.
7. Oral leukoplakia/ lichen planus.
8. Intensive keratinization of the feet (alabaster's coloring).
9. Thickining of nails.
10. Ulcer.
11. Stomatitis angularis.
12. Rubeosis diabetica (rosy cheeks).
13. Xanthomatosis (yellowish nodules on the palms, soles, buttocks, the back surfaces of elbow joints).

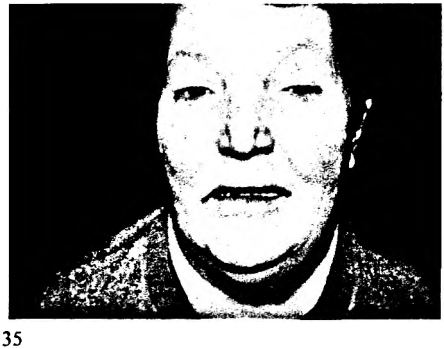


Fig. Stomatitis angularis. Rosy cheeks.

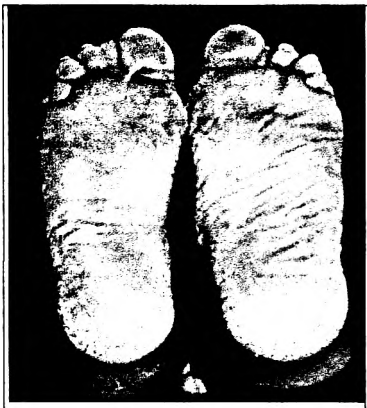


Fig. Alabaster's coloring

Fig. Thickining of the nails

Necrobiosis lipoidica diabeticorum.

- Occurs in 0,3% of diabetics.
- Seen in young adults and middle aged in setting of DM type 1.
- May have a history of preceding trauma.
- Not always associated with diabetes. Consider a glucose tolerance test to pick up 20% non-overt diabetics.
- Lesion due to alteration in collagen.

Signs

- Distinctive,sharply circumscribed, multicolored (yellow, red,brown)papule that expandsto aplaque. Mostly occurs on the anterior and lateral surfaces of the lower legs (shins), may occur on the face, trank and arms. Lesion slowly evolves over months, lasts years. Intralesional ulcers may occur, often painful.
- Very resistant to treatment
- Spontaneous remission in 15%

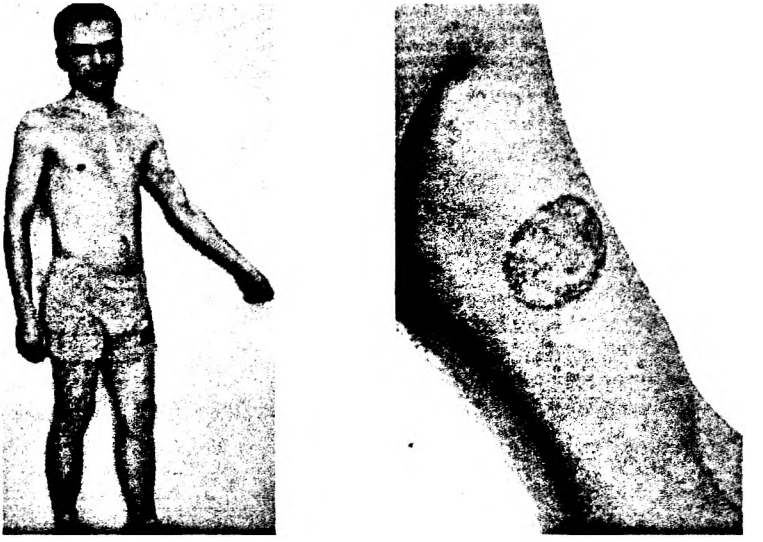


Fig. 26-years-old patient with Diabetes mellitus type 1. Necrobiosis lipoidica diabeticorum.

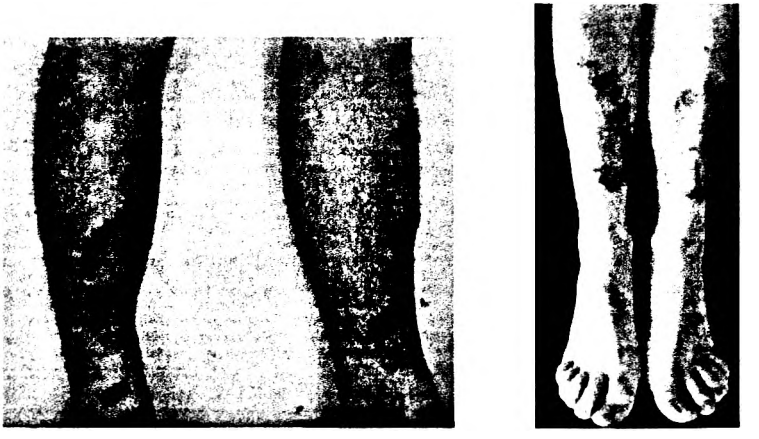


Fig. Necrobiosis lipoidica on the skin of shins.

Bone and Joint disease Associated with Diabetes. "Diabetic Foot".

- The term refers to foot problems caused directly by diabetes, damage to the nerves and blood vessels occurs in the foot, reducing the ability to feel properly.

- The insensate, poorly perfused foot is a risk for ulcers from pressure necrosis or inflomation from repeated skin stress and unnoticed minor trauma. These can evolve into cellulitis, osteomyelitis, or nonclostridial gangrene and end in amputation.

- Charcot foot affects the metatarsal, tarsometatarsal, and tarsal joints, which are located in the forefoot and midfoot

Risk Factors and Causes

- Chronic hyperglycemia
- diabetic peripheral neuropathy

Problems can begin from any small sore or injury to the foot, most especially:

- Blisters that becomes a large sore
- A simple cut that goes untreated
- Ingrown toenails
- Small wounds from rubbing shoes or socks

Symptoms and signs

- Lack of feeling in the foot
- Dull or sharp pain in the foot
- Swelling of the foot or leg
- Redness can be a sign of infection, especially when surrounding a wound, or a place where the foot has been rubbed by shoes or socks
- Loss of hair on the lower leg, often with the skin becoming hard and shiny
- Warmth in specific parts of the foot can be a sign of infection
- Fever or chills associate with a foot wound that is not healing
- Thickining of foot dorsum or ankle joint
- Osteolysis, osteosclerosis
- Osteoporosis, periostosis
- Frutures, paraosseal calcification
- Foot bones are mostly affected: metatarsals and tarsal bones.
- Diabetes is the leading cause of nontraumatic lower-extremity amputation.

Symptoms of Charcot foot

- Dislocation of the joint
- Heat
- Insensitivity in the foot
- Instability of the joint

- Redness
- Strong pulse
- Swelling of the foot and ankle (caused by synovial fluid that leaks out of the jont capsle)
- Subluxation (misalignment of the bones that form a joint)
- Osteomyelitis and septic arthritis may develop

Laboratory and Investigations

- X-rays or MRI to detect joint effusions, large osteophytes, fractures, joint misalignment and/or dislocation, osteoporosis
- Drawing fluid from the joint

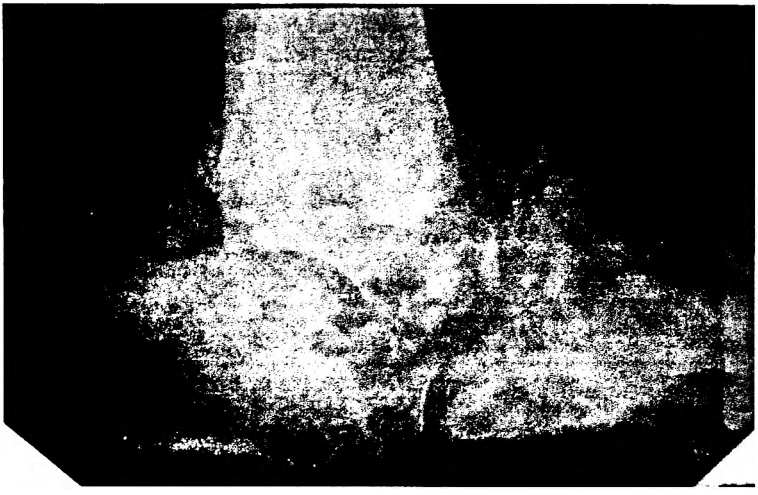


Fig. X-ray : osteolysis, osteosclerosis of tarsal bones.

Treatment

- Patients with wounds, infections, or ulcers of the foot should be treated intensively.
- Antibiotics for Gramm -, + and anaerobes I/V.
- Use crutches, wheelchairs; bed rest.
- Local treatment + vascular evaluation in conjunction.
- Surgery may be necessary to treat severe deformities or recurring ulcers by reshaping structures within the foot or removing bony protrusions that cause ulcers
- Osteoctomy used to treat Charcot foot
- Amputation if gangrene

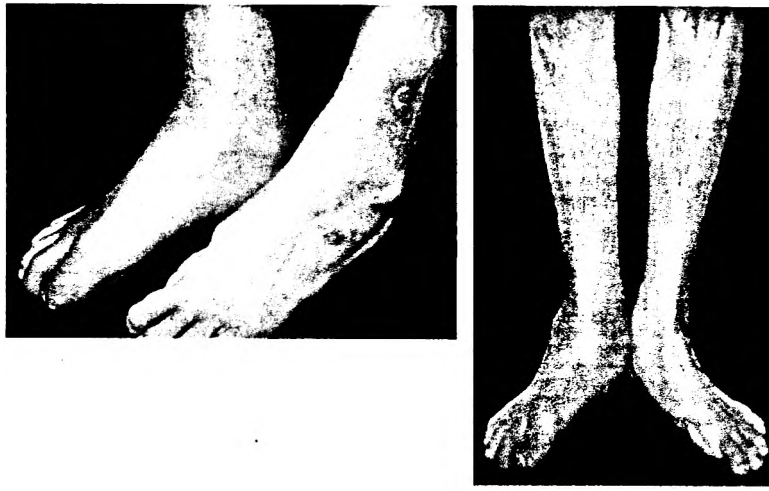


Fig. Charcot foot.

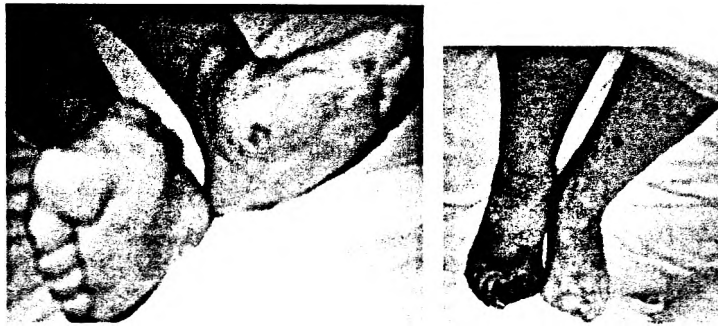


Fig. "Diabetic foot". Ulcer.

Fig. Glycemic Dry Gangrene.

Fig. Glycemic Gangrene.

Cardiovascular complications of diabetes.

The main cardiovascular complications of diabetes are accelerated atherosclerosis, and increased platelent adhesiveness, possibly due to enhanced thromboxane A2 synthesis, and decreased prostacyclin synthesis.

The atherosclerosis lesions can manifest in a variety of ways:

- Intermittent claudication, gangrene and impotence.
- Coronary artery disease leading to ischaemic heart disease, especially silent myocardial infarctions.
- Dilated cardiomyopathy (diadetic "cardiomiopathy").
- Cerebrovascular accident

Chapter III. Treatment of Diabetes Mellitus.

1. Insulin
2. Oral hypolycemic agents
3. Lifestyle modification
4. Diet.

1. Treatment of Diabetes Mellitus Type 1.

The target in the management of diabetes mellitus is maximum compensation of the disturbed metabolic processes.

Criteria of compensation of diabetes mellitus
(Europen NiDDM POLICY Group, 1993)

- Fasting glucose. - 6,1 mmol/l and after meal < 8,0 mmol/l
- Aglucozuria
- HbA1c < 6.5%
- Tg < 1.7 mmol/l, Holesterol < 5,2 mmol/l
- BMI < 24 (female), < 25 (male)
- BP < 140/90mm Hg

Insulin.

Insulin is required for treatment of all patients with DM type 1 and many patients with DM type 2. The goals of insulin therapy are:

1. Normal grougth and development in children.
2. Normal pregnancy, delivery, and conceptus in women.
3. Mininal interference with psychological adjustment.
4. Acceptable glycaemic control, with minimal hypoglycaemia.
5. Prevention of complication.

Insulin is commercially available in concentrations of 100 U/ml . There is an additional U500 preparation of regular insulin.

Different types and species of insulin have different pharmacological properties. Insulin type and species, injection technique, insulin antibodies, site of injection, and individual patient response differences can all affect the onset, degree, and duration of insulin activity. Insulin in use may be kept at room temperature to limit local irritation at the injection site, which may occur when cold insulin is used. Abdominal injection above umbilicus has quickest absorption followed by arm, thigh and hip. Intramuscular injection has faster than subcutaneous. Smaller doses faster than larger. Insulins available in the world are recombinant human or human insulin analog origin. NPH = neutral protamin Hagedorn.

Indication for the insulin therapy.

1. Typel DM.
2. Diabetic coma/precomatoes states, ketoacodosis.
3. Type 2 DM with complication nephropathy, hepatic insuffisiance
4. Type 2 DM: first/secondary resistance for the oral hypoglycemic agents.
5. Diabetes during pregnancy.
6. Post-renal transplantation diabetic patients

Temporary prescription for the insulin therapy

1. Concomitant diseases
2. Surgical intervention/injury

Insulin Administration

- Subcutaneous injections
- Continuous subcutaneous insulin pump - CCII
- intra venus injection (regular insulin only)
- doses adjusted for individual patients needs to meet glycemic control

Insulin Preparations

Insulin preparation can be classified:

- Based on source as bovine, porcine, and human insulins.
- Based on time course of action as rapid, intermediate, and long acting insulins.
- Based on strength as 40 U/mL, and 100 U/mL.
- Newer insulin analogues.

Human Insulin

Human insulin differs from porcine insulin by one amino acid residue and from bovine insulin by tree amino acid residues. The changes in the amino acid residues of these three insulins are given in Table.

Amino acid position	A8	A10	B30
Human	Threonine	Isoleucine	Threonine
Porcine	Threonine	Isoleucine	Alanine
Bovine	Alanine	Valine	Alanine

Two types of human insulins.

1. **Semisythetic human insulin.** This is an enzymatically modified pork insulin. The monocomponent porcine insulin is enzymatically dealaninated from the B30 position which is then replaced by threonine to make the structure identical to human insulin.
2. **Recombinant DNA biosynthetics.**

Characteristics of Insulins According Its Times Action.

1. Rapid-acting Insulins Analogs: **(Humalog, Novolog, Apidra)**. Human analogs. Give before 20 minutes before the meal subcutaneously above umbilicus. Tree - four injections daily or more if it need. When intravenous insulin *is needed for hyperglycemic emergences, the rapid-acting insulin analogs have no advantage over regular human insulin,* which is instantly converted to the monomeric form when given intravenously.

Insulin Humalog (lispro) is an insulin analog produced by recombinant technology utilizing a non-pathogenic strain of *E.coli*, wherein two amino acids near the carboxyl terminal of the B chain have been reversed in position: Proline at position B28 has been moved to B29 and lysine has been moved from B29 to B28.

Insulin Novolog (aspart) is a single substitution of praline by aspartic acid at position B28.

Insulin Apidra (glulisine) differs from human insulin in that the amino acid asparagines at position B3 is replased by lysine and the lysine in position B29 by glutamic acid. These changes result in these three analogs having less tendency to form hexamers, in contrast to human insulin. When injected subcutaneously, the analogs quicly dissociate into monomers and are absorbed very rapidly, reaching peak serum values in as soon as 1 hour - in contrast to regular numan insulin, whose hexamers require considerably more time to dissociate and become absorbed. The amino acid changes in these analogs do not interfere with their binding to the insulin receptor, with the circulating halfOlife, or with their immunogenicity, which are all identical with those of human regular insulin.

The rapid-acting analogs used in insulin pups.

2. Short-acting Regular Insulins (R). Human. Slowly being replaced Humalog. Give before the meal subcutaneously above umbilicus, intramuscular or intravenous.

It is crystalline zinc insulin whose useful in treatment of diabetic ketoacidosis and during the perioperative management of insulin-requiring diabetics or during acute infections.

For marked insulin-resistant persons who would otherwise require large volumes of insulin solution a U500 preparation of human regular insulin is available. Since a U500 preparation syringe is not available, a U100 insulin syringe or tuberculin syringe is used to measure doses. The phisian should carefully note dosages in both units and volume to avoid overdosage.

3. Long-acting (Basal) Insulins: (N/NPH,L /Lente, Humulin N). Human. Be given subcutaneous by arm, thigh and hip but not intravenous. Two injeactions daily.

It is **intermediate**-acting neutral protamine Hagedorn (NPH) insulin – NPH (neutral protamine Hagedorne or isophane) insulin whose onset of action is delayed by combining 2 parts soluble crystallane zinc insulin with 1 part protamine zinc insulin. This produces equivalent amounts of insulin and protamine, so that neither is present in an uncomplexed form ("isiphane").

Lente Insulin :a mixture of large and small crystals, has a large variation in absorbtion.

1. **Ultra Long-acting (Basal) Insulins: (U or Ultralente, Lantus, Levemir**). Human. Be given subcutaneous by arm, thigh and hip but not intravenous.

Ultralente is groups of large crystals to give it a slow dissolution into the blood, however its rate of absorption is very variable depending on the temperature, blood supply and hormone levels, thus avoid in women.

Lantus (insulin glargine) – is an insulin analog in which the asparagines at position 21 of the A chain of the human insulin molecule is replaced by glycine and two arginines are added to the carboxyl terminal of the B chain. The arginines raise the isoelectric point of the molecule closer to neutral, maiking it more soluble in an acidic environment. *Given as a single injection at bedtime to type 1 DM. Cannot be mixed with the other human insulins because of its acidic pH. Not recommended in pregnancy.*

Levemir (insulin detemir) – is an insulin analog in which the tyrosine at the position 30 of the B chain has been removed and a 14-C fatty acid chain (tetradecanoic acid) is attached to the lysine at position 29 by acylation. The fatty acid chain makes the molecule more lipophilic than native insulin and the addition of zinc stabilizes the molecule and leads to formation of hexamers. After inlection, self-association at the injection site and albumon binding in the circulation via the fatty acid side chain, leads to slower distribution to peripherial target tissues and prolonged duration of action. Given once or twice daily.There is a vast excess of albumin binding sites available in plasma per insulin detemir molecule, it is unlikely that hypoalbuminemic states will affect the ratio of bound to free insulin detemir.

The longer-acting insulin analogs cannot be mixed with either regular insulin or the rapid-acting insulin analogs.

5. Premixed (NPH/Regular) Insulins: Humalog 75/25 – Human /U100, onset 10-30 min, peak 1-3 hours, duration of action 18 -22 hours. **Humulin 50/50:** human, onset 30 -60 min, peak 2-4 hours, duration of the action 16 -22 hours.

Stable premixed insulins are available as a convenience to patients who have difficulty mixing insulin because of visual problems or impairment of manual dexterity. Premixed insulins not recommended for Type 1 DM as does not allow enough flexibility. Premixed preparations of insulin lispro and NPH insulins are unstable because of exchange of insulin lispro with the human insulin in the protamine complex. Consequently, the soluble component becomes over time a mixture of regular and insulin lispro at varying ratios. In an attempt to remedy this, an intermediate insulin composed of isiphane complexes of protamine with insulin lispro was developed called NPL (neutral protamine lispro). This insulin has the same duration of action as NPH insulin.

Table. Kinetics of the Insulins

Insulin	Duration	Onset (hours)	Peak (hours)	Usual Effective Duration of Action
Humalog Novolog Apidra	Very short	5-10 min 10 -30 min 5- 15 min	30 -40 min 40 -50 min 1 – 1,5	2 -3 3 – 5 3 -4
Human Regular	short	½ -1	2	6 -8
Human NPH/Lente	long	2- 4	6 -7	14 - 20
Ultralente/ Lantus Levemir	ultralong	4- 5 1,5 1	 Flat Flat	18 -28 ~24 17

Commercial insulin preparations

1. Rapid-acting human insulin analogs
   Insulin lispro (Humalog, Lilly)
   Insulin aspart (Novolog, Novo Nordisk)
   Insulin glulisine (Apidra, Sanofi Aventis)
2. Short –acting regular insulin
   Regular insulin (Lilly, Novo Nordisk)
3. Intermediate- acting insulins
   NPH insulin (Lilly, Novo Nordisk)
4. Premixed insulins
   70% NPH/30% regular (70/30 insulin – Lilly, Novo Nordisk)
   50% NPH/50% regular (50/50 insulin – Lilly)
   70%NPL/30% insulin lispro (Humalog Mix 75/25 – Lilly)
   50% NPL/50% insulin lispro (Humalog Mix 50/50 – Lilly)
   70% insulin aspart protamine /30% insulin aspart (Novolog Mix 70/30 – Novo Nordisk)
5. Long- acting human insulin analogs
   Insulin glargine (Lantus, Sanofi Aventis)
   Insulin detemir (Levemir, Novo Nordisk).

Insulin Theraphy

Starting dose an adult DM1 patients on insulin = 0, 5 -0, 6 U/kg/daily (weight x 0,5U). A single dose of insulin usually does not exceed 30-40 U. It should be kept in mind that the physiological demands in insulin are 40 – 60U/24 h.

Different insulin regimen

1. Regular short acting insulin . Adjusting dose based on premeal hyperglycemia, anticipated meal size and physical activity. 1U used for every 15g of carbohydrates in the meal. If carbohydrates count not possible, estimate by using ~ prebreakfast /prelunch/ presupper ratio 3 :2:1 and then modified by postmeal blood glucose and added to the sliding scale.

2. Multiple Daily Injection Program (Basal- bolus therapy) – multiple injections of insulin in conjunction with self-blood glucose monitoring. If near-normalization of blood glucose is attempted, at least three or four measurements of capillary blood glucose and tree or four insulin injections are necessary.

- NPH as basal insulin :- best to initiate at 0,3 U/kg/d total insulin dose starting at a twice daily NPH-regular dose: 2/3 given 20 -30 min prebreakfast and remaining 1 : 3 presupper:- NPH/Regular ratio is 2 :1 prebreakfast and 1:1 presupper
- Insulin glargin as a basal insulin: 1 injection bedtime to provide 24-hour coverage usually, but sometimes it needs to be given twice a day/and rapid-acting insulin analogs premeal

3. "Sliding Scale Insulin" – Variable Insulin Dose Schedule

- patient takes fixed doses of intermediate-acting insulin but varies doses of rapid-acting insulin based on blood glucose reading at time of dose
- use baseline R dose when in blood glucose target range: add or subtract units when above or below target
- allows patient to make corrections to avoid long periods of hyper- or hypoglycemia

4. Insulin pump therapy by portable battery-operated pump

- dosage based on providing 50% of the estimated insulin dose as basal and intermittent boluses prior to meal
- the meal bolus would depend on the carbonhydrate content of the meal and the premeal blood glucose value
- 1U per 15g of carbohydrate +1U for 50mg/dL of blood glucose above a target value
- farther adjustments to basal and bolus dosages would depend on the results of blood glucose monitoring

A combination of rapid-acting insulin analogs and long-acting insulin analogs allows for more physiologic insulin replacement.

5. Travel and Insulin Regimen. If large change in time zones (8 -10 hours) and staying only 1-3 days keep on regimen at home as not enough time for body to even adjust. *Day is lengthened*: day of departure take normal AM dose, wait 10 -12 hours to take normal PM dose with a snack/meal. After 6 hours check blood glucose, if <11 mmol/L wait until next AM to give next dose. IF >11 mmol/L take 1/3 of normal AM dose now. On first day at destination reset watch to local time and take normal doses. *Day is shortened*: day of departure

take normal AM, then PM doses. On first day of destination take 2/3 of normal AM dose, after 10 hours, re-check blood glucose before supper. If < 11 mmol/L take normal PM dose. If > 200mmol/L take remaining 1/3 of morning dose along with PM dose. On second day at destination take normal AM dose and re-set watch to local time, take normal evening dose before supper.

Complications of Insulin Therapy

- Hypoglycaemia
- Local allergic reactions at the injection site including local incting, erythematous and indurated lesions, and discrete subcutaneous nodules.
- Fat atrophy or fat hypertrophy may develop at the injeation sires. Fat atrophy is usually due to impurities in the insulin preparation. Fat hypertrophy is attributed to the local lipogenic effects of the injected insulin.

Therapeutic problems and its therapy

Somogyi syndrome.

Patients with DM Type 1 is determining the proper adjustment of insulin dose when the prebreakfast blood glucose level is high. 3 AM hypoglycemia leads to a surge of counterinsulary hormones to produce high blood glucose level by 7 AM.

- 3AM hypoglycemia leads to rebound hyperglycemia in 7AM, from excessive PM NPH
- Avoid by periodically check 3AM blood glucose: if increased bedtime +increased dinner regular or decreased evening snack;if bedtime blood glucose normal, but increased 3AM, then increased bedtime NPH by 2U;if decreased 3AM, then decreased bedtime NPH by 2U
- Be treated by eliminating the dose of intermediate insulin at dinnertime and giving it at a lower dosage at bedtime or by supplying more food at bedtime

"Dawn phenomenon"

- Present in a patients with type 1 diabetes
- Reduced tissue sensitivity to insulin between 5 AM and 8AM can aggravate the hyperglycemia (in absence of Somogyi)
- Diagnosis of the cause of prebreakfast hyperglycemia can be facilitated by self-monitoring of blood glucose at 3 AM in addition to the usual bedtime and 7AM measurements
- The dosage of intermediate insulin can be divided between dinnertime and bedtime, must increased PM NPH

Methods of insulin administration

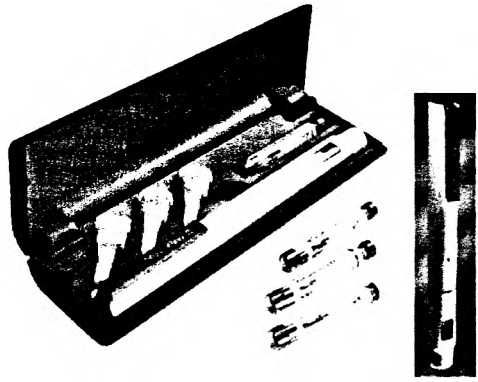
1. Insulin syringes.

Plastic disposable syringes are available in 1-ml, 0.5-ml,and 0,3-ml sizes. Two lengths of needles are available short (8mm) and long (12,7mm). Long needles are preferable in obese patients to reduce variability of insulin absorption. Ultrafine needles as small as 31 gauge reduce the pain of injections. "Disposable" syringes may be reused until blunting of the needle occurs (3- 5 injections).Sterility adequate to avoid infection with reuse appears to maintained by recapping syringes between uses. Cleansing the needle with alcohol may not be desirable since it can dissolve the silicone coating and can increase the pain of skin puncturing.

2. Insulin pen injector devices (Novo Nordisk, Sanofi Aventis, Becton Dicknson).

- eliminate the need for carring an insulin bottle and syringes during the day
- gently mix the suspension before each use
- easy-to-use, convenient and accurate
- helps improve compliance, less dosage errors in arthritis, vision or poor motor coordination, or children

Cartridges of regular insulin, NPH insulin, insulin aspart, insulin glargin and 70% NPH30% regular insulin are available for reusable pens. Thirty-one gauge needles (5,6 and 8mm long) for these pens make injections painless.



3. Insulin pumps (Medronic Mini-Med, Animas, Deltec Cozmo, Disetronic H-Tron – v100 insulin) – continuous subcutaneous insulin infusion - **CSII therapy**

- prime candidate for the insulin pump : pregnant diabetic ,patient with irregular work schedules
- external, battery-operated pump continuously delivers basal dose of rapid-acting insulin through small subcutaneous catheter
- basal insulin infusion should maintain constant blood glucose between meals.
- at meals, patient programs pump to deliver extra insulin bolus
- basal dose may be increased or decreased based on activity, sleep etc.
- can be disconnected, allowing the patient to remove the pump temporarily
- advantages: more flexible lifestyle
- disadvantages: very expensive, increased risk of ketoacidosis if pump disconnected

2. Inhaled insulin (Exubera).

A novel method for delivering preprandial powdered form of insulin by inhalation. Inhaled insulin is administrated 10 minutes prior to meal using a combination of 1 and 3 mg unit doses; 1 mg of inhaled insulin is equivalent to 3 unit subcutaneous insulin injection.This insulin preparation is contraindicated in patients who smoke and who have discontinued smoking for less than 6 months. Pulmonary function tests has recommended every year.

Site of injection

- the abdomen with the exception of a circle with a 2-inch radius around the navel and rotate sites within that region; recommended for subcutaneous injections of short-acting insulins
- thighs: anterior and lateral aspects - subcutaneous
- upper arms - subcutaneous
- flanks and upper buttocks -subcutaneous
- intramuscular injection recommended for DKA or dehydration but not for routine injections (faster onset)
- only regular insulin intravenously
- rotation sites of injection – avoid lipoatrophy or lipohypertrophy

Technique Portable Insulin Pen Devises. The needle is inserted subcutaneous and the plunger is depressed via a button to deliver dose. Slightly longer injection time compared to traditional syringe as need to keep needle in place 5 sec after plunger is completely depressed.

- have a disposable needle
- cartridges can be kept at room temperature for up to 30 days
- Two types (Min/max/increments):

1. Prefilled (disposable): **Humalog, Humulin** (each pen contains 300U of R, NPH, 70/30) 3ml – (1/60/1). **Novolin Prefilled** (R, NPH,70/30) 1,5 ml – (2/58/2).

2. Reusable (replaceable cartridge): potential for loss of sterility. Can deliver as little as 0,5U with short 30g needles. **B-D Pen Classic**, 1.5 ml – (1/30/1). **Autopen AN3000** - (1/16/1)**&AN3100** - (2/32/2). **NovaPen** 1.5 ml – (1/40/1). **Disetronic Pen** 3,15 ml – (1/80/1)

Technique Insulin Infusion Pumps. Insert subcutaneous Teflon cannula or 26-27-g stainless steel needle into abdomen or buttocks, change every 3-5 days. For regular of Lispro insulin ½ is used as basal infusion over 24 hours, the rest is bolus insulin for meals, snacks using 1U/10-15 g of carbohydrates.

Inhaled Insulin

- can take right before 1st bite of meal
- faster onset than subcutaneous
- Not yet approved

Blood Glucose Monitoring (Self-Management training)

- Self-monitoring and recording of blood glucose is now standard management
- Blood glucose monitoring is useful for monitoring patient's long-term diabetes control

- Goals :HbA1C should be no higher than 1% above the upper limit of the normal range for any particular laboratory
- Initially monitor blood glucose 4 times a day, before each meal. Follow closely when make changes
- Once on stable dose can monitor twice a day 4 days/week (8 finger sticks). Follow closely when make changes
- When blood glucose stable check every day in rotating fashion: AM, next day lunch, then dinner, then every night before bedtime
- Once under control, patient can check 1- 2 times/week
- some patients may learn to self titrate their doses; Is affected so markedly by daily fluctuations in environmental stress, exercise, diet, infections

The Average Home Blood Glucose meter (Glucometer)

One Touch Fast Take: uses blood from arm, less painful, uses 40% less blood (1,5 uL of blood or 2,5 uL) and automatically drags blood drop to test strip on contact. Results in 15 sec, store 150, gives the 14 day average.

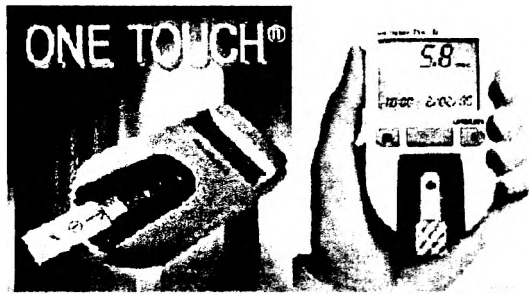
GlucoWatch Biographer: automatic, up to 3 reading/hour for 12 hours, alarm sounds if out of set ranges.Uses ionophoresis that has the enzyme glucose oxidase as a biosensor, then measures electrons from oxidation. Improved quality of life as less finger-sticks.

Mini-Med makes a continuous glucose monitoring system as well. **Lasette:** uses laser to puncture for testing, less painful.

Glucometer Dex: stripless, uses disposable cartridge good for 10 tests.

AtLast System; creates a small break in the arm or thigh using a custom-made lancet.

Microlet Vaculance: helps draw-up blood after skin in lanced in thigh, abdomen or palm so long as meter does not reguire a "hanging drop"



Diabetic Diet

Today there is no "diabetic" diet. The medical nutritional therapy for people with diabetes should be individualized, with consideration given to usual eating habits and other lifestyle factors.

Balanced diet

- protein -15% of daily calories
- fat -20% calories (saturated < 10%, polyunsaturated < 10%) of daily calories
- carbohydrates -65 % of daily calories
- preferred distribution of calories 2/10 breakfast, 3/10 lunch, 4/10 supper, 1/10 bedtime snack
- 50g of dietary fiber each day
- Eat lots of whole grains, vegetables, beans and fruits as 40-50% of daily calories

Carbohydrate counting - 15 :1 rule. 1U of rapid-acting insulin needed for each 15 grams of carbohydrate taken in. Every 15g carbohydrate consumed with meal requires 1U of rapid-acting insulin administered just before eating the meal is particaulary important in insulin-requiring diabetics

- Glycemic index; a ranking of carbohydrates according to their effect on blood-sugar levels.
- Sugar substitutes (nonnutritive sweeter)

Table. 15 grams of Carbohydrates

Bread/Starch Group	Fruit Group	Milk Group	Candy/junk Food
1 slice of bread,1/3 cup of cooked rice, 3/4 cup of unsweetened cereal, 1/2 cup of sweetened cereal, 1/2 cup of corn or peas or ½ a cup of pasta	Small apple/other piece of fruit, 1/2 cup of fruit juice, 2 tablespoon of raisins, 1-1/4 cup of strawberries	1 cup of any milk, ¾ cup of regular fruit yogurt, 1 cup of aspartame sweetened yogurt	Nart candy (six lifesavers),1/2 cup of ice cream/frozen yogurt, ¼ cup of sherbet, 1 tablesoop honey or jam, 2 sugar packets or 1 tablespoon of sugar, 9 jelly beans,3 graham crackers or two small cookies

Table. Glycemic Index

Glycemic Load + gram carbohydrates in serving x Glycemic Index

Baguette	=	136	Pasta	=	71
Baked potato	=	121	Chocolate	=	70
While bread	=	100	All-Bran/Dry beans	=	60
Grape-nuts	=	96	Apple	=	54
White rice	=	81	Carrots	=	49
Wild rice	=	81	Lentis	=	40
Wild rice	=	78	Peanuts	=	21

Refined carbohydrates such as sugar, bread, spaghetti, macaroni, bagels, crackers, cookies and rice. Refined carbohydrates have glycemic indices close to those of refined sugars. Whole grains are absorbed at a significantly slower rate, therefore do not drive up HbA1C as high.

Dietary Management of Diabetes Mellitus: Stepped care.

This involves the estimation of the total daily caloric requirement of the individual patient. This must be estimated after considering a number of variable factors like as age, sex, actual weight, desirable weight, activity, and occupation of the patient.

First step.

Total daily caloric requirement can be calculated as:

- Sedentary individuals 30 Kcal/kg/day.
- Moderately active individual 35 Kcal/kg/day.
- Heavity active individuals 40 Kcal/kg/day.

Second step.

This involves allocation of the calories in a proper proportion to carbohydrate, protein and fat. The recommended proportion of calories to be derived from each of them:

- Carbohydrate 50-60%
- Protein 10-20%
- Saturated fat <10% (<7% if LDL is elevated)
- Polyunsaturated fat <10%
- Monounsaturated fat 10 -15 %.

A few more important factors need be considered at this stage. They are:

- Minimal protein requirement for a good nutritious diet is about 0,9 g/kg/day.
- Carbohydrates should be taken in the form of starches and other complex sugars. Rapidly absorbed simple sugars like glucose should generally

be avoided. Use of caloric sweeteners including sucrose is acceptable in many patients.

- Fish oils cantaining omega 3 fatty acids have been reported to be beneficial, as antiatherogenic.
- High-fiber diet is beneficial as it has an antiatherogenic effect mediated through lowering of blood lipids.

Third step.

This involves distribution of the calories throughout the day. This is particaulary important in insulin-requiring diabetics, to avoid hypoglycaemia. Different distributions may be required for different lifestyles.

A typical pattern of distribution of calories is:

- 20% of the total calories for breakfast.
- 35% of the total calories for lunch.
- 30% of the total calories for dinner.
- 15% of the total calories for late-evening feed.

2. Treatment of Diabetes Mellitus Type 2.

Lifestyle modification

In well-controlled studies that included a lifestyle intervention arm, substantial efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. In the Finnish Diabetes Prevention Study, weight loss averaged 9.2 lb at 1 year, 7.7 lb after 2 years, and 4.6 lb after 5 years ; "moderate exercise," such as brisk walking, for 30 min/day was suggested. In the Finnish study, there was a direct relationship between adherence with the lifestyle intervention and the reduced incidence of diabetes. In the DPP , the lifestyle group lost ~12 lb at 2 years and 9 lb at 3 years (mean weight loss for the study duration was ~12 lb or 6% of initial body weight). In both of these studies, most of the participants were obese (BMI >30 kg/m^2). A low-fat (<25% fat) intake was recommended; if reducing fat did not produce weight loss to goal, calorie restriction was also recommended. Participants weighing 120–174 lb (54–78 kg) at baseline were instructed to follow a 1,200-kcal/day diet (33 g fat), those 175–219 lb (79–99 kg) were instructed to follow a 1,500-kcal/day diet (42 g fat), those 220–249 lb (100–113 kg) were instructed to follow an 1,800-kcal/day diet (50 g fat), and those >250 lb (114 kg) were instructed to follow a 2,000-kcal/day diet (55 g fat).

Oral drugs for treating hyperglycemia

Medications for type 2 diabetes are designed to:

1. Drugs that stimulate insulin secretion(insulin secretagogue). : sulfonylureas and meglitinide.

2. Drugs that alter insulin action (insulin sintetaizer): Metformin and Thiazolidinediones.

3. Drugs that principally affect absorption of glucose (digestion modifiers): acarbose and miglitol.

4. Combination edications: Glucovance.

Design of Oral Glycemics Medications

1. Drugs that stimulate insulin secretion (insulin secretagogue). Premeal Medication .

Second generation of sulfonylureas: glyburide and glipizide.
Third generation of sulfonylureas: glimeperide.

