Gerd Herold and colleagues

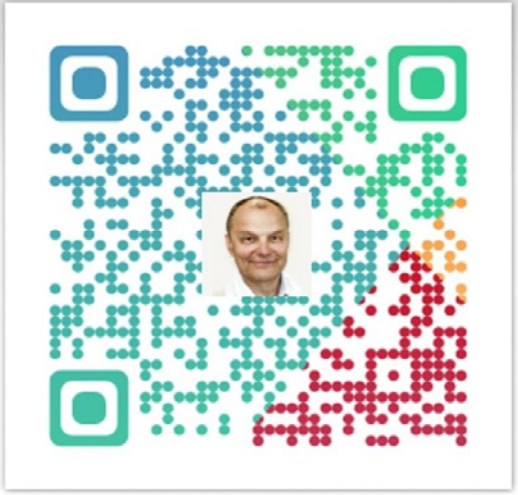
INTERNAL MEDICINE

second edition

Vol. I+II

A lecture oriented systematic and accurate representation of the complete topic catalogue for the medical examination for physicians

Systematically the complete topics of internal medicine · Accentuation of "pitfalls" which are important for exams · Taking account of the most important German and American textbooks · Therefore also recommended for the American ECFMG examination · Tables of biochemistry and haematology reference intervals with SI units · Taking account of "evidence based medicine" · ICD-10 codes within the text and the index



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Be careful about reading health books. You may die of a misprint. (Mark Twain)

Abbreviations

AAA	Abdominal aortic aneurism
AB	Antibodies
ACE	Angiotensin converting enzyme
ACE-I	ACE-Inhibitor
ADB	Anti-Desoxyribonucleotidase B
ADH	Antidiuretic hormone
AET	Aetiology
AF	Atrial fibrillation
AG	Antigen
AIDS	Acquired Immunodeficiency Syndrome
AIHA	Autoimmune haemolytic anaemia
AN	Autonomic neuropathy
ANA	Anti nuclear antibodies
ANCA	Anti neutrophile cytoplasmatic antibodies
ANP	Atrial natriuretic peptide
A.O.	And others
APC	Activated Protein C
APS	Antiphospholipid syndrome
APPROX	Approximately
ARDS	Adult respiratory distress syndrome
ARF	Acute renal failure
ASAP	As soon as possible
ASD	Atrial septum defect
ASL	Antistreptolysin
AT	Antithrombin
AT	Antithrombin
ATP	Adenosine Triphosphate
AXR	Abdominal X-ray
BMI	Body Mass Index
BMT	Bone marrow transplant
BNP	brain natriuretic peptide
BP	Blood pressure
BU	Bread unit
BW	Body weight
C	Celsius
CA	Carcinoma
CA.	Circa
CDC	Centres for disease control
CH	Carbohydrate
CHD	Coronary heart disease
CI	Contraindications
CK	Creatine Kinase
CL	Clinical picture
CMV	Cytomegalovirus
CNP	Type C natriuretic peptide
CNS	Central Nervous System
CO	Complications
CON	Contagiousness
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CRF	Chronic renal failure
CRP	C-reactive protein
CSE	Cholesterol Synthesis Enzyme
CSF	Cerebrospinal Fluid
CT	Computer tomography
CU	Carbohydrate unit
CVI	Chronic venous insufficiency
CVP	Central venous pressure
CXR	Chest X-ray
DD	Differential diagnosis
DEF	Definition
DHD	Dengue haemorrhagic fever
DHS	Dengue haemorrhagic shock
DI	Diagnosis
DIC	Disseminated intravascular coagulation
DNA	Deoxyribonucleic acid
DSA	Digital subtraction angiography
DVT	Deep vein thrombosis
EBV	Epstein Barr Virus
ECF	Extracellular fluid
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Effects
EHEC	Enterohaemorrhagic E. coli
ELISA	Enzyme linked immunosorbent assay
EN	Enteral nutrition
ENT	Ear Nose & Throat
EP	Epidemiology
ESP	Especially
ESR	Erythrocyte Sedimentation Rate
ET	Aetiology
EU	European Union
F	Female
FFP	Fresh Frozen Plasma
FH	Family History
FUO	Fever of unknown origin
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GI	Gastrointestinal
GN	Glomerulonephritis
HBV	Hepatitis B Virus
HCT	Haematocrit
HI	Histology
HIT	Heparin induced thrombocytopenia
HIV	Human Immunodeficiency Virus
HLT	Half life time
HOCM	Hypertrophic obstructive cardiomyopathy
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
HUS	Haemolytic uraemic syndrome
HX	History
IA	Interaction
IBS	Irritable bowel syndrome
ICA	Internal carotid artery
ICD	Implantable Cardioverter - Defibrillator
ICF	Intracellular fluid
ICP	Intracranial pressure
ICU	Intensive care unit
IFAT	Indirect immunofluorescence antigen test
IG	Immunoglobulin
IHA	Indirect Haemagglutinin test
I.M.	Intramuscular
INC	Incidence
IND	Indication
INR	International normalised ratio
ISF	Interstitial fluid
ITP	Idiopathic thrombocytopenia
IU	International units
I.V.	Intravenous
IVF	Intravascular fluid
LAB	Laboratory tests
LAS	Lymphadenopathy syndrome
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LDV	Lymphocyte doubling time
LMWH	Low molecular weight Heparin
LOC	Localization
M	Male
MDS	Myelodysplastic syndrome
MI	Mentzer index
MI	Myocardiac infarction
MIO	Million
MM	Multiple myeloma
MOA	Mode of action
MRI	Magnet resonance imaging
MW	Molecular weight
NK (cells)	Natural killer (cells)
NSAID	Non steroidal anti-inflammatory drug
OAC	Oral anticoagulation
OAD	Occlusive atherosclerotic disease
OCC	Occasionally
OCC	Occurrence
OD	Overdose
PA	Pulmonary artery
PAT	Pathogen
PAT	Pathology
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PEP	Post exposure prophylaxis
PET	Positron emission tomography
PFO	Persistent foramen ovale
PG	Pathogenesis
PI	Protease inhibitor
PID	Pelvic inflammatory disease
PM	Pacemaker
PMC	Pseudomembranous Enterocolitis
PN	Parenteral nutrition
PNH	Paroxysmal nocturnal haemoglobinuria
P.O.	Per os
POSS	Possibly
PPC	Phenprocoumon
PPH	Pathophysiology