Table. Sulfonylureas (second and third generation sulfonylureas). **Long acting drugs.**

Pharmacological Name	**Commercial Name**	**Tablet Size**	**Daily Dose**	**Duration of Action**
Glyburide	DiaBeta, Micronase	1,25; 2,5, and 5 mg	1,25 – 20 mg as single dose or in 2 divided doses	Up to24 hours
Glipizide	Glucotrol	5 and 10 mg	2,5 – 40 mg as a single dose or in 2 divided doses on an empty stomach	6 – 12 hours
	Glucotrol XL	5 and 10 mg	Up to 20 or 30 mg daily as a single dose	Up to24 hours
Glimepiride	Amaryl	1,2 and 4 mg	1 – 4 mg	Up to 24 hours

Action

Sulfonylureas primarily lower blood glucose levels by increasing the release of insulin from the pancreas. Specific receptors on the surface of pancreatic B-cells bind sulfonylureas in the rank order of their insulintropic potency. Activation of this receptors closes potassium channels, blocks K channels, resulting it depolarization of the B-cell and increase exocytosis of stored insulin.

- Use in patients with residual B-cell function
- Well absorbed
- Work well in combination with Acarbose, Metformin, Troglitazone

Side-effects:

- Hypoglycemia
- Weight gain
- Exfoliative dermatitis
- hepatitis

Table. Meglitinides - short acting drugs. Pre-meal- medication .

Pharmacological Name	Commercial Name	Tablet Size	Daily Dose	Duration of Action
Repaglinide	Prandin	0,5, 1, and 2 mg	4 mg in two divided doses given 15 minutes before breakfast and dinner	3 hours
Nateglinide	Starlix	60 mg and 120 mg	60 or 120 mg 3 times a day before meals	1,5 hours

Primary effect is hepatic glucose output, "Insulin Pill", no renal adjustment needed. A meglitinide derived from benzoic acid, its acts similar to an extremely short-acting sulfonurea but less insulin increase thus less weight gain and fewer hypoglycemic episodes.

Action

- new class of drugs unlike sulfonureas that bind to receptors on the insulin producing cells,
- meglitinides work through a separate potassium based channel on the cell surface allowing for Ca infux
- given before a meal it reduces the postprandial hyperglycemia
- may cause hypoglycemia but less frequent than the hypoglycemia seen with sulfonylurea agents
- works well with Metformin

- very good for young,healthy active patients who eat at unpredictable times
- safe in sulfaureas allergy
- titrate cautiously if elderly with renal or hepatic dysfunction

2. Drugs that alter insulin action. Insulin sensitizer.

These increase sensitivity of insulin by decreasing hepatic gluconeogenesis (primary effects) and increasing peripheral insulin sensitivity (secondary effects). They do not increase insulin levels or weight gain. Alone, they do not cause hypoglycemia.

Table. Biguanides. Pre-meal -medications.

Pharmacological Name	Commercial Name	Tablet Size	Daily Dose	Duration of Action
Metformin	Glucophage	500,850 and 1000mg	1 -2,5 g; one ablet with neals 2 or 3 imes daily	7 – 12 hours
Extended-release metformin	Glucophage XR	500 mg	500 – 2000 ng once a day	Up to24 hours

Action

- Increase glucose utilization in muscle, intestine, fat
- Decrease hepatic glucose output by 30%
- Won't cause hypoglycemia's requires insulin to work and does not stimulate its release
- Decreases Tg by 50%,total and LDL with slight increase HDL.

Titration of Metformin (ADA, 2009).

- Begin with low-dose Metformin (500mg) taken one or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
- After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850, or 500 mg tablets, twice per day (before breakfast and/or dinner).
- If gastrointestinal side apper as doses advanced, decrease to previos lower dose and try to advance the dose at a later time.
- The maximum effective dose can be up to 1,000 mg per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.
- Based on cost considerations, genetic metformin is the first choice of therapy. A longer-acting formulation is available in some countries and can be given once per day.

Side-effects

- Diarrhea
- Metallic taste, nausea,anorexia
- Decrease B-12 and folate absorbtion
- Mild inhibition of lactate metabolism

Table. Thiazolidinediones (TZDs or "Glitazones") .

Pharmacological/ Commercial Name	Tablet Size	Daily Dose	Duration of Action
Rosiglitazone (Avandia)	2, 4 , and 8 mg	4 8 mg daily (can be divided)	Up to 24 hours
Pioglitazone (Actos)	15, 30, and 45 mg	15 -45 mg daily	Up to 24 hours

Action

- Decreases resistance to insulin by at cell membrance (PPAR-gamma receptor) by altering nuclear transcription in muscle (90%0 ("muscle drug") and liver (10%). The major metabolic defect (insulin resistance) in DM2 is in the muscle.
- No increase hypoglycemia as requires insulin to be presenr.
- Increase fertility (ovulation if anovulatory),.
- Addition contraception in anovulatory premenopausal women
- Good for obesity and insulin resistant in combination with insulin or sulfonureas
- Insulin sparing like Metformin.

Side-effects:

- Increased cholecterol.
- Weight gane
- Anemia
- Edema (fluid retention)
-

3. Drugs that principally affect absorption of glucose (digestion modifiers).

Table. Alfa-glucosidase inhibitors. Pre-meal medications.

Pharmacological/ Commercial Name	Tablet Size	Daily Dose	Duration of Action
Acarbose (Precose)	50 and 100 mg	75 – 300 mg in 3 divided doses with first bite of food	4 hours
Miglitol (Glyset)	25, 50, and 100 mg	75- 300 mg in 3 divided doses with first bite of food	4 hours

Action

- In small bowel to delay the breakdown of ingested carbohydrates
- Decrease postprandial glucose 50% and fasting 15%
- No hypoglycemia
- Good for children
- Not absorbed
- No systemic side-effects
- Synergistic with sulfonureas
- Good if mild liver or renal impairment

Side-effects

- Abdominal pain
- Diarrhea
- Terminal flatulence from colonic breakdowns of carbohydrates.

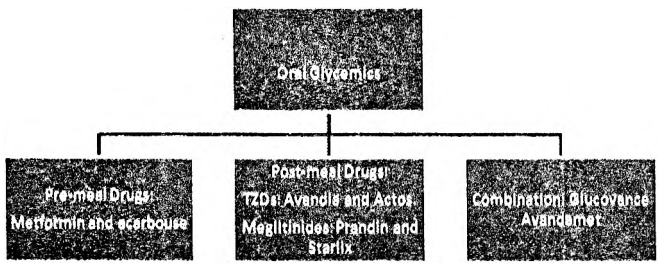
4. Combination medications.

Glucovance = Metformone+Glyburide (1,25/250;2,5/500;5/500 mg).

Avandamet= Rosiglitazone+metformin (1/500;2/500;4/500mg).

- Can be used for initial therapy.

Design. Oral Glycemics according meal



Design. Oral Glycemics according mechanism action

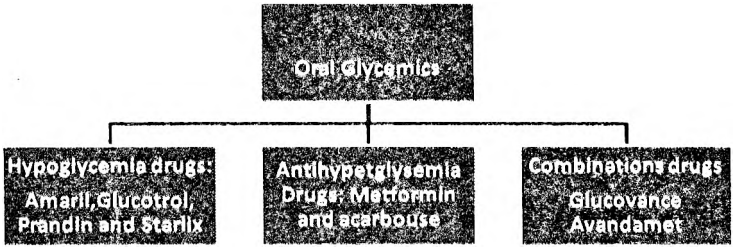


Table. Oral antidiabetic drugs that stimulate insulin secretion.

Drug	Tablet size	Daily dose	Duration of action
SYLFONYLUREAS			
Glyburide (Micronase,Diabeta)	1,25 mg; 2,5 mg; 5mg	1,25-20 mg as single dose or in 2 divided doses	Up to 24 hours
Gllipizide (Glucotrol)	5 and 10 mg	2,5 -40 mg as single dose or in 2 divided doses on empty stomach	6 – 12 hours
Glucotrol XL	5 and 10 mg	Up to 20 or 30 mg daily as a single dose	Up to 24 hours
Glimeperide (Amaril)	1,2 and 4 mg	1 – 4 mg as single dose	Up to 24 hours
MEGLINIDE ANALOGS			
Repaglinide (Prandin)	0,5mg,1mg, and 2 mg	4 mg in two divided doses giver 15 minutes before breakfast and dinner	3 hours
d-PHENYLALANINE DERIVATIVE			
Nateglinide (Starlix)	60 mg and 120 mg	60 or 120 mg 3 times a day before meals	1,5 hours

Table. Oral antidiabetic drugs that are insulin-sparing.

BIGUANIDES			
Metformin (Glucophage)	500, 850, and 1000 mg	1 – 2,5 g; one tablet with meals 2 or 3 times daily	7 – 12 hours
Extended-release Metformin (Glucophage XR)	500 mg	500 – 2000 mg once a day	Up to 24 hours
THYAZOLIDINEDIONES			
Rosiglitazone (Avandia)	2, 4 , and 8 mg	4 8 mg daily (can be divided)	Up to 24 hours
Pioglitazone (Actos)	15, 30, and 45 mg	15 -45 mg dai-ly	Up to 24 hours
ALFA-GLUCOSIDASE INHIBITORS			
Acarbose (Precose)	50 and 100 mg	75 – 300 mg in 3 divided doses with first bite of food	4 hours
Miglitol (Glyset)	25, 50, and 100 mg	75- 300 mg in 3 divided doses with first bite of food	4 hours

Table.Combination oral antidiabetic drugs.

Glyburide/Metformin (Glucovance)	1,25 mg/250 mg 2,5 mg/500 mg 5 mg/500 mg	Maximum daily dose of 20 mg glyburide/2000 mg metformin	See individual drugs
Rosiglitazone/metformin (Avandamet)	1 mg/500 mg 2 mg/500 mg 4 mg/500 mg	Maximum daily dose of 8 mg ro-siglitazone/2000 mg metformin	See individual drugs

Injeccted antihyperglycemic medications for use in patients with DM type 2

New medications that effect glycemic control.

1. **Amylin agonists - Symlin (pramlintide).**

Symlin (pramlintide) is the first in a new class of injected antihyperglycemic medications for use in patients with DM type 2 or DM type 1 treated with insulin.

- Synthetic analog of human amylin (neuroendoctine hormone synthesized from pancreatic B-cells that contributes to glucose control during the postprandial period)
- When used with insulin,this compound can help improved glycemic control
- Cannot be realized with insulin alone

Action

- Redused postprandial glucouse peaks
- Reduces glucouse fluctuations throughout the day
- Enhances satiety leading to potential weight loss
- Lowers mealtime insulin requirements

Indication

- DM type 2,as an adjunct treatment in patients who use mealtime insulin therapy(regular insulin or rapid-acting insulin analogs) and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin
- DM type1, as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy.

Administration

- Taken just prior to meals, tree time a day subcutaneus (injection form).

2. **Glucagon-like peptide-1 agonists (GLP-1)- Byetta (exenatide).**

Byetta is the first in a new class of a drugs for the treatment of DM type2 called incretin mimetic.It's origins ia an interesting place- the Gila monster's saliva. This small lizard noted it could go a long time wiyhout eating. This substance found in it's saliva that slowed stomach empting, thus making the lizard feel fuller longer. This substance similar in nature to a gut hormone found in humans GLP-1.

GLP-1 a naturally occurring peptide produced by the *l*-cells of the small intestine, potentiates glucose-stimulated insulin secretion.Exenatide has homology with the human GLP-1 sequence but has longer circulating half-life. It binds

avidly to the GLP-1 receptor on the pancreatic B-cell and augments glucose-mediated insulin secretion.

Action

- To have many effects on glucose regulation as GLP-1
- Mimics the body's natural physiology for self-regulating blood sugar
- Enhance glucose-dependent insulin secretion by B-cells
- Suppresses inappropriately elevated glucagon secretion
- Slow gastric empting.

Side effects

- Nausea, vomiting, diarrhea

Administration

- Two time a day subcutaneous 5 mcg bid within 1 hour in morning and evening (injection form).
- Is approve for use with sulfonylurea, metformin, and/or a TZD.

Treatment Approach Diabetes Mellitus Type 2:

Stepped care.

Choice of specific antihyperglycemic agents is predicated on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expence.

Step 1.If fasting glycemia < 160 mg/dL start with nutritition, lifestayle modification, smoking cessation, exercise, self monitoring glucose, aspirin every day, vitamin E 400 IU/d to decrease oxidative stress, decries BP to <130/80.

Step 2. If not at target after 2-4 month or initial fasting glycemia is >160 mg/dL add on combination of oral hypoglycemic.

Step 3. Add a 3rd oral glycemics agent.

Step 4. Add insulin.

Step 5. If HbA1C still hugh, stop orals and intensify insulin by giving NPH before breakfast and every night before bedtime + regular or Lizpro before meals or 70/30 before breakfast and dinner.

Step 6. Add Metformin or Troglitazone to insulin therapy.

Poorly controlled diabetes mellitus type 2 – use 3-4 oral agents of different classes. May need to add NPH insulin every night before bed time.

Treatment Approach Diabetes Mellitus Type 2 the Overweight patients.

- Diet and exercise
- + Metformin or @-Glucosidase or TZd's to treat insulin resistance
- + Sulfonylurea
- + every night before bedtime NPH insulin
- +NPH or Lente before bedtime.

Consider Orlistat.

Treatment Approach Diabetes Mellitus Adult Patient 20-30 years old

Screen for DM Type 1 with stimulated C-peptide measurement:

- If low – DM Type 1, high – DM type 2
- If 20-30years old with high C-peptide – diet, exercise, weight loss.
- If fasting glucose > 180 start medicines.
- Thin, youger adult patients or if low C-peptide is more likely to have a B-cell defect and will respond better to Sulfonylureas or Repaglinide or Insulin as the initial treatment.

Insulin therapy Diabetes Mellitus Type 2.

Start insulin if:

- fail 3 month nutritional and exercise therapy and oral drugs not working ,
- ketosis
- imminent surgery,
- gestational
- renal damage.

Starting insulin dose 0,5 -0,6 units/kg/day: 2/3 am(70%NPH,30%R), 1/3 pm (50 -50) also start Metformin at 500 mg*7d then twice a day. Dose should cover expected carbohydrates intake (1U per 10-15 g carbohydrates).

- Athletes may only need 0,5 U/kg
- Females may need 0,7 U/kg during the peak hormonal time of their cycle, 0,8U/kg during the 2nd trimester, and 0,9 -1 U/kg during 3rd trimester
- Up to 2U/kg may be need if very sick or during puberty. A child in DKA with an infection during puberty may need 4 U/kg.

Starting NPH or intermediate acting: weight in kg /4 = dose in units at 10 pm.

Start 70/30 at weight in kg/2 = dose in units.

Algorithm of Insulin Therapy for DM Type 2 (ADA, 2009).

1. Start with bedtime intermediate-acting insulin or bedtime or morning NPH (can initiate with 10 U or 0,2 U/kg.
2. Check fasting glucose (fingerstic) usually daily and increase dose, typically by 2 U every 3 days until fasting levels are consistently in target range

(3,9 – 7,2 mmol/L – 70 -130 mg/dL).Can increase dose in larger increments, e.g. by 4U every 3 days, if fasting glucose is > 10 mmol/L (180 mg/dL).

3. If hypoglycaemia occurs, or fasting glucose level < 3,9 mmol/L (70 mg/dL), reduce bedtime dose by 4 U or 10% - whichever is gteater.

4. If HBA1c>7% after 2-3 months and if fasting blood glucose is in target range (3.9 -7,2 mmol/L -70 -130 mg/dL), check blood glucose before lunch, dinner and bed. Depending on blood glucose results, add second injection as below. Can usually begin with 4 U and adjust by 2 U every 3 days until blood glucose is in range:

a) Pre-lunch blood glucose out of range add R-insulin at breakfast

b) Pre-dinner blood glucose out of range add NPH-insulin at breakfast or R-insulin at lunch

c) Pre-bed blood glucose out of range add R-insulin at dinner

5. If not HBA1c>7% after 2-3 months – continue regimen and check HBA1c every 3 month, if HBA1c >7% after 3 months recheck pre-meal .blood glucose levels and if out of range, may need to add another injection. If HBA1c continues to be out of range, check 2 hour postprandial levels and adjust pre-prandial R-insulin.

Control levels:

- Fasting blood glycemia – 65-126 mg/dL
- 2 hour postmeal – 180mg/dL, 2-4 am -60 -80 mg/dL
- Hba1c < 7%.
- If poorly control and patient on oral glycemics: add every night before bedtime NPH 0,1 units /body weight or single dose of 70/30 before dinner while continue oral medicines. As less weght gain than am NPH.

Chapter IV. The Comatose States in Diabetes Mellitus.

Definition

"Coma" is derived from Greek "Koma" meaning deep sleep. Coma has been defined as absence of any psychologically understandable response to external stimuli or inner need.

Signs of Coma

1. Altered physiological function.
2. Raised intracranial tension.
3. Herniations syndromes.

1. Altered physiological function.

In comatose patient five parameters altered which are assessed.

A. State of consciousness: This is a level of the individual awareness and the responsiveness of his mind to himself, the environment and the impressions made by his senses. Various terms used in the past to define different degrees of coma are:

a) Coma: There is a complete loss of consciousness from which the patient cannot be aroused by painful stimuli, all reflexes are lost including corneal, light cough, swallowing, etc.

Evaluation of Severity of Coma
(Edinburgh Classification).

Grade 0. Fully conscious.
Grade 1. Drowsy, but responds to verbal commands.
Grade 2. Unconscious, but responds to minimal pain stimulus.
Grade 3. Unconscious, but responds to strong pain stimulus.
Grade 4. Unconscious with no response pain.

b) Stupor. This is a state of partial loss of response to the environment. The patient is difficult to arouse and though he can be briefly aroused, it is slow and inadequate. The patient is otherwise not aware of his environment and falls back into the stuporous state.

c) Hypersomnia or lethargy: Thia is morbid drowsiness or prolonged sleep from which the patient can be aroused or awakened. He appeareas to be in complete possession of his senses but goes back to sleep as soon as the stimulation is remived.

d) Syncope: this is traisient, partial or complete suspension of consciousness with impaired circulation and respiration, pallor, perspiration and cold skin.

e) Fugue state: This is a disturbance of consciousness, lasting hours or days, in which the patient performs purposeful acts, but later, consciously fails to remember actions out during that period.

f) Confusion. This is a mild lowering of the level of consciousness. This is impaired, capacity to think clearly and with customary rapidity, and to perceive, to respond to and remember guestions or directions.

g) Delirium. This is characterized by confusion, disorded perception and loss of attention. This is marked disorientation in time, excitement and hyperkinesias.

B. Respiratory patterns: Comatose patients often have characteristic pattern depending upon the site of lesion and its etiology.

a) Hyperventilation: This is present with hypoxia, acidosis, salicylate poisoning, severe psychogenic causes.

b) Hypoventilation; This is present with respiratory failure, sedative-narcotic overdosage and braine-stem compression.

c) Cheyne-Stokes respiration: This is characterized by alternate periods of hyperpnea and apnea. It is present with bilateral cerebral hemisphere dysfunction as in hypertensive or metabolic diseases. It also occurs with impending transtentoprial herniation.

d) Central Neurogenic Hyperventilation: This is characterized by a sustained repid, regular and deep hyperpnea. It is seen in lesions of Ascending

Reticular Activating System and often suggests transtentorial herniation with mid-brain compression.

e) Apneustic breathing: This is characterized by apause at full inspiration indicating lesion of lower pons.

f) Ataxic or cluster breathing: This is characterized by irregularly irregular breathing pattern and is seen with compression of medulla oblongata.

C. Pupils: Equal and normally reactive pupils suggest that the oculomotor nerve and the upper brain-stem are intact. Full and conjugate eye movements suggest that midbrain and pontine tegmentum are intact.

a) Pupillary reaction helps to differentiate structural from metabolic causes of coma. Pupillary pathways are relatively resistant to metabolic insult and hence in metabolic disorders, pupils are reactive to light. Absence of light reflex suggests structural lesion, asphyxia, hypothermia and drugs.

b) Fixed and dilated pupils suggest instillation of mydriatic drops or direct trauma to the orbit or oculomotor nerve.

c) Hippus: This is spontaneous, rhythmic constriction and dilatation of pupils which suggest mid-brain damage.

d) Irregular pupils: 1-2 mm irregularity may be normally present or may occur with early oculomotor nerve palsy, trauma or mydriatic eye drops.

D. Eye movements and Ocular reflexes:

a) Conjugate gaze to one side suggests ipsilateral frontal lobe lesion or contralateral pontine lesion.

b) Sundowm dewiation is seen with mid-brain compression.

c) Ocular bobbing occurs with primary pontine hemorrhage.

d) Horizontal eye roving is seen with mild metabolic coma.

e) Doll"s eye movements or oculocephalic reflex: On vertical or horizontal rotation of the head, conjugate deviation of the eyeballs occur on the opposite side if brainstem is intact. If brainstem is intact. If brainstem is damaged the eyes follow the direction of the head rotation. In hypoglycemia and hepatic encephalopathy this response is brisk. However, as the metabolic coma progresses, the abnormal response eventually ensues. This reflex must not be attempted if there is doubt about trauma to the cervical spine.

f) Caloric response or oculovestibular reflex: After the external auditory canal is cleared of wax, the patient is put in supine position with head elevated to 30o and the external canal is then irrigated with cold water. Thia will result in horizontal nystagmus with fast component to the opposite side if vestibule-oculomotor brainstem pathways are intact. In metabolic or structural brainstem lesion, there is dysconjugate ocular movement.

g) Cilio-spinal reflex: A noxious stimulus over the skin of the neck, face or upper trunk causes bilateral papillary dilatation if the sympathetic pathways are intact.

h) Corneal reflex: On touching the cornea with a wisp of cotton, there is blinking of both the eyelids if fifth and seventh cranial nerves are intact. This reflex is absent early in posterior fossa or brainstem lesion.

E. Motor response: Distinct motor response can occur in various levels and types of coma. Application of noxious stimuli leads to varios postures:

a) Decorticate posture: Flexion of any or all the limbs suggests lesion in the descending motor pathways above rostal mid-brain.

b) Decorticate posture: Extension of the limbs suggests lesion in the midbrain and upper pons due to herniation or toxic or metabolic disorder.

c) Triple flexion; Decerebrate upper extremities with lower limb flexion is triple flexion response which results from the spinal reflex secondary to damaged descending motor tracts.

d) Cortical response: When there is lesion of the cerebral hemispheres, several motor and behavioral patterns, similar to those of a normal infant functioning at the thalamic level appear. They are bilateral symmetrical such as sucking, snorting, grasping, motor perseveration and gegenhalten (increased muscle tone to passive movements).

F. **Raised intracranial pressure (ICP).**

The normal ICP is 2-15 mm of Hg. It is raised with any space-occupying lesion in the brain. The symptoms and signs of raised ICP are headache, vomiting, papilledema, bradycardia, hypertension, Cheynes-Stokes respiration, yawning and hiccupping.

F. Herniation syndromes.

G. There are two herniation syndromes-uncal and transtentorial which can rapidly cause irreversible brain-stem damage if untreated at an early stage. A third type infratentorial herniation is not common.

a) Uncal herniation: This results from an expanding intracranial lesion in the temporal lobe or lateral cranial vault. Uncus and the hippocampal gyrus compresses the adjacent midbrain the oculomotor nerve and the posterior nerve and the posterior cerebral artery. Initially there is ipsilateral papillary dilatation with contralateral hemiplegia. Later, there is is decorticate and decerebrate posturing and loss of ocular reflexes. As the pons in compressed, the corneal reflex is lost and when medulla is involved there may be apnea, hypotension and cardiac arrest.

b) Transtantorial or central herniation: This is associated with lesions in frontal, parietal or temporal lobes. Diencephalon or midbrain is displaced.

c) Infratentorial: The signs and symptoms are due to herniation of the cerebellum and mesencephalon upward through the transtentorial notch, obstructing CSF and venous return or a downward herniation through the foramen magnum causing fatal cardio-respiratory failure.

1.Diabetic Hypoglycemia.

Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin. Occurs most often in insulin-treated diabetics, usually due to problems with matching insulin dose to estimated blood glucose levels.Hypoglycemia is a dangerous comopication, and in the short time run more serios than hyperhlycemia. Prolonged hypoglyucemia may cause permanent brain damage.

Less commonly, hypoglycemia occurs in non-diabetics persons (alcohol intoxication, insulin-secreting tumors, oral hypoglycemic drugs, pentamidine).

"Re-explain" Renal failure, Exogenous, **Pituitary**, Liver failure, Alcohol, Insulinoma/Infection, Neoplasm

Ethiology (Risk in Diabetics):

- Insulin excess (intensive therapy, dosing errors, erratic absorption due to lipohypertrophy)
- Medicines(sulfonamides, sulfonylureas, beta-blockers)
- Not enough carbohydrate
- Too much glucose use by the body
- Unusual physical exertion

Pathogenesis

Protection against hypoglycaemia is normally provided by two mechanisms as plasma glucose concentration falls:

1. Cessation of insulin release.
2. Secretion of counter-regulatory hormones.

The 4 counter-regulatory hormones are glucagon, catecholamines (epinefrin and norepinefrine), cortisol and growth hormone. They counter hypoglycemia by increasing hepatic glucose prodactiion and decreasing glucose utilization by non-hepatic tissues. Glucagon is the primary counter-regulatory hormone, while catecholamines serve as the major backup. Cortisol and growth hormone do not function acutely, but come into play sustained hypoglycemia.

3.Diabetic patients are vulnerable to hypoglycaemia due to two reasons:

- insulin excess
- counter-regulatory failure. In the early stages inself, DM Type 1 patients lose the capacity to increase glucagone release in response to hypoglycaemia. Many patients also lose the capacity to release cathecholamines in response to hypoglycaemia, as a result of diabetic autonomic neuropathy.

Symptoms and signs:

Hypoglycemia may be:

- Mild
- Severe
- Proper comatose state
-

Symptoms and signs of the mild hypoglycemia

- Anxiety, Hunger
- Irritability restlessness
- Trouble concentrating
- Dizziness
- diplopia, blurred vision
- Sweating
- Tremor
- Palpitation
- Skin moist
- Respiration, body temperature normal

Laboratory

- Fasting blood glucose <2,8 mmol/l (les then 40 mg%) and <2,2 mmol/l after meal
- Glucose absent in urine, no acetone

Treatment of the mild hypoglycemia

- By eating or drinking carbohydrates;
- orange juice, tea
- sugar candies
- glucose tablets

Symptoms and signs of severe hypoglycemia

- personality changes, mood changes
- trizm
- Muscle rigidity, exaggerated tendon reflexes, tonic and clonic spasms
- Pupils dilated

Treatment severe hypoglycemia

- Glucagon - 1 mg im/iv/sc (onset 5-20 min)
- Glucose - 40% - 20 -40 ml i/v

Deep hypoglycemic comatose state

- Consciousness is fully lost
- Hypotention or hypertention,arrhythmia
- areflexia, lowered body temperature,
- adynamia, cessation of sweating and convulsions
- Oedema of the brain and lungs
- Cerebrocirculatory disorders, hemiplegia
- Death

Treatment of hypoglycemic coma

- 40% Glucose i/v strem 40 -100 ml

- Hydrocortisone150-200 mg i/v, i/m or prednisolon 30 -90 mg i/v
- Adrenaline 0,1% -0,5 -1 ml s/c,i/v
- Mannitol 15 -20% 0,5 -1g/kg i/v,Magnezium sulphate 25%-5 -10ml i/v

Prognosis

- Favourable when diagnosis/treatment are timely
- Fatal outcome when treatment are absence

Complications in hypoglycemic coma

- Edema of the brain and lungs
- Cerebrocirculatory disorders
- Myocardial infarction

Insult and hemiplegia

Somagui phenomenon (posthypoglycaemia hyperglycaemia)

- Refers to rebound hyperglycaemia following an episode of hypoglycaemia, due to counter-regulatory hormone release.
- Manifests as morning fasting hyperglycaemia, in response to unrecognized nocturnal hypoglycaemia
- The significance of the Somagui phenomenon is that the correction of the morning hyperglycaemia depends on reducing, and not increasing the evening dose of intermediate-acting insulin.

Clues to the presense of Somagui phenomenon

The classical clinical picture is one of the worsening diabetic control in the presense of increasing insulin doses and is manifested especially by fasting hyperglycaemia.

a) excessive hunger and weight gain occurring in the context of worsening hyperglycaemia

b) subtle clinical signs of nocturnal hypoglycaemia, such as mild nocturnal swaating, morning headacheas, and hyportermia

c) Wide fluctuations in the plasma glucose and urine glucose occurring over short time intervals, and not related to meals

d) Can be confirmed by documenting hypoglycaemia at 3AM and hyperglycaemia in the fasting state

e) The ultimate criterion for the diagnosis is improvement in diabetic control after a decrease in the insulin dose

The Dawn Phenomenon

- Closely related to the Somagui phenomenon in that there is fasting hyperglycaemia, but no hypoglycaemia during the night
- The mechanism of the dawm phenomenon is thought to be nocturnal surge of growth hormone release or increased clearance of insulin in the mornings
- -can be confirmed and differentiated from the Somagui phenomenon by documenting at 3AM and in the morning

- The significance of the dawn phenomenon is that, the correction of the fasting hyperglycaemia depends on increasing, and not decreasing the insulin.

2. Diabetic Ketoacidosis.

It is acute complication of the diabetes mellitus which characterized by hyperglycemia, dehydration , acidosis, ketonemia, ketonuria

Ethiology

-Too little/no insulin injected

-Too much carbohydrate intake

- Fevers

- Infections
- Heart attacks
- stress
- Medicines: thiazide water pills
- corticosteroids
- birth control pills
- protease inhibitors

Pathogenesis

Diabetic ketoacidosis results from insulin deficiency and glucagon excess. Hyperglycaemia resulting in a hyperosmolar state, which induces an osmotic leading to volume depletion and dehydration. Activation of lipolysis in adipose tissue, resulting in release of increased amounts of free fatty acids into a plasma, which are taken up by the liver.Accelerated hepatic gluconeogenesis and impaired peripheral utilization of glucose, both resulting in severe hyperglycaemia. This hyperglycaemia induces an osmotic dieresis leading to volume depletion and dehydration. Activation ketogenic process resulting in ketosis and metabolic acidosis. The mechanism is complex and invololves the following sequences: the exess glucagon causes a resetting of the hepatic metabolism of fre fatty acids. This is achieved throuth an increased activity of the enzyme, carnitine acyltransferase. The result is that hepatic mitochondria convert free fatty acids to ketone bodies which accumulate in the body fluids. The ketone bodies mainly include acrtoacetic acid and beta-hydroxybutyrie acid, but to minor amount, acetone also.They are responsible for the acidotic state. These acids dissociate completely, releasing hydrogen ions into the body fluids with a resultant fall in pH. The fall in pH is countered by the buffers, especially bicarbonate, which is used up.

Pathogenesis of DKA - Summary

- Insulin deficiency combined with increased counter-regulatory hormones
- Unrestricted hepatic glucose production – extreme hyperglycemia
- Lipolisis - free fatty acids – ketoacids – acidosis

- Osmotic diuresis causes dehydration and electrolyte abnormalities

Ketoacidotic coma degree

- Mild - stage DKA I
- Manifested – DKAII
- Severe – DKA III
- Coma proper – DKA IY

Symptoms and signs:

- Confusion or drowsiness
- Nausea/ vomiting
- Fruity smelling breath –acetone odor
- Rapid, deep breathing – Kussmaul respiration's
- diffuse abdominal pain
- Increased thirst/urination
- dehydration

DKA I

- Sharp weakness
- Lassitude
- Somnolence
- Vomiting
- Headache, dizziness
- Abdominal pain –"pseudoperitonites"

DKA II and DKA III

- Sopor (deep pathological sleep)
- Pain sensation, swallowing, pupillary and corneal reflexes are preserved

DKA IY (proper coma)

- Consciousness is fully lost, diminished muscle tonus
- Respiration is gasping, deep with prolonged inspiration and brief expiration (Kussmaul's respiration) with frutty (aceton) smelling breath
- pink, pale, dry, cold, inelastic skin
- eyeball hypotension
- Pupils constricted
- Collapse, arrythmia

Oliguria, anuria

Laboratory Findings

- Hyperglycemia 20 to > 30 mmol/l
- PH 7.2 – 6.8, ketonemia
- Decreased Na, K, CI, HCO3
- Glucosuria, acetonuria, proteinuria, cylindruria, microhaematuria
- neutrophilic leucocytosis, accelerated ESR

ECG -signs of the hypokaliemia such as:

- Segment ST dearease
- low T wave
- QRST complex elongeed
- Patological U >T (2:1) V1 – V2
- Fibrillation, exstrasystole

Diagnosis criteria for DKA:

1. Blood glucose > 250 mg/dL, arterial pH < 7,3, serum bicarbonate < 15 mEq/L and moderate degree of ketonemia and/or ketonuria.
2. The anion gap of > 12 mEq/L is usually present.
3. Assesment of ketonemia and/or ketonuria is usually performed by nitroprusside test which provides srmiquantitave assay of acetoacetate and acetone levels. Tis assay underestimates the severity of ketoacidosis as it does not recognize the presence of beta-hydroxybutyric acid, the main ketoacid in DKA.

Treatment

- Rehydration 1-2 L 0,9%NaCI in 1st 1-2 hr (15cc/kg/hr) and 0,5 -1L per hour (2-9-2hr).
- Insulin infusion:10 -20U(0,15U/kg) bolus, then 0,1 U/kg infusion (add 500U insulin to 1L 0,9%NaCl for concentration of 0,5U/ml)
- When blood glucose <15mmol/l add 5% glucose and reduce insulin infusion by 1/2
- Avoid hypokaliemia
- K+ lost from cells due to insulin deficiency and general catabolic state
- Blood levels do not reflect total body losses which may be 400 - 500mEq
- K+ falls during treatment due to rehydratation and insulin action(drives K+ into cells)
- Replace as KCL
- When K<3mEq/L add 40mEq/L
- When K<4 -4,5mEq/L add 10 -20mEq/L
- When K is 3 -4 add 30mEq/L
- When K is 5-6 add<10mEq/l
- If pH<6,9 give 100mol in 4000 ml H2O at 200 ml/hr
- If Ph 6,9 -7 give 50mmol (200mlbicarb in H2O at 200ml/hr)
- Mannitol 15% -20% 0,5 -1 g/kg (treatment cerebral edema)

Prognosis in ketoacidotic coma

- Most favourable if coma not more 6 hr
- Is poor in according of myocardial infarction or cerebrocirculatory disturbances
- Fatal outcome without treatment

Complications of diabetic ketoacidosis

- Acute gastric dilatation or erosive gastritis
- Cerebral oedema.
- Hyperkalaemia.
- Hypoglyucaemia.
- Infections.
- Insulin resistance.
- Myocardial infarction.
- Vascular thtombosis Somagui phenomenon.

3. Hyperglycaemic Hyperosmolar State.

This is a syndrome characterized by extreme dehydration resulting from sustained hyperglycaemic dieresis under circumstances in which the patient is unable to drink sufficient water. The biochemical hallmark of the syndrome is extreme hyperglycaemia in the absence of significant ketoacidosis.

- Usually complication of DM type 2
- High mortality rate, of more than 50%

Ethiology

- Profaund dehydration resulting from hyperglycemia
- Precipitating events: infection, stroke, myocardial infarction, trauma
- Drugs :glucocorticoids, immunosuppressives, diuretics
- Medical procedures – dialysis
- Reduced fluid intake, especially in elderly, bedridden patients
- Bleeding
- Acute pancreatitis

Pathogenesis

- Extreme hyperglycemia
- Hyperosmolality
- Volume depletion and CNS signs

Laboratory

- High serum osmolality >350mOsm/L
- Blood glucouse >30 to 55 mmol/L(range 600 – 2,400 mg/dL)
- Urine negative for ketones, high urine glucose
- Prerenal azotaemia with elevation of blood urea nitrogen and creatinine
- A mild metabolic acidosis with marginal decrease in plasma bicarbonate (<10 mmol/L) indicates lactic acidosis
- Hyponatriemia, hyperchloremia, hyperazotmia
- Leucocytosis, high haemoglobin

Symptoms and signs

- Coma develops in periods - 2hour to 1-2 days
- Rapid dehydration
- Dry mucous and skin, eyeball tonus diminished
- Pupils constricted
- Hypotension, colanse, tachycardia, arrhythmia
- Tachypnoea without acetone odor
- Oliguria, anuria
- CNS signs: bilateral,spontaneous nystagmus, muscular hypertonus, epileptoid fits, transient hemiplegia
- Venos and arterial trombosis

Treatment

- Rehydration with 0,45% NaCl
- Insulin infusion 0,1U/kg/hr
- Cerebral edema may result if osmolality is treated too aggressively

Heparin 5000 -10 000 U i/v

4. Hyperlactacidaemic coma.

Lactic acidosis occurs when lactic acid is produced at accelerated rates, due to anaerobic metabolism in skeletal muscles and other tissues.

Ethiology

- Very rare occurrence
- Hypoxia of any genesis:cardiac and respiratory failure, anaemia, shock, hemorrahges
- Drugs: biguanides, salicylates
- Renal or hepatic insufficiency

Pathogenesis

- Develops acutely during a few hour
- Excess production of lactic acid
- Pyruvic acid is accumulated and converted into lactic acid
- Activated the processes of anaerobic glycolysis

Laboratory

- Mild hyperglicaemia <20mmol/l, negative ketonaemia
- Mild glucosuria, negative ketonuria
- Increased blood ratio lactic/pyruvate
- Diagnosis is confirmed by alow arterial pH (<7,2), increased anion gap, decreased plasma bicarbonate, and a high concentration (>5,0 mmol/L) of lactic acid in the blood.

Symptoms and signs

- Nausea, vomiting
- Somnolence, delirium, loss of consciosness
- Kusmaul's respiration without acetone odor

- Low body temperature
- Hypotension, collanse
- Motor anxiety
- anuria

Treatment

- To neutralize and remove the excess of lactic acid:2,5% sodium bi-carbonate -336mml/hr(100mmol/hr i/v drip
- Oxygen
- Insulin i/v drip 6-8U in 500ml -5% Glucouse
- Plasma, substituting solutions i/v
- Hydocortisone 250 -500mg i/v
- Haemodialysis in severe cases(ineffective therapy, anuria)

Prognosis

- Doubtful
- Mortality 50%

Chapter V. Insulinoma.

Insulinoma is a pancreatic insulin secreting tumor:

- Median age is 50 years old, but 23 years old if have MEN-1.
- Most are solitary, spherical, size varies from 2 mm to 10 sm, very rarely to 15 sm.
- 10% multiple, 10% malignant, 10% MEN-1 related.
- If malignant, matastases spread into the liver.
- Located in the tail, head, and body of the pancreas
- Sometimes are located extra pancreatically :in the duodenal wall, splenic hilum

Pathogenesis

Dificient supply of the brain with glucose and oxygen leads to stimulation of the sympathetic nervus system and subsequent increase of catecholamains in the blood. Reduced oxidation processes and disorders of all types of metabolism in the brain are as a result of hypoglycaemia lead to the loss of normal tonus by the walls of the cerebral vessels. The last circumstance is the cause of vascular dilatation and increased permeability not only under the effect of catecholamaines, but also as a consequence of theaugmented flow of blood to the brain because of the constriction of the peripheral vessels. Dilatation of the vessels and the increase of their permeability lead to development of cerebral oedema, deceleration of the rate of blood flow, and the formation of thrombi with subsequent development of atrophic and degenerative changes in the brain. Histological examination of the brain revels diffuse changes in the nerve cells: petechiae, haemorrage.

Symptoms and signs

- Attack of hypoglycaemia occuк suddenly

- In the morning: diplopia, blurred vision, palpitation, sweating, weakness, confusion, amnesia, hunger or nausea.
- Face is flushed, the skin moist, profuse sweating
- Increased muscular tonus, tendon and periosteal reflexes, convulsions, Babinski"s sign +, Rossolimo's sign +.
- Pupils wide

Deep coma

The period of excitation is replaced by loss of consciousness :

- Areflexia
- Fall in body temperature
- Bradicardia, shallow breatning.

During latent period between hypoglycaemic attacks patient complain of loss of memory, impaired mental working capacity, apathy, sometimes muscular pain, weigth gain

Laboratory

- Range of glucouse 0.55 – 1,1 mmol/L (52-10 mg/dL) or lower in hypoglucaemic attack.
- Immunoreactive insulin increased,C-peptide and proinsulin increased.
- Fasting glycaemia <1.65 mmol/l (30 mg/dL),blood glucose testing on a fasting stomach and during 24 hours with the patient reciving ba diet ordinarly prescribed.
- Plasma sulfonyreas test
- MRI/CT confirm.

Treatment

-Surgery

Prognosis

- Favorable if surgery treatment.
- If radical treatment is not applied, the prognosis is poor
- Letal outcome may occur during a hypoglycaemia coma.

Chapter VI. Diseases of the Thyroid Gland.

Anatomy of the Thyroid Gland

Thyroid gland is located in the neck, below Adam's apple, in front of windpipe, with two connecting lobes and isthmus and is well supplied with blood vessels, the right lobe is often bigger than the left. The isthmus is located in the region of the 2^{nd} to 4^{th} tracheal rings. In an adult the thyroid gland weight about 15-20g and after 50 years it diminishes.

Histology of Thyroid gland

The thyroid gland consist of follicles, the cavity of its is filled with viscous colloid, a product of the epithelial cells of the follicles. Colloid consists of

thyroglobulin. The intrafollicular islets in the stroma between follicles. These islets serve as a source for the new of llicles.

The thyroid gland contains of the 3 types of the epithelial cells by the fine-needle biopsy :

A-cell – folliculare epitelium

- B-cell (Ashkinazi's cell, onkocytes)
- C –cell produced calcitonin

Thyroid gland secreted:

- T4 –thyroxin,
- T3 –triiodothyronine;
- - calcitonin

Biochemistry

- Free T4 and free T3 represent the hormonally active fraction
- The remainder is hormonally inactive, mainly bound to T4 binding globulin (TBG) and albumin
- T3 is more biologically active then T4
- Some T4 is converted to T3 in peripheral tissues by 5'-dejodinase
- Metabolized by most tissues; metabolites reach liver are excreted in bile

Regulation of the Thyroid Gland:

Extrathyroid

Stimulation by the pituitary gland – TSH, epinephrine, prostaglandins

When the levels of T4 and T3 fall, the pituitary secretes more TSH. When T4 and T3 levels rise, the pituitary secretea less TSH.

Intrathyroid (autoregulation) of Thyroid Gland:

- Response to iodide-with increasing iodide supply, inhibition of iodide organification decreasing T3 and T4 synthesis (Wolf-Chaikoff effect)
- Varying thyroid sensitivity to TSH in responce to iodide availability
- Increased ratio of T3 to t4 in iodide deficiency

Thyroid hormones effects:

- Circulation and cardiac rate (force and output)
- Central nervous system function
- Appetite, blood fat and sugar levels , regulation of fat
- Energy levels, carbons and protein metabolism
- Bowel function
- Body temperature
- Growth and skeletal development
- Muscle tone and agility
- Speed of metabolism

Thyroid hormones are therefore essential for life, growth and development

Terminology and Classification of the Thyroid gland disorders

Thyroid disorders include:

1. Goitre (generalized enlargment of the thyroid gland that does not result from inflammatory or neoplastic processes): diffuse toxic goiter, diffuse non-toxic goiter, nodule or multinodules goitre
2. Hyperthyroidism (where the thyroid releases too much hormone and the body's metabolism goes too fast)
3. Hypothyroidism (where the thyroid releases too little hormone so the body's metabolism goes too slowly): hypothyroidism&myxedema
4. Thyroiditis (inflammation of thyroid gland by specific agents or autoimmune processis): Hashimoto's thyroiditis, subacute thyroiditis, post-partion thyroiditis
5. Thyroid Nodules and swellings: benign and malignancy. May be adenoma, colloid nodule, cyst, primary thyroid malignancy, metastatic neoplasm

Ethyology

Common following signs:

- genetic predisposition
- autoimmune reactions
- outside factors such as: iodine and microelements deficiency, radiation, virus infection, stress

Diagnosis

a. Physical examination: palpation of the thyroid gland
b. Laboratory findings,
c. Ultrasound
d. Fine needle biopsy
e. Iodine thyroid scan

a. Physical examination

Goitre may be:

- diffuse (thyromegaly), nodular, multinodular, diffuse-nodular
- Euthyroid, hypothyroid, hyperthyroid .

Thyroid hormones act like chemical messengers and deliver instructions to various tissues and target organs via the bloodstream and clinical symptoms may be different. But approximatly 40% diagnosis of the thyroid gland diseases can make diagnosis with clinical examination.

"Portrait's" diagnosis of the patients with thyroid gland disorder function

	Hyperthyroidism	Hypothyroidism
CNS	Young-looking, anxiety, nervousness and/panic attacks, make a lot of rapid unnessary movements and verbose, absence concentration, easily upset, insomnia, feel hotter than those around them, sweeting, trembling of the hands and a hard muscle weakness	Old-looking, sluggishness, indecisiveness, slowness of thought processes(brain fog), poor memory and concentration, feeling cold even on warm day, fatigue, exhaustion and low energy, slow reflexes, deepening, hoarse voice
Facial expression	An angry frightened look, staring gaze	Poor mimic, swelling of face and feet
Skin, hair, weight	Warm, thin, transparent, velvet, moist, lose weight	Thick, dry, coarse, pale, skin rashes, brittle hair and nails, hair loss, alopecia thining eyebrows, overweight
Thyroid gland	Diffuse or multinodular goitre, soft, mobile, not fused with the underlying tissues	Enlarged thyroid gland or diminished
CVS	Palpitations, fast pulse, arrithmia, increased systolic blood pressure, chest pain	Slow, weak pulse, bradicardia, increased diastolic and decrease systolic blood pr.
GDT	Increased appetite but weight lost, diarrhoea	chronic constipation
Sexual disturbances	Menstrual cycle disturbances or scant mensis, infertility, imponence in man, reduced libido	Menstrual cycle disturbances or scant mensis, infertility, imponence in man, reduced libido
Temperature	Normal or subfebril	Low basal temperature

b. Laboratory findings and investigation

Immunoassay techniques for diagnosing thyroid disorders measure the amount of circulating hormones in the blood very accurately.

Table. Thyroid Function Test.

Hormone	Range
TSH	0,30 -5,00mIU/L
Free T4	11 – 23pmol/L
Free T3	3,5 – 6,7 pmol/L

The TSH level is a good indicator of thyroid function and is considered the most important hormone to be initially tested. It is the first hormone assessed when suspecting a thyroid disorder.

- hypothyroidism: TSH level decreased, T3 and T4 decrease;
- hyperthyroidism: TSH level LOW , T3 and T4 increase.

If the TSH levels are not low, then other tests must be run:

Thyroid antibody test

Thyroid constituents	Range
Antibody against thyroid thyroglobulin	Less then 40 ME/ml
Antibody against thyroperoxidase	Less then 35 ME/ml

Miscellaneous Tests

- Thyroid antibodies: antithyroglobulin antibodies, microsomal antibodies increased in Hashimotoe's thyroiditis
- TSH receptor antibodies: thyroid stimulating immunoglobulin (TSI) or TSAb increased in Graves disease

Accurate and widely available blood tests can confirm or rule out the diagnosis quite easily within a day or two. Other special tests are occasionally use to distinguish among the varios causes of hyperthyroidism

c. Ultrasound

Ultrasound may be used for:

- surveillance, localization of thyroid gland and lymphatic nodules
- quantitation of thyroid gland : normal volume in female – 18ml, normal volume in mail – 24ml;
- quantitation of residual recurrent tumor;.

d. Fine -Needle Thyroid Biopsy.

Aspiration of thyroid tissue with a 25-gauge (fine needle) is helpful in the diagnosis of thyroid disorders, especially nodular lesions. Small nonpalpable (less then 10 mm) nodules are detected in half of "normal" thyroids and are rarely malignant

- to guide fine-needle aspiration biopsy of clinically suspicious thyroid nodules and nodes

e. Iodine Thyroid Scan

Will show if the cause is a single nodule ("hot" nodule) or the whole gland.

Because the thyroid gland normally takes up iodine in order to make thyroid hormones, measuring how much radioactive iodine or technetium is captured by the gland can be a very useful way to measure its function. The dose of radiation with this test is very small and has no side effects. Such radioactive

thyroid scan and uptake tests are often essential to know what treatment should be used in a patient with hyperthyroidism.

1. Non-toxic goiter.

Non-toxic endemic goitre

- is generalized enlargement of the thyroid gland in a euthyroid individual .
- does not result from inflammatory or neoplastic processes in persons .
- dwelling in areas of iodine deficiency (approximately 115 countries).
- 5% of the world's population have goiters.
- Endemic in the regions of the world with low-iodine diets: increased rate of congenital hypothyroidism and cretinism

- Most adults endemic goitre are found to be euthyroid; however, some are hypothyroid or hyperthyroid
- may become multinodular and grow to great size
- high rate of congenital hypothyroidism and cretinism

Sporadic non-toxic goitre - in which only the individual is affected in persons living outside the areas of iodine deficiency.

Classification of the Goitre (WHO, 1994)

- Grade 0- the thyroid unpalpable and invisible
- Grade 1 –palpable, not visible in normal position of the neck; the thickiened mass moves up during swalloving
- Grade 2 - neck swelling, visible when the neck is in normal position

Risk factors

Appearance of a goitre is more likely during:

- adolescence,
- pregnancy and lactation
- goitrogens:thiocynates(cabbage, turnip, soy, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid because of icreased thyroid hormone requirements

Risk factors for sporadic goiter

1. Family history
2. diet
3. age over 40 years

4. gender (w>m)

Ethiology and Pathogenesis

- Iodine deficiency or excess
- Goitrogens: brassica vegetables (cassava, sorghum, millet, maize)
- Drugs: iodine, lithium, para-aminosalisylic acid
- Any disorder of hormone synthesis with compensatory growth
- Periphereal resistance to thyroid hormone
- Early stages: goiter is usually diffuse. Later stages: multinodular nontoxic goiter with nodule, cyst formation and areas of ischemia, hemorrage , and fibrosis

Fig.Non-toxic goiter in 41 years-old women.

Complications

- Compression of neck structures, causing stridor, dysphagia, pain, hoarseness
- attempts to shrink such goiters with iodine supplements or thyroxine are usually unsuccessful and may cause thyrotoxicosis
- since noduler goiters tends to become autonomous over time

- Multinodular goiter may become autonomous leading to toxic multinodular goiter and thyrotoxicosis

Diagnosis and laboratory

- Physical examination: palpation of the thyroid gland and lymphatic nodules
- TSH normal or slightly increase, T4 normal, antithyroid anibodies in low titres or undetectable, thyroglobulin elevated
- Ultrasound scan
- Fine needle biopsy if nodules are present, different with malignancy
- Radioactive iodine scan

Treatment

Treatment depends on the underlying cause:

- Remove goitrogens
- Suppression with L-T4 may be effective in any TSH-depended goitre
- Goitre caused by iodine deficiency - Iodine-therapy : KJ, "Euthyrox". Prevention – the introduction of iodinerich foods into the diet(seafood and iodised salt). Iodine supplementation 20 mg/kg salt. The minimum dietary requirement for iodine is about 50 mg daily, with optimal iodine intake being 150- 300 mg daily. Iodine sufficiency is assessed my measurement of urinary iodine excretion, the taget being more than 100 mg of iodide per gram of creatinine.
- Hyperthyroidism – is managed with drugs that slow the activity of the thyroid or surgically removed
- Hypothyroidism – by lifelong hormone replacement T4 therapy
- Adults with large multinodular goiter may require thyroidectomy for cosmesiss, compressive symptoms, or hyrotoxicosis

2.Hyperthyroidism & Thyrotoxicosis

The term refers two main categories:

Hyperthyroidism due to excessive glandular synthesis of thyroid hormone and thyrotoxicosis/hyperthyroidism due to exogenous intake of thyroid hormone or inflammatory process or ectopic production of thyroid hormone

Thyrotoxicosis are a series of clinical disorders associated with increase circulating levels of free thyroxine or triiodothyronine.

The various causes include the following a clinical diagnosis:

A. Graves' Disease .

B.Toxic Nodular Goitre.

C.Toxic Nodule.

D. Thyroiditis a) classical subacute thyroiditis b)silent thyroiditis c)post-partum thyroiditis

E. McCune-Albrigth Syndrome.

F. Jod Basedow (Jodine-induced)

G. Extra-thyroidal Sources of Thyroid Hormone a)endogenous (struma ovariae< ovarian teratoma metastases from follicular carcinoma) b) exogenous (drugs)

H. Excessive Thyroid Stimulation a) pituitary thyrotrophoma b) pituitary thyroid hormone receptor resistance) > hCG (e.g. molar pregnancy)

3. Graves' Disease.

- Know as diffuse toxic goitre in Russia.
- Know as Basedow's in Europe.
- Know as Grave's in USA.

Definition.

Diffuse toxic goitre is an autoimmune endocrine disease with congenital defect of the immune control system.

- Characterized by an increase in synthesis and release of thyroid hormones .
- The thyroid gland is typically diffuse enlarged in 98% of young females, associated with exophthalmos).
- In the elderly, toxic multi-nodular thyroid goiter is a close 2nd.
- Iis encountered everywhere, peaks in 4th decade of the ages.
- much more common in women than in men (8:1).
- Caused by a mixture of genetics and environment.

General Considerations

- autoimmune disease
- thyromegaly or goiter
- excess production of thyroid hormone
- Decreased TSH, increased T4, free T4 and free T4 index
- increased TSI or TSAb
- family history,may be associate with other autoimmune disorders in family (DM1,alopecia areata, myasthenia gravis)
- age 30- 40y.o , F>M (8:1)
- Association with HLA-B8/HLA-DR3.
- Associated with DM Type 1, Addisons, vitiligo, pernicious anemia, alopecia areata, celiac disease, myasthenia gravis.

Determines factors

- The neouro-endocrine incitement (pregnancy, lactation, climax)
- Psychic trauma, craniocerebral trauma
- Excessive insolation
- The intake of large doses of iodine
- Acute and chronic infections

Etiology and Pathogenesis.

The pathogenesis of the hyperthyroidism due to thyroid stimulating IgG (TSH-R AB, antithyroglobulin, antimicrosomal Ab's) that bind to the TSH receptor in thyroid cell membranes which increase secretion of thyroxine and triiodothyronine by thyroid. No direct correlation between serum concentration of Ab's and serum thyroid hormones.

- Autoimmune disorder due to a defect in T-suppressor cells
- B-lymphocytes produce thyroid stimulating immunoglobulins directed against TSH receptor that mediate thyroid stimulation.

Clinical Features

There are actually three distinct parts of Graves' disease:

1. **Hyperthyroidism** : overactivity of the thyroid gland .
2. **Ophtalmopathy** : autoimmune inflammation of the tissues around the eyes causing swelling .
3. **Pretibial myxedema** : thickening of the skin over the lower legs .

In the degree of severity hyperthyroidism is classified as mild, moderate and severe.

Symptoms and Signs

- Merzerburg's triad : diffuse , symmetric, soft, smooth , nontender goitre, Ophthalmopathy/exophthalmos , tachicardia
- Dalrimpl's syptom: stare, sparkl glare glance, exophtalmos
- Graefes' sign : is lagging of the upper lid behind the globe when the person fixes his gaze on some slowly descending object; as a result, a white strip of the sclera is seen between the upper lid and the iris.
- Kochers' sign: is explained by the increased retraction of the upper lid, due to which a white strip of sclera appears between the upper eyelid and iris when the patient fixes his gaze on an object moving up.
- "Thyrotoxic heart": severe tachycardia/atrial fibrillation, enlargement of the heart or dilated cardiomyopathy, heart failure.
- Ophtalmopathy: proptosis (exophtalmos) , lid lag ,lid retraction , diplopia (double vision), characterictic stare , conjnctival injection
- Dermopathy: pretibial myxedema peau d'orange-like thickening and redness at anterolateral shin due to lymphocytic infiltrate

■ Onycholysis, acropathy(elephant skin), swelling and clubbing in extremities (improves with topical glucocorticoid with nocturnal plastic occlusive dressing)

Most people with Graves' disease have no obviose eye involvement. Their eyes may feel irritated or they may look like they are staring. About one of 20 people with Graves' disease will suffer more severe eye problem, which can include bulging of the eyes, severe inflammation, double vision, or blurred vision. If these serious problems are not recognized and treated, they can permanently damage the eyes and even cause blindness. Thyroid and eye involvement in Graves' disease generally run a parallel course with eye problems revolving slowly after hyperthyroidism is controlled.

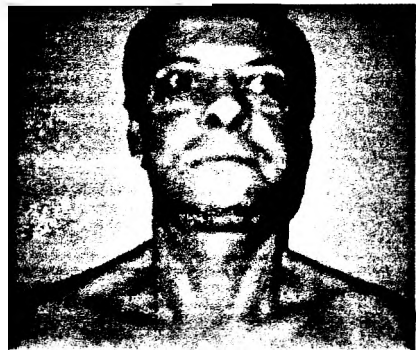


Fig. Dalrimpl's syptom: stare, sparkl glare glance, exophtalmos

Fig. Graefes' sign (left) and Kochers' sign (right).

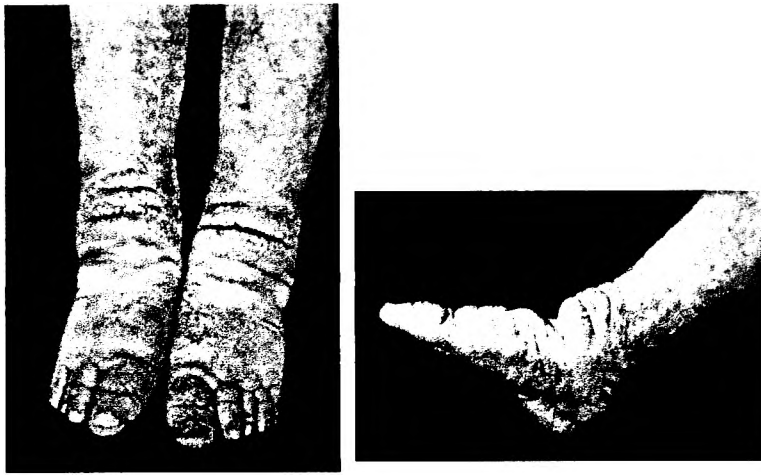


Fig .Pretibial mixedema

Diagnosis

- Physical examination
- Suppressed TSH
- Increased T4, free T4 and free T4 index

Treatment

- Medical therapy ("antithyroid" or "thyrostatics drugs")
- Radioactive 131J therapy
- subtotal thyroidectomy

Drugs

Thiourea drugs:

- methimazole, propylthioracil, iodide agents.

Action

- inhibit thyroid hormone synthesis

Methimazol: orally in initial doses of 30 -60mg once a day duration 3-6 weeks. orbital radiation: surgical decompression and as the free thyroxine level becomes normal (5-10 mg orally once a day or 5-10 mg methymazol + 50 mkg levothiroxine orally once a day,1-2 years).

Indication

- young adults
- patients with mild thyrotoxicosis
- small goiters
- fear of isotopes

- preparing hyperthyroid patients for surgery and elderly patients for radioactive iodide treatment

Side-effects and complications

- pruritus, allergic dermatitis
- nausea, dyspepsia
- agranulocytosis (control white blood count and stop methymazol-therapy)
- sore throat and febrile illness,
- onset is generally abrupt
- posttreatment primary hypothyroidism
- high rate of recurrent hyperthyroidism (about 50%, patients with thyroperoxidase and thyroglobulin antibodies remain high after 2 years of therapy)

Propylthiouracil in initial doses of 100 -150mg daily in four divided doses duration 3 – 4 weeks. The dosage is generally reduced as a manifestation of heperthyroidism resolve and as the free thyroxine level becomes normal (50 - 100 mg orally once a day +50 mkg levothiroxine orally once a day,1-2 years).

Side-effects and complications

- arthritis
- lupus erythematosus
- aplastic anemia, thrombocytopenia, hypoprothrombinemia
- acute hepatitis
- Such complications as acute hepatitis and agranulocytosis/ aplastic anemia, thrombocytopenia, hypoprothrombinemia is administration with prednisone treatment.

Iodide contrast agents :

iopanoic acid (Telepaque), ipodate sodium (Bilivist, Oragrafin). Lugol's solution (10 drops 3 times daily orally).

Treatment periods of 8 - 10 months, but efficacy tends to wane with time.

Action

- inhibit peripheral 5'-monodeiodination of thyroxine, thereby blocking its conversion to active T3.

Indication

- severe thyrotoxicosis
- thyrotoxic "storm"
- thyroxine overdosage
- subacute thyroiditis
- amiodarone-induced thyrotoxicosis
- intolerant to thioureas
- newborns with thyrotoxicosis

Symptomatic treatment

Beta-blockers

Propranolol -10 -80mg

- orally a day under the pulse and BP control. Initial doses 10mg orally and increased progressively until an adequate response is achieved.

- Athenolol 50 - 100mg orally a day.

- Methoprolol 50 – 150mg orally a day.

It effectively relives the tachycardia, tremor, anxity, diaphoresis, periodic parslysis. Propranolol is available in a long-acting formulation that provides more consistent relief.

Treatment of Ophthalmopathy:

- Prednisone 60- 80 mg orally a day for 3-4 weeks or retroorbital injection 1 time a day. The dosage is generally reduced as a manifestation of ophtalmopathy

- Orbital radiation

- Surgical decompression

Therapeutic option:

- severe cases of ophtalmopathy;

- Note that propilthiouracil or methimazole may worsen ophthalmopathy.

Cessation of the smoke. Smoking increasees the risk of having a flare in ophtalmopathy following 131J treatment and also reduces the effectiveness of prednisone treatment.

Treatment of cardiac complication ("thyrotoxic heart")

- Digoxin is treated atrial fibrillation and heart failure

- Diuretics i/v (furosemid)

- beta-blockers (propranolol,) –80 120 mg orally a day

- Standart antianginal therapy, if angina pectoris present

- Anticoagulation therapy for prevent arterial thromboembolism in thyrotoxicosis-induced atrial fibrillation (0,325mg aspirin orally tonight)

Radioactive Iodine (131J) Therapy

Indication

- Non effective medical therapy
- Elderly patients
- Patients with coronary disease

Radioactive iodine therapy not be given to pregnant women

Complication

- hypothyroidism: L-T4 lifelong therapy with measurements of free T4 and TSH when indicated.

Thyroid surgery: subtotal thyroidectomy

Indication

- Toxic nodular goiter
- Pregnant women

- Significant chance of malignancy
- Very large goitre

Complications

- hypothyroidism: L-T4 lifelong therapy with measurements of free T4 and TSH when indicated.

4.Thyrotoxic crisis ("storm")

Definition

This disorder is an extreme form of thyrotoxicosis.

- It is a severe state of uncontrolled hyperthyroidism
- Occur with stressfull illness, infection, trauma, surgery in hyperthyroid patient, radioactive iodine administration

Clinics

- Hyperthyroidism
- Vomiting, diarrhea, dehidration
- Very high fever, often with dry skin
- Severe tachycardia, arrithmia, congestive heart failure, pulmanary edema
- Mental status changes ranging from delirium to coma

Laboratory

- Increased T3,T4,undetectable TSH
- +/_- anemia, leukocytosis, hypercalcemia

Treatment

Initiate promt therapy, don't wait for confirmation from laboratory findings

- Thiourea drugs: propylthiouracil 150-250 mg every 6 hours, or methimazole,15-25 mg every 6 hours.Ipodate sodium (500mg/d orally if begun 1 hours after the first dose of thiourea
- Iodine to inhibit release of thyroid hormone :iodine is given 1 hours later as Lugol's solution (10 drops 3 times daily orally) or as sodium iodine (1g intravenously slowly).
- Hydrocorttisone to block peripheral conversion and to lower body temperature:50mg every 6 hours
- Propranolol 0,5-2 mg intravenously every 4 hours or 20 -120 mg orally every 6 hours
- Aspirin is avoided since it displaces T4 from thyroid-binding globulin, raising free T3 serum levels
- Fluid and electrolyte maintenance, vasopressors as indicated

Definitive treatment with 131J or surgery is delayed until the patient is euthyroid.

5. Other less Common Causes of Hyperthyroidism

1.Toxic Nodule

- may be single or multiple nodules
- autonomous thyroid hormone production, may arise from a nodule in a multinodular goitre
- occurs in a elderly patients
- not associated with infiltrative ophthalmopathy or dermopathy.
- thyroid function tests mandatory; TSH-R - Ab negative
-most small thyroid nodules are asymptomatic
-Scanning techniques: uptake of 123J, ultrasonogram
- be treated : propanolol, surgery or radioactive iodine therapy

Fig. Toxic Nodule

2. Subacute Thyroiditis (DeQuervain's Thyroiditis) (see below)

3. Struma Ovarii

- thyroid tissue is contained in about 3% dermoid tumors and teratomas.
- increase intraabdominal J131 uptake
- surgery treatment

4. Pituitary tumor (TSH Hypersecretion by the pituitary)

- caused by a pituitary adenoma or pituitary hyperplasia (know as "non-neoplastic inappropriate secretion of thyrotropin)

- TSH increase/or normal
- treatment to bromocriptine or octreotide /transfenoidal surgery or radiation therapy

5. Hashimoto's thyroiditis (see below)

6. Pregnancy and trophoblastic tumors

- occur in 5 -9% of women in the first 6 months after delivery
- may occur during the first 4 months of pregnancy
- transient hyperthyroidism results from the release of stored thyroid hormone following damage to the thyroid by thyroperoxidase antibodies whose IgG subclasses activate the complement cascade
- high serum level of HCG may cause sufficient teceptor activation to cause thyrotoxicosis
- eventually return to euthyroid state, 1/3 remain hypothyroid
- treated by propranolol during the hyperthyroid phase, followed by thyroxine during hypothyroidism

6. Hypothyroidism & myxedema.

Definition.

Hypothyroid is the syndrome of relative or absolutely insufficiency of thyroid hormones by thyroid glands with complete loss of its action on the target organs. In the degree of severity hypothyroid is classified as mild, moderate and severe. Unrecognizing hypothyroid severe states is striking myxedema ("mucous edema").

Classification

Hypothyroidism may be due to primary disease of the thyroid gland itself or lack of pituitary TSH, congenital or acquired:

1. Primary (thyrogenic) :
   - post-surgical thyroidectomy or post-ablative 131J;
   - autoimmune –Hachimoto's thyroidites;
   - iodine deficiency - congenital
2. Secondary (pituitary):
   - insufficiency of pituitary TSH
3. Tertiary (hypothalamic) :
- decreased TRH from hypothalamus
4. Peripheral tissue resistance to thyroid hormone
5.

Determienes factors, ethiology and pathogenesis

1. Age >50 years old
2. Hashimoto's thyroiditis

3. Autoimmune diseases
4. Iodide deficiency
5. Genetic thyroid enzyme defects
6. Drug goitrogenes : lithium, iodide, propilthyiouracil/methimazole, phenylbutazone, sulfonamides, amiodarone, interferon-alfa, interleukin-2.
7. Food goitrogenes in iodidedeficient areas
8. Infiltrating diseases (cancer, sarcoidosis) due to peripheral resistance to thyroid hormones
9. Hypothyroid phase in subacute viral thyroiditis following initial hyperthyroidism
10. Neck radiation therapy
11. Thyroidectomy

The fluid retention seen in myxedema is caused by the interstitial accumulation of hydrophilic mucopolysaccharides, which leads to lymphedema. Hyponatriemia is due to impaired renal tubular sodium reabsorption due to reductions in Na+ -K+ ATpase. Cellular proteins are also affected in myxedema.

Epidemiology

- 2-3% of general population
- F>M 10:1

Clinical Features

- Slowing of mental and physical performance, slow speech, memory loss, lethargy, delayed return of deep tendon reflexes
- Cold intolerance, hypothermia
- Cool, dry, rough, pilling skin, yellow (carotenemic) skin color
- Puffiness of face, per orbital edema, peripheral edema
- Hoarseness, enlarged tongue and lips
- Hair dry and coarse, eyebrows thinned (lateral 1/3)
- Constipation , meteorism, hypo/achlorhydria
- Weight change ("not true obesity") due to pleural effusion , peritoneal effusion cavities (intestinal edema), peripheral edemoes
- "Myxedema heart": cardiac enlargement , pericardial effusion , bradicardia, generalized atherosclerosis, diastolic hypertension, heart sounds dull, systolic murmur at the apex of the heart
- Anemia, hyponatremia
- Menorrahagia/ amenorrea, galactorrhea, infertility, decrease libido

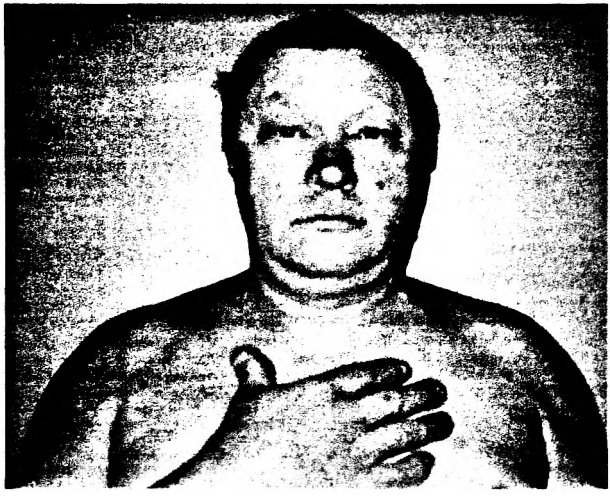


Fig. Hypothyroidism (myxedema) in a 46 years-old patient :puffiness of face, per orbital edema, peripheral edema ,hair dry and coarse, eyebrows thinned .

Fig. 50 years –old patient with hypothyroisis.Enlargment of a tongue.

Laboratory Findings

- T4 and radioiodine uptake low. Serum T3 is not good test
- TSH increased
- Subclinical hypothyroidism:

- if TSH >10 mU/L check anthythyroid antibodies and start therapy

- if TSH 5 -10 mU/L + goitre – check antibodies, if negative re-check in 1 -6 months; if positive start thyroxine therapy

- Titers of antibodies against thyroperoxidase and thyroglobin high in Hashimoto's thyroiditis
- ECG; small voltage of waves, bradicardia, decreased S-T interval below the base line, elongation P-Q
- Pituitary enlargement due to hyperplasia of TSH-secreting cells by CT or X-ray
- Increase serum cholesterol, liver enzymes, creatine kinase, hyponatriemia, hypoglycemia

Treatment

1. **Levothyroxine (L- T4)**: (dose range usually 0.05 - 0.2mg/kg/day) under the monitor TSH is in the middle of its normal range. Brand preparations of levothyroxine in the world appear to be bioequivalent to each other and certain genetics (Euthyrox, Levoxine, Levothroid). Take on empty stomach.

- Initial doses elderly : 12,5 – 25 ug/ day ; with cardiac problems start 12,5 ug/day and increase gradually
- Initial doses age 30 -60 : 75 -100 ug/day
- Lifelong therapy

Side-effects

- tachycardia, arrhythmias
- tremor, anxity
- diarrhea, cramps

Contraindication

- acute infarct myocardial, thyrotoxicosis

2. **T4 + T3 combination (Liothyronine, Liotrix)** ratio of 10:1. This combination has been improve mood and neurophysiologic function compared to T4 alone.

3. **Liothyronine (Cytomel)** 25 ug twice a day. Synthetic T3,short half life, lots of peaks and valleys throughout the day.

4. **Liotrix (Thyrolar) :** 20 mg/daily. Combination of synthetic T4 (100mg) + T3 (25 ug)

Complications of hypothyroidism

1. Increase susceptibility to infection
2. Megacolon in long-standing hypothyroidism
3. "Myxedema coma"
4. "Myxedema madness" –organic phychoses with paranoid delusions
5. Infertility
6. Hypoventilation, hypoxia, hypercapnia
7. Hypotention.

7. Hypothyroid (myxedema) coma.

Definition

Most severe complication of hypothyroidism. It is a rare syndrome usually seen in an elderly female with longstanding hypothyroidism.

Determienes factors

1. Longstanding unrecognized hypothyroidism
2. Severe infections (pneumonia)
3. Surgery,
4. Stroke
5. Trauma , castrointestinal bleed
6. Drugs : narcotics, sedatives, diuretics
7. Cold exposure, hypotermia

Clinics

- Hypothyroidizm, stupor, hypoventilation, hypothermia, bradicardia, hypertention
- Decreased T3 and T4, increased TSH, decreased glucose
- Check ACTH and cortisol for evidence of adrenal insufficiency

Treatment

- Cortiosteroids (due to the possibility of concomitant adrenal insufficiency)100mg bolus, folloved by 50 mgi/v D
- L-T4 0,2 – 0,5 mg (400ug) i/v loading dose, then 0,1 mg (100 ug) i/v or BID untill oral therapy tolerated
- Correct hypoventilation (intubation)
- T3 100mg i/v daily then 25mg BID
- Fluid and electrolyte correction.

8. Hashimoto's thyroiditis

Definition

Hashimoto's thyroiditis or autoimmune thyroiditis is an autoaggressive with lymphoid and plasmocytic infiltration of thyroid gland by thyroid antigens.

Patients develop hyperthyroidism as a result of release of stored thyroid hormone during severe Hashimotoe's thyroiditis.

Two variants of Hashimoto's Thyroiditis :

1. Goitrous: presents with a euthyroid /or hypothyroid goiter.
2. Atrophic: hypothyroid state and atrophic gland

Ethiology and Pathogenesis

- Genetic predisposition/associated with HLA B8/ HLA DR3
- More common in female of middle age, F : M = 17 :1
- Defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles

■ B-lymphocytes produce antithyroglobulin and anthythyro peroxidase (anti-TPO or antimicrosomal antibody)

■ Hypothyroidism or a euthyroid state, increased TSH compensatory; followed by decreased free T4 and eventually decreased free T3

■ Antimicrosomal and anti-thyroglobulin antibodies

Clinical picture

- Develop gradually
- No complaints or weakness may be present
- In severe cases attended by thyrotoxicosis
- Goitrous form usually presents with a rubbery goiter and euthyroidism, then hypothyroidism becomes evident
- If thyroid very firm and enlarged, patient complain of pressure of the neck and sometimes difficalty in swalloving (compression symptoms)
- Thyroid gland not painful, mobile
- Atrophic variant patient are hypothyroid from start
- Associated with thyroid lymphoma

Laboratory finding

- TFT reveals hypothyroidism, or a euthyroid state with a compensatory increase in TSH; followed by decreased free T4 and eventually decreased freeT3
- Antimicrosomal and anti-thyroglobulin antibodies

Treatment

■ Treated according thyroid status

■ If hypothyroid, replace with L-thyroxine 1,6 -1,8 mkg/kg/daily , start by initial dose 25 mkg orally daily

■ If euthyroid, also treat with L-thyroxine if significant anti-thyroid antibody present.

9.Subacute thyroiditis.

Definition.

Subacute thyroiditis is acute inflammation of the thyroid, probably viral in origin, characterized by giant cells and lymphocytes.

Ethiology and Pathogenesis

■ Viral infection (epidemic parotitis, meals, rubella, grip,etc)

■ Often preceded by upper respiratory tract infection (URTI)

■ F:M =7:1, ages 30 -50

■ Disruption of thyroid follicles by inflammatory process results in the release of stored hormone

Clinical picture and laboratory finding

- Pain worse to turn heard, swallow, may radiate to ear, jaw or chest
- Hyperthyroidism is followed by hypothyroidism
- Symptoms mimic a manic episode such as that the diagnosis missed
- Thyroid gland enlarged and tender

Two forms of subacute thyroiditis:

1. Painful tender thyroid ("DeQuervain's"Thyroiditis); * Acute onset with fever, pain in the neck with the turn of the head, swallowing, cough; pane radiates to jaw, occiput, ears.

2. Painless untender ('Silent") thyroid; symptoms mimic

- thyrotoxicosis stage duration 1-2 months
- During thyrotoxicosis thyroid radioiodine uptake is low
- Lab: WBC elevated without leukosytosis, < ESR, <thyroglobulin, <or> TSH,< T4,T3

Treatment

- **Prednisone 30 -60mg/daily** with a gradual reduction by 5 to 2,5 mg every 10 days under the WBC control

- **Symptomatic treatment: beta-blockers (propranolol,) -10 -80mg** orally a day under the pulse and BP control. Initial doses 10mg orally and increased progressively until an adequate response is achieved. - **Athenolol 50 - 100mg orally a day. - Methoprolol 50 – 150mg orally a day.**

- **Ipodate sodium or iopanoic acid 500mg orally** daily promptly corrects elevated T3, continue for 15 -60 days until free T4 normalize

- ASA can be used for painful form (increases peripheral conversion) for 3-5 months

- If symptomatically hypothyroid may treat short-term with thyroxine

10. Thyroid nodules and thyroid cancer.

Thyroid nodules

Nodular (irregular) goitre is a common term which refer all formation which more then 10 mm in a volume detectible by palpation or other visual methods. It is clearly defind discrete mass, separated from the thyroid parenchyma.

Ethiology

- iodine deficiency
- family history of goitre
- F:M = 7:2 ; suspicious -19%, malignant -4%
- If less then 1,5 cm volume of nodules usually benign

Classification

- benign tumors: follicular adenoma (adenoma may produce thyrotoxicosis)
- thyroid cancer
- hyperplastic area in a multinodular goiter
- cystic nodule : true thyroid cyst, area of cystic degeneration in a multinodular goiter. Less then 4 cm with serous fluid usually benign.
- thyroid incidentalomas: nodules not palpable on examination, but detected on imaging study for another purpose (size <1cm volume)

Clinics

- small thyroid nodules asymptomatic
- large nodular goiter become a cosmetic embarrassment, caused discomfort, dysphagia, hoarseness
- Pemberton's sign: large substernal goiters caused superior vena cava syndrome (facial erythema and jugular vein distention that progress to cyanosis, facial edema when both arms are kept raised over the head)

Diagnosis

- fine needle aspiration (FNA): read by an experienced cytopathologist (benign or malignant). Two or more biopsies may be obtained.
- thyroid function test
- ultrasound investigation
- thyroid scan : minimal 131J uptake into nodule is "cold" nodules. 15 -20% of its are maligmant.; very low malignant potential if warm or "hot" (significant 131J uptake into nodule).