PPSB	Prothrombin proconvertin Stuart-Prower factor antihaemophilic factor B
PRG	Prognosis
PRO	Prophylaxis
PTCA	Percutaneous transluminal coronary angioplasty
PTH	Parathyroid hormone
PTS	Post Thrombotic Syndrome
PTT	Prothrombin time
RA	Rheumatoid arthritis
RBBB	Right Bundle Branch Block
RES	Reticular Endothelial Syncythium
RF	Rheumatoid factor
RNA	Ribonucleic acid
RS	Raynaud's Syndrome
RV	right ventricular
S.C.	Subcutaneous
SE	Side effects
SIADH	Syndrome of inadequate ADH secretion
SK	Streptokinase
S.L.	sublingual
SLE	Systemic lupus erythematosus
SOB	Shortness of breath
SPECT	Single Photon Emission Computed Tomography
SR	Slow release
SR	Sinus rhythm
ST	Stage
STD	Sexually transmitted disease
SU	Sulfonyl urea
SVT	Supraventricular tachycardia
SYM	Symptoms
SYN	Synonym
TAA	Thoracic aortic aneurism
TCA	Tricyclic antidepressants
TEA	Thrombendarteriectomy
TEE	Transoesophageal echocardiography
TH	Therapy
THR	Total hip replacement
TIA	Transitory ischaemic attack
TOA	Thrombangiitis obliterans
TOS	Thoracic Outlet Syndrome
TPHA	Treponema Pallidum Haemagglutinin
TPN	Total parenteral nutrition
TSH	Thyroid stimulation hormone
TURP	Transurethral resection of the prostate
UFH	Unfractioned Heparin
URTI	Upper Respiratory Tract Infection
US	Ultrasound
UTI	Urinary tract infection
UV	Ultraviolet
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VUR	Vesico-ureteric-renal reflux
VV	Varicose veins
VZV	Varicella Zoster Virus
WHO	World health organization
Y	

Find more medical abbreviations at *www.medizinische-abkuerzungen.de*

Find more general abbreviations at *www.acronymdb.com*
www.chemie.fu-berlin.de/cgi-bin/acronym

VI. E N D O C R I N O L O G Y

Internet infos: *www.dgae-info.de; www.endokrinologie.net; www.diabetes.cme.de www.aace.com; www.endosociety.org*

DIABETES MELLITUS ("sweetened with honey") [E14.9]

Internet infos: *www.diabetes-deutschland.de; www.diabetes-webring.de; www.diabetes-world.net; www.diabetes.ca; www.deutsche-diabetes-gesellschaft.de; www.diabetes.org*

Def.: Diabetes mellitus is a group of heterogenic diseases characterized by chronic hyperglycaemia, which is caused by a defect either in the insulin secretion, the insulin effects or by a combination of those two.