High index of suspicion

- firm, fixed with cervical nodes higher>2 cm
- hoarseness, vocal cord paralysis, enlarged lymph nodes
- young adults
- men
- increase growth higher>0,5 cm per 6 months by ultrasound
- solitary (single or dominant)
- therapeutic radiation of head, neck, or chest
- ultrasound signs: irregular margins, intranodular vascular spots, microcalcification
- cyst with bloody fluid or if reaccumulates

Treatment

1. Medical therapy.
2. Surgery
3. Ultrasound guided ethanol injection
4. Radioiodine 131J
5. Photocauterization

1. Medical therapy: Levothyroxine treatment("suppressive Levothyroxine treatment")

Indication

- TSH increase /normal –"suppression" 0,05 -0,1 mg daily x 6 months
- TSH low (indication of autonomus thyroid secretion)– L-T4 ineffective and liable to cause clinical thyrotoxicosis , L-T4 should be not administrated.
- Most suitable for younger for larger nodules >2 cm

Side-effects

- small loss of bone density

Patients at risk for osteoporosis are advised to have periodic therapy for osteoporosis .

Contraindication

- thyroid incidentalomas (nonpalpable thyroid nodules)
- cyst
- small nodules less 1cm
- certain cardiovascular disorders (angina pectoris, arrhythmia)

2. Surgery

Indication

- if growing nodule
- compressive symptoms
- if "cold" nodule and high clinical suspicion
- microfollicular adenoma if non-autonomas
- macrofollicular nodule
- large retrosternal goitre

3. Ultrasound guided ethanol injection

Indication

- autonomous nodule
- cystic nodule; cystic nodules yielding serous fluif are usually benign, but fluid should be submitted for cytology
- macrofollicular nodule
- toxic nodule

2. Radioiodine 131J therapy

Indication

- autonomus nodule
- toxic nodule
- multinodulat toxic goitre

The great majority of thyroid nodules are benign. Conversion to a malignant nodule is rare. Patients with small nonpalpable thyroid nodules are at very low risr for malignancy, and even those are malignant have a minor effect on morbidity and mortality.

Multinodular goires tend to persist or grow slowly.The prognosis for patients with thyroid nodules that prove to be malignant is determined by cytology

All patients with benign irregular goitre need to be followed by regular periodic palpation of the thyroid gland (one time 3 months), ultrasound examination (one time 6 months), and rebiopsied one time a year or if growth nodule occurs.

Thyroid cancer

Thyroid cancer is diagnosed about 40 per million population. Most thyroid cancers remain microscopic and indolent. Those cancers that do become aggressive often have mutations in the *p53* tumor suppressor gene or the *ras* and *gsp* oncogenes.

Determines factors

- increases in age
- F:M=3:1
- External x-ray treatment to the neck/head during childhood
- Childhood exposure to radioactive isotopes of iodine in nuclear fallout (Chernobyl accident, Nagasaki accident)
- familial (3%)
- associated with multiple hamartomas of the skin and mucous membranes
- associated with breast cancer or adenomatous poliposis coli

Classification

Thyroid cancer is either parafollicular (medullary) or follicular (papillary, follicular, anaplastic). Most present with a thyroid mass and cervical lymphadenopathy.

1. **Papillary carcinoma** is the most common thyroid malignancy.

Remember the P's (R.Silver, J.Shin, 2002): -

- Papillary: well-differentiated
- Popular : the most common thyroid malignancy: seen more commonly in younger patients, associated with radiation exposure
- Psammoma: multicentric, some follicular components histologicaly
- Palpable nodes and usually metastasizes to regional lymph nodes first
- Positive Prognosis: lifespan not affected if confined to one lobe and < 2cm
- Positive 131 I uptake

2. **Follicular carcinoma**

Remember the "F's (R.Silver, J.Shin, 2002) :

- Female
- Follicular :more aggressive then papillary

- Far away metastases : angioinvasive, spreading to lung, bones, distant sites without lymph node involvement.Hurtle cell cancer is aggressive variant of this cancer with frequent pulmonary metastases
- FNA biopsy not diagnostic
- Favourable prognosis

3. Anaplastic carcinoma.

- old age
- rapidly progressive
- poor prognosis

4. **Medullary carcinoma.**

Remember the M"S (R.Silver, J.Shin, 2002):

- Medullary: worse prognosis than papillary or follicular cancer
- Men – associated with multiple endocrine neoplasia (MEN) IIa or IIb, high familial aggregation
- aMyloid; may produce calcitonin, ACTH, serotonin, prostaglandins, kallikrein, bradikinin (these substances can be used as tumor markers)
- Median node dissection

5. Lymfoma.

- seen in the context of a nodule or an enlarging goitr in a patient with Hashimoto's thyroiditis

Diagnosis

FNA

Treatment: surgery, radiation, chemotherapy

Surgery

1. Total thyroidectomy
2. Subtotalthyroidectomy for adults under age 45 who have a single tumor less then 1 cm in diameter
2. Nodal dissection

Complication

1. Airway problems
2. Hypoparathyroidism : tetany
3. Recurrent laryngeal nerve damage
4. Hypothyroidism

Adjuvant therapy

1. Thyroxine is prescribed in dose of 0,05 – 0,1 mg daily immediately postoperatively (suppressed TSH) long-term treat.

Chapter VII. Diseases of the Parathyroid Gland.

Anatomy

The parathyroid glands are small endocrine glands.

- Lie closely to the posterior surface of the thyroid
- Usually represented by two pairs.
- The superior pair is located on the borderline between the superior and median thirds of the thyroid at the level of the cricoids cartilage.
- The inferior pair is located at the inferior pole of the thyroid.
- In some cases may be located in the tissue of the thyroid, the thymus.
- Sizes 0,6 x 0,3 x 0,15 cm, weight is about 0,05 -0,3g.
- Secreted parathormone (PTH)

Effects of the parathormone

- Regulated the constant content of phosphorus-calcium metabolism together with thyrocalcitonin, a hormone of the thyroid gland.
- Under the influence of the parathormone the blood calcium content rises, and under the effect of the thyrocalcitonin diminishes.

Regulation

- Is mainly autoregulating and depends on the content of calcium in the blood.
- ACTH, glucocorticoids,the growth hormone,T4, androgens,oestrogens, vitamin D also participate in the regulation of phosphorus-calcium metabolism. Unlike the parathormone ,this hormones produce a hypocalcaemic effect.
- Vitamin D intensifies the absorbtion of calcium and phosphorus in the intestine and also augments the reabsorption of phosphorus in the kidney.

Role of Calcium

- It reduces the excitability of the peripheral nervous system and permeability of cell membranes.
- Is plastic material for the formation of bone tissue. The amount of calcium in the bone tissue amounts to about 95-99% of its contain in the body.
- It participates in regulating blood coagulation.
- The daily requirement of calcium in adults is 0,5- 1,0g.
- The total content of calcium in the blood –s 2,4 -2,9 mmol/L (9,6 - 11,6 mg/dL).
- The total content of phosphorus in the blood is 3,2 -4,8 mmol/L (10 -15 mg/dL).
-

1. Hyperparathyroidism.

Definition

Hyperpathyroidism is caused by hyperproduction of the parathormone (PTH) and characterized by pathological changes first of all in the bones and kidneys.

Epidemiology

-Age 20 -50 years old

- w > m

Ethiology

-A single or multiple adenomas or hyperplasia of the parathyroid glands.

- The causes of the formation of adenomas remain unknown.

Pathogenesis

- Overproduction of PTH has a direct effect on the bones
- Increased activity of osteoclasts which discharge citric acid
- Local acidosis causes mobilization of phosphate and calcium from the bones and their passage into the blood.
- Impoverishment of bone tissue in calcium and phosphate causes its cystic reorganization, replacement of destroyed bone tissue with fibrous tissue, osteomalacia, ftractures of the bones.
- PTH inhibits the reabsorption of phosphorus in the renal tubules, which results in its intensified excreation in the urine and low concentration in the blood.
- Compensatory flow of inorganic phosphorus compounds from the bones into the blood.
- By inhibiting the secretion of calcium by the kidneys excess PTH induces hypercalcaemia.
- Promotes nephrocalcinosis and nephrocalculosis.
- Hypercalcaemia and hupercalciuria inhibit ADH, which results in polyuria with eventual polydipsia.

Classification

1. Primary Hyperpathyroidism (Recklinghausen's disease):

- Autonomous secretion of PTH by parathyroid.
- Serum calcium and PTH are raised.
- Causes – single adenoma, multiple adenoma, nodular hyperplasia and carcinoma.

Primary hyperpathyroidism secondary to a parathyroid adenoma may be a part of multiple endocrine neoplasia syndrome :

MEN1 (Werner's syndrome): tumors of pituitary, pancreas and parathyroid glands. Other abnormalities seen include Zollinger-Ellison syndrome.

MEN2A: phaeochromocytoma ,medullary carcinoma of thyroid as well as hyperpathyroidism.

MEN2B has additional multiple neuromas but hyperpathyroidism is not present.

2. Secondary Hyperpathyroidism

- Parathyroid hyperplasia with increased PTH secretion in an attempt to compensate for prolonged hypocalcaemia.
- Serum calcium is low, PTH raised.
- Causes – chronic renal failure, malabsorption, osteomalacia and rickets.

3. Tertiary Hyperpathyroidism

- Adenoma formation and autonomous PTH secretion occurring in cases of secondary hyperparathyroism.
- Serum calcium and PTH are raised.

Symptoms and signs

Non-specific symptoms

- Anorexia, nausea, vomiting, constipation
- Peptic ulceration
- Hypertension, tachycardia, arrithmia
- Myopathy
- Weight loss, weakness, lassitude and tiredness
- Drowsiness, poor concentration, depression, memory loss.

Skeletal manifestations:

- Bone pane, fractures and deformity due to osteitis fibrosa and osteitis fibrosa cystic.
- Localised bone swelling, especially of the mandible.

Denerative arthritis and attacks of acute pseudogout, especially of the knee joints, due to chondrocalcinosis affecting the menisci

Renal manifestation

- Polyuria and polydipsia
- Recurrent calculus formation
- Deposition of calcium salts in the renal parenchyma – nephrocalcinosis
- Impairment of renal function with uraemia, hypokalaemia, hyperuricaemia, hyperchloraemic acidosis and dilute urine.
- Calcification of arterial walls and soft tissues of hand
- Corneal calcification, best seen by slit-lamp examination

Laboratory finding

- Raised serum calcium and raised PTH.
- Serum phosphate low
- Raised serum chloride
- Serum alkaline phosphatase may be raised depending on the degree of bone involvement

ECG

- Shortened QT interval
- Cardiac arrhythmias

X-Ray examination

- Nephrocalcinosis
- Demineralisation and subperiostal eosions of phalanges, most marked on the radial side of middle phalanx.
- Resorption of the terminal phalanges.
- Diffuse osteoporosis of long tubular bones, cranium. Cysts are located near epiphises of long tubular bones
- "Peper-pot" appearance of the skull on lateral view.
- Soft tissue calcification
- DEXA (dual-energy X-ray absorptiometry) and CT scan reduced bone density.

Visual diagnostics for localization of the tumor

- Ultrasonography
- Selective neck vein catheterization with PTH measurements
- CT scanning and subtraction imaging

Treatment

- Ademoma is treated by surgical removal
- Hyperplasia is treated by removal of all four glands and transplantation of some of the excised tissue to the forearm.

Prognosis

- In operative treatment is usually favourable.
- Without operative treatment patients with primary hyperparathyroidism become invalids and die from mounting cachexia and renal failure.

2.Hypercalcaemic Crisis

Definition

Hypercalcaemic crisis is acute calcium intoxication of the body associated with hyperproduction of 3EP to lead to rapid and abrupt rise in the blood calcium to critical values – 3,5 – 4,25 mmol/L.

- Seen in elderly patients with primary hyperparathyroidism.
- The pathogenesis is not clear enough.

Clinical picture

- Develops abruptly but sometimes gradually
- Temperature rises to 40oC
- Anorexia, thirst, nausea, vomiting
- Abdominal spastic pain that can simulate acute appendicitis, can be attended by gastric haemorrhage, acute pancreatitis, ulcer perforation
- Muscular weakness, pain in the joints and muscles
- Somnolence, pyrexia and altered conscious level

- Renal form of hypercalcaemic crisis is characterized by the clinical picture typical for acute renal insufficiency or uraemic coma
- Dehydration
- Hypotention, collapse
- Leucocytosis, accelerated ESR, anaemia
- Proteinuria
- ECG may show AV block, prolonged PR interval and QRS, bundle branch blocks and shortened QT interval.

Laboratory Findings

- hypercalcaemia is considered mild if the total serum calcium level is between 2,6 – 3 mmol/l (10,5 – 12 mg/dL)
- hypercalcaemia is considered severe if the total serum calcium level is above 14 mg/dL

Treatment

- In mild hypercalcaemia < 12mg/dL simple oral hydration along with increased salt intake is sufficient.4-6 litres of 0,9% saline I/V over 24 hours.
- Diuretics : furosemide 40 -160 mg/day or ethacrynic acid 50 -200 mg/day – after correction of volume.
- Forced diueresis with 4-6 litres of I/V fluid per day and furosemide 2 hourly.Sodium, potassium and magnesium
- Salmon calcitonin 200 -400 IU subcutanrusly 8 hourly for 24 hours.
- Mithramycin 25 mcg/kg I/V over 6 hours for 3-8 days.
- Neutral phosphate (0,1 M) 500 mL I/V over 6-8 hours.
- Corticocteroids : Prednisolone 5-15 mg 6 hourly orally or hydrocortisone 50 -100 mg I/V , hourly.
- Bisphosphonates : oral phosphate 250 mg 6 hourly.
- Indomethacin 25 mg 6 hourly orally.
- Haemodialysis with a low-Ca bath

Prognosis

- Depends on timely diagnosis and treatment
- Mortality reaches 65%.

3. Hypoparathyroidism.

Definition

Hypoparathyroidism or tetany is caused by insufficient production of PTH and is characterized :

- The common clinical manifestation is tetany.
- Serum calcium is low (hypocalcaemia) and serum phosphate high.

Ethiology

The disease may be caused by:

- The accidental removal of the parathyroid glands in resection of the thyroid.
- Inflammatory processes in parathyroid glands (tuberculosis, amyloidosis, measles).
- Trauma.
- Congenital insufficiency.
- Autoimmune processes.
- Malignant metastases
- Radioactive iodine therapy used in the management of toxic goitre

Pathogenesis

PTH deficiency leads :

- To the reduced passage of calcium from the bone tissue into the blood.
- Increased phosphorus reabsorption in the proximal parts of the renal tubules.
- To cause hypocalcaemia and hyperphosphatemia.
- Hypocalcaemia gives rise to the imbalance between the ions of sodium and potassium, calcium, magnesium, which, in its turn, sharply stimulates neuromascular excitation.

Classification

- Postoperative hypoparathyroidism.
- Congenital hypoparathyroidism.
- Idiopathic hypoparathyroidism.
- Pseudohypoparathyroidism (resistance to PTH).

Symptoms and signs

According to the clinical course, acute, chronic and subclinical forms of hypoparathyroidism are distinguished.

Chronic form of hypoparathyroidism .

- In congenital or idiopatic hypoparathyroidism .
- In spring and autumn.
- Cold hands and feet.
- Numbness' gooseflesh, parastesia and feeling of spasms.
- Painful tonic spasms which affect symmetrical groups of muscles and are selective character.
- Trophic disorders: brittle and reedy nails, defects of the teeth, caries.
- Cataract, focal or total baldness, early appearance of grey hair.
- Episodes of migraine, angiana pectoris bronchial asthma.

Illnesses of the genitor-urinary system .

Diagnostic tests

- Chvostek's sign is manifested by tapping the facial nerve in front of the tragus of the conha auriculae with a finger or percussion hammer.This sign may be of the I,II,III degree. Chvostek II and Chvostek III are usually detected in the latent form of the disease.
- Chvostek I :muscle contraction of the entire region innrvated by the facial nerve is characteristic of obvious tetany.
- Chvostek II: muscular contraction occurs in the region of the wing of the nose and the corner of the mouth.
- Chvostek III: contraction of just the muscle of the corner of the mouth.
- Trousseau's twitching is detected by applying a rubber tourniquet or rubber cuff compressing the patient's arm till the pulse disappears for two to tree minutes.
- Schlesinger's sign is demonstrated by the rapid passive flexing of the patient's leg at the hip joint when it is extended at the knee joint.In latent tetany the extensor muscles of the hip contract convulsively with extreme supination of the foot.
- Erb's sign: contraction of the muscles of the limbs under the effect of galvanic current even of the small intensity.

Laboratory

- Hypocalcaemia, hyperphosphataemia
- ECG lengthening of the Q-T wave

Treatment

- In the acute phase, calcium chloride 10% - 20 ml I/V slow.
- Substitution therapy is provided by alfacalcidol or calcitriol, both at a dose of 0,25 -2 mg/day.

4. Tetany crisis. (Acute form).

The bout of spasms may last from several minutes to several hours, sometimes several times a day or week.

Causes

- Infections
- Psychic trauma
- Overcooling or overheating

Symptoms and signs

- Consciousness may be present or lost in severe cases
- "Fish's mouth", a sardonic smile
- Trismus –spasms of the masticatory muscles of the jaw.

- "Accoucheeur's hand" – a characteristic position of the hand .The fingers are flexed and bent to the palm slightly, the thumb is flexed, the hand bent at the wrist joint.
- In spasm of the muscles of the lower extremities the thighs and shins are stretched out, the feet turned inward, the toes flexed.
- Opistothonus; spasm of the muscles of the back causes the trunk to be bowed foreward.
- Sharp disorders of respiration: result of the convulsive contractions of the intercostals muscles, muscles of the abdomen and diaphragm.
- Laryngospasm, which can leads to asphyxia and fatal outcome.
- Pyloric spasm, diarrehoea, polyuria
- Tachicardia
- Hypertention
- Acute psychosis
- Brain oedema, extrapyramidal symptoms.

Diagnostic tests

- Chvostek's sign is manifested by tapping the facial nerve in front of the tragus of the conha auriculae with a finger or percussion hammer.This sign may be of the I, II, III degree. Chvostek II and Chvostek III are usually detected in the latent form of the disease.
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- Erb's sign: contraction of the muscles of the limbs under the effect of galvanic current even of the small intensity.

Fig. " Trousseau's symptom .

Laboratory

- Hypocalcaemia, hyperphosphataemia
- ECG lengthening of the Q-T wave

Treatment

- Slow I/V 20ml of 10% solution of calcium gluconate
- If tetany is not relieved, administration of the magnesium
- Persistent vomiting is treated with I/V isotonic saline and potassium.
- In alkali excess, their withdrawal and if nessesary, ammonium chloride 2g 4 hourly will control tetany.

Prognosis

- In timely and correct replacement therapy is favourable
- In the occurrence of laryngospasm is very serious : death from asphyxia

Chapter VIII. Diseases of the Adrenals.

Anatomy

The adrenals are a paired, vital organ of internal secretion:

- two small structures situated one a top each kidney.
- Weight 10 – 20 g
- Length 40-60mm, width 20 -35mm,thickness 6-10mm

Adrenal glands consist of two distinct regions:

- Of a yellow outer -the adrenal cortex, which surrounds
- and an inner layer -the adrenal medulla, which has a reddish-brown tinge

The adrenal cortex secreted 3 classes of steroid hormons:

- Mineralocorticoids (aldosterone) from zona glomerulosa (outermost layer="salt").
- Glucocorticoids (cortisol) from zona fasciculata (middle layer="sugar")
- Adnrogens (dehydroepiandrosterone sulphate, dehydroepiandrosterone, androstenedione) from zona reticularis (innermost layer ="sex").

Effects of Mineralocorticoids and Its Regulation

Aldosterone regulates the water-salt metabolism:

- on the kidney promoting the reabsorption of sodium ions (Na+) in to the blood. Water follows the salt and this helps maintain normal blood pressure.
- acts on sweat glands to reduce the loss of sodium in perspiration.
- acts on taste cells to increase the sensitivity of the taste buds to sources of sodium.

The secretion of aldosterone is stimulated by:

- a drop in the level of sodium ions in the blood.
- a rise in the level of potassium ions in the blood.
- angiotensin II.
- ACTH .

Glucocorticoids effects and Its Regulation:

- Stimulate gluconeogenesis.
- Increase insulin resistance (diabetogenic action).
- Increase protein catabolism.
- Stimulate leukocytosis and lymphopenia.
- Inhibit bone formation; stimulate bone resorption.
- Inhibit fibroblasts, causing collagen and connective tissue loss.
- Suprese inflammation.
- Regulate extracellular fluid volume; promote renal solute-free water clearance.

Androgens effects and Its Regulation:

- Primarily responsible for adrenarche (pubic and axillary hair).
- in F is a major source of androgens/hypersecretion may produce a masculine pattern of body hair and cessation of menstruation.
- In M excessive production can cause premature puberty .
- Regulated by ACTH.

The adrenal medulla releases:

- adrenaline (also called epinephrine)
- noradrenaline (also called norepinephrine)
- Both are derived from the amino acid tyrosine
- Controlled by the sympathetic NS and hypothalamus

Catecholamines effects and Its Regulation:

- increase in the rate and strength of the heartbeat resulting in increased blood pressure;

- blood shunted from the skin and viscera to the skeletal muscles, coronary arteries, liver, and brain;
- rise in blood sugar;
- increased metabolic rate;
- bronchi dilate;
- pupils dilate;
- hair stands on end ("gooseflesh" in humans).
- clotting time of the blood is reduced;
- increased ACTH secretion from the anterior lobe of the pituitary

Adrenals Regulation

- ACTH stimulates growth of adrenal cortex and secretion of its hormones.
- Primary control by CRH from hypothalamus.
- Feedback inhibition by cortisol on pituitary, hypothalamus and CNS.
- By sleep-wake cycle and stress.

1. Adrenal insufficiency.

- Hyposecretion of the adrenal cortices hormones
- ACTH excess

Classification Adrenal Insufficiency

- Primary (adrenal causes) :
- Addisson"s Disease
- Congenital
- Acquired enzyme defects
- Secondary Adrenal Insufficiency (pituitary, inadequate ACTH):
- Hypothalamic
- Pituitary
- Glucocorticoid therapy
- Abrupt onset
- Slow onset

Ethiology of the Primary abrupt onset Adrenal Insufficiency (Waterhouse-Friedrickson Syndrome)

- Adrenal hemorrage (Waterhouse-Friedrickson Syndrome)
- Necrosis/trombosis (sepsis, leucemia, haemophilia e.t.c.)
- Trauma
- Clinical presentation is acute adrenal/Addissonian crisis

Ethiology of the Primary chronic adrenalocortical insufficiency (Addisson"s Disease).

- Autoimmune adrenalitis (destruction of cells in the adrenal cortex)
- Tuberculous drenalitis
- Adrenal metastases
- AIDS
- Bilateral adrenalectomy
- Drugs (ketoconazole)

Ethiology of the Pituitary Hypocorticism

- Autoimmune hypophisitis
- Tumor
- Infictions
- Trauma
- necrosis

Symptoms and signs

Both primary and secondary chronic adrenal insufficiency characterised by:

- weakness and fatigue
- postural hypotension
- weight loss, anorexia, nausea, vomiting
- Diarrhea
- Abdominal, muscle and joint pain

Syptoms and signs of Addisson's diasease

- Golden brown pigmentation (a dusky bronze =melanoderma) of the skin and mucous membranes : palmar creases, buccal mucosa, pressure areas, creases, hipples, face, the folds of the palms, the dorsal surface of the hands and feet, postoperative cicatrices . Pigmentation marked on the open parts of the body: areas against which the clothes rub,the axilla and the groin, elbows, knees, the small of the back , skin folds, nipples of the mammary glands, the genitals.
- Dehydration, salt craving.
- Hypotention (systolic blood pressures under 100 mm Hg), small heart.
- Amenorrhea, scant axillary and pubic hair.
- Associated with vitiligo, Hashimoto's thyroiditis, pernicious anaemia, type 1 DM, primary ovarian failure and hypoparathyroidism.
- The association of two or more of these endocrinopathies is known as type II polyglandular autoimmune syndrome.
- The combination of adrenal insufficiency, hypoparathyroidism and chronic mucocutaneous candidiasis constitutes type I polyglandular autoimmune syndrome.

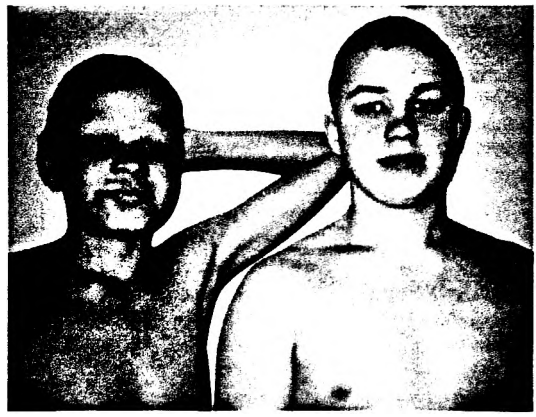


Fig..Pigmentation of the skin, scant axillary hair, birth mark (left)in the both Caucasion patient's. Normal color of the skin in healthy person (right).

Fig. Addison's disease. Pigmentation marked on the open parts of the body: areas against which the clothes rub, nipples.

Fig. Hyperpigmentation of fold on the palme skin and nails. Normal color of the skin of healthy person.

Fig.Hyperpigmintation in the palmar skin creases and nails.

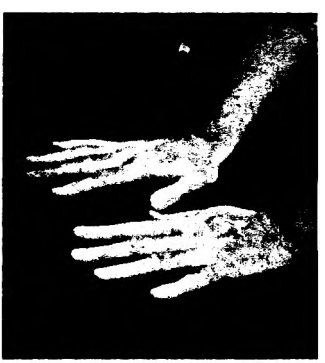


Fig . Hyperpigmintation in the palmar skin creases (left), but depigmentation of the skin (vitiligo).

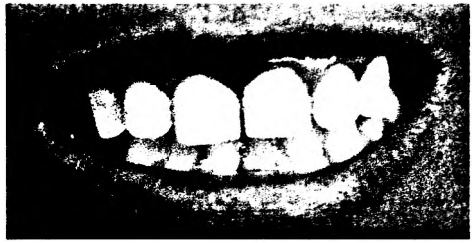


Fig. Pigmentation of the gums and buccal mucosa.

Laboratory Finding

A diagnosis of Addison's disease is made by laboratory tests. The aim of these tests is first to determine whether levels of cortisol are insufficient and then to establish the cause.

- low cortisol
- high ACTH
- ACTH stimulation test
- CKP stimulation test
- adrenal antibodies if autoimmune ethyology
- huponatriemia, hyperkaliemia,hypoglycaemia
- Plasma rennin activity is high and plasma aldosterone levels low or normal
- chronic anemia
- In tuberculous adrenalitis, chest radiograph may show evidences of pulmonary tuberculosis. CT scan and plain radiograph of abdomen may show adrenal calcification.

Treatment

Patient with Addison's disease require life-long glucocorticoid and mineralocorticoid replacement therapy.

- Cortisone acetate 25 mg per or os on getting up in the morning. and 12,5 mg in the evening at 6 PM. Alternatively, prednisolone is given in a dose of 5 mg in the morning and 2,5 mg in the evening.
- Florinef (mineralocorticoid) 0.05mg-0,2 mg per os daily
- Increase dose of steroid in times of illness or for surgery/stress
- Tubercuolous adrenalitis should be treated with antituberculous chemotherapy.

Special problems. Surgery

- If need surgery with general anesthesia are treated with injections of hydrocortisone and saline on the evening before surgery and continue until the patient is fully awake and able to take medication by mouth.

2.Pituitary adrenal insufficiency.

Ethiology

- Tumor, pituitary metastases
- Lymphocytic hypophysitis
- Pituitary trauma/radiation
- Long term glucocorticoid therapy

Clinical picture

- Usually more chronic than primary
- Slow onset
- Pallor, not hyperpigmentation
- Secondary hypogonadism : amenorrhea, decreased libido, scant axillary and pubic hair, small testicles.
- Secondary hypothyroidism.
- Prepubertal growth deficit, delayed puberty.

Laboratory finding and investigations

- X ray examination of the sella turcica : sella turcica is enlarged with a widened entrance and deepened fundus osteoporosis of the posterior wall of the sella turcica, calcinats (pituitary adenomas).
- Low cortisol
- Low ACTH
- Usually normal K+
- Pituitary adenomas by CT scan

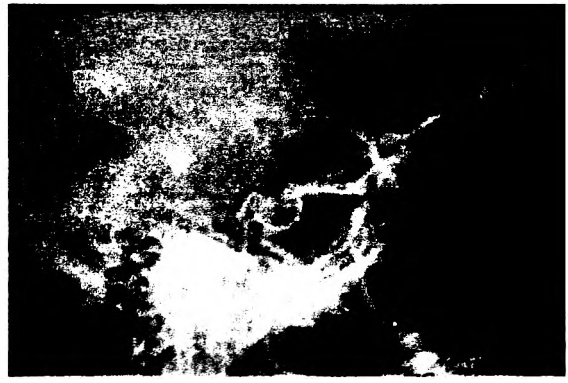


Fig. Normal X-ray of the sella turcica.

Fig. Pituitary adenomas by X-ray exam.

Treatment

- Surgery (transsphenoidal resiction)
- radiation of the tumor
- Cortisone acetate 25 mg per or os on getting up in the morning. and 12,5 mg in the evening at 6 PM. Alternatively, prednisolone is given in a dose of 5 mg in the morning and 2,5 mg in the evening.
- Florinef (mineralocorticoid) 0.05mg-0,2 mg per os daily .

3. Acute adrenal crisis&addisonian crisis.

Acute adrenocortical insufficiency is a crisis state threatening the life of the patient and developing as a result of the rapid or sudden decrease in the functional reserves of adrenal cortex.

Causes of Addison's disease

- Infection
- Stress.
- After bilateral adrenal infarction or bilateral haemorrhage
- Adrenal haemorrhage and often death has been associated with meningococcaemia (Waterhouse-Friderichsen syndrome).

Causes of Secondary adrenal inssuficiancy

- Postpartum pituitary necrosis (Sheehans).
- Necrosis of pituitary macroademoma.
- Surgical trauma (transient).

Pathogenesis

Sharp deficiency in corticosteroid hormones forms the basis of the pathogenesis.

Clinical

Clinical features of acute adrenal deficiency result from glucocorticoid deficiency, mineralocorticoid deficiency, androgen deficiency.

- Loss of mineralocorticoid activity is associated with development of hypotension, hyponatraemia and hyperkalaemia.
- The predominant manifestation of adrenal crisis is shock, but the patient often have nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, confusion or coma.
- Two other common symptoms are abdominal tenderness and fever.
- Patients with long-standing adrenal insufficiency who present in crisis may be hyperpigmented and have weight loss, serum electrolyte abnormalities, and other manifestations of chronic adrenal insufficiency.

Treatment

If acute onsrt of hypoetension, shock and volume repletion that is unexplained and catecholamine resistant always consider this and treatment with steroids, do not wait for laboratory confirmatory tests.

- Hydrocortisone 100 mg 6 hourly and taper it over 24 to 48 hours to amaintenance dose once the underlying stress resolves.
- Correct hypovolaemia and sodium depletion with normal saline.
- Glucose solution 5% if patient is hypoglycaemic.

Prognosis

- Farourable if timely treatment had been applied
- If no treatment is given, death occurs in one or two days.

4. Hupercortisizm.

Hypercorticizm is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol.

- It is relative rare.
- Age 20 to 50

Classificaion and ethiology

- Cushing's disease: Pituitary Cushing's.Corticosteroid excess caused by an ACTH secreting pituitary adenoma
- Cushing's Syndrome: iatrogenic,adrenal adenoma, micro-macronodular hyperplasia
- ACTH-independent Cushing's Syndrome: ectopic ACTH or ectopic corticotropin hormone syndrome

■ Pseudo-Cushing's: due to a supraphisiological doses of glucocorticoids drugs, pregnancy, pubertat period, obesity .

Table. Causes of Cushing's syndrome.

ACTH dependent	ACTH independent
Cushing's disease	Iatrogenic (use of corticosteroids)
Ectopic ACTH syndrome(tumor)	Adrenal adenoma
Iatrogenic (ACTH therapy)	Adrenal carcinima
Ectopic corticotrophin-releasing hormone syndrome (rare)	Micronodular carcinoma (rare)
Macronodular hyperplasia (initial stages)	Macronodular hyperplasia (rare)

- Cushing's disease is corticosteroid excess due to pituitary-dependent bilateral adrenal hyperplasia. The pituitary tumors in Cushing's disease are usually microadenomas (< 10 mm in size) which generally do not cause symptoms by local mass effect.
- Cushing's syndrome of pituitary origin is more common in women.
- Ectopic ACTH syndrome, usually due to small cell carcinoma of lung, is more common in men. Other tumors include carcinoid of Thymus, pancreatic carcinoma and bronchial adenoma.

Syptoms and signs

■ Weakness, headache
■ Pain in the back and limbs
■ Gonadal dysfunction: oligo/amenorrehea in women, decreased libido/impotence in a men
■ Hypertrichosis by the masculine type in F
■ Emotional lability, frank psychosis, euphoria or depression, headache and backache ,sleep disorders.
■ Acne and furuncles, dry and desquamating, with a purplish-marble patern skin, haemorrages

Signs

■ Weight gain.Centripetal (truncal) obesity but thin extremities, supraclavicular fat pads, posterior cervical fat "buffalo hump", "moon faces"
■ Facial plethora, hirsutism in women
■ Wide purple striae around the breasts/abdomen, thights;
■ acne, easy bruising, poor wound healing
■ Hypertension.
■ Osteoporosis, pathologic fractures, a vascular necrosis.
■ Truncal obesity (Cushing's obesity)

Selective localization of fat on the face –"moon face" (a rounded face), purplish-red, facial plethora.

- Chest, abdomen,neck over the7th cerebral vertebra –"buffalo hump".
- Thin limbs . proximal myopathy
- Hirsutism but with loss of hair on the head, downy hair prevails on the face
- Masculine type in female.
- Ginecomastia .
- Female balding
- Skin infections, bruising.

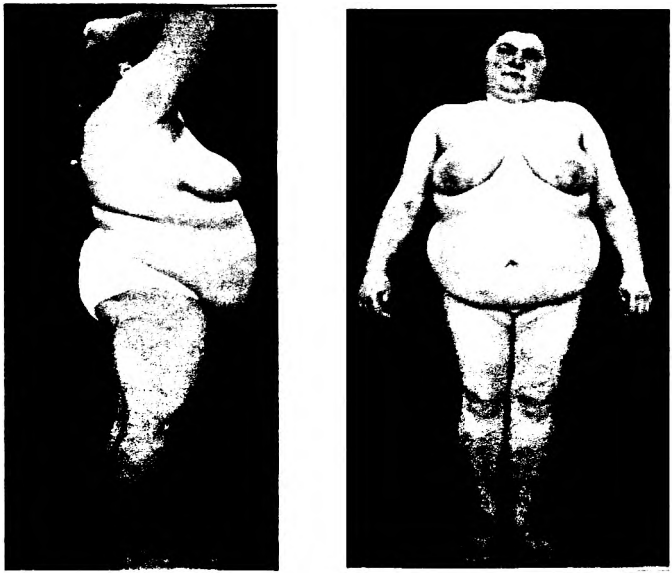


Fig. Cushing's obesity:centripetal (truncal) obesity, but thin extremities. 32-years-old patient.

Fig. "Moon face".

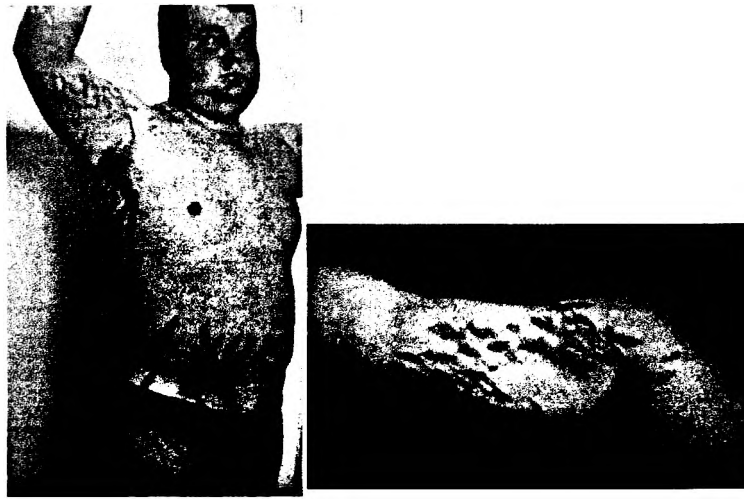


Fig. Wide purple striae around the breasts, abdomen, hips.

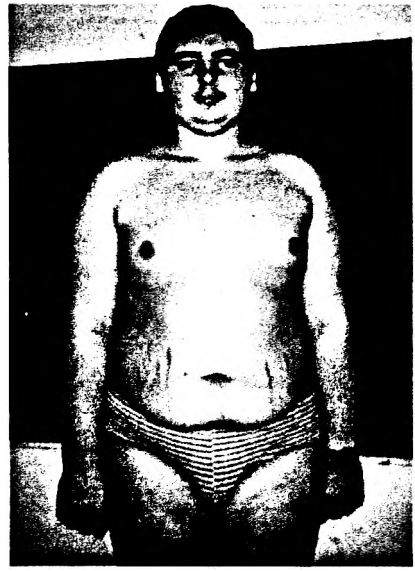


Fig. Multiple narrow stria in a15 years-old boy with hypothalamic pubertal syndrome.

Laboratory findings and investigations of Cushing's disease

- Cushings disease: high cortisol, urinary 17-cs and uriary 17-ketosteroids: slightly increased ACTH, no suppression with low dose Dexamethasone.
- Plain radiograph of the pituitary fossa may show one or more of the following abnormalities:
  - Enlargement of the sella turcica.
  - Erosion of clinoid pr5ocesses.
  - Suprasellar calcification.
  - Double floor of the sella turcica
- X- ray marked osteoporosis of the vertebral bodies "fish" vertebrae
- hyperglycaemia, glucosuria, leukocytosis, hypokaliemia, hyperlipidemia,, nephocalcinosis .

Fig. X-ray diagnosis: macroadenoma.Destruction of posterior wall of the sella turcica. Destraction of clinoid processes.

Laboratory and investigations of Cushing's syndrom

- Cushing's syndrom; high cortisol, low ACTH
- X-ray examination of adrenal (adenoma)
- Adrenal huperplasia: normal serum ACTH, no supression with low dose dexamthasone, supresesses with high dose
- ACTH secreating Tumor: increased ACTH, no suppression

Treatment

Treatment for hypercoticizm are designed to lower the high level of cortisol

1. Medical therapy :hypothalamic 5-HT antagonist:medical adrenalectomy with Ketoconazole (Nizoral), Aminoglutethimide, Bromocriptine, Metyrapone (Metopirone), which inhibit adrenal steroid biosynthesis perioperatively
2. Surgery. Transsphenoidal resection of microadenoma or adrenalectomy.
3. Radiation therapy:stereotactic radiosurgery or gamma-knife radiation.
4. Reducing corticosteroid use.

5.Hyperaldosteronism. (Conn's syndrome).

Definition

State of hypersecretion of the mineralocorticoid aldosterone .

Classification

1. Primary Hyperaldosteronism is due to an abnormality in the zona glomerulosa.

2. Secondary Hyperaldosteronism results from the stimulation of aldosterone secretion by angiotensin II following activation of rennin-angiotensin system.

Primary Hyperaldosteronism

Ethiology

- Aldosterone-producing adrenal adenoma (Conn"s syndrome)
- Bilateral adrenal hyperplasia :
- Idiopathic
- ACTH-dependent (glucocorticoid-responsive or dexamethasone-suppressible). In this type of hyperaldosteronism, the secretion of aldosterone is under ACTH control. Therefore, treatment is by administering glucocorticoids which suppresses ACTH release.

Pathogenesis

Excess aldosterone produces sodium retention, potassium loss and metabolic alkalosis.

Symptoms and signs

- Fatigue.
- Muscle weakness from hypokalaemia.
- Parasthesias, tetany due to metabolic alcalosis.
- Headaches.
- Hypertension uncontrolled by standard therapy.
- Hypokaliaemia off diuretics.
- Polyuria, polydipsia, nocturia due to nephrogenic diabetic insipidus.

Labarotory

- Hypokalaemia: elevated urinary potassium (>30 mEg/day during hypokaliaemia in inappropriate).
- High normal Na+.
- Metabolic alcalosis.
- High 24 hr"s urinary or plasma aldosterone .
- Low random plasma renin .

Diagnostic criteria:

- Dastolic hypertention without edema.
- Decreased renin .
- Increased aldosterone secretion both unresponsive to increases in volume.

Treatment

- Medical: spirinolactone (aldosterone antagonist) – up to 400 md/day.A few patient develop gynaecomatia with spirinolactone. In them, amiloride 10 -40 mg/day may be substituted.

- Surgical: removal of adenoma is curative (unilateral adrenalectomy).
- ACE inhibitors may be given for control of hypertension.

Secondary hyperaldosteronism

- Results from aldosterone excess mediated throuth the renninangiotensin system.

Ethiology

- Physiological : salt depletion from inadequate intake or excessive loss through kidney or gastrointestinal tract.
- Pathological : excessive diuretic therapy, nephritic syndrome, cirrhosis with ascites , congestive heart failure, accelerated or malignant phase of hypertension, severe renal artery stenosis.

Laboratory

- Hypokalaemia
- Plasma aldosterone levels are elevated.
- Plasma rennin activity is elevated.

Treatment

- Salt depletion is treated with intravenous saline.
- Congestive heart failure is treated with spirinolactone and ACE inhibitors.
- Barterer's syndrome is treated with spirinolactone and indomethacin.
- Malignant hypertension is treated with antihypertensive drugs.
- Renovascular disease is treated with ACE inhibitors, but definitive therapy is angioplasty or surgical correction.
- If excessive diuretic therapy is the cause (Thiazide), it should be substituted or supplemented with one of the potassium-sparing diuretics like spirinolactone, amiloride or triamterene.

6. Pheochromocytoma.

Definition

Tumor which synthesized and release cathecholamines which leading to malignant hypertension

Epidemiology

- Occur with equal frequency in males and females in any age.
- Rare tumor arising from chromaffin cells of the sympathetic nervous system (occur anywhere from the base of the brain to the urinary bladder).
- Most commonly a single tumor of adrenal medulla
- 10% extra-adrenal,10% multiple tumors,10% malignant,10% familial.
- Most pheochromocytomas are noncancerous (benign) and don't spread to other part of the body.

- Rare cause of hypertension

Ethiology

- Tumor cause unclear

Classification

- Adrenalosympathetic (paroxysmal) form.
- Stable form (stably increased arterial pressure without crises).
- Asymptomatic form.

Symptoms and signs

- Symptoms often paroxysmal, may be triggered by stress, exertion, certain foods.
- Classic triad: "pounding" headache, palpitations, diaphoresis.
- Blood pressure >260/160mm Hg .
- Postural hypotension:this result from volume contraction.
- Tremor, anxiety, chest or abdominal pain.
- Tachyarrythmias.
- Cardiomyopathy.
- Nausea, vomiting.
- Skin and mucous are pale, limbs cold, pupils dilated.
- Fever.
- Café au lait spots:these are patches of cutaneous pigmentation, which vary from 1 -10 mm and occur any place on the body.Characteristic locations include the axillae and intertridinous areas (Groin). They vary from light to dark brown, hence the name café au lait.

Laboratory and investigation

- Increased urinary catecholamines usually sufficient to confirm diagnosis.
- Elevated plasma epinephrine unsuppressed by central @-adrenergic.
- Hyperglycemia, hypercalcemia, erythrocytosis.
- Positive adrenal CT scan and MRI
- Meta-iodo-benzoguanidine uptake by tumor site during scan; useful to locate for surgery

Treatment

- Surgical resection.
- Adequate pre-operative preparation: -@-blockade pre-operation

- Doxazozine, Phentolamine , Labetalol. Peri-opetative: beta-blokade – propranolol .

- Rescreen urine one month post-operatively.

7. Pheochromocytoma's crisis. (Hypertensive crisis).

- It is acute malignant hypertention due to excessive production of cathecholamine by hormone active tumor.
- May vary in occurrence from monthly to several times per day.
- The duration may vary from seconds to hours.
- Worsen with time, occurring more frequently and becoming more severe as the tumor grows.

Aggravatings factors

- Stress .
- Exertion.
- Certain foods.
- Palpation of the abdomen.

Clinical signs

- Ubrupt onset.
- Headache.
- Palpitations.
- Diaphoresis.
- Blood pressure >260/160 mm Hg .
- Epigastric and flank pain.
- Polyuria.

Treatment

- Phentolamine (Regitin) 0.05 mg I/V titrated to desired effect or Nitroprusside begin infusion 0,3 – 0,5 mcg/kg/min I/V titrate to desired effect; Doxazozine (Cardura) 2mg per os titrate to 16 mg to titrate effect.

Complications

- Stroke.
- Tacchiarritmiaas.
- Heart failure

Prognosis

- Curable if recognized and properly treated, but fatal if not.

Chapter IX. Diseases of the Hypothalamic-Pituitary System.

Pituitary Gland (Hypophisis)

Anatomy

- A small endocrine gland situated in the sella turcica of the sphenoid bone, bridged over by diaphragm sellae.
- It is related to sphenoidal aie sinuses below, optic chiasma above and cavernous sinuses laterally.

- The anteroposterior dimention is about 10 , it is 12 -15 mm wide and 5 -6 mm high. Weights about 0,7 g.
- The sagittal demention of the sella turcica are about the 10 -15 mm and vertical 8 -12 mm.
- Consists of two parts: the anterior lobe(adenohypophysis) and the posterior lobe(neurohypophisis).

Anterior Pituitary

- Forms the adenohypophysis comprising 75% of the hypophysis
- Consists of basophil, eosinophol and chromophobe cells

Anterior Pituitary Produced Six Different Hormones:

Electron microscopically 5 distinct types of cells can be identified:

- Somatotrophs secreting Growth hormone (GH).
- Lactotrophs secreting Leutenizing hormone (LH).
- Lactotrophs secreting Follicle stimulating hormone (FSH).
- Thyrotrophs secreting Thyroid stimulating hormone (TSH).
- Corticotrophs secreting Adrenocorticotropin hormon (ACTH)
- Lactotrophs secreting Prolactin (PRL)

Posterior Pituitary

The posterior lobe, pituitary stalk and eminentia medialis of the tuber cinereum are components of the neurohypophysis.

Posterior Pituitary Produced Hormones:

- Oxytocin .
- Antidiuretic hormone (ADH)= arginine vasopressin hormone.

Table. The Pituitary Hormones and its action.

Hormone	Actions
Thyroid stimulating hormone (TSH)	Stimulates the production of T4 and T3
Luteinising hormone (LH), Follicle stimulating hormone (FSH)	In males, both FSH and LH are nessesary for spermatogenesis.In males, FSH stimulates Sertoli cells to secrete androgen binding protein (ABP),transferring, plasminogen activator and inhibin. In males, LH stimulates Leyding cells to produce testosterone. In females, FSH promotes growth and development of ovarian follicles during the follicular phase of menstrual cycle. In females, the mid-cycle peak of LH (LH surge) induces ovulation.

Hormone	Actions
	In females, both FSH and LH are nessesary for the development of corpus luteum during the luteal phase of menstrual cycle.
Growth Hormone (GH)	Promotes growth
Prolactin (PRL)	Exerts its main effects on the breasts, stimulating lactation
Adrenocorticotrophic Hormone (ACTH)	Controls cortisol release from adrenal cortex, and skin pigmentation
Arginine Vasopressin (AVP) -ADH	Promotes reabsorption of water by renal tubules
Oxytocin	Promotes uterine contraction and expression of milk from the breasts

Hypothalamus

- The higher regulator of the neuro-endocrine system
- It is a region of the brain located in its basal part within the limits of the middle cranial fossa.
- There are 32 pairs of nuclei, which participate in the regulation of the most vital vegetative functions of the organism.: arterial pressure, vascular permesbility, appetite, sleep and wakefulness, psychic activity, activity of the peripheral endocrine glands("target" glands).
- The feedback system or "plus-minus" interaction ensures the normal production of hormones in the organism, thus maintaining the consistency of the internal medium and various functions of the organism.
- There are releasing factors for all the tropic hormones,
- Monoamines (dopamine, noradrenaline, serotonin) regulate the secretion of releasing factors and their entry into the circulation. They are produced by the nerve cells located in the middle part of the hypothalamus.
- Activity of the hypothalamic centres is controlled by other parts of the central nervus system and particularly by the cerebral cortex.

Hypothalamic Control of Pituitary

The hypothalamus and hypophysis constitute a single interconnected system of the organism. The hypothalamus nuclei are connected with the hypophysis by means of neurosecretory pathways

- Tropic (releasing) and inhibitory factors control the release of the anterior pituitary gland and by direct feedback inhibition.
- The posterior pituitary receives ADH and oxytocin from hypothalamus, secreting them under CNS control .

Table.Hypotalamic Hormones and its Action.

Hormone	Action
Corticotrophin releasing factor (CRF), Arginine vasopressin (AVP)	Stimulating ACTH and LPH
Gonadotrophin releasing factor (GnRF)	Stimulating LH and FSH
Somatostatin or Somatotropin release inhibiting factor	Inhibiting GH and TSH
Thyrotrophin releasing hormone (TRH)	Stimulating TSH and PRL
Dopamine (D) or prolactin release inhibitory factor	Inhibiting PRL

1. Hypopituitarism. (Panhypopituitarism).

It is state of hyposecretion of anterior pituitary.

- Can be caused by either hypothalamic or pituitary dysfunction.
- Patients may have single or multiple hormonal deficiencies.
- May be genetic or idiopatic(acquired)

Etiology of hypopituitarism

- Invasive: generally primary tumors.
- Infarction: e.g. Sheehan;s syndrome.
- Infiltrative: e.g. sarcoidosis, histiocytosis .
- Immunologic: autoimmune destruction.
- Infections: e.g. TB, syphilis.
- Injury: severe head trauma.
- Iatrogenic: following surgery or radiation.
- Idiopathic: familial forms, congenital midline defects.

Classification

1. Congenital hypothalamic: Deficiencies of GnRP (Kallmann's syndrome), TRH, GHRH, CRF.
2. Acquired hypothalamic: craniopharyngioma, sarcoidosis, tuberculosis,histiocytosis-X, radiotherapy, tumors.
3. Pituitary : pituitary adenoma, post-partum necrosis (Sheehan's syndrome),surgery, autoimmune, radiotherapy, haemorrage, empty sella syndrome.

Clinical

Manifestation of hypopituitarism depending upon which specific hormones are lacking and whether their deficiency is partial or comletely .

Symptoms

- Sexual dysfunction.
- Weakness.
- Loss of weght
- Easy fatigability.
- Lack of resistance to stress, cold, and fasting.
- Axillary and pubic hair loss.
- Hypotention;
- Pituitary tumors may cause visual field defects.
- LH deficiency: leads to loss of libido and impotence in males, and oligomenorrhoea or amenorrhoea in females.Later бшт males, there may be gynaecomastia and decreased frequency of shaving. In both sexes, axillary and pubic hair becomes sparse and later absent. The skin is finer and wrinkled.
- ACTH deficiency: leads to cortisol deficiency resulting in symptoms and signs of adrenal insufficiency, with skin pallor due to lack of melanin and normal plasma electrolytes.

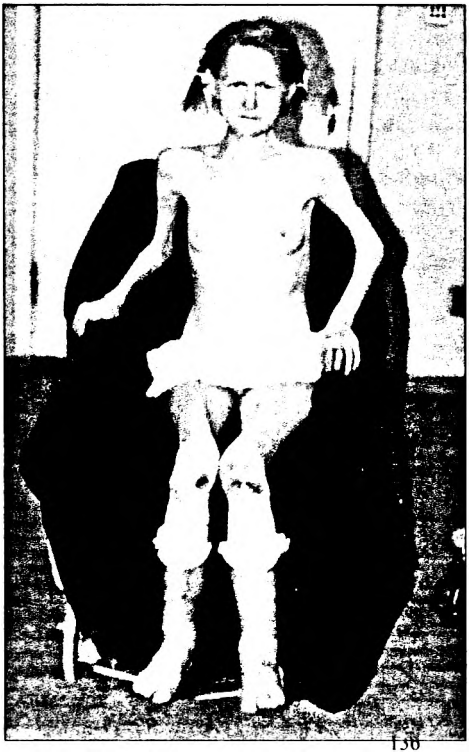


Fig. Hypothalamic-pituitary cachexia (Simmonds' syndrome) : secondary hypocorticoidism,a secondary hypothyrosis,a secondary hypogonadotrophic hypogonadism; an amenorrhea, an oligotrophy of mammary glands, absence hair of apubis and an axillary fossae. Secondary somatotropic insufficiency: an atrophy of muscles, anoedontus. A secondary polyfactorial anaemia of serious degree. Hypoprotein edemas. Growth - 158 sm, weight - 26 kg.

- TSH deficiency: leads to symptom and signs of secondary hypothyroidism.
- PRL deficiency: leads to failure of lactation.
- Ultimately, the patient goes into coma resulting from hypoglycaemia, water intoxication and hypothermia.

Essentials of diagnosis

- Fall in LH/FSH and PRL leads to sexual dysfunction; axillary and pubic hair loss, amenorrea or infertility in women, erectile dysfunction in men.
- TSH deficiency leads to hypothyroidism.
- ACTH deficiency leads to adrenal insufficiencyeasy fatigability, weakness, lack of the resistasnce to stress, hypotension .
- Fall in GH, clinically not apparent.

Fig. 20 years-old women with anorexia veurosa.
Growth – 160 cm, weight - 42 kg. Normal growth of hair .

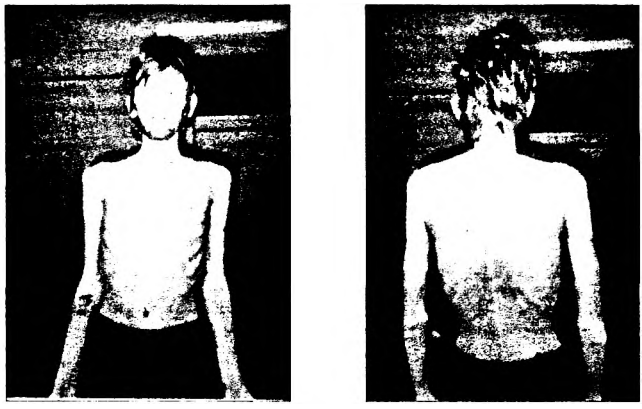


Fig.23 years-old patient. Panhypopituitarism(tumour of a bottom of IV ventricle of a brain). Secondary hypocorticoidism.Cachexia. Growth - 172 cm, weight - 45 kg.

Laboratory

- Low free T4 with low or inappropriately normal TSH.
- Low testosterone without elevation of LH and FSH.
- Provocation tests may be required to assess pituitary reserve

Treatment

- Transsphenoidal removal of pituitary tumors.
- Radiation therapy with x-ray, gamma knife, heavy particles.
- Lifetime hormone replacement therapy:

- ACTH deficiency is treated with cortisol 20 mg in the morning and 10 mg in the evening or prednisolone 5 mg in the morning and 2,5 mg in the evening.
- TSH deficiency is treated with T4 0,1 – 0,15 mg daily.
- Gonadotrophin deficiency is treated with sex hormone replacement, based on the age and sex of the patient.

2. Diabetes insipidus. Posterior Hypopituitarism.

Definition

It is state of absolute deficiency of ADH or of resistance to ADH.

Hypothalamic diabetes insipidus may be either an independent disease, or a symptom of certain endocrine and non-endocrine diseases. It is encountered in patient of all ages, but most often occur in young people from 18 to 25 years of age.

Classification

1. Deficient production of ADH (hypothalamic):
- Primary diabetes insipidus: familial or idiopathic
- Secondary diabetes insipidus .

2. Deficient action of ADH : nephrogenic diabetes insipidus ("renal diabetes insipidus"):total or considerable insensitivity of the distal part of the kidney tubules to ADH).

3. Vasopressinase-induced diabetes insipidus of pregnancy.

Ethiology

1. Primary deficiency of ADH:
- Trauma
- Infection
- Tumor
- Granulomas
- Inflammatory(autoimmune hypophisitis)
- Vascular
- Genetic defects
- idiopathic

2. Secondary deficiency of ADH :
- Psychogenic polydipsia
- Dipcogenic polydipsia (abnormal thirst)
- Iatrogenic

3. Nephrogenic diabetes insipidus:
- Drugs :Lithium,amphotericin B, aminoglycosides, rifampicin
- Metabolic :hypercalcaemia, hypokalaemia
- Amiloidosis
- Genetic
- Idiopathic.

Pathogenesis

The lack of ADH leads to a reduced reabsorption of water in the distal segments of the convoluted tubules of the kidneys, which causes an increase in dieresis (polyuria). Dehydration is attended by stimulation of the "thist centre" in the hypothalamus resulting in thirst (polydipsia).

Clinical

- Polyuria, excessive thirst and polydipsia are the cardinal manifestations
- Daily urine output may reach as high as 10-15 litres.

Laboratory and investigations

- The urine is clear, and of low specific gravity.
- The osmolality is low, usually less then that polasma. However in primary polydipsia, plasma osmolality may be lower than urinary osmolality.
- Serum sodium is borderline high indicating water loss.
- MRI of pituitary and hypothalamus

- Water deprivation test: the diagnosis of hypothalamic diabetes insipidus depends on demonstrating that a rise of plasma osmolality induced by withholding fluids is not accompanied by a normal rise in the osmolality or specific gravity of urine. The later test is necessary to show that kidney is capable of concentrating the urine which it cannot do in nefrogenic diabetes insipidus.

Treatment

- Desmopressin 10 -20 mcg intranasally once or twice a day.
- Chlorpropamide enhances the renal responsiveness to vasopressin.
- Carbamazepine is an alternate drug with similar action.
- Thiazide diuretics are the only effective drugs for nefrogenic diabetes insipidus.

Growth Hormone Disorders

GH functions:

- is essential for body growth
- to regulate body composition, fluid homeostasis,
- glucose and lipid metabolism,
- skeletal muscle and bone growth, and possibly cardiac functioning.
- sleep, exercise, and stress

3. Acromegaly.

Definition

Acromegaly is an endocrine disease characterized by the disproportional growth of the skeleton, soft tissues, and internal organs, which as a result of the GH hypersecretion occurring in adult life after epihyseal clousure.

Ethiology

- Pituitery tumor or diffuse hyperplasia of eosinophil cells in the anterior pituitary.
- Rare causes: excessive growth hormone secretion from pancreatic islet cell tumor, or excessive secretion of growth hormone-releasing hormone from hypothalamic lesions, bronchial carcinoid and small cell lung carcinoma.

Pathogenesis

GH exerts much of its growth-promoting effects through the release of IGH-1 produced in the liver and other tissues.Hyperproduction of the GH leads to hypertrophy of the bones of the skeleton, joint cartilages, capsules and tendons, and hyperplasia of the internal organs. GH-secreting pituitary tumors usually cause some degree of hypogonadism, either by cosecretion of prolactin or by direct pressure upon normal pituitary tissue.In the initial phase of the disease the endocrine glands (thyroid, parathyroid glands, pancreas) are hyperplasia and their function is increased, but at a later period of the disease hypoplasia of endocrine glands develops with reduction of function.

Symptoms and signs

- Headaches, impairment of vision and memory, apathy, drowsiness

- Arthralgias and muscular pain
- Hypertention, cardiomegaly and heart failure with a dilated left ventricle.
- Decreased libido and impotence.
- Irregular menses or amenorrhea.

Portret's diagnosis:

- Enlargement of the superciliary arches, zygomatic bones, the hollow of the auricles, nose, lips, tongue; prognatism and malocclusion, tooth spacing widens (diastema).
- Macroglossia, hypertrophy of pharyngeal and laryngeal tissue; this causes a deep, coarse voice.
- The skin manifest hyperhydrosis, thickening, cystic acne, and areas of acanthosis nigricans, skin papillomas.
- The hands enlarge and a doughy, moist handshake,the fingers widen, causing patients to enlarge their rings.
- Hypertrichosis.
- Degenerative arthritis,overgrowth of vertebral bone; the thorax increases in sizes, making the patient barrel-chested; the intercostals spaces widened.
- Kyphosis and scoliosis of the spine.
- The sternum, clavicles, and ribs thicken.
- Weigth gain.
- Obstructive sleep apnea.
- Goiter.
- Splanchnomegaly.
- Bitemporal hemianopsia (blindness in the temporal half of the field of vision in each eye), primarily to the red and white colors

Fig. Acromegaly in a 56 year –old patient. Hand of acromegaly patient (left) and hand of healthy person (right).

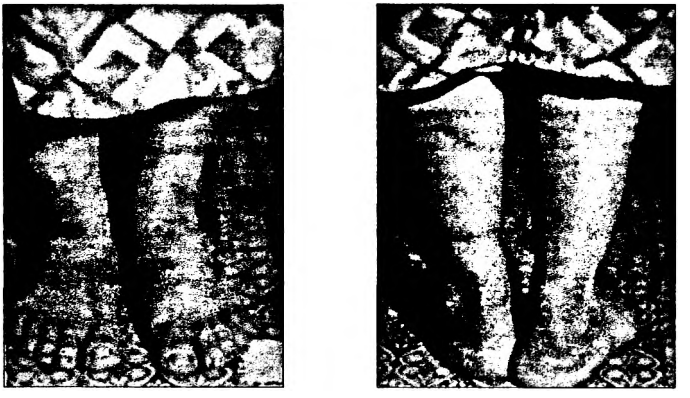


Fig. Foot of acromegaly patient.

Fig. Foot of acromegaly patient.

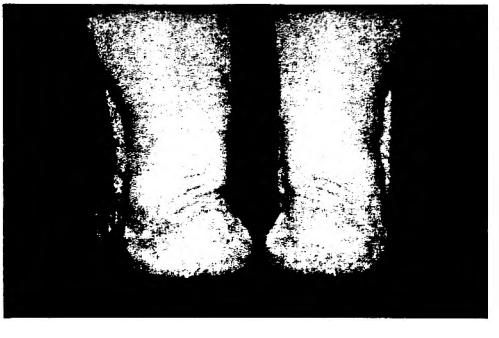


Fig. Foot of acromegaly patient.

Fig. Acromegaly in a 42 year-old female. Hyperthrophy of the soft tissue of the face. Diastema, prognatism.

Fig . Acromegaly in 61 years-old patient.. Enlargement of the tongue (macroglossia).

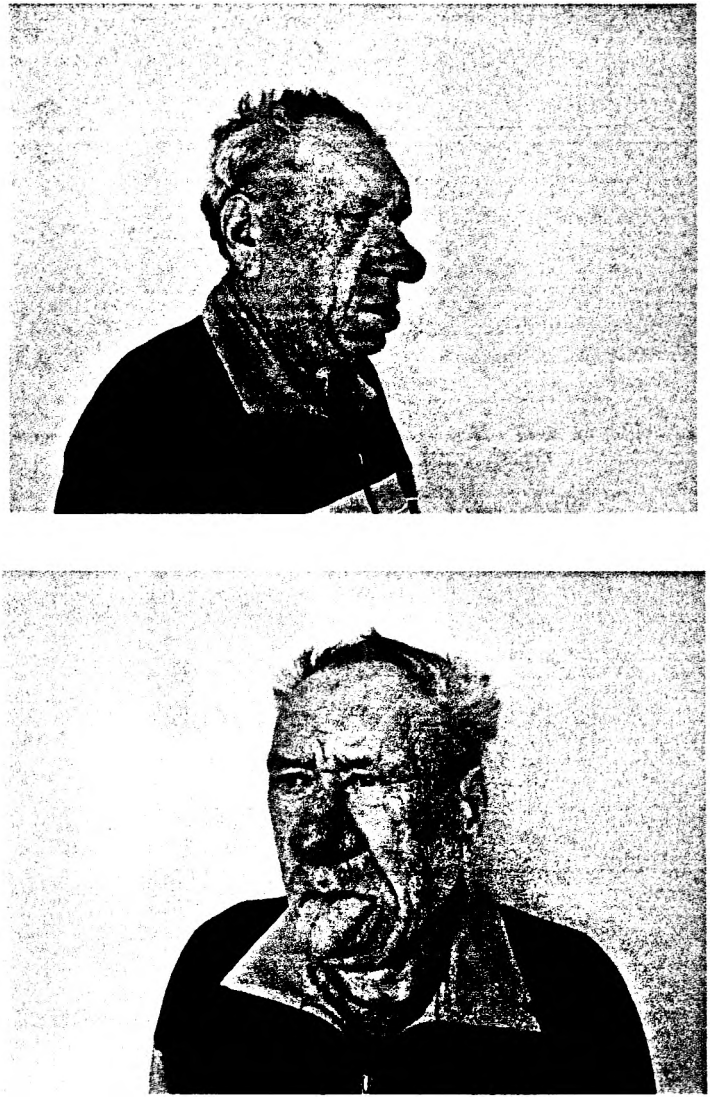


Fig. Acromegaly in 64 years-old patient.

Laboratory and investigations

- X –rays shows: the long bones are wide, thick, with coarse bony trabecular pattern tufting of the terminal phalanges.
- X –rays shows: the vault of the scull is increased in thickness, paranasal sinuses are large, mandible shows prognathism and malocclusion of the teeth .
- Plain Radiograph of the pituitary fossa: sella turcica is widened, deep and ballooned.
- CT scan or MRI shows a pituitary tumor in 90% of acromegalics.
- Elevated IGF -1 levels (normal 202 – 453 ng/ml).
- Basal GH level (normal 0-264 nmol/L in male ,and 0-440 nmol/L in female).
- GH levels are measured during an oral glucose tolerance test. A failure of suppression or paradoxical rise of GH indicates acromegaly.
- Demonstration of GH rise after TRH administration.
- Insulin resistance causing diabetes mellitus (30%).
- Collon polyps are common, especially in patients with skin pappilomas

Picture. Different types of sella turcica (by M.Julles , I. Hollo)

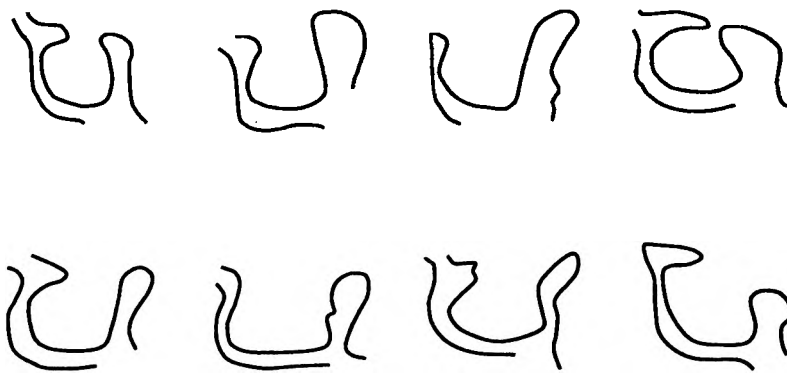


Table.IGF -1 levels according the age.

Age, years	Normal response nmol/L
19 -24	48 - 450
25 -29	62 -280
30 -39	40 -280
40 -49	40 -256
50 -59	66-310
> 60	118 -314

Treatment

1. Surgery.
2. Medical therapy.
3. Radiosurgery.

Surgery

- Endoscopic transnasal, transsphenoidal pituitary microcrosurgery removes the adenoma.

Medical therapy

- Dopamine agonist (Bromocriptine or Carbergoline). The initial dose is 0,25 mg orally twice weekly, which is gradually increased to a maximum dosage of 1 mg twice weekly
- Somatostatin analogue (Octreotide or Lanreotide).Short-acting Octreotide acetate in doses of 50μg is injected subcutaneously 3 times daily. Responders who tolerate the drug are swirched to long-acting octreotide acetate injectable suspension in a dosage of 20 mg intragluteреally per month. The dosage may be adjusted – up to maximum of 40 mL monthly – to maintain the serum GH between 1 and 2,5 ng/mL, keeping IGF-1 levels normal.Lanreotide SR is given by subcutaneous injection at a dosage of 30 mg every 7-14 days. Lanreotide Autogel is a newer formulation that is administrated by deep subcutaneous injection in doses of 60-120 mg every 28 days.
- GH receptor antagonist. Pegvisomant: the starting dosage is 10 mg subcutaneously daily. The maintenance dosage can be increased by 5-10 mg every 4-6 weeks, based on serum IGF-1 levels and liver transaminase lrvrls. This drug does not shrink GH-secreting tumors.

Radiosurgery

- External radiotherapy by gamma knife, heavy particle radiation, or adapted liner accelerator
- Stereotactic radiosurgery :implantation of yttrium into the pituitary .

Prognosis

- Patients with untreated or persistent acromegaly tend to have premature cardiovascular disease and progressive acromegalic symptoms.

- Transsphenoidal pituitary surgery is successful in 80-90% of patients with tumors less than 2 cm in diameter and GH levels less than 50 ng/mL.
- Conventional radiation therapy (alone) produces a remission in about 40% of a patients by 2 years and 75 % of patients by 5 years after treatment.
- Hypopituitarism may occur, due to the tumor itself, pituitary surgery, or radiation therapy.

4. Gigantism.

Definition

- Gigantizm is a disease characterized by a proportional intensified growth of the skeleton and other organs and tissues as a result of the GH hypersecretion occurring in the period of sexual maturation.
- Gigantism is considered the height more than 200 sm at male and more than 190 sm at female.
- A child is considered to be tall when the height is greater than 2 standart deviations above the mean for the age.

Ethiology

- Pituitery tumor or diffuse hyperplasia of eosinophil cells in the anterior pituitary.
- Pituitary neuroinfection or a trauma.

Pathogenesis

- Excessive GH causes tall stature and gigantism if it occurs before closure of epiphyses.
- Hyperproduction of the GH leads to intensified proportional growth of the skeleton and of other organs.
- Fast uncontrollable growth of a body at the length, proceeding throughout all life, resulting to posture disturbance, peripheric angiopathy, polyneuropathy, insulinresistance.
- 30 % of patients have depression of libido, a potency and a dysmenorrhea because of hyperprolactinemia.
- 80 % of patients are IGT, and at 25 % the obvious diabetes with ketoacidosis develops.
- In the course of time there are signs of disproportionality of the body

Symptoms and signs

Normally, in adults, the height of the person is equal to the length of arm span. The apper segment (from vertex to the pubic symphysis) is equal to the lower segment (from pubic syphysis to the heel).

There are signs of disproportionality of a gigant persone:

- long-legged, long arms ,but short trunk,and reduced head;
- acromegalic features (so-called acromegalic gigantism).

- height of giants measure in position standing, sitting, laying because at them the scoliosis, a kyphoscoliosis, shift vertebra disks take place;
- the length of arm span exceeds length of feet;
- The sizes of a head small;
- The length of feet is more than length of a trunk;
- Augmentation of the sizes of a brush at length (from the beginning of a brush till the end of a long finger);
- Augmentation of the sizes of feet.
- Secondary sexual signs are developed badly. The hypogenitalism are at young men.
- Dysmenorrheal/amenorrhea/ anovulatory menstrual cycles are at girls .A mammary glands are developed badly.
- Quite often have trophic ulcers or gangrene of the bottom extremities
- A secondary hypothyrosis, adrenal insufficiency, diabetes insipidus may occur with the age

Complaints:

- headache,giddinesses, fast fatigability ,the memory impairment
- unpleasant sensations in the field of heart
- paresthesias in distal departments of extremities, cold intolerance of the extremities ,
- Good-quality tumour can not be accompanied by other symptoms.

Differencial diagnosis

GH-induced gigantism must be differentiated:

1. Simple or primary gigantism: Racial, familial or constitutional
   - Great heaight and body weight of the parents, normal sexual and physical development.
2. Endocrine: sexual precocity, hypogonadism.
   - Sexual precocity may be due to premature secretion of gonadotropic hormones.Acceleration of linear growth occurs with simultaneously with signs of premature sexual development.
   - Primary hypogonadism is marked by high disproportional growth; a relatively short trunk, a small head, long extremities with signs of underdevelopment of sexual organs and absence of secondary sex characters.
3. Genetic: Klinefelter's syndrome.
   - Lower segment more than the upper segment, gynicomastia, small,firm testes, azoospermia, chromatin (Barr) body usually present, 47xxy.
4. Metabolic: Marfan's syndrome
   - Abnormal shape of the ears, congenital heart defects, dolichocephalic cranium, arachnodactyly, high arched palate, arm span greater than the height and the lower segment more than the upper segment.
5. Miscellaneous: Cerebral gigantism (Soto's syndrome)

- Large elongated head, prominent forehead, large ears and jaws, elongated chin, antimongoloid slant to the eyes and coarse facial features.They have subnormal intelligence and impaired coordination. The cause is not known.

Treatment (see "Acromegaly").

5. Dwarfism. (Short Stature, Nanism, Microsomia).

General consideration

Dwarfism is the term applied when the patient's height is 2 standart deviations less than that for his/her age and sex (adult males no higher than 130 sm and adult females below 120 sm).

Definition

Pituitary nanism is a genetic disease caused by an absolute or relative deficiency of GH, which leads to the retarding of the growth of the skeleton and other organs and tissues.

- Is characterized by deficient stature in adul males no higher than 130 sm and adult females below 120 sm
- Bigins after two-three years of age.

Ethiology

- A genetic disease which is inherited as an autosomal-recessive trait,or more seldom, as an autosonal-dominant trait
- Occur as a result of the isolated insufficiency of the GH
- Occur in people with a normal level oa GH , but when GH is not biologically active or the peripheral tissues not sensitivity to it (somatomedins insufficiency).
- May develop as a conswquence of the lesion of the pituitary by trauma, tumors or vascular.

Phatogenesis

- Genetic defects : prop-1, pit-1 gene deficiency
- GH deficiency leads to the retarding of the growth of the skeleton and internal organs, hypoplasia and atrophy in the thyroid gland, sexual glands.

Symptoms and signs

- The infantile body proportion (the apper srgment is greater than the lower segment and the height is greater than the arm span).
- Skeletal age and dental age delayed by more than 2 years
- The growth rate is less than 4 sm/year
- The skin pale, at times with a yellowish shade, wrinkled, dry
- The subcutaneous fat is poorly developed but obesity over abdomen, in the area of the mammary glands, the pubis and thighs
- The muscular system is poor
- Splanchnomicria, but the function of the internal organs is usually not disturbed

- The sexual system is underdeveloped.Male sometimes have cryptorchidism (failure of the testes to descend into the scrotum). Female do not have menstruation.Secondary sex characters and libido are absent
- In nanism caused by tumor or hydrocephalus general cerebral symptoms present, may occur bitemporal hemianopia
- MRI shows hypoplastic or aplastic pitutaries

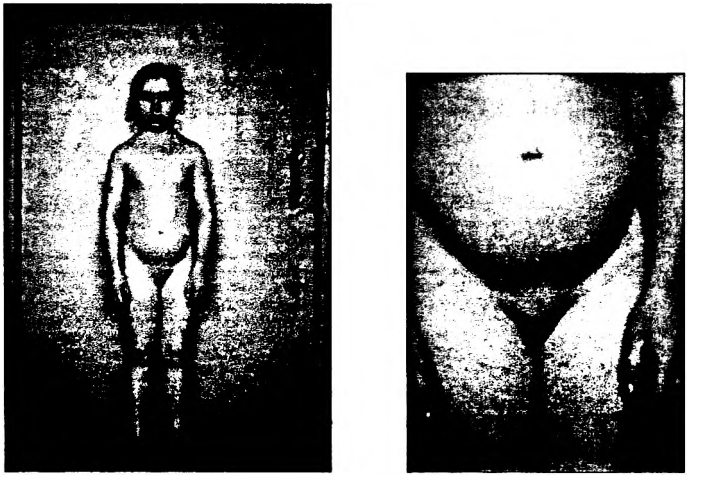


Fig. Pituitary nanism in a 18 -year-old female (height – 110 cm, weigth -26 kg).

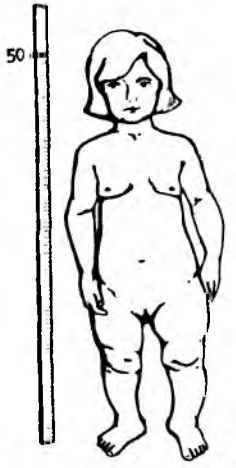
Differencial diagnosis

Short stature are divided into two broad categories:

1. Disproportionate dwarfism.

- If body size is disproportionate, some parts of the body are small and others are of average size or above-average size. Disorders causing disproportionate dwarfism inhibit the development of bones.

Fig. 46 years –old patient with disproportional short stature. Chondrodisplasia (Pseudopseudohypoparathyroidism).



Picture. Chondrodystrophy.

2. Proportionate dwarfism.

- A body is proportionately small if all parts of the body are small to the same degree and appear to be proportioned like a body of average stature.

Causes

1. Herediatary/ Genetic.
- If there is a family history of short stature – genetic.
- If there is no family history of short stature – primordial short stature
- The bone age and dental age are normal.
- They are short, they grow at a constant rate of 4 -5 csm a year
- Normal body proportions for age.
- There is no endocrine abnormality and require no endocrine treatment.