Ep.: Prevalence of manifest diabetes is age dependent: Age < 50 y. 1 - 2 %, age > 60 y. circa 10 %, age > 70 y. up to 20 %. > 90 % are type 2 diabetics and circa 5 % are type 1 diabetics. In the USA 4 % of the obese juveniles are type 2 diabetics! The number of type 2 diabetics in a population increases with the extent of overnutrition.

Aetiologic classification : (WHO and ADA = American Diabetes Association, 1997)

I. Type 1 diabetes: β cell destruction, which leads to absolute insulin deficiency
   A) Immune mediated
      Special form: LADA (latent autoimmune diabetes (with onset) in adults): Type 1 diabetes with manifestation in adult age (> 25 y.), in which insulin deficiency develops rel. slowly. In the first 6 months no insulin requirement, detection of GAD-antibodies.
   B) Idiopathic (infrequent in Europe)

II. Type 2 diabetes: 3 causes of various degrees: An Insulin resistance, a secretory defect of the β-cells or a progressing apoptosis of the β-cells.

III. Other specific types:

   A) Genetic defects of β cell function (autosomal dominant pathway):
      „Maturity-onset Diabetes of the Young (MODY) without auto-Ab detection and without adiposity: Manifestation is before 25 years of age; circa 1 % of all diabetics:

MODY type	Gene	Abbreviation	Chromo-some	PPh	Notes
MODY 1	Hepatocyte nuclear factor 4 alpha	HNF-4alpha	20q	Reduced insulin secretion, decreased glycogen synthesis	Low triglycerides
MODY 2 (15 %)	Glucokinase	GK	7p	Reduced insulin secretion	Mild course, mostly without late complications
MODY 3 (65 %)	Hepatocyte nuclear factor 1 alpha	HNF-1 alpha	12q	Reduced insulin secretion	Renal glycosuria
MODY 4	Insulin promotor factor-1	IPF-1	13q	Reduced insulin secretion, defective receptor for sulfonylureas	
	Pancreatic duodenum homebox-1	PDX-1			
MODY 5	Hepatocyte nuclear factor 1 beta	HNF-1beta	17q	Reduced insulin secretion	Renal cysts, malformations of genitalia
MODY 6	Neuro D1 or BETA2	Neuro D1	2q	Abnormal trans-scription regulation of the Beta cells	

B) Genetic defects in insulin action

C) Diseases of the exocrine pancreas (chronic pancreatitis)

D) Endocrinopathies: Acromegaly, Cushing´s syndrome, phaeochromocytoma, hyperthyroidism, somatostatinoma, glucagonoma, aldosteronoma

E) Drug induced, e.g. glucocorticoids, thyroid hormones, beta-adrenergic agonists, thiazides, oral contraceptives

F) Infections, e.g. congenital rubella, CMV

G) Uncommon forms of immune-mediated diabetes, e.g. anti-insulin receptor antibodies

H) Genetic syndromes, which are sometimes associated with diabetes, e.g. Down´s syndrome, Klinefelter´s syndrome, Turner´s syndrome etc.

IV. Gestational diabetes (GDM)

Classification according to the clinical severity (WHO, 2000):

- IGT: Impaired glucose tolerance
- NIR: Noninsulin requiring (type 2 diabetics)
- IRC: Insulin required for control (type 2 diabetics, who need oral antidiabetic agents + insulin)
- IRS: Insulin required for survival (type 1 diabetics and type 2 diabetics without own insulin production)

Aet.: ■ **Type 1 diabetes** (< 10 %):

Destruction of beta cells in the islets of Langerhans caused by autoimmune insulitis with absolute insulin deficiency. Blood glucose levels increase, when circa 80 % of all beta cells are destroyed. Genetic factors play a predisposing role: 20 % of type 1 diabetics have a positive family Hx (for type 1 diabetes) and HLA types DR 3 and/or DR 4 are present in > 90 % of patients. The following findings point to an autoimmune insulitis in the case of a newly diagnosed type 1 diabetic:

■ Detection of autoantibodies:

- cytoplasmic islet cell Ab (ICA): antigen: gangliosides
- anti-GAD-Ab (GADA): antigen: glutamic acid decarboxylase
- anti-IA-2-Ab: antigen: tyrosine phosphatase 2
- insulin auto-Ab (IAA): antigen: (pro)insulin
- anti-ZnT8 (antigen: zinc-transporter 8)

Detection of the ICA by immune fluorescence very costly, therefore most commonly replaced by anti-GAD-Ab and anti-IA-2-Ab.