2. Chromosomal(Turner's syndrome ,Down's syndrome, Noonan's syndrome)

Turner's syndrome (SHOX gene deficiency):

- Are girls who have agenesis of their ovaries
- The chromosomal pattern is 45 XO
- Grow at the rate of less than 4 sm each year with normal bone age and dental age but absent pubertal growth spurt, so that during adolescence, the skeletal age is delayed due to the absence of sex hormones

- A characteristically short webbed neck, low hairline, square and shield-like chest, cubitus valgus and mental retardation
- Puffy hands and feet at birth and during infancy
- Heart and blood vessel defects
- Kidney problems
- No development of breasts or onset of menstruation during adolescence
- Infertility
- Oxandrolone 0,15 mg/kg/day with growth hormone from early adolescence till puberty can increase the height.After the age of 15 years cyclical estrogen replacement therapy in physiological doses is given for life.GH replacement is recommended before epiphyseal fusion.

3. Constitutional growth delay and Delayed puberty.
- Is common among adolescent boys
- There is a history of delay in growth and pubertal development in the father and other male relatives
- Is no true endocrine deficiency
- They grow at a constant rate of about 4 sm a year but their bone age and dental age is delayed by about 2 years
- Immature but later normal
- If puberty does not occur spontaneously by 15 years og age, it can be induced by testosterone enanthate 250 mg intramuscular once a month for 3 months.

4. Nutritional,Malnutrition,Malabsorption
5. Rickets
6. Endocrine: Hypothyroidism,Cushings syndrome,Congenital adrenal hyperplasia
- Hypothyroidism:
- Mental retardation since birth
- Dry skin,body proportions is infantile (upper segment is more than lower segment), constipation
- Lifelong thyroxine replacement is required

7. Skeletal:Achondroplasia, skeletal dysplasias,spinal deformities
- Achondroplasia
- Short limbs resulting in short stature
- The lower segment is always less than the upper segment
- Mental and dental ages are normal
- Endocrine functions are normal

8. Systemic diseases:Uremia, renal tubular acidosis, Cirrhosis of liver, Congenital cyanotic heart disease
- Can cause growth failure during childhood
- Growth failure is a secondary problem
- Can be recognized by their own specific clinical features

Laboratory and investigations

- Decrease GH, LH, FSH, TRH, ACTH
- Diagnostic tests (Thyroliberin test)
- X-rays: the zones of growth do not close ,the cranium has the proportions typical of a child, the skull-cap is thin
- When there is a tumor: sella turcica is enlarged, deformed with its walls destroyed
- MRI

Treatment

The treatment of Dwarfism's depends on the cause of the disease.

- If pituitary tumor is revealed, radiotherapy is applaid or the tumor is removed surgically.
- Somatotromine therapy is prescribed in insufficient GH secretion: using recombinant DNA technology, two forms of synthetic GH were developed, somatropin and somatrem. Somatropin is identical to the endogenous pituitary-derived GH, whereas somatrem has an extra amino acid on the N-terminus. Both synthetic forms have similar biological actions and potencies as the endogenous GH polypeptide.
- GH is administered by subcutaneous or intramuscular injection. The circulating half-life of GH is relatively short (20-30 minutes), while its biological half-life is much longer (9-17 hours) due to its indirect effects.
- Symptomatic adults with severe GH deficiency (serum IGF-1 below 85 mcg/L) may be treated with subcutaneous recombinant human GH (rhGH) injection starting at a dosage of about 0,2 mg (0,6IU)/day, administered three or four times weekly. The dosage of recombinant human GH is increased every 2-4 weeks by increments of 0,1 mg (0,3IU) until side effects occur or a sufficient salutary response and a normal serum IGF-1 level are achieved.A sustained-release injectable suspension of GH has been developed. It can be given once monthly and is therefore more convenient than standard rhGH preparations.If the desired effects are not seen within 3-6 months at maximum tolerated dosage, rhGH therapy is discontinued.
- Side effects of rhGH therapy: peripheral edema, hand stiffness, arrthralgias, myalgias, headache, pseudotumor cerebri, gynecomastia, carpal tunnel syndrome, hepertension, proliferative retinopathy
- Thyroid hormones, synthetic anabolic steroids, chorionic gonadotropin to stimulate and develop the sexual glands, androgens and oestrogens for individuals plans.
- The indication for the treatment termination is the osteal age of 13 years and growth of 160 sm at girls, osteal age of 15 years and growth of 170 sm at boys. Now there is an opinion on expediency of continuation of treatment of

the adult persons GH having its deficiency since the childhood, in connection with necessity of metabolic effect GH (anabolic, lipolytic).

Prognosis

Working capacity is broken. The group of physical inability since the childhood is defined. Patients are infertility.

Chapter X. Obesity

Definition

Obesity is a discord in system of regulation of mass of the body, leading excessive deposition of fat of a body, characterised by superfluous stocks of triglycerides in adiposites, that promotes occurrence of some serious metabolic diseases which lead to increased health risk.

- This is a chronic disease with no known cure.
- 20 % or greater above ideal body weight
- 170% of ideal body weight or BMI>40 is morbid obesity
- BMI <20 or >27 to increased health risk

Extends such accompanying diseases:

- cardiovascular: hypertention,CAD, varicose veins,sudden death from arrhythmia
- respiratory: sleep apnea, dyspnea, pulmonary embolus, infections
- gastrodigestinal: fatty liver, gallbladder disease
- metabolic and endocrine: DM type 2, IGT, hyperlipidemia,hyperuricemia,dismenorrea, infertility, hirsutism
- increased risk of neoplastic diseases:endometrial, post-menopausal breast, prostate, colorectal cancers.

Fat tissue is not uniform in its metabolic characteristics. Fat cells from the organs are more likely to break down under the influence of catecholamines (brain trancmitters). Making matters worse, these abdominal fat cells do not allow insulin to come to their rescue and slow their breakdown. Fat cell breakdown liberates FFA from the cell. While FFA are important metabolic fuels, they may well be the villains in a number of metabolic processis. It is suspected that FFA prevent the body from using glucose, which may cause insulin resistance and glucose intolerance, hyperinsulinemia and increased glucose prodaction by the liver, a typical finding in DM Type 2. FFA's also stimulate the synthesis of TG in the liver, VLDL, LDL.

Epidemiology

- Incidence reaches 50% among females and 30% among males, and 10% among children
- Occurs at any age but obesity prevails in age groups after 50 years.

- Hereditary predisposition: if mother and father have obesity risk at the child - 78 %; if one of parents is sick risk to have obesity at the child - 56 %. The chance development of obesity in the child who was born from parents without adiposity - 14 %.

Risk Factors

- Increasing age
- Genetic variants in energy expenditure
- Behaviour and lifestyle : regular overeating, particularly abuse of foodstuffs rich in carbonhydrates and fats; a sedentary lifestyle
- Secondary causes:endocrine:Cushing"s syndrome, hypothyroidism; drugs.
- Hypothalamic injury:trauma, surgical, lesions in ventromedial or paraventricular median nucleus

Pathogenesis

- Positive energy balance:energy input >energy output
- Functional disorders of the feeding centre of the hypothalamus:satiety centres of the ventromedial nuclei and appetite centres of the ventrolateral nuclei of the hypothalamus
- Increased supply of food due to stimulation of the feeding centre in insufficient physical activity leads to the accumulation of the fat in the fat depots: in the skin, subcutaneous fat, mesentery, omentum, pararenal and mediasttinal tissue,epicardium, myocardium, liver, and pancreas.
- Several novel hormones appear to act upon brain receptors to regulate appetite and metabolism:

Leptin

- Congenital leptin deficiency accounts for 1-2% of early-onset morbid obesity
- Is a hormone secreted by subcutaneous adipose tissue in response to fat storage or overfeeding.
- -It binds to brain @-melanocortin receptors and influences the secretion of neuropeptides, inhibiting neuropepttide Y and agouti-related peptide
- It promotes satiety and increase the body's metabolic rate
- It required for gonadotropin secretion.

Grelin

- Is a 28-amino-acid hormone
- Is secreted by the empty stomach
- It stimulate appetite

@-MSH

- Alfa-melanocyte-stimulating hormone is a neuropeptide that regulates the hypothalamic control of food intake
- Defect in the @-MSH receptor are present in up to 5% of morbidly obese patients

Citocins

- FNO-@- factor necrosis of tumor is a product of adipocites secretion response insulinresistance by decreasing of GluT4 excretion
- **Classification**
- The generally accepted classification of obesity does not exist.

Anatomo-morphological classification

Is based on morphology of a fatty tissue:

- 1. Hypertrophic type
- Arises at mature age;
- It is characterised by augmentation of the sizes adiposites without augmentation of their general number.

2. Hyperplastic type

- It is characterised by augmentation of total of fatty cells.
- 3. The admixed or hypertrophic-hyperplastic type

Table. Classification of overweight and obesity (WHO, 1998).

Fenotype	BMI	Risk of comorbided diseases
	< 18,5	The low risk, but risk of other clinical problems increases
Normal mass of a body	18,5 – 24,9	usual
Overweight		
Overweight	25,0 – 29,9	moderated
Obesity of 1st degree	30,0 – 34,9	raised
Obesity of 2nd degree	35,0 -39,9	high
Obesity of 3rd degree	>40,0	Very high

Degree of obesity should be defined with the account of a sex, age and growth surveyed and BMI is not authentic and does not reflect degree of adiposity at certain categories of the population:

- persons aged is more senior 65 years;
- sportsmen and at people with very developed musculation;

- teenagers with the neoterminated period of growth;
- at pregnant women.

Worldwide tables are developed for calculation of ideal body mass in different age groups for persons from the asthenic, normosthenic and hypersthenic constitution, and also for children of various age groups.

Topography and terminology

Allocate various types of adiposity depending on an aetiology,of the fat localization and its anatomo-histologic characteristics. Adipose tissue distribute differently in men and women.

- The term "android" to describe the upper body (abdominal) distribution. Abdominal obesity are an increase association with DM, CVD and gout.
- The term "gynoid" to discribe for the lower body (gluteo-femoral) fat accumulation more commonly seen in women.
- Proportional.
- Disproportional.

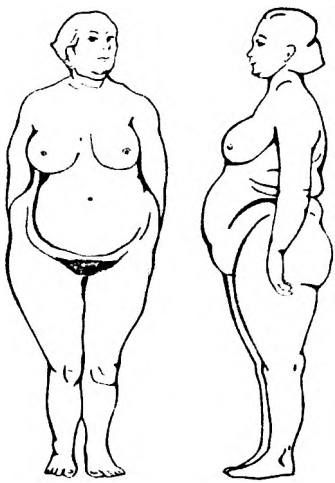
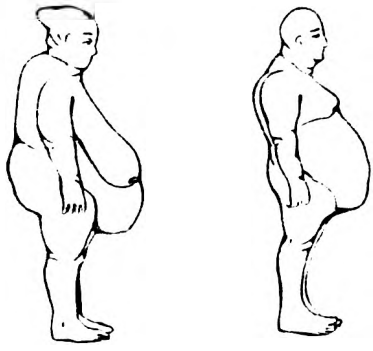


Fig. Femenine type of obesity.

Fig. Android obesity in 56-years-old women with DM Type 2.



Picture. Abdominal obesity in climacteric period in female and in a male.

Fig. A45-years-old patient: hypothyroidism, obesity (BMI =39), secondary hypogonadism, DM type 2.

Calculations Body Fat

- Gold standart is hydrodensitometry (underwater weighing) and dual-energy x-ray absorptometry (both for research)
- Clinics use BMI(Body Mass index) : weight in kg/(height in meters) squared (Wt/Ht2):
- Clinics use WHR (waist:hip circumference ratio): at men less than 1,0 and women less - 0,85.This is the most objective sign of abdominal adiposity.The waist is measured at its narrowest point and hip circumference at its widest, while standing.

Table. Obesity Classification according of BMI

	Males ,BMI	Females, BMI
Underweight	21	19
Average	21	25
Overweight	27 - 28	30- 32
Moderately Obese	31 -40	32 -40
Extreme Obesity	41 -45	41-45
Morbidly Obese	>45	>45

Table. Obesity Classification according of WHR

Sex	Normal	Overweight	Obesity
Males	<94 sm	94 – 102 см	>102sm
Females	<80 sm	80 – 88 см	> 88sm

Classification of Obesity according of the Ethiology

I.Primary obesity (exogenous causes of obesity)

1. Alimentary constitutional obesity
2. Acquired hypothalamic lesion: tumor,infection,trauma,vascular lesion.

II. Secondary obesity (endogenous causes of obesity)

1. Acquired hypothalamic lesion due to infection,sarcoid, vascular malformation
2. Hormonal: hypothyroid, hypo-ovarian; climacteric; adrenal, primary hyperinsulinism.

II. Genetic syndroms: Prader-Willi; Alstrom syndrome; Carpenter syndrome; Cohen syndrome;

III. Medications causing weight gain: insulin, sulfonaureas, atypical neuroleptics, antidepressants, glucocorticoids, cyproheptadine, progestins, alfa-1 and beta -2 adrenergic antagonists

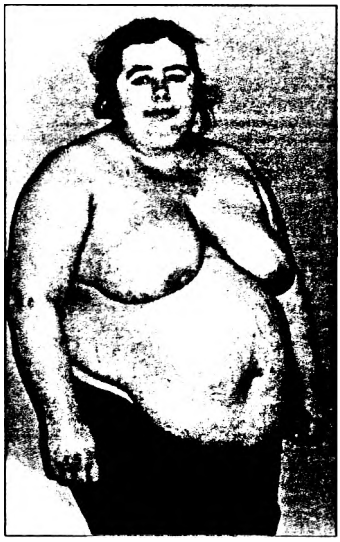


Fig. Hypothalamic obesity in 32-years-old patient.

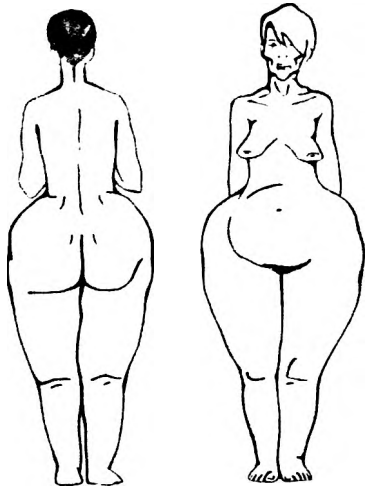


Fig. Disproportional accumulation of the fat: lypodysthrophy of the upper part of the body ("witch's face") but excessive accumulation of the fat for the lower part of the body.

Symptoms and signs

- Increased appetite,lassitude, apathy, somnolence, fatiguability, headache, poor memory
- Excessive sweating (hyperhidrosis), eczema, pyoderma, furunculosis
- Umbilical and inguinal hernias
- The cardiac sounds are dull, the heart boundaries are distended, arterial hypertention, bradicardia
- Ischaemic heart disease and circulatory insufficiency: pain in the region of the heart, dyspnoea, cyanosis, odema
- Respiratory: the vital, respiratory, and reserve lung capacity diminishes, which leads to oxygen lack in the body.; bronchitis and pneumonia occurs often.

- Gactrointestinal: gastroptosis,fatty liver, cholecystitis and cholangitis, cholelitiasis, acute and chronic pancreatitis
- Urinary: pyelitis, urethritis, cystitis, urolithiasis
- Genital :dismenorrea, infertility, spontaneous abortion;decrease libido and potency
- *Pickwick syndrome:* is characterized by morbidly obesity combined with hypersomnia,difficult breathing, particularly during sleep and often cyanosis of the mucous membranes and skin.

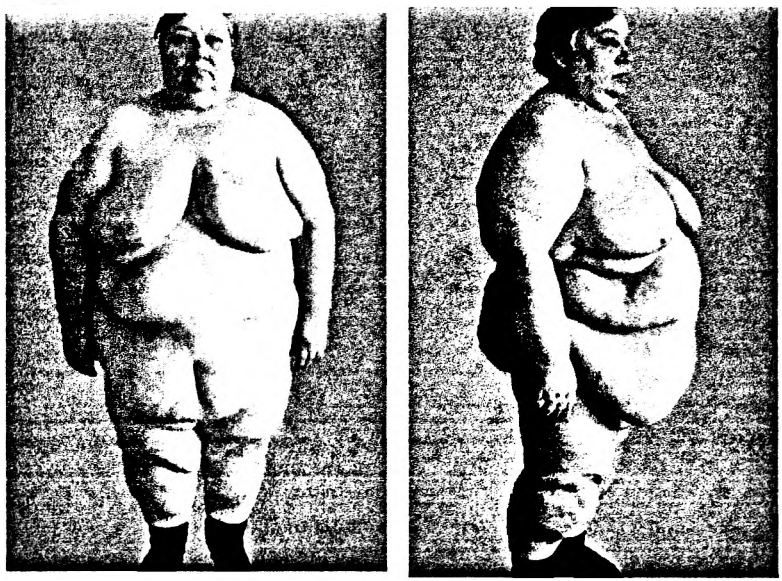


Fig. Extreme Obesity (BMI>40)) in a 65 years-old patient with DM Type 2, dislipidemias, ischemic disease and atrial hypertention.

Laboratory

- ACTH,LH,ADH,insulin is often increased
- TRH,PRL decreased
- Cholesterol, beta-lipoproteins, and free fatty acids increased
- DM type 2 or IGT
- Uric acd in the blood increased often
- The total amount of protein decreased
- Secondary aldosteronism may occur

- The basal metabolism and the iodine cumulative capacity of the thyroid are often diminished

Diagnosis and differential diagnosis

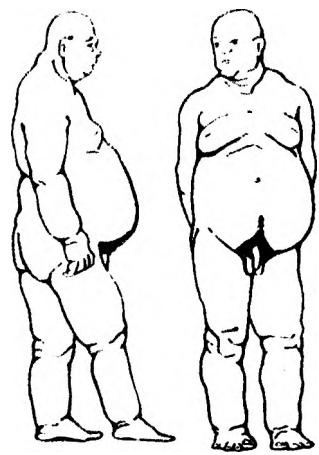
Alimentary obesity is differentiated from obesity in Cushing's syndrome and adipose-genital dystrophy, hypothyroidism,hyperinsulinism, primary hypogonadism and diseases of the central nervus system.

As distinct from ordinary obesity:

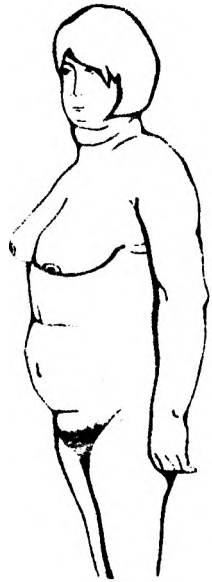
- Cushing's syndrome: selective deposition of fat on the face,neck,chest,abdomen combined with thin limbs;hirsutism; the corresponding laboratory data and the x-ray examination and CT scan of the adrenals or sella turcica.
- Adipose-genital dystrophy: feminine-type accumulation of fat – on the chest, pubis, hips, and pelvis combined with hypoplasia of the genitals.
- Hypothyroidism: the uniform accumulation of fat is combined with symptoms of hypothyroidism and the low values of the thyroid hormons
- Hyperinsulinism: is characterized by uniform deposition of fat and by attacks

of hypoglycaemia

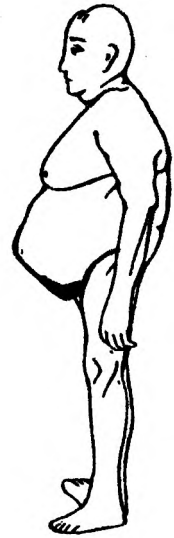
- Hypogenital obesity; is characterized by feminine-type deposition of fat, eunuchoid proportions of the body(tall height and long limbs with a relatively short trank) is combination with underdeveloped genitals and secondary sex characters.
- Hypothalamic obesity:is a rapid gain of the body weight within a few months,feminine-type obesity,combination with bulimia and polydipsia,and with symptom of an organic lesion of the central nervous system



Picture. Climacteric's obesity in a male.



Picture. Cushing's obesity.



Picture. Eunuchoid fenotype and obesity

Treatment

6 Step Treatment of Obesity

Goal is 10-15% reduction from baseline in 6 -12 month.

Step 1.General recommendation.Doctor Advice: "I belive it is important to your health and well being that you lose weight. Together we can come up with a simple program for weight loss that will work for you if you follow it at lwast 80-90% of the time. I don't expect you to be perfect all the time".

- Caloric reduction must be individualized

Step2. Diet.

- **Doctor Advice:** Do nothing else when eating, eat only at the kitchen without watching TV. Wait 5 minits before another helping of foot. Do not "clean" your plate. Leave the table after eating. Advise patient to brush their teeth right after dinner or when they feel the urge to snack. Toothpaste taste does not mix well with foods and they may forgo eating a snack rather than having to re-brush, especially before bedtime.Shop from a list, do not shop when hungry.Keep no snack foods in the house.Lay out exercise clothes the night before as a reminder to walk/jog in the morning.Avoid "night-eatingsyndrom", seen as morning anorexia, evening hyperphagia and insomnia.

- Avoid trigger foods: nuts 9use air-popped popcorn), cheese, ice cream/frozen yogurt,chips,butter,cakes, red meat,salad dressings with oil,fatty fish.
- Change 3 eating habits that contribute to weight problem.Snacking during day, eating after dinner, overeating at social events, eating in response to negative moods
- To change where/when/how they eat
- Need to emphasize weight control, not merely losing weight, but keeping it off.
- Smoking cessation, stress reduction, exercise and group support

Diet

- *Meal –replacement plans*: use meal-replacement bars or shkes (Ultra-slim fast or nectle sweet success) for up to 2/3 meals. Can also get prescription drinks such as Pro-Cal or medifast which have less total calories due to less sugars, but not as palatable.Aim for 1200 caloria intake.This plan is continued for 121 weeks.
- *Very low calorie diet* – 1000- 1200 calorie diet.Patient needs to check vital signs 2 time a day (BP,temperature,pulse).

1. Protein - 1,5g/kg/daily IBW (or 75g protein, 50g carbohydrates daily).
2. Potassium 30mEq/daily
3. Multiple vitamin with minerals
4. NaCL 5g daily
5. Ca-carbonate 4 tablets daily (total dose 800 mg Ca)
6. 2,0 liters of fluid or more.

- *Weight Watchers Diet*: attend weekly meetings, can only eat a certain number of food ppoints from each category. A healthy diet low in calories.
- *Jenny Craig Diet*: carbohydrates are 60%, concentrating on complex ones. Low fat foods. A healthy diet low in calories.

Dr.Dean Ornish Diet: avoid fat.Eat healthy natural food like fruits and vegetables, oatmeal, soy. Very healthy, but hard to maintain.Fatis <105, carbohydrates 70%, protein 20%.Cholesterol intake of <5 mg/daily with vitamin supplements and fish oil.

- *Zone diet*: (40/30/30 diet), 40% complex carbohydrates, 30% protein and fat, with each meal in proper ration to avoid carhydrates craving from insulin bumps.
- *Low Carbohydrate Diets*: Atkin's Diet high protein low carbohydrates (<20g/daily).Can eat bacon,eggs,cheeseburger, shrimp, fish,steak,cheese,sugarless foods. Have risk of loss of vitamine B, Ca and P. Induces a ketosis that leads to water loss and anorexia.
- *Suzanne Summers Diet*: No fats with carbohydrates and if eat fruit need to wait at least 20 min before eat more carbohydrates.

Step3. Exercise

- Does not have to be unpleasant or punishing.
- The best exrsise regime is the one the patient can perform comfortable and regulary
- Start by walking: aim for 3.500 -5.000 extra steps per day (30-40 min). 10.000 steps per day is optimal fro full health benefits
- 30 minutes/day of vigorous or 60-80 min of moderate intensity.Walr, stationary bike,low-impact aerobic video,clean house,park far away,take stairs

Step4. Behavior therapy

- Individual or group therapy
- Self-monitoring, stimulus control, stress management, cognive change

Step5. Anti - Obesity Drugs.

- No drugs cure obesity. Approved anti-obesity drugs only for short-term use.

- If BMI >30 kg/m2 or if >27 with comorbidities (CVD,DM,dyslipidemia)
- Appetite Suppressants : work at the appetite center.

1. Noradrenergic agents (Xen-Phen) 15 mg 4 time daily.
2. Serotonergic agents : Prozac(Fluoxetine) 10-20 mgdaily, titrate to 60 mg/daily.Antidepressant that does cause weight loss, but tend to regain by 1 year.
3. Adrenergic/serotonergic agents : Meridia (Sibutramine): start 10 mg three time daily ,give 1 month, then 15 mg if inadequate loss.

- Metformin: antidiabetic drug has been proposed to be possible beneficial in improving insulin resistance and ultimately in weight loss.
- Pancreatic lipase inhibitor: Xenical (Orlistat) found to be mildly to moderately effective. 120 mg per os three time daily with meals or within 1 hour after,give 3 month. Take multivitamin supplement 2 hours before or after dose.
- Leptin: a Protein that inhibits neuropeptide –y.
- Cholecystokinin antagonists: feelings of satiety.
- Fat substitutes: olestra (Olean)

Contraindications to obesity medsins

- BMI<27
- Catabolic systemic illness
- Closed-angle glaucoma
- General anesthesia
- Medication specific contra
- Pregnancy or lactation
- Stroke
- Unstable CVD

- Recent suicide attempt

Step6. Surgery therapy.

- Stomach band: the Lap-Band is an adjustable silicone band that is placed around the upper part of the stomach to create a small pouch.It's limits a person's food consumption and creates an earlier feeling of being full.Placed laparoscopicaly.
- Gactroplasty ("stomach stapling") is treatment of last resort
- Jieunal bypass: induced global malabsorbtion. The cardia of the stomach is stapled is stapled across vertically leaving a small 10 ml gastric pouch. This helps to limit intake and prevent intake of high calorie sweets
- Liposuction

Prognosis

- With early and regularly applied treatment is favorable
- Cardiovascular diseases (myocardial infarction, cerebral stroke) and pneumonia are the main causes of death.

Chapter XI . Diseases of the Sexual Glands.

There are following concepts of a sex:

- *Chromosomal*: 46XX - a female, 46XY - a male.
- *Gonadal:* presence of ovaries at girls and testicles at boys.
- *Genital:* is defined on a structure of external genitals, and hormonal on development of corresponding sexual hormones.
- *Psychological* - conformity of feeling of the sex to character of external genitals.

Definition and terminology

Function of sexual glands, as well as all other glands of internal secretion, can be lowered and raised. Diseases of sexual glands can be parted on tree big groups:

- *1. Hypogonadism* (Hypogenitalism)
- - is a syndrome of deficiencies in gametogenesis or the secretion of gonadal hormones. The hypogonadism arises during the various periods of a life.
- - Eunuchoidism :the most expressed form of a hypogonadism characterised by disproportions of a skeleton and adiposity.
- 2. *Hypergenitalism* ("early puberty")
- *3. Delay of sexual development*:
- - is called physiological feature of development of the organism
- - not accompanied by any disorders
- - often family.

1. Diseases of the Male's Gonads

Man's sexual system.

- The testes are a paired glandulat organ situated in the scrotum
- Sizes 3-5 cm ling, 2-3 cm wide (lower limit = 4 x 2,5 cm), weights 15 -30 g, the right testicle is usually a little more than the left.
- Testosterone (from the Leydig cell) is a male sex hormone .

Testosteron ation .

- The external genitals form and grow.
- The secondary sex characters develop.
- The prostate and seminal vesicles grow and develop.
- The skeletal and muscular systems form.
- Increased protein metabolism.
- The growth zones in the bones close.
- Determines libido.
- To delay of sodium, water, nitrogen.
- Provide man's socially-role behaviour.

- Both positive and negative feedback may occur by androgens directly or after conversion to estrogen
- Primarily involved in negative feedback on LH, whereas inhibin (from the Sertoli cell) suppreses FSH secretion.

Sexual development of boys.

At newborn boys testicles have length of 8-10 mm, width of 8 mm. The right testicle is more than left. In sexual development of boys distinguish two periods: 10-15 years when there is a development of genitals and secondary sexual signs and after 15 years - the genesial period, the spermatogenesis period. Sexual development occurs gradually and begins with disappearance of hypodermic Adeps in a scrotum, its pigmentation. The doctor of the general practice, as well as the pediatrist should own a technique of a palpation of testicles and an estimation of results of their research. The mass of testicles of the adult man are on the average 25 g. The penis of the adult malei s on the average 10-12 cm. At survey of genitals pay attention to volume of both half of scrotum, presence or absence in them of testicles (cryptorchism, an ectopia of testicles). To palpate testicles it is necessary fingers of both arms in vertical and horizontal position of the patient. At survey and a palpation it is necessary to note:

1) the scrotum should be the bulb-shaped form droops (not to be tightened to a pubis), should be have pigmentation with numerous fine cords,

2) testicles should be lowered for a bottom of a scrotum, their configuration should appear accurately visually and they should be palpated as roundish, elastic, mobile formations.

In the absence of one or both testicles in a scrotum it is necessary to search for them by pappation in the inguinal channel in horizontal and vertical positions of the patient.

There are various models testikulometer-orhidometer, representing a set ellipse's models of testicles with gradual ascending of their volume from 1 to 25 ml, with the indicating of age fluctuations of volume of testicles.

Man's secondary sexual signs:

- "A male's figure.
- Growth of hair on a stomach in the form of a rhombus ("path" to a belly-button), in axillary fossas. Presence of growth of moustaches, beards, and high temples in temporal areas.
- On a neck well developed guttural cartilages ("an Adam's apple")
- A Low voice timbre

Classification and ethiology

Depending on the maintenance of sexual and gonadotrophic hormones in blood and urine .

1. Primary Testicular Failure (hypergonadotrophic) hypogonadism.This is a syndrome caused by the direct effect of the pathological processis on the testis.

- characterized by increased LH/FSH
- Congenital: chromosomal defects (Klinefelter syndrome, Noonan syndrom), cryptorchidism, male pseudohermaphrodotism, bilateral anorchia
- germ cell defects (Sertoli cell only syndrome; Leyding cell aplasia)
- Infection – TB, mumps
- Trauma, irradiation
- Drugs, alcohol
- Poor secondary sexual development, poor muscle development

2. Secondary (hypogonadotrophic) hypogonadism. This is a syndrome as a result of hypothalamic-pituitary insufficiency which leads to diminished production of gonadotropic hormones and decreased secretion of androgens.

- characterized by decreased/normal LH
- endocrine (Cushing's syndrome, hypothyroidism, hypopituitarism, oestrogen-secreting tumors)
- chronic illness
- malnutrition
- drugs (spirinolactone, GnRH agonists)
- alcohol, narcotics
- Regression of secondary sex signs: diminished of the external genitals (penis and testes), less of hair in axillary fossas, face, stomach, diminished of the muscle,ginecomastia

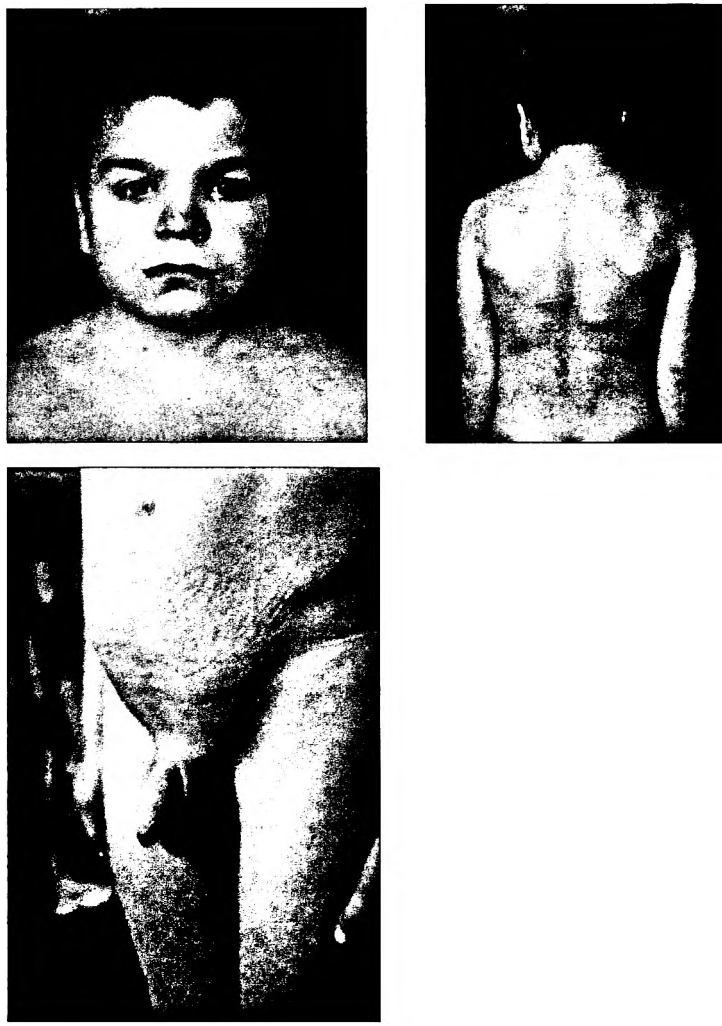


Fig. Congenital hypothyroidism (cretinizm) in 17 –years-old boy. Height - 139 cm, weight - 39 kg. Absence of physical flexures of a backbone, hair on a pubis, in axillary fossa, a short neck, is not formed "an Adam's apple", testes is 1,5 cm in diameter, the penis corresponds to age of the 9-year-old child.

3. Defects in Androgen Action
- Testicular feminization (Complete androgen insensitivity)
- Incomplete androgen insensitivity (5-@-reductase deficiency)

Symptoms and signs

Clinical presentation depends on age of onset

1. Fetal life
- Ambiguous genitalia and male pseudohermaphroditism

2. Prepubertal period
- Poor secondary sexual development, poor muscle development
- Eunuch-like body proportions
- Underdeveloped the penis, testes, prostate gland

3. Postpubertal period
- There is no disproportion of the body
- Decreased libido, erectile dysfunction, infertility
- Decreased facial and body hair if very significant androgen deficiency
- Fine wrinkles in the corners of mouth and eyes
- Decreased in musculature
- Osteoporosis with longstanding hypogonadism

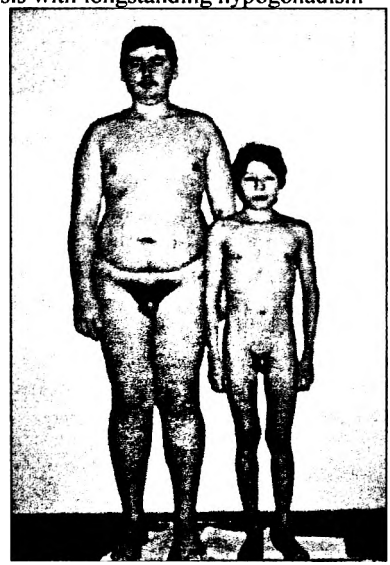


Fig. 16-years-old guys.Gynoid obesity and gynecomastia (left), infantile morfotype (right).

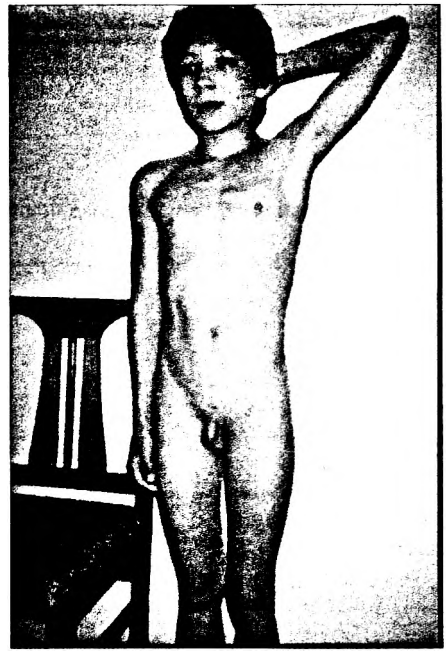


Fig. Congenital hypogonadism .Cryptorchidism in 16-years-old. Height 142 cm, weight -38 kg.

Diagnosis and differential diagnosis

- Is made on the basis of the medical history
- Clinical picture: eunuchoidism, undevelipment of the testes, penis and secondary sex characters, increased LH/FSH are caracterised for primary hypogonadism
- Development of hypogonadism following diseases of the hypothalamic-pituitary system, tumor of the pituitary(confirmed by x-ray examination), decreased LH is confirmed secondary hypogonadism

Treatment

- Consider testosterone replacement

Prognosis

- Primary hypogonadism: is favorable for life, to full recovery is poor.
- Secondary hypogonadism: is determined by the principal disease.

2.Gynecomastia

- Proliferation of the glandular component of the malr breast
- Estrogen/androgen imbalance – increased estrogen/androgen ratio

Ethiology

- Physiologic: neonatal (maternal hormone), puberty, aging
- Pathologic
- Primary hypogonadism,hyperthyroidism, adrenal disease, hyperprolactinemia
- Tumors – pituitary,breast, testicular, adrenal
- Chronic disease – liver, renal, mulnutrutition
- Congenital/genetic – Klinefelter's syndrome
- Drugs – cimetidine,spirinolactone,digoxin,chemotherapy,narcotics
- Familial, idiopathic

Fig. Pubertal dispituitarizm . Gynecomastia in 16 years-old boy.

Diagnosis

- Is based on history, age, onset, chronic disease,pain, drugs
- Physical examination: feminization, general observe (thyroid, liver, testicular exam)
- Laboratory and investigations:serum TSH,PRL,LH,FSH, testosterone,estradiol

Treatment

- Medical: androgens for hypogonadism.Anti-estrogens – tamoxifen,clomiphene
- Surgical: required if gynecomastia present for > 1 year (reduction mmamoplasty).

3.Congenital Disorders of Sex Differentiation: Klinefelter's Syndrome

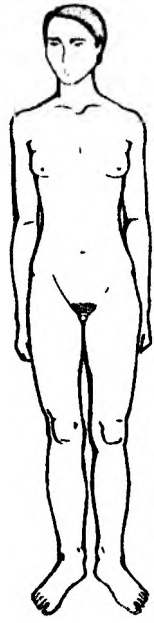
Definition

Dysgenesis of the siminiferous tubules (Klinefelter's syndrome) is a disease caused by anomaly of the sex chromosomes

- Is disturbed spermatogenesis
- Occur is 1:1100 with male phenotype, among sterile 1:9

Ethiology and Pathogenesis

- The cause of the disease is unknown
- Is due to chromosome anomaly: extra X-chromosome kariotype 47XXY, 48XXXY, 49XXXXY or mosaicism 46XY/47XXY
- The formation of the testicles and the male genitals in the embrional period is normal because of the presence of the Y-chromosome in the kyriotype.
- In the pubertal period, degerative changes occur in the testis with impairment of its normal development and insufficient secretion of testosterone
- Deficiency of testosterone leads to increase in gonadotropic hormones



Picture. Klinefelter's syndrome in a boy with karyotype 47XXXY.

Syptoms and signs

- Is manifested during puberty
- Patients are tall, with eunuchoid body proportions: the limbs are disproiportially long in relation to the trunk
- Is female-type fat localization, gynaecomastia, wide pelvis, narrow shoulders
- Absence of hair growth on the fase and in the axillae, growth of hair on a pubis in the form of a triangle
- The testes are small, flabby, firm; cryptorchidism
- The penis is usually normal in size
- Libido is preserved, but patient are sterile because of azoospermia
- Mental retardation

Diagnosis and differencial diagnosis

- Increased GH,LH,FSH,PRL
- Testosterone decreased, but estrogens may be increased
- Is azoospermia

- Kariotype 47XXy or mosaicism with negative sex chtomatin
- Differentiated from pubertal gynecomastia and hypogonadism

Treatment

- Male sex hormone or their synthetic analogs replacement therapy

Prognosis

- Is unfavorable for full recovery
- Sterility
- The working capacity depends on the degree of mental retardation

4. Diseases of the Female Gonads : Hypogonadism

The female's sexual system

- The ovary is one of the paired organs, each ovary is 3-4 cm long, 2 -2.5 cm wide, weighs 6-7g.
- Situated in the small pelvis
- Two female sexual hormones (oestradiol and progesterone) are producted of the follicles in ovaries and reticular zone of the adrenals cortex. In pregnancy progesterone is also formed in the placenta.
- The cells of the inner theca and the hilum of the ovary produce a small amount of androgens
- Is controlled by pituitary FSH/LH

Estogens action

- Promote enlargent of the uterus and vagina, proliferation of the endo- and myometrium
- Provide the development of female secondary sex characters : the development of the mammary glands, shaping of a feminine figure and the corresponding features of the skeleton
- Accelerate the differentiation and ossification of the skeleton
- Possess a protein anabolic effect
- stimulate a glycogenolysis.

Progesterone action

- In the uterus creates conditions for receiving the fertilized ovum and maturation of the foetus
- Inhibits the contractile muscular excitability of the uterus
- Stimulates the growth of the alveoli in the mammary glands
- Suppresses the effect of estrogens on the uterine mucosa during the menstrual cycle

In a man's organism estrogens are formed as a result of conversion of androgens of testicles and adrenals in a fatty tissue and a liver in estrogens.

Sexual development of girls. The length of ovaries of the newborn girl to 3 cm., by 16 years-old they become more are enlarged at length. In the first days of newborn girls can have a special condition - *a hormonal crisis or, so-called "small puberty":* it becomes perceptible enlargement of the mammary glands, a desquamative vulvovaginitis, a cutaneous dropsy of external genitals. And by 5-8 day later there is a short metrorrhagia (1-2 days). It is bound by that in an organism of mother the placenta sates an organism of a foetus with estrogens, and in the first days after sorts their level falls. In sexual development of girls allocate two periods: prepuberty - since 8 years to menarche, puberty - from menarche till a full sexual maturity. At children growth of a follicle does not wear cyclic character, there is no ovulation. In the first 1-2 years the menses comes owing to sharp depression of level of estrogens at the moment of an atresia of follicles.

Female secondary sexual signs: "feminine" figure, the developed peripapillary mugs with the palpated glandular tissue, acting dummies; growth of hair on a pubis in the form of a triangle, presence of hair in axillary fossas, a regular menstrual cycle.

Hypogonadism

Classification and Ethiology

1. Primary Female's hypogonadism :

- Is a syndrome caused by direct effect of a pathological process on the activity of the ovaries as a result of which the secretion of the estrogens is reduced
- Congenital : disorders of sexual differentiation (gonadal dysgenesis)
- Damage to the ovaries by infection (mumps, TB)
- Surgical removal

2. Secondary Female's hypogonadism:

- Is a syndrome caused by diminished production og gonadotrophic hormones as a result of which the secretion of estrogens is reduced
- Congenital : anrenocortical dysfunction
- May be caused by pituitary disease: tumor,ischemia,necrosis, trauma,infection (panhypopituitarism, Simmonds-Sheehan's syndrome, craniopharyngiom)
- Endocrine diseases: hypothyroidism, Cushing's disease, adrenal insufficiency
- Mulnutritition or obesity
- Amenorrhoea
- Regression of secondary sex signs : hypoplasia of the external genitals and uterus, mammary glands

Symptoms and signs

Clinical presentation depends on age of onset

1. Fetal life
   - Ambiguous genitalia and female pseudohermaphroditism
2. Prepubertal period
   - Poor secondary sexual development, poor muscle development
   - Underdeveloped the uterus, vagina and ovaries
   - Primary amenorrhoea
   - Eunuch-like body proportions
3. Postpubertal period
   - Decreased LH,FSH,PRL,estrogens
   - There is no disproportion of the body
   - Involution of secondary sex signs: mammary glands, loss of hair in axillary fossas and pubis, obesity
   - Secondary amenorrhoea, infertility
   - Hypoplasia of the uterus and external genitals

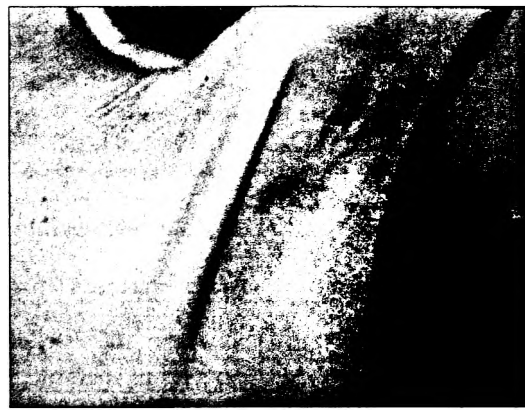


Fig. Loss of hair in axillary fossae. In 38 years-old woman.Secondary hypogonadism.

Treatment

- Consider testosterone replacement

Prognosis

- Primary hypogonadism: is favorable for life, to full recovery is poor.
- Secondary hypogonadism: is determined by the principal disease.

5. Hirsutism and Virilization

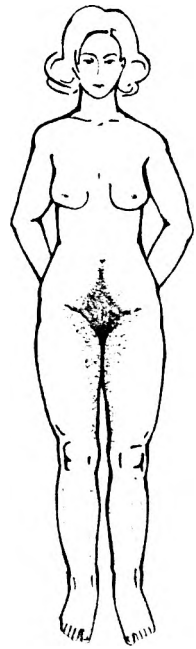
Definition and Terminology

- Both term refer to states of androgens exess

Hirsutizm& Hyperthrichosis

- Hirsutism this is male patern of hair growth in women: back, chest, upper abdomen
- Hyperthrichosis this is excessive growth of hair in the non-androgen-mediated areas of the body (upper and low extremities)

Fig. Hirsutism but with loss of hair on the head as in men. Downy hair prevails on the face in a 52- years- old female.



Picture. Hisutizm

Virilization

- Hirsutizm, frontal balging
- Deepening of voice
- Clitoral enlagment
- Increase in musculature
- Acne

Defeminization

- Amenorrhea
- Decreased breast size

Ethiology

1. Constitutional : family history, ethnic background

2. Adrenal : congenital hyperplasia or tumor

3. Ovarian: polycystic ovarian disease (PCOD) or tumor

4. Pituitary : Cushing's disease

5. Medications. Androgen-mediated: ACTH, anabolic steroids, androgens, progestational agents. Non-androgen-mediated : cyclosporine, diazoxide, phenytoin

Laboratory

- Increased testosterone
- Increased LH/FSH, seen commonly in PCOD as ratio >2.5
- DHEA-s as measure of adrenal androgen production

Treatment

- Discontinue causative medicatuins: oral contraceptives, low dose glucocorticoid
- Peripherial androgen antagonist : spirinolactone
- Diane -35 (combination of cyproterone acetate and estradiol) :blocks receptor binding

6. Congenital Disorders of Sex Differentiation; Shereshevsky –Turner syndrome.

Definition

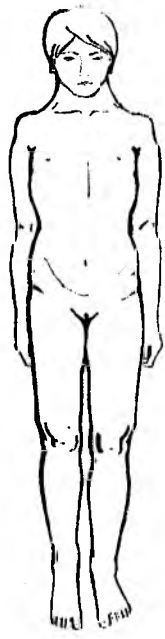
Gonadal dysgenesis or Shereshevsky-Terner syndrome is caused by anomaly of the sex chromosomes as a consequence of which gonadal development in the erly embrional period is disturbed.

- Occur rare 1:3000 girls that are born

Ethiology and Pathogenesis

The cause of the disease is unknown

- Non-separation of the sex-chromosomes during meiosis in the parents
- Kariotype 45XO or varios mosaic variants: 45XO?46XX; 45XO/46XY; 45xO/47XXX etc.
- Congenital absence of the gonads causes hypogenitalism
- Varios congenital defects : anomalies of the kidneys, congenital heart diseases, retarded growth, double ureters, occlusion of the renal arteries
- The gonads are absent are replaced by connective-tissue strands
- The uterus is hypoplastic



Picture. Turner syndrome in a female patient with 45 X-chromosome complex:webbed neck,absence of secondary sex characters, retarded growth.

Symptoms and signs

- Proportional short stature (< 150 cm)
- The ears are situated lower than usual, the lower jaw is often shortened
- The hairline at ther nape of the neck is low, the neck is usually short
- Webbed neck – skin folds pass from the head to the shoulders giving the patient a sphinx-like appearance
- Skeleton abnormality: the chest is broad;a depression in the region of the sternum;a shortening of the fourth and fifth metacarpal bones, a moderate retardation of bone age from the actual age; a high hard palate
- Eayes defects: daltonism,ptosis, strabismus
- Absent secondary sex characters, hypoplasia of the large and small pudendal lips and uterus ana a narrow vagina

Diagnosis and differential diagnosis

- Is based on the characteristic clinical picture
- Kariotype and sex chromatin investigation

- X-ray exam of the skeleton
- Differential diagnosis with Dwarfism

Treatment

- Hormone replacement therapy: femail sex hormones, anabolic steroids
- Surgery of the congenital defects of the viscers (ventricular septal defect, the isthmus of the aorta etc)

Prognosis

- Is unfavourable to full recovery
- The patients remain sterile
- Death may occur from congenital defects of the viscera
-

Chapter XII. Medical Documentation. Recomendatios for the Taking case history of the patient with endocrine pathology.

The case history is the accounting, legal, archival and historical document in which the part of a life of the patient is reflected, concerning its states of health and a site during the certain moment of time. On a case history it is possible to judge chronology of a current of disease at the concrete patient, about that what diagnostic and medical actions were spent to the patient and planned in the future at an outpatient observation for the patient. Consultations of experts of a different profile, consultations and their conclusions and the reference are reflected in a case history. On a case history it is possible to judge not only how the doctor estimates a state of health of the patient, what plan of its treatment and inspection, but also about a skill level of the attending physician, adequacy of spent medical-diagnostic actions. Features of a writing of a case history of the patient with an endocrine pathology depend on the information on some additional symptoms which allow to tap possible disturbances from endocrine system and from the analysis and correct generalisation of already available data on the patient. Your problem at a case history writing consists not in simple transfer of that you were informed by the patient and that you have taped at physical and laboratory-tool inspection, and in generalisation of the received information for the purpose of an establishment of the correct diagnosis, drawing up of the clear and logically bound report on strategy and tactics of inspection, treatment and aftertreatment of the patient. The practical and clinical experience, a certain lexicon, practical both theoretical knowledge and skills is necessary for ordering of data. Pay attention to following principles:

- Study to state the thoughts competently, in detail stating the information received from the patient;
- Write down all information received by you necessary for an establishment of the diagnosis, it is not necessary to make the diagnosis if you do not have sufficient for this purpose information;-allocate separate headings of sections, write them on the centre of a line or with the big spaces;
- Complaints describe only in section "complaints of the patient at the moment of entering" and "complaints at the moment of inspection". If the patient does not show complaints from cardiovascular system, do not write it in section "breath organs". It is better to write down words of the patient, instead of how you interpret them. For example, the patient cannot show the complaint to a polyuria and a polydipsia as he does't know medical terminology, is better to write down, that the patient notes the expressed thirst and frequent urination. Sometimes the patient states the purpose of the entering to hospital: "for high-grade inspection", "for passage of a course of special treatment".

- Anamnesis data write in section "the anamnesis of the present disease", instead of at the description of clinical inspection of organs and systems;

Especially significant information underline, designate a point, an asterisk or allocate with other colour;

- Distinguish the essential information from minor which can be lowered. Lower the most part negative results and note in a case history only what have the immediate relation to complaints of the patient and a substantiation of your judgements in the course of a diagnosis establishment.

- Do not list all deviations which you *have not found out* in the patient, be limited to the indicating only the most important in the clinical relation of symptoms. For example, "at auscultation breath over lungs vesicular, rhonchuses are not present". Do not describe, that breath at the patient through a nose free and выделений from both nasal courses is not present. You even can not describe in detail border of lungs on all pulmonary fields if at the patient such pathology is not taped. *Describe that you have taped at inspection, instead of that that is not present.*

- Try to describe a condition of organs of systems it is compressed, laconically and positively, using short phrases and separate words *which should be written it is legible;*

- The sizes describe in centimetres, not using for comparison in the sizes of fruit and vegetables. For example, "in the right share of a thyroid gland formation in the sizes about 3 cm in diameter" (but not in size with a string bean or a bean as such record does not reflect the true sizes of formation) is palpated.

Before the beginning of conversation with the patient be presented and, explain to the patient your role of the student as the future doctor, the purpose of your conversation. Address to the patient on a name and a patronymic, instead of on a surname or using a sexual sign "man" - "woman" or the term of "patient" it is tactless and disrespectful in relation to the person.

Pay attention to that it was convenient to patient to conduct with you conversation: if it is necessary, let will visit a toilet, will say goodbye to relatives, signs nutrition. Short expectation will allow to frame necessary contact and will arrange to you of the patient. Speak with the patient considering its educational level, age, the social state. Start reception of the information, which preliminary write down in a notebook not to miss and to forget further the valuable information, relying only on your memory, after all you can start to make out a case history in other day.

Case History

Biodata of the patient
Name___Age_____Sex____
Home Adress_____Occupation____Religion____Marital status_____

Date of hospitalization

Complaints of the patient

1. In the beginning complaints of the patient are stated at entering in a hospital and their detailed elaboration on systems. Begin with questions of the general character: "As you now feel yourselves?", "that you has resulted in a hospital?" Give to the patient the initiative that he has told about herself (himself) easy. In the beginning of conversation you do not know with what patient and in what mood you should deal. It can be закнутый and the silent patient or the patient too talkative. Probably is a patient in a grave condition it is difficult to them to communicate or with hostility adjusted patient. That it to find out behave activly. Activly listen to the patient encouraging it to conversation the behaviour, interest, benevolent confidence, inducing it to give about itself the additional information. Will feel for it the sympathy words "Yes, I understand you", a head nod, a sympathetic view, correctly understanding a situation. Do not encourage patients to insignificant stories about difficulties of travel to a hospital or about incompetence of doctors, a carelessness and callousness of medical staff and furthermore do not cry together with the patient. Activly listen to the patient and activly interfere with a narration, referring its story in the necessary direction for you.

2. Set direct questions :"Where is you ill ? On what the pain and when it has appeared is similar?" Prompt to the patient some possible answers: "This pain a constant or arises only after meal or to meal is not bound? A pain of stupid character or acute?"During conversation with the patient it is necessary to avoid leading questions of type of the help: "you love salty nutrition?" It is better to ask doubly: "That you prefer more salty or sweet?" Do not set at once some questions. If the patient speaks: " I had a strong pain in a pancreas "- concretise its complaint. Why he considers, that this pain has arisen in a pancreas, will define its localisation. Do not state the sceptical relation to knowledge to patients of anatomy, especially do not lose time for the collecting of the necessary information, leading discussion about pancreas topography. Be attentive, friendly, benevolent and remember, that contact between the doctor and the patient promotes finding-out of the major details of the anamnesis of disease and a life of the patient which can affect diagnostic and medical tactics essentially. Besides, a number of complaints of the patient is that, that the patient cannot tell about them to anybody, except the attending physician, and sometimes hesitates to inform on them even to it, therefore it is necessary to adhere to medical ethics and a deontology.

Anamnesis morbi (Origin, duration and progress):

Details of each symptom must be recorded separately.The mode of onset, whether sudden or gradual, the duration of each symptom and its progress and finally the present status of the symptom must be noted

Find out at what age there were first signs of disease and to what reasons binds its occurrence the patient: the transferred infection, a trauma, stress, influence of physical factors and others.

- What were dynamics of symptoms of illness before hospitalization, the reasons of the present hospitalisation (an illness exacerbation, treatment of complications etc.);
- What medicinal preparations were accepted by the patient and their efficiency (the name, a dose, the reception scheme, side effects).

The description of the present disease should include the relation of the patient to the condition: that promoted occurrence of complications or disease exacerbations, whether the way of life of the patient and its working capacity has changed. All symptoms which have forced the patient to address for the first time to the doctor, it is necessary to state in a chronological order. The information is given to you by the patient, but correctly to interpret it and not to miss the important episodes are an indicator of your level of clinical thinking and medical qualification

History of the past illness

Similar illness in the past with their time of occurrence, duration and results should be noted. Chilhood illnesses, tuberculosis, hypertention, jaundice etc. must be inquired into. Past injuiries, accidents, operations or hospital stay and blood transfusion history must also be noted in details.

Anamnesis vitae (Personal history)

Patient's appetite, food habits, type of diet, bowel and micturition habits, sleep and addictions like alcohol, smoking, narcotics etc., must be inquired into.

Family history:

The state of health of parents, peers and children should be noted. If any member is deceased, the cause of death should be noted. Some genetically transmitted disease should be noted into .

Physical examination

Status presents (Objective examination of the patient's.)

To define a morphotype of the patient growth and body proportions:

- To pay attention to conformity of growth to age and the sex of the patient. The relation of length of feet to length of a trunk (at children - short; at adults the length of feet is more than length of a trunk; the distance between fingers of the arms extended in the parties is more than length of a body). An appreciable shorting of arms and feet ("children's proportions of a structure of a body") - at the hypothyrosis congenital or got in the early childhood, Dwarfism's. Short and thin arms and feet - at Dwarfism; short and thick - at premature puberty. Long arms and feet are at a primary hypogonadism. The brushes enlarged in the cross-section size and stops, the wide thorax acting forward a mandible and arch of a eyebrow; big tongue and the big auricles are taped at an acromegalia.

- Definition of a phenotype of the patient: adiposity degree and its topography; at

Progressing depression of mass of a body at the kept appetite is characteristic for a thyrotoxicosis, DM.

- To define conformity of the sexual development to calendar age , sex, and degree of expression of secondary sexual signs

- To estimate of topography of growth of hair and their properties (dry, fat, fragile, the early grey hair, abaissement) to consider racial features of the patient, a heredity. More expressed growth of hair becomes perceptible at southern nationalities. Magnificent growth of thin hair on a head at men at weakly developed secondary sexual signs, rare moustaches and a beard - a hypogonadism sign, however at blondes and brown-haired persons The rare type of a pilosis becomes perceptible at normally developed external genitals. Abaissement of hair in axillary fossas and on a pubis both at men, and at women is a sign of a secondary hypogonadism.Growth of hair on the person at women in the form of the Scottish small beard, on a stomach in the form of a rhombus - a virilescence sign

Low line of growth of hair on a nape and in the field of a forehead in a combination to small growth, wide pterygoid cords of a skin between mastoid and acromial processes ("a sphinx neck"), widely placed not developed dummies of mammary glands, absence in them a glandular tissue it is characteristic for a Shereshevsky-Tuerner syndrome.

- To pay attention to: colour, humidity, presence on a skin of separate elements, puffiness, a hyperpegmentation. Colour of the skin of sunburn on sites of a friction of clothes (ulnar, knee joints, girdle area, axillary hollows, palmar cords) in a combination to pigmentation of gums, a mucosa of cheeks are a symptom, characteristic for the primary adrenal failures .

Pigmentation of is dirty-brown colour on elbows, a neck is characteristic for Cushing's syndrome; a hyperpegmentation of a skin round eyes is for a diffusive toxic goiter; a hyperpegmentation palmar creases and on a brush of interphalanx joints and open sites of a body are at chronic primary adrenal insufficiency.

Brown with various shades in the form of maculae xanthopathy of feet against shining, the varnished cold skin is a dermopathy at DM.

Hot, diffusively wet on all body, velvety skin is characteristic for a thyrotoxicosis. Cold, shelled, dense skin in a combination to edemas of back of brushes, supraclavicular fossas (at pressing by a finger of hydropic fossas it is not formed) is characteristic for a hypothyrosis . The rugosity, thin, dry, flabby, yellowish skin in a combination to an atrophy of face muscles is typical for Dwarfism and panhypopituitarism.

Strips of a stretching of purple-red colour (stria) - places of local disappearance of the fat on a stomach, an internal surface of hips, a breast, lumbar area are typical for a hypercorticoidism . Shorter and light pink colour strias are typical for a hypothalamic pubertal syndrome.

- Spend a palpation of a thyroid gland and define degree of its augmentation; to estimate gland structure, mobility, morbidity; to define a condition of cervical, submandibular and peripheric lymph nodes. Moderately dense, painful, rather quickly enlarged thyroid gland testifies about subacute thyroiditis. Dense, irregularly enlarged, with the indistinct contours, bound to surrounding tissues testifies a malignant degeneration of a struma. Diffusively enlarged, dense - autoimmune thyroiditis. At an endemic struma a thyroid gland moderately dense, smooth, equal, mobile, enlarged in sizes.
- Spend if necessary the special methods of objective inspection taping diseases thyroid and parathyroid glands, diabetes complications.

Independently carry out research of cardiovascular, nervous, respiratory, digestive, genitourinary, joints system, sense organs and result their description, using the skills received at studying of propaedeutics of internal illnesses. Formulate the preliminary diagnosis on the basis of anamnestic data and results of objective inspection of the patient

Respiratory system_____

Circulatory system_____

Digestive system_____

Genitourinary system_____

Nervous system_____

Laboratory finding and special investigations

In the beginning state results of traditional laboratory researches and tool data: the general analysis of blood, the general analysis of urine, biochemical blood analysises, an electrocardiogram, a X-ray inspection of organs of a thoracal cavity.

Conclusions of consulting physician

Substantiation of the provisional diagnosis

Differential diagnosis

- Make the differentsialn diagnostic table, where bring data of the supervised patient (the complaint, objective data, additional methods of research) in comparison with diseases with similar semiology.
- At each concrete disease the differential diagnosis is based on the main symptoms of disease at the supervised patient.

Substantiation of clinical diagnosis

- Should state in the short form the main complaints and the disease signs, anamnesis morbid and vitae, objective inspection with the indicating of the major clinico-biochemical, hormonal, radiological researches in concrete units of measure for the supervised patient, and in brackets to specify normal parametres of the given research.
- To cite data of additional methods of research, the conclusion of advisers (the neuropathologist, the oculist etc.), allowing to prove the diagnosis.
- should prove a disease stage (compensation, a decompensation, subcompensation). In the presence of complications of the given disease it is necessary to prove and define them severity level. Then the definitive diagnosis of disease is formulated: nosological unit, a stage of disease, complication and degree of their expression, disease severity level.

Treatment

- Calculate to your patient a daily calory depending on disease and its state, performed work to the supervised patient
- To define necessary quantity of alimentary ingredients in grammes and calories (fibers, fats, carbohydrates) to the supervised patient

The student should show ability to combine medicinal preparations, ways of their introduction. Medicinal preparations to be noted in Latin transcriptions with the indicating of a dose, a rhythm and how use.

Name of medicine (pharmacology)	Trade name	How use (per orally, i/v, s/c, i/m)

Prognosis

- The forecast is underlined concerning a life, recovery, working capacity .
- Give to the supervised patient doctor's advices

List of diabetes-related terms and their definitions.

(ADA Diabetes World – Professional education, 2008 Adapted from NIDDK.)

Below is a list of diabetes-related terms and their definitions. Use the letter groupings to jump to words beginning with those letters.

A1C

a test that measures a person's average blood glucose level over the past 2 to 3 months. Hemoglobin (HEE-mo-glo-bin) is the part of a red blood cell that carries oxygen to the cells and sometimes joins with the glucose in the bloodstream. Also called hemoglobin A1C or glycosylated (gly-KOH-sih-lay-ted) hemoglobin, the test shows the amount of glucose that sticks to the red blood cell, which is proportional to the amount of glucose in the blood.

acanthosis nigricans (uh-kan-THO-sis NIH-grih-kans)

a skin condition characterized by darkened skin patches; common in people whose body is not responding correctly to the insulin that they make in their pancreas (insulin resistance). This skin condition is also seen in people who have pre-diabetes or Type 2 diabetes.

acarbose (AK-er-bose)

an oral medicine used to treat Type 2 diabetes. It blocks the enzymes that digest starches in food. The result is a slower and lower rise in blood glucose throughout the day, especially right after meals. Belongs to the class of medicines called alpha-glucosidase inhibitors. (Brand name: Precose)

ACE inhibitor

an oral medicine that lowers blood pressure; ACE stands for angiotensin (an-gee-oh-TEN-sin) converting enzyme. For people with diabetes, especially those who have protein (albumin) in the urine, it also helps slow down kidney damage.

acesulfame potassium (a-see-SUL-fame puh-TAS-ee-um)

a dietary sweetener with no calories and no nutritional value. Also known as acesulfame-K. (Brand name: Sunett)

acetohexamide (a-see-toh-HEX-uh-myde)

an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by helping the pancreas make more insulin and by helping the body better use the insulin it makes. Belongs to the class of medicines called sulfonylureas. (Brand name: Dymelor)

acute

describes something that happens suddenly and for a short time. Opposite of chronic.

adhesive capsulitis (ad-HEE-sive cap-soo-LITE-is)

a condition of the shoulder associated with diabetes that results in pain and loss of the ability to move the shoulder in all directions.

adult-onset diabetes
former term for Type 2 diabetes.

AGEs (A-G-EEZ)
stands for advanced glycosylation (gly-KOH-sih-LAY-shun) end products. AGEs are produced in the body when glucose links with protein. They play a role in damaging blood vessels, which can lead to diabetes complications.

albuminuria (al-BYOO-mih-NOO-ree-uh)
a condition in which the urine has more than normal amounts of a protein called albumin. Albuminuria may be a sign of nephropathy (kidney disease).

alpha cell (AL-fa)
a type of cell in the pancreas. Alpha cells make and release a hormone called glucagon. The body sends a signal to the alpha cells to make glucagon when blood glucose falls too low. Then glucagon reaches the liver where it tells it to release glucose into the blood for energy.

alpha-glucosidase inhibitor (AL-fa-gloo-KOH-sih-days)
a class of oral medicine for Type 2 diabetes that blocks enzymes that digest starches in food. The result is a slower and lower rise in blood glucose throughout the day, especially right after meals. (Generic names: acarbose and miglitol)

amylin (AM-ih-lin)
a hormone formed by beta cells in the pancreas. Amylin regulates the timing of glucose release into the bloodstream after eating by slowing the emptying of the stomach.

amyotrophy (a-my-AH-truh-fee)
a Type of neuropathy resulting in pain, weakness and/or wasting in the muscles.

anemia (uh-NEE-mee-uh)
a condition in which the number of red blood cells is less than normal, resulting in less oxygen being carried to the body's cells.

angiopathy (an-gee-AH-puh-thee)
any disease of the blood vessels (veins, arteries, capillaries) or lymphatic vessels.

antibodies (AN-ti-bod-eez)
proteins made by the body to protect itself from "foreign" substances such as bacteria or viruses. People get Type 1 diabetes when their bodies make antibodies that destroy the body's own insulin-making beta cells.

ARB
an oral medicine that lowers blood pressure; ARB stands for angiotensin (an-gee-oh-TEN-sin) receptor blocker.

arteriosclerosis (ar-TEER-ee-oh-skluh-RO-sis)
hardening of the arteries.

artery
a large blood vessel that carries blood with oxygen from the heart to all parts of the body.

aspart insulin (ASS-part)
a rapid-acting insulin. On average, aspart insulin starts to lower blood glucose within 10 to 20 minutes after injection. It has its strongest effect 1 to 3 hours after injection but keeps working for 3 to 5 hours after injection.

aspartame (ASS-per-tame)
a dietary sweetener with almost no calories and no nutritional value. (Brand names: Equal, NutraSweet)

atherosclerosis (ATH-uh-row-skluh-RO-sis)
clogging, narrowing and hardening of the body's large arteries and medium-sized blood vessels. Atherosclerosis can lead to stroke, heart attack, eye problems and kidney problems.

autoimmune disease (AW-toh-ih-MYOON)
disorder of the body's immune system in which the immune system mistakenly attacks and destroys body tissue that it believes to be foreign.

autonomic neuropathy (aw-toh-NOM-ik ne-ROP-uh-thee)
a type of neuropathy affecting the lungs, heart, stomach, intestines, bladder or genitals.

background retinopathy (REH-tih-NOP-uh-thee)
a type of damage to the retina of the eye marked by bleeding, fluid accumulation and abnormal dilation of the blood vessels. Background retinopathy is an early stage of diabetic retinopathy. Also called simple or nonproliferative (non-pro-LIF-er-uh-tiv) retinopathy.

basal rate
a steady trickle of low levels of longer-acting insulin, such as that used in insulin pumps.

beta cell
a cell that makes insulin. Beta cells are located in the islets of the pancreas.

biguanide (by-GWAH-nide)
a class of oral medicine used to treat Type 2 diabetes that lowers blood glucose by reducing the amount of glucose produced by the liver and by helping the body respond better to insulin. (Generic name: metformin)

blood glucose
the main sugar found in the blood and the body's main source of energy. Also called blood sugar.

blood glucose level
the amount of glucose in a given amount of blood. It is noted in milligrams in a deciliter, or mg/dL.

blood glucose meter
a small, portable machine used by people with diabetes to check their blood glucose levels. After pricking the skin with a lancet, one places a drop of blood on a

test strip in the machine. The meter (or monitor) soon displays the blood glucose level as a number on the meter's digital display.

blood glucose monitoring
checking blood glucose level on a regular basis in order to manage diabetes. A blood glucose meter (or blood glucose test strips that change color when touched by a blood sample) is needed for frequent blood glucose monitoring.

blood pressure
the force of blood exerted on the inside walls of blood vessels. Blood pressure is expressed as a ratio (example: 120/80, read as "120 over 80"). The first number is the systolic (sis-TAH-lik) pressure, or the pressure when the heart pushes blood out into the arteries. The second number is the diastolic (DY-uh-STAH-lik) pressure, or the pressure when the heart rests.

blood urea nitrogen (BUN) (yoo-REE-uh NY-truh-jen)
a waste product in the blood from the breakdown of protein. The kidneys filter blood to remove urea. As kidney function decreases, the BUN levels increase.

blood vessels
tubes that carry blood to and from all parts of the body. The three main types of blood vessels are arteries, veins and capillaries.

body mass index (BMI)
a measure used to evaluate body weight relative to a person's height. BMI is used to find out if a person is underweight, normal weight, overweight or obese.

bolus (BOH-lus)
an extra amount of insulin taken to cover an expected rise in blood glucose, often related to a meal or snack.

borderline diabetes
a former term for Type 2 diabetes or impaired glucose tolerance.

brittle diabetes
a term used when a person's blood glucose level moves often from low to high and from high to low.

bunion (BUN-yun)
a bulge on the first joint of the big toe, caused by the swelling of a fluid sac under the skin. This spot can become red, sore and infected.

C-peptide (see-peptide)
"Connecting peptide," a substance the pancreas releases into the bloodstream in equal amounts to insulin. A test of C-peptide levels shows how much insulin the body is making.

callus
a small area of skin, usually on the foot, that has become thick and hard from rubbing or pressure.

calorie
a unit representing the energy provided by food. Carbohydrate, protein, fat and

alcohol provide calories in the diet. Carbohydrate and protein have 4 calories per gram, fat has 9 calories per gram, and alcohol has 7 calories per gram.

capillary (KAP-ih-lair-ee)
the smallest of the body's blood vessels. Oxygen and glucose pass through capillary walls and enter the cells. Waste products such as carbon dioxide pass back from the cells into the blood through capillaries.

capsaicin (kap-SAY-ih-sin)
an ingredient in hot peppers that can be found in ointment form for use on the skin to relieve pain from diabetic neuropathy.

carbohydrate (kar-boh-HY-drate)
one of the three main nutrients in food. Foods that provide carbohydrate are starches, vegetables, fruits, dairy products and sugars.

carbohydrate counting
a method of meal planning for people with diabetes based on counting the number of grams of carbohydrate in food.

cardiologist (kar-dee-AH-luh-jist)
a doctor who treats people who have heart problems.

cardiovascular disease (KAR-dee-oh-VASK-yoo-ler)
disease of the heart and blood vessels (arteries, veins and capillaries).

cataract (KA-ter-act)
clouding of the lens of the eye.

cerebrovascular disease (seh-REE-broh-VASK-yoo-ler)
damage to blood vessels in the brain. Vessels can burst and bleed or become clogged with fatty deposits. When blood flow is interrupted, brain cells die or are damaged, resulting in a stroke.

certified diabetes educator (CDE)
a health care professional with expertise in diabetes education who has met eligibility requirements and successfully completed a certification exam.

Charcot's foot (shar-KOHZ)
a condition in which the joints and soft tissue in the foot are destroyed; it results from damage to the nerves.

chlorpropamide (klor-PROH-pah-mide)
an oral medicine used to treat Type 2 diabetes. It lowers blood glucose levels by helping the pancreas make more insulin and by helping the body better use the insulin it makes. Belongs to the class of medicines called sulfonylureas. (Brand name: Diabinese)

cholesterol (koh-LES-ter-all)
a type of fat produced by the liver and found in the blood; it is also found in some foods. Cholesterol is used by the body to make hormones and build cell walls.

chronic
describes something that is long-lasting. Opposite of acute.

circulation
the flow of blood through the body's blood vessels and heart.

coma
a sleep-like state in which a person is not conscious. May be caused by hyperglycemia (high blood glucose) or hypoglycemia (low blood glucose) in people with diabetes.

combination oral medicines
a pill that includes two or more different medicines. See Glucovance.

combination therapy
the use of different medicines together (oral hypoglycemic agents or an oral hypoglycemic agent and insulin) to manage the blood glucose levels of people with Type 2 diabetes.

complications
harmful effects of diabetes such as damage to the eyes, heart, blood vessels, nervous system, teeth and gums, feet and skin, or kidneys. Studies show that keeping blood glucose, blood pressure, and low-density lipoprotein cholesterol levels close to normal can help prevent or delay these problems.

congenital defects (kun-JEN-ih-tul)
problems or conditions that are present at birth.

congestive heart failure
loss of the heart's pumping power, which causes fluids to collect in the body, especially in the feet and lungs.

conventional therapy
a term used in clinical trials where one group receives treatment for diabetes in which A1C and blood glucose levels are kept at levels based on current practice guidelines. However, the goal is not to keep blood glucose levels as close to normal as possible, as is done in intensive therapy. Conventional therapy includes use of medication, meal planning and exercise, along with regular visits to health care providers.

coronary heart disease (KOR-uh-ner-ee)
heart disease caused by narrowing of the arteries that supply blood to the heart. If the blood supply is cut off, the result is a heart attack.

creatinine (kree-AT-ih-nin)
a waste product from protein in the diet and from the muscles of the body. Creatinine is removed from the body by the kidneys; as kidney disease progresses, the level of creatinine in the blood increases.

D-phenylalanine derivative (dee-fen-nel-AL-ah-neen)
a class of oral medicine for Type 2 diabetes that lowers blood glucose levels by helping the pancreas make more insulin right after meals. (Generic name: nateglinide)

dawn phenomenon (feh-NAH-meh-nun)
the early-morning (4 a.m. to 8 a.m.) rise in blood glucose level.

dehydration (dee-hy-DRAY-shun)
the loss of too much body fluid through frequent urinating, sweating, diarrhea or vomiting.

dermopathy (dur-MAH-puh-thee)
disease of the skin.

desensitization (dee-sens-ih-tiz-A-shun)
a way to reduce or stop a response such as an allergic reaction to something. For example, if someone has an allergic reaction to something, the doctor gives the person a very small amount of the substance at first to increase one's tolerance. Over a period of time, larger doses are given until the person is taking the full dose. This is one way to help the body get used to the full dose and to prevent the allergic reaction.

Dextrose, also called glucose (DECKS-trohss)
simple sugar found in blood that serves as the body's main source of energy.

Diabetes Control and Complications Trial (DCCT)
a study by the National Institute of Diabetes and Digestive and Kidney Diseases, conducted from 1983 to 1993 in people with Type 1 diabetes. The study showed that intensive therapy compared to conventional therapy significantly helped prevent or delay diabetes complications. Intensive therapy included multiple daily insulin injections or the use of an insulin pump with multiple blood glucose readings each day. Complications followed in the study included diabetic retinopathy, neuropathy and nephropathy.

diabetes educator
a health care professional who teaches people who have diabetes how to manage their diabetes. Some diabetes educators are certified diabetes educators (CDEs). Diabetes educators are found in hospitals, physician offices, managed care organizations, home health care and other settings.

diabetes insipidus (in-SIP-ih-dus)
a condition characterized by frequent and heavy urination, excessive thirst and an overall feeling of weakness. This condition may be caused by a defect in the pituitary gland or in the kidney. In diabetes insipidus, blood glucose levels are normal.

diabetes mellitus (MELL-ih-tus)
a condition characterized by hyperglycemia resulting from the body's inability to use blood glucose for energy. In Type 1 diabetes, the pancreas no longer makes insulin and therefore blood glucose cannot enter the cells to be used for energy. In Type 2 diabetes, either the pancreas does not make enough insulin or the body is unable to use insulin correctly.

Diabetes Prevention Program (DPP)
a study by the National Institute of Diabetes and Digestive and Kidney Diseases conducted from 1998 to 2001 in people at high risk for Type 2 diabetes. All

study participants had impaired glucose tolerance, also called pre-diabetes, and were overweight. The study showed that people who lost 5 to 7 percent of their body weight through a low-fat, low-calorie diet and moderate exercise (usually walking for 30 minutes 5 days a week) reduced their risk of getting Type 2 diabetes by 58 percent. Participants who received treatment with the oral diabetes drug metformin reduced their risk of getting Type 2 diabetes by 31 percent.

diabetic diarrhea (dy-uh-REE-uh)
loose stools, fecal incontinence, or both that result from an overgrowth of bacteria in the small intestine and diabetic neuropathy in the intestines. This nerve damage can also result in constipation.

diabetic ketoacidosis (DKA) (KEY-toe-ass-ih-DOH-sis)
an emergency condition in which extremely high blood glucose levels, along with a severe lack of insulin, result in the breakdown of body fat for energy and an accumulation of ketones in the blood and urine. Signs of DKA are nausea and vomiting, stomach pain, fruity breath odor and rapid breathing. Untreated DKA can lead to coma and death.

diabetic mastopathy
a rare fibrous breast condition occurring in women, and sometimes men, with long-standing diabetes. The lumps are not malignant and can be surgically removed, although they often recur.

diabetic myelopathy (my-eh-LAH-puh-thee)
damage to the spinal cord found in some people with diabetes.

diabetic retinopathy (REH-tih-NOP-uh-thee)
diabetic eye disease; damage to the small blood vessels in the retina. Loss of vision may result.

diabetogenic (DY-uh-beh-toh-JEN-ic)
causing diabetes. For example, some drugs cause blood glucose levels to rise, resulting in diabetes.

diabetologist (DY-uh-beh-TAH-luh-jist)
a doctor who specializes in treating people with diabetes.

diagnosis (DY-ug-NO-sis)
the determination of a disease from its signs and symptoms.

dialysis (dy-AL-ih-sis)
the process of cleaning wastes from the blood artificially. This job is normally done by the kidneys. If the kidneys fail, the blood must be cleaned artificially with special equipment. The two major forms of dialysis are hemodialysis and peritoneal dialysis.

dietitian (DY-eh-TIH-shun)
a health care professional who advises people about meal planning, weight control and diabetes management. A registered dietitian (RD) has more training

dilated eye exam (DY-lay-ted)

a test done by an eye care specialist in which the pupil (the black center) of the eye is temporarily enlarged with eyedrops to allow the specialist to see the inside of the eye more easily.

Dupuytren's contracture (doo-PWEE-trenz kon-TRACK-chur)
a condition associated with diabetes in which the fingers and the palm of the hand thicken and shorten, causing the fingers to curve inward.

edema (eh-DEE-muh)swelling caused by excess fluid in the body.

electromyography (EMG) (ee-LEK-troh-my-AH-gruh-fee)
a test used to detect nerve function. It measures the electrical activity generated by muscles.

Endocrine gland (EN-doh-krin)
a group of specialized cells that release hormones into the blood. For example, the islets in the pancreas, which secrete insulin, are endocrine glands.

endocrinologist (EN-doh-krih-NAH-luh-jist)
a doctor who treats people who have endocrine gland problems such as diabetes.

enzyme (EN-zime)
protein made by the body that brings about a chemical reaction, for example, the enzymes produced by the gut to aid digestion.

euglycemia (you-gly-SEEM-ee-uh)
a normal level of glucose in the blood.

exchange lists
one of several approaches for diabetes meal planning. Foods are categorized into three groups based on their nutritional content. Lists provide the serving sizes for carbohydrates, meat and meat alternatives, and fats. These lists allow for substitution for different groups to keep the nutritional content fixed.

fasting blood glucose test
a check of a person's blood glucose level after the person has not eaten for 8 to 12 hours (usually overnight). This test is used to diagnose pre-diabetes and diabetes. It is also used to monitor people with diabetes.

fat
1. One of the three main nutrients in food. Foods that provide fat are butter, margarine, salad dressing, oil, nuts, meat, poultry, fish and some dairy products.
2. Excess calories are stored as body fat, providing the body with a reserve supply of energy and other functions.

fluorescein angiography (fluh-RESS-ee-in an-gee-AH-grah-fee
a test to examine blood vessels in the eye; done by injecting dye into an arm vein and then taking photos as the dye goes through the eye's blood vessels.

fructosamine test (frook-TOH-sah-meen)
measures the number of blood glucose molecules (MAH-leh-kyools) linked to protein molecules in the blood. The test provides information on the average blood glucose level for the past 3 weeks.

fructose (FROOK-tohss)
a sugar that occurs naturally in fruits and honey. Fructose has 4 calories per gram.

gangrene (GANG-green)
the death of body tissue, most often caused by a lack of blood flow and infection. It can lead to amputation.

gastroparesis (gas-tro-puh-REE-sis)
a form of neuropathy that affects the stomach. Digestion of food may be incomplete or delayed, resulting in nausea, vomiting, or bloating, making blood glucose control difficult.

gestational diabetes mellitus (GDM) (jes-TAY-shun-ul MELL-ih-tus)
a type of diabetes mellitus that develops only during pregnancy and usually disappears upon delivery, but increases the risk that the mother will develop diabetes later. GDM is managed with meal planning, activity, and, in some cases, insulin.

gingivitis (JIN-jih-VY-tis)
a condition of the gums characterized by inflammation and bleeding.

gland
a group of cells that secrete substances. Endocrine glands secrete hormones. Exocrine glands secrete salt, enzymes and water.

glargine insulin (GLAR-jeen)
very-long-acting insulin. On average, glargine insulin starts to lower blood glucose levels within 1 hour after injection and keeps working evenly for 24 hours after injection.

glaucoma (glaw-KOH-muh)
an increase in fluid pressure inside the eye that may lead to loss of vision.

glimepiride (gly-MEH-per-ide)
an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by helping the pancreas make more insulin and by helping the body better use the insulin it makes. Belongs to the class of medicines called sulfonylureas. (Brand name: Amaryl)

glipizide (GLIH-pih-zide)
an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by helping the pancreas make more insulin and by helping the body better use the insulin it makes. Belongs to the class of medicines called sulfonylureas. (Brand names: Glucotrol, Glucotrol XL)

glomerular filtration rate (glo-MEHR-yoo-lur)
measure of the kidney's ability to filter and remove waste products.

glomerulus (glo-MEHR-yoo-lus)
a tiny set of looping blood vessels in the kidney where the blood is filtered and waste products are removed.

glucagon (GLOO-kah-gahn)
a hormone produced by the alpha cells in the pancreas. It raises blood glucose.

An injectable form of glucagon, available by prescription, may be used to treat severe hypoglycemia.

glucose

one of the simplest forms of sugar.

glucose tablets

chewable tablets made of pure glucose used for treating hypoglycemia.

Glucovance

an oral medicine used to treat Type 2 diabetes. It is a combination of glyburide and metformin.

glyburide (GLY-buh-ride)

an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by helping the pancreas make more insulin and by helping the body better use the insulin it makes. Belongs to the class of medicines called sulfonylureas. (Brand names: DiaBeta, Glynase PresTab, Micronase; ingredient in Glucovance)

glycemic index (gly-SEE-mik)

a ranking of carbohydrate-containing foods, based on the food's effect on blood glucose compared with a standard reference food.

glycogen (GLY-koh-jen)

the form of glucose found in the liver and muscles.

glycosuria (gly-koh-SOOR-ee-ah)

the presence of glucose in the urine.

gram

a unit of weight in the metric system. An ounce equals 28 grams. In some meal plans for people with diabetes, the suggested amounts of food are given in grams.

HDL cholesterol, stands for high-density-lipoprotein cholesterol (kuh-LESS-tuh-rawl LIP-oh-PRO-teen)

a fat found in the blood that takes extra cholesterol from the blood to the liver for removal. Sometimes called "good" cholesterol.

heredity

the passing of a trait from parent to child.

honeymoon phase

Some people with type 1 diabetes experience a brief remission called the "honeymoon period." During this time their pancreas may still secrete some insulin. Over time, this secretion stops and as this happens, the child will require more insulin from injections. The honeymoon period can last weeks, months, or even up to a year or more.

hormone

a chemical produced in one part of the body and released into the blood to trigger or regulate particular functions of the body. For example, insulin is a hormone made in the pancreas that tells other cells when to use glucose for energy. Synthetic hormones, made for use as medicines, can be the same or different from those made in the body.

human leukocyte antigens (HLA)
proteins located on the surface of the cell that help the immune system identify the cell either as one belonging to the body or as one from outside the body. Some patterns of these proteins may mean increased risk of developing Type 1 diabetes.

hyperglycemia (HY-per-gly-SEE-mee-uh)
excessive blood glucose. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours. Postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

hyperinsulinemia (HY-per-IN-suh-lih-NEE-mee-uh)
a condition in which the level of insulin in the blood is higher than normal. Caused by overproduction of insulin by the body. Related to insulin resistance.

hyperlipidemia (HY-per-li-pih-DEE-mee-uh)
higher than normal fat and cholesterol levels in the blood.

hyperosmolar hyperglycemic nonketotic syndrome (HHNS) (HY-per-oz-MOH-lur HY-per-gly-SEE-mik non-kee-TAH-tik)
an emergency condition in which one's blood glucose level is very high and ketones are not present in the blood or urine. If HHNS is not treated, it can lead to coma or death.

hypertension (HY-per-TEN-shun)
a condition present when blood flows through the blood vessels with a force greater than normal. Also called high blood pressure. Hypertension can strain the heart, damage blood vessels, and increase the risk of heart attack, stroke, kidney problems and death.

hypoglycemia (hy-po-gly-SEE-mee-uh)
a condition that occurs when one's blood glucose is lower than normal, usually less than 70 mg/dL. Signs include hunger, nervousness, shakiness, perspiration, dizziness or light-headedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. Hypoglycemia is treated by consuming a carbohydrate-rich food such as a glucose tablet or juice. It may also be treated with an injection of glucagon if the person is unconscious or unable to swallow. Also called an insulin reaction.

hypoglycemia unawareness (un-uh-WARE-ness)
a state in which a person does not feel or recognize the symptoms of hypoglycemia. People who have frequent episodes of hypoglycemia may no longer experience the warning signs of it.

hypotension (hy-poh-TEN-shun)
low blood pressure or a sudden drop in blood pressure. Hypotension may occur when a person rises quickly from a sitting or reclining position, causing dizziness or fainting.

IDDM (insulin-dependent diabetes mellitus)
former term for Type 1 diabetes.

immune system (ih-MYOON)
the body's system for protecting itself from viruses and bacteria or any "foreign" substances.

immunosuppressant (ih-MYOON-oh-suh-PRESS-unt)
a drug that suppresses the natural immune responses. Immunosuppressants are given to transplant patients to prevent organ rejection or to patients with autoimmune diseases.

impaired fasting glucose (IFG)
a condition in which a blood glucose test, taken after an 8- to 12-hour fast, shows a level of glucose higher than normal but not high enough for a diagnosis of diabetes. IFG, also called pre-diabetes, is a level of 100 mg/dL to 125 mg/dL. Most people with pre-diabetes are at increased risk for developing type 2 diabetes.

impaired glucose tolerance (IGT)
a condition in which blood glucose levels are higher than normal but are not high enough for a diagnosis of diabetes. IGT, also called pre-diabetes, is a level of 140 mg/dL to 199 mg/dL 2 hours after the start of an oral glucose tolerance test. Most people with pre-diabetes are at increased risk for developing type 2 diabetes. Other names for IGT that are no longer used are "borderline," "subclinical," "chemical," or "latent" diabetes.

implantable insulin pump (im-PLAN-tuh-bull)
a small pump placed inside the body to deliver insulin in response to remote-control commands from the user.

impotence (IM-po-tents)
the inability to get or maintain an erection for sexual activity. Also called erectile (ee-REK-tile) dysfunction (dis-FUNK-shun).

incidence (IN-sih-dints)
a measure of how often a disease occurs; the number of new cases of a disease among a certain group of people for a certain period of time.

incontinence (in-KON-tih-nents)
loss of bladder or bowel control; the accidental loss of urine or feces.

inhaled insulin
an experimental treatment for taking insulin using a portable device that allows a person to breathe in insulin.

injection (in-JEK-shun)
inserting liquid medication or nutrients into the body with a syringe. A person with diabetes may use short needles or pinch the skin and inject at an angle to avoid an intramuscular injection of insulin.

injection site rotation
changing the places on the body where insulin is injected. Rotation prevents the formation of lipodystrophies.

injection sites
places on the body where insulin is usually injected.

insulin
a hormone that helps the body use glucose for energy. The beta cells of the pancreas make insulin. When the body cannot make enough insulin, it is taken by injection or through use of an insulin pump.

insulin adjustment
a change in the amount of insulin a person with diabetes takes based on factors such as meal planning, activity and blood glucose levels.

insulin analogues
An insulin analogue is a tailored form of insulin in which certain amino acids in the insulin molecule have been modified. The analogue acts in the same way as the original insulin, but with some beneficial differences for people with diabetes. Analogues are sometimes referred to as "designer" insulins.

insulin pen
a device for injecting insulin that looks like a fountain pen and holds replaceable cartridges of insulin. Also available in disposable form.

insulin pump
an insulin-delivering device about the size of a deck of cards that can be worn on a belt or kept in a pocket. An insulin pump connects to narrow, flexible plastic tubing that ends with a needle inserted just under the skin. Users set the pump to give a steady trickle or basal amount of insulin continuously throughout the day. Pumps release bolus doses of insulin (several units at a time) at meals and at times when blood glucose is too high, based on programming done by the user.

insulin reaction
when the level of glucose in the blood is too low (at or below 70 mg/dL). Also known as hypoglycemia.

insulin receptors
areas on the outer part of a cell that allow the cell to bind with insulin in the blood. When the cell and insulin bind, the cell can take glucose from the blood and use it for energy.

insulin resistance
the body's inability to respond to and use the insulin it produces. Insulin resistance may be linked to obesity, hypertension, and high levels of fat in the blood.

insulin-dependent diabetes mellitus (IDDM)
former term for Type 1 diabetes.

insulinoma (IN-suh-lih-NOH-mah)
a tumor of the beta cells in the pancreas. An insulinoma may cause the body to make extra insulin, leading to hypoglycemia.

intensive therapy
a treatment for diabetes in which blood glucose is kept as close to normal as possible through frequent injections or use of an insulin pump; meal planning; adjustment of medicines; and exercise based on blood glucose test results and frequent contact with a person's health care team.

intermediate-acting insulin
a type of insulin that starts to lower blood glucose within 1 to 2 hours after injection and has its strongest effect 6 to 12 hours after injection, depending on the type used. See lente insulin and NPH insulin.

intermittent claudication (IN-ter-MIT-ent CLAW-dih-KAY-shun)
pain that comes and goes in the muscles of the leg. This pain results from a lack of blood supply to the legs and usually happens when walking or exercising.

intramuscular injection (in-trah-MUS-kyoo-lar)
inserting liquid medication into a muscle with a syringe. Glucagon may be given by subcutaneous or intramuscular injection for hypoglycemia.

islet cell autoantibodies (ICA) (EYE-let aw-toe-AN-ti-bod-eez)
proteins found in the blood of people newly diagnosed with Type 1 diabetes. They are also found in people who may be developing Type 1 diabetes. The presence of ICA indicates that the body's immune system has been damaging beta cells in the pancreas.

islet transplantation
moving the islets from a donor pancreas into a person whose pancreas has stopped producing insulin. Beta cells in the islets make the insulin that the body needs for using blood glucose.

islets
groups of cells located in the pancreas that make hormones that help the body break down and use food. For example, alpha cells make glucagon and beta cells make insulin. Also called islets of Langerhans (LANG-er-hahns).

jet injector (in-JEK-tur)
a device that uses high pressure instead of a needle to propel insulin through the skin and into the body.

juvenile diabetes
former term for insulin-dependent diabetes mellitus (IDDM), or Type 1 diabetes.

ketone
a chemical produced when there is a shortage of insulin in the blood and the body breaks down body fat for energy. High levels of ketones can lead to diabetic ketoacidosis and coma. Sometimes referred to as ketone bodies.

ketonuria (key-toe-NUH-ree-ah)
a condition occurring when ketones are present in the urine, a warning sign of diabetic ketoacidosis.

ketosis (ke-TOE-sis)
a ketone buildup in the body that may lead to diabetic ketoacidosis. Signs of ketosis are nausea, vomiting, and stomach pain.

kidney failure
a chronic condition in which the body retains fluid and harmful wastes build up because the kidneys no longer work properly. A person with kidney failure needs dialysis or a kidney transplant. Also called end-stage renal (REE-nul) disease or ESRD.

kidneys
the two bean-shaped organs that filter wastes from the blood and form urine. The kidneys are located near the middle of the back. They send urine to the bladder.

Kussmaul breathing (KOOS-mall)
the rapid, deep, and labored breathing of people who have diabetic ketoacidosis.

lancet
a spring-loaded device used to prick the skin with a small needle to obtain a drop of blood for blood glucose monitoring.

laser surgery treatment
a type of therapy that uses a strong beam of light to treat a damaged area. The beam of light is called a laser. A laser is sometimes used to seal blood vessels in the eye of a person with diabetes. See photocoagulation.

latent autoimmune diabetes in adults (LADA)
a condition in which Type 1 diabetes develops in adults.

LDL cholesterol, stands for low-density lipoprotein cholesterol (kuh-LESS-tuh-rawl LIP-oh-PRO-teen)
a fat found in the blood that takes cholesterol around the body to where it is needed for cell repair and also deposits it on the inside of artery walls. Sometimes called "bad" cholesterol.

lente insulin (LEN-tay)
an intermediate-acting insulin. On average, lente insulin starts to lower blood glucose levels within 1 to 2 hours after injection. It has its strongest effect 8 to 12 hours after injection but keeps working for 18 to 24 hours after injection. Also called L insulin.

limited joint mobility
a condition in which the joints swell and the skin of the hand becomes thick, tight, and waxy, making the joints less able to move. It may affect the fingers and arms as well as other joints in the body.

lipid (LIP-id)
a term for fat in the body. Lipids can be broken down by the body and used for energy.

lipid profile
a blood test that measures total cholesterol, triglycerides, and HDL cholesterol. LDL cholesterol is then calculated from the results. A lipid profile is one measure of a person's risk of cardiovascular disease.

lipoatrophy (LIP-oh-AT-ruh-fee)
loss of fat under the skin resulting in small dents. Lipoatrophy may be caused by repeated injections of insulin in the same spot.

lipodystrophy (LIP-oh-DIH-struh-fee)
defect in the breaking down or building up of fat below the surface of the skin, resulting in lumps or small dents in the skin surface. (See lipohypertrophy or li-

poatrophy.) Lipodystrophy may be caused by repeated injections of insulin in the same spot.

lipohypertrophy (LIP-oh-hy-PER-truh-fee)
buildup of fat below the surface of the skin, causing lumps. Lipohypertrophy may be caused by repeated injections of insulin in the same spot.

lispro insulin (LYZ-proh)
a rapid-acting insulin. On average, lispro insulin starts to lower blood glucose within 5 minutes after injection. It has its strongest effect 30 minutes to 1 hour after injection but keeps working for 3 hours after injection.

liver
an organ in the body that changes food into energy, removes alcohol and poisons from the blood, and makes bile, a substance that breaks down fats and helps rid the body of wastes.

long-acting insulin
a type of insulin that starts to lower blood glucose within 4 to 6 hours after injection and has its strongest effect 10 to 18 hours after injection. See ultralente insulin.

macrosomia (mack-roh-SOH-mee-ah)
abnormally large; in diabetes, refers to abnormally large babies that may be born to women with diabetes.

macrovascular disease (mack-roh-VASK-yoo-ler)
disease of the large blood vessels, such as those found in the heart. Lipids and blood clots build up in the large blood vessels and can cause atherosclerosis, coronary heart disease, stroke, and peripheral vascular disease.

macula (MACK-yoo-la)
the part of the retina in the eye used for reading and seeing fine detail.

macular edema (MACK-yoo-lur eh-DEE-mah)
swelling of the macula.

mastopathy, diabetic
a rare fibrous breast condition occurring in women, and sometimes men, with long-standing diabetes. The lumps are not malignant and can be surgically removed, although they often recur.

maturity-onset diabetes of the young (MODY)
a kind of Type 2 diabetes that accounts for 1 to 5 percent of people with diabetes. Of the six forms identified, each is caused by a defect in a single gene.

meglitinide (meh-GLIH-tin-ide)
a class of oral medicine for Type 2 diabetes that lowers blood glucose by helping the pancreas make more insulin right after meals. (Generic name: repaglinide)

metabolic syndrome
the tendency of several conditions to occur together, including obesity, insulin resistance, diabetes or pre-diabetes, hypertension, and high lipids.

metabolism
the term for the way cells chemically change food so that it can be used to store or use energy and make the proteins, fats, and sugars needed by the body.

metformin (met-FOR-min)
an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by reducing the amount of glucose produced by the liver and helping the body respond better to the insulin made in the pancreas. Belongs to the class of medicines called biguanides. (Brand names: Glucophage, Glucophage XR; an ingredient in Glucovance)

mg/dL
milligrams (MILL-ih-grams) per deciliter (DESS-ih-lee-tur), a unit of measure that shows the concentration of a substance in a specific amount of fluid. In the United States, blood glucose test results are reported as mg/dL. Medical journals and other countries use millimoles per liter (mmol/L). To convert to mg/dL from mmol/L, multiply mmol/L by 18. Example: 10 mmol/L x 18 = 180 mg/dL.

microalbumin (MY-kro-al-BYOO-min)
small amounts of the protein called albumin in the urine detectable with a special lab test.

microalbuminuria (MY-kro-al-BYOO-min-your-EE-ah)
the presence of small amounts of albumin, a protein, in the urine. Microalbuminuria is an early sign of kidney damage, or nephropathy, a common and serious complication of diabetes. The ADA recommends that people diagnosed with type 2 diabetes be tested for microalbuminuria at the time they are diagnosed and every year thereafter; people with type 1 diabetes should be tested 5 years after diagnosis and every year thereafter. Microalbuminuria is usally managed by improving blood glucose control, reducing blood pressure, and modifying the diet.

microaneurysm (MY-kro-AN-yeh-rizm)
a small swelling that forms on the side of tiny blood vessels. These small swellings may break and allow blood to leak into nearby tissue. People with diabetes may get microaneurysms in the retina of the eye.

microvascular disease (MY-kro-VASK-yoo-ler)
disease of the smallest blood vessels, such as those found in the eyes, nerves, and kidneys. The walls of the vessels become abnormally thick but weak. Then they bleed, leak protein, and slow the flow of blood to the cells.

miglitol (MIG-lih-tall)
an oral medicine used to treat Type 2 diabetes. It blocks the enzymes that digest starches in food. The result is a slower and lower rise in blood glucose throughout the day, especially right after meals. Belongs to the class of medicines called alpha-glucosidase inhibitors. (Brand name: Glyset)

mixed dose

a combination of two types of insulin in one injection. Usually a rapid- or short-acting insulin is combined with a longer acting insulin (such as NPH insulin) to provide both short-term and long-term control of blood glucose levels.

mmol/L

millimoles per liter, a unit of measure that shows the concentration of a substance in a specific amount of fluid. In most of the world, except for the United States, blood glucose test results are reported as mmol/L. In the United States, milligrams per deciliter (mg/dL) is used. To convert to mmol/L from mg/dL, divide mg/dL by 18. Example: 180 mg/dL ч 18 = 10 mmol/L.

monofilament

a short piece of nylon, like a hairbrush bristle, mounted on a wand. To check sensitivity of the nerves in the foot, the doctor touches the filament to the bottom of the foot.

mononeuropathy (MAH-noh-ne-ROP-uh-thee)

neuropathy affecting a single nerve.

myocardial infarction (my-oh-KAR-dee-ul in-FARK-shun)

an interruption in the blood supply to the heart because of narrowed or blocked blood vessels. Also called a heart attack.

nateglinide (neh-TEH-glin-ide)

an oral medicine used to treat Type 2 diabetes. It lowers blood glucose levels by helping the pancreas make more insulin right after meals. Belongs to the class of medicines called D-phenylalanine derivatives. (Brand name: Starlix)

necrobiosis lipoidica diabeticorum (NEK-roh-by-OH-sis lih-POY-dik-ah DY-uh-bet-ih-KOR-um)

a skin condition usually on the lower part of the legs. Lesions can be small or extend over a large area. They are usually raised, yellow, and waxy in appearance and often have a purple border.

neovascularization (NEE-oh-VASK-yoo-ler-ih-ZAY-shun)

the growth of new, small blood vessels. In the retina, this may lead to loss of vision or blindness.

nephrologist (neh-FRAH-luh-jist)

a doctor who treats people who have kidney problems.

nephropathy (neh-FROP-uh-thee)

disease of the kidneys. Hyperglycemia and hypertension can damage the kidneys' glomeruli. When the kidneys are damaged, protein leaks out of the kidneys into the urine. Damaged kidneys can no longer remove waste and extra fluids from the bloodstream.

nerve conduction studies

tests used to measure for nerve damage; one way to diagnose neuropathy.

neurologist (ne-RAH-luh-jist)

a doctor who specializes in problems of the nervous system, such as neuropathy.

neuropathy (ne-ROP-uh-thee)
disease of the nervous system. The three major forms in people with diabetes are peripheral neuropathy, autonomic neuropathy, and mononeuropathy. The most common form is peripheral neuropathy, which affects mainly the legs and feet.

noninsulin-dependent diabetes mellitus (NIDDM)
former term for Type 2 diabetes.

noninvasive blood glucose monitoring (NON-in-VAY-siv)
measuring blood glucose without pricking the finger to obtain a blood sample.

NPH insulin
an intermediate-acting insulin; NPH stands for neutral protamine Hagedorn. On average, NPH insulin starts to lower blood glucose within 1 to 2 hours after injection. It has its strongest effect 6 to 10 hours after injection but keeps working about 10 hours after injection. Also called N insulin.

nutritionist (noo-TRIH-shuh-nist)
a person with training in nutrition; may or may not have specialized training and qualifications. See dietitian.

obesity
a condition in which a greater than normal amount of fat is in the body; more severe than overweight; having a body mass index of 30 or more.

obstetrician (ob-steh-TRIH-shun)
a doctor who treats pregnant women and delivers babies.

ophthalmologist (AHF-thal-MAH-luh-jist)
a medical doctor who diagnoses and treats all eye diseases and eye disorders. Opthalmologists can also prescribe glasses and contact lenses.

optician (ahp-TI-shun)
a health care professional who dispenses glasses and lenses. An optician also makes and fits contact lenses.

optometrist (ahp-TAH-meh-trist)
a primary eye care provider who prescribes glasses and contact lenses. Optometrists can diagnose and treat certain eye conditions and diseases.

oral glucose tolerance test (OGTT)
a test to diagnose pre-diabetes and diabetes. The oral glucose tolerance test is given by a health care professional after an overnight fast. A blood sample is taken, then the patient drinks a high-glucose beverage. Blood samples are taken at intervals for 2 to 3 hours. Test results are compared with a standard and show how the body uses glucose over time.

oral hypoglycemic agents (hy-po-gly-SEE-mik)
medicines taken by mouth by people with Type 2 diabetes to keep blood glucose levels as close to normal as possible. Classes of oral hypoglycemic agents are alpha-glucosidase inhibitors, biguanides, D-phenylalanine derivatives, meglitinides, sulfonylureas, and thiazolidinediones.

overweight
an above-normal body weight; having a body mass index of 25 to 29.9.

pancreas (PAN-kree-us)
an organ that makes insulin and enzymes for digestion. The pancreas is located behind the lower part of the stomach and is about the size of a hand.

pancreas transplantation
a surgical procedure to take a healthy whole or partial pancreas from a donor and place it into a person with diabetes.

Pediatric endocrinologist (pee-dee-AT-rik en-doh-krih-NAH-luh-jist)
a doctor who treats children who have endocrine gland problems such as diabetes.

pedorthist (ped-OR-thist)
a health care professional who specializes in fitting shoes for people with disabilities or deformities. A pedorthist can custom-make shoes or orthotics (special inserts for shoes).

periodontal disease (PER-ee-oh-DON-tul)
disease of the gums.

periodontist (PER-ee-oh-DON-tist)
a dentist who specializes in treating people who have gum diseases.

peripheral neuropathy (puh-RIF-uh-rul ne-ROP-uh-thee)
nerve damage that affects the feet, legs, or hands. Peripheral neuropathy causes pain, numbness, or a tingling feeling.

peripheral vascular disease (PVD) (puh-RIF-uh-rul VAS-kyoo-ler)
a disease of the large blood vessels of the arms, legs, and feet. PVD may occur when major blood vessels in these areas are blocked and do not receive enough blood. The signs of PVD are aching pains and slow-healing foot sores.

pharmacist (FAR-mah-sist)
a health care professional who prepares and distributes medicine to people. Pharmacists also give information on medicines.

photocoagulation (FOH-toh-koh-ag-yoo-LAY-shun)
a treatment for diabetic retinopathy. A strong beam of light (laser) is used to seal off bleeding blood vessels in the eye and to burn away extra blood vessels that should not have grown there.

pioglitazone (py-oh-GLIT-uh-zone)
an oral medicine used to treat Type 2 diabetes. It helps insulin take glucose from the blood into the cells for energy by making cells more sensitive to insulin. Belongs to the class of medicines called thiazolidinediones. (Brand name: Actos)

podiatrist (puh-DY-uh-trist)
a doctor who treats people who have foot problems. Podiatrists also help people keep their feet healthy by providing regular foot examinations and treatment.

podiatry (puh-DY-uh-tree)
the care and treatment of feet.

point system

a meal planning system that uses points to rate the caloric content of foods.

polydipsia (pah-lee-DIP-see-uh)
excessive thirst; may be a sign of diabetes.

polyphagia (pah-lee-FAY-jee-ah)
excessive hunger; may be a sign of diabetes.

polyuria (pah-lee-YOOR-ee-ah)
excessive urination; may be a sign of diabetes.

postprandial blood glucose (post-PRAN-dee-ul)
the blood glucose level taken 1 to 2 hours after eating.

pre-diabetes
a condition in which blood glucose levels are higher than normal but are not high enough for a diagnosis of diabetes. People with pre-diabetes are at increased risk for developing Type 2 diabetes and for heart disease and stroke. Other names for pre-diabetes are impaired glucose tolerance and impaired fasting glucose.

premixed insulin
a commercially produced combination of two different types of insulin. See 50/50 insulin and 70/30 insulin.

preprandial blood glucose (pree-PRAN-dee-ul
the blood glucose level taken before eating.

prevalence
the number of people in a given group or population who are reported to have a disease.

proinsulin (proh-IN-suh-lin)
the substance made first in the pancreas and then broken into several pieces to become insulin.

proliferative retinopathy (pro-LIH-fur-ah-tiv REH-tih-NOP-uh-thee)
a condition in which fragile new blood vessels grow along the retina and in the vitreous humor of the eye.

prosthesis (prahs-THEE-sis)
a man-made substitute for a missing body part such as an arm or a leg.

protein (PRO-teen)
1. One of the three main nutrients in food. Foods that provide protein include meat, poultry, fish, cheese, milk, dairy products, eggs, and dried beans. 2. Proteins are also used in the body for cell structure, hormones such as insulin, and other functions.

proteinuria (PRO-tee-NOOR-ee-uh)
the presence of protein in the urine, indicating that the kidneys are not working properly.

rapid-acting insulin
a type of insulin that starts to lower blood glucose within 5 to 10 minutes after injection and has its strongest effect 30 minutes to 3 hours after injection, depending on the type used. See aspart insulin and lispro insulin.

rebound hyperglycemia (HY-per-gly-SEE-mee-ah)
a swing to a high level of glucose in the blood after a low level. See Somogyi effect.

Recognized Diabetes Education Programs
diabetes self-management education programs that are approved by the American Diabetes Association.

regular insulin
short-acting insulin. On average, regular insulin starts to lower blood glucose within 30 minutes after injection. It has its strongest effect 2 to 5 hours after injection but keeps working 5 to 8 hours after injection. Also called R insulin.

renal (REE-nal)
having to do with the kidneys. A renal disease is a disease of the kidneys. Renal failure means the kidneys have stopped working.

renal threshold of glucose (THRESH-hold)
the blood glucose concentration at which the kidneys start to excrete glucose into the urine.

repaglinide (reh-PAG-lih-nide)
an oral medicine used to treat Type 2 diabetes. It lowers blood glucose by helping the pancreas make more insulin right after meals. Belongs to the class of medicines called meglitinides. (Brand name: Prandin)

retina (REH-ti-nuh)
the light-sensitive layer of tissue that lines the back of the eye.

risk factor
anything that raises the chances of a person developing a disease.

rosiglitazone (rose-ee-GLIH-tuh-zone)
an oral medicine used to treat Type 2 diabetes. It helps insulin take glucose from the blood into the cells for energy by making cells more sensitive to insulin. Belongs to the class of medicines called thiazolidinediones. (Brand name: Avandia)

saccharin (SAK-ah-rin)
a sweetener with no calories and no nutritional value.

secondary diabetes
a type of diabetes caused by another disease or certain drugs or chemicals.

self-management
in diabetes, the ongoing process of managing diabetes. Includes meal planning, planned physical activity, blood glucose monitoring, taking diabetes medicines, handling episodes of illness and of low and high blood glucose, managing diabetes when traveling, and more. The person with diabetes designs his or her own self-management treatment plan in consultation with a variety of health care professionals such as doctors, nurses, dietitians, pharmacists, and others.

sharps container
a container for disposal of used needles and syringes; often made of hard plastic so that needles cannot poke through.

short-acting insulin
a type of insulin that starts to lower blood glucose within 30 minutes after injection and has its strongest effect 2 to 5 hours after injection. See regular insulin.

side effects
the unintended action(s) of a drug.

sliding scale
a set of instructions for adjusting insulin on the basis of blood glucose test results, meals, or activity levels.

Somogyi effect, also called rebound hyperglycemia (suh-MOH-jee)
when the blood glucose level swings high following hypoglycemia. The Somogyi effect may follow an untreated hypoglycemic episode during the night and is caused by the release of stress hormones.

sorbitol (SORE-bih-tall)
1. A sugar alcohol (sweetener) with 2.6 calories per gram. 2. A substance produced by the body in people with diabetes that can cause damage to the eyes and nerves.

split mixed dose
division of a prescribed daily dose of insulin into two or more injections given over the course of the day.

starch
another name for carbohydrate, one of the three main nutrients in food.

stroke
condition caused by damage to blood vessels in the brain; may cause loss of ability to speak or to move parts of the body.

subcutaneous injection (sub-kyoo-TAY-nee-us)
putting a fluid into the tissue under the skin with a needle and syringe.

sucralose
a sweetener made from sugar but with no calories and no nutritional value.

sucrose
a two-part sugar made of glucose and fructose. Known as table sugar or white sugar, it is found naturally in sugar cane and in beets.

sugar
1. A class of carbohydrates with a sweet taste, including glucose, fructose and sucrose. 2. A term used to refer to blood glucose.

sugar alcohols
sweeteners that produce a smaller rise in blood glucose than other carbohydrates. Their calorie content is about 2 calories per gram. Includes erythritol, hydrogenated starch hydrolysates, isomalt, lactitol, maltitol, mannitol, sorbitol, and xylitol. Also known as polyols (PAH-lee-alls.)

sugar diabetes
former term for diabetes mellitus.

sulfonylurea (sul-fah-nil-yoo-REE-ah)
a class of oral medicine for Type 2 diabetes that lowers blood glucose by help-

ing the pancreas make more insulin and by helping the body better use the insulin it makes. (Generic names: acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide)

syringe (suh-RINJ)
a device used to inject medications or other liquids into body tissues. The syringe for insulin has a hollow plastic tube with a plunger inside and a needle on the end.

team management
a diabetes treatment approach in which medical care is provided by a team of health care professionals including a doctor, a dietitian, a nurse, a diabetes educator, and others. The team acts as advisers to the person with diabetes.

thiazolidinedione (THIGH-uh-ZOH-lih-deen-DYE-own)
a class of oral medicine for Type 2 diabetes that helps insulin take glucose from the blood into the cells for energy by making cells more sensitive to insulin. (Generic names: pioglitazone and rosiglitazone)

triglyceride (try-GLISS-er-ide)
the storage form of fat in the body. High triglyceride levels may occur when diabetes is out of control.

Type 1 diabetes
a condition characterized by high blood glucose levels caused by a total lack of insulin. Occurs when the body's immune system attacks the insulin-producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin. Type 1 diabetes develops most often in young people but can appear in adults.

Type 2 diabetes
a condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can appear in young people.

ulcer (UL-sur)
a deep open sore or break in the skin.

ultralente insulin (UL-truh-LEN-tay)
long-acting insulin. On average, ultralente insulin starts to lower blood glucose within 4 to 6 hours after injection. It has its strongest effect 10 to 18 hours after injection but keeps working 24 to 28 hours after injection. Also called U insulin.

unit of insulin
the basic measure of insulin. U-100 insulin means 100 units of insulin per milliliter (mL) or cubic centimeter (cc) of solution. Most insulin made today in the United States is U-100.

United Kingdom Prospective Diabetes Study (UKPDS)
a study in England, conducted from 1977 to 1997 in people with Type 2 di-

abetes. The study showed that if people lowered their blood glucose, they lowered their risk of eye disease and kidney damage. In addition, those with Type 2 diabetes and hypertension who lowered their blood pressure also reduced their risk of stroke, eye damage, and death from long-term complications.

urea (yoo-REE-uh)
a waste product found in the blood that results from the normal breakdown of protein in the liver. Urea is normally removed from the blood by the kidneys and then excreted in the urine.

uremia (yoo-REE-mee-ah)
the illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion.

urine
the liquid waste product filtered from the blood by the kidneys, stored in the bladder, and expelled from the body by the act of urinating.

urine testing
also called urinalysis; a test of a urine sample to diagnose diseases of the urinary system and other body systems. Urine may also be checked for signs of bleeding. Some tests use a single urine sample. For others, 24-hour collection may be needed. And sometimes a sample is "cultured" to see exactly what type of bacteria grows.

urologist (yoo-RAH-luh-jist)
a doctor who treats people who have urinary tract problems. A urologist also cares for men who have problems with their genital organs, such as impotence.

vascular (VAS-kyoo-ler)
relating to the body's blood vessels.

vein
a blood vessel that carries blood to the heart.

very-long-acting insulin
a type of insulin that starts to lower blood glucose within 1 hour after injection and keeps working evenly for 24 hours after injection.

very-low-density lipoprotein (VLDL) cholesterol
a form of cholesterol in the blood; high levels may be related to cardiovascular disease.

vitrectomy (vih-TREK-tuh-mee)
surgery to restore sight in which the surgeon removes the cloudy vitreous humor in the eye and replaces it with a salt solution.

vitreous humor (VIH-tree-us)
the clear gel that lies behind the eye's lens and in front of the retina.

void
to urinate; to empty the bladder.

wound care

steps taken to ensure that a wound such as a foot ulcer heals correctly. People with diabetes need to take special precautions so wounds do not become infected.

xylitol (ZY-lih-tall)
a carbohydrate-based sweetener found in plants and used as a substitute for sugar; provides calories. Found in some mints and chewing gum.

50/50 insulin
premixed insulin that is 50 percent intermediate-acting (NPH) insulin and 50 percent short-acting (regular) insulin

70/30 insulin
premixed insulin that is 70 percent intermediate-acting (NPH) insulin and 30 percent short-acting (regular) insulin.

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Учебное издание

Янголенко Вера Васильевна

Эндокринология

пособие
(на английском языке для иностранных студентов 4 и 6 курсов лечебного факультета)

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Подписано в печать 3.10.2017 г. Формат бумаги 64 х 84 1/16.

Бумага типографская №2. Гарнитура Times. Усл. печ. л. 12,55

Уч. изд. л. 8,0 Тираж 200 экз. Заказ № 757

Издатель и полиграфическое исполнение

УО «Витебский государственный медицинский университет»

Лицензия ЛИ № 02330/05494444 от 08.04.2009

Отпечатано на ризографе в Витебском государственном медицинском университете

210023, Витебск, Фрунзе, 27.