Detection of ICA in type 1 diabetes 80 %, GADA and IA-2A together > 90 %, IAA age dependent 20 – 90 % (diagnostically not relevant)

■ Temporary remissions with immunosuppressive therapy

■ Histology: Infiltration of the islets of Langerhans by autoreactive T lymphocytes

If GADA and IA-2-Ab are present in a healthy individual, the risk to develop diabetes type 1 within the next 5 years lies around 20 %.

■ **Type 2 diabetes** (> 90 %):

Pathogenetic 2 defects play a role:

■ Impaired insulin secretion

In type 2 diabetics the early postprandial insulin secretion is defective; this leads to postprandial hyperglycaemia.

■ Apoptosis of islet cells

An apoptosis of more than 50% of the islet cells leads to hyperglycaemia.

■ Decreased insulin action (insulin resistance)

Cause: Pre-receptor defect, receptor defect with down regulation, post-receptor defect = impairment of the signal transduction, e.g. of the tyrosine kinases

Note: Healthy individuals express only one iso form of the Human-Insulin-Receptor on the cell membrane: HIR-A. Type 2 diabetics express both iso forms: HIR-A and HIR-B.

■ Reduced incretin secretion (→ see GLP-1-based therapy)

Remember: The majority of diseas develops because of a metabolic syndrome (= prosperity syndrome): Frequent concurrence of the 4 risk factors: Obesity with emphasis on the trunk (visceral), dyslipoproteinaemia (triglycerides ↑, HDL cholesterol ↓), essential hypertension and impaired glucose tolerance or type 2 diabetes mellitus. At the onset of the metabolic syndrome an insulin resistance of the insulin dependent tissues (e.g. skeletal muscle cells) is found, so that increased insulin levels are required for the cellular utilization of glucose. The hyperinsulinaemia increases the feeling of hunger, leads to obesity, and favours the development of early arteriosclerosis.

Definition of the metabolic syndrome (IDF, 2005):

- Abdominal obesity with a waist circumference ≥ 94 cm (m) or ≥ 80 cm (f) in Caucasians (different values apply for other ethnic groups)
- Plus two of the following factors:
  - Triglycerides > 150 mg/dl (1,7 mmol/l)*)
  - HDL cholesterol < 50 mg/dl (1,29 mmol/l)*) f
    < 40 mg/dl (1,04 mmol/l)*) m
  - Blood pressure > 130/85 mm Hg*)
  - Fasting plasma glucose > 100 mg/dl (5,6 mmol/l) or type 2 diabetic

*) or previous therapy of one of these impairments

Note: There are definitions of the metabolic syndrome, that differ from this (WHO, NCEP-ATP III).

Remember: Overnutrition combined with obesity and lack of physical activity are the determining factors for the manifestation of type 2 diabetes mellitus! Circa 80 % of type 2 diabetics are overweight.
High insulin levels reduce the sensitivity and density of insulin receptors (= down regulation) and thus the effect of insulin. This results in a further increase of insulin levels (vicious circle). Therapeutic principle is the elimination of overeating and obesity ➔ resulting in a reduction of insulin levels again, and restoration of the sensitivity and density of insulin receptors!

Note: 35% of patients with metabolic syndrome have a sleep apnea syndrome

Other manifestations of type 2 diabetes:
- Stress factors: Infections, trauma, operations, stroke, myocardial infarction etc.
- Endocrinopathies and drugs are considered separately in the diabetes classification.

	Type 1 diabetes	**Type 2 diabetes**
Pathogenesis	insulin deficiency	insulin resistance
Anatomy	asthenic	mostly pyknic/obese
Onset	often rapidly	slowly
Predominant age of manifestation	12. - 24th year	> 40th year
B cells	reduced to < 10 %	reduced only moderately
Plasma insulin / C peptide	low or lacking	initially increased
Autoantibodies (IAA, GADA, IA-2A)	+	–
Metabolic status	unstable	stable
Ketosis tendency	strong	low
Response to sulfonyl ureas	lacking	good
Insulin therapy	necessary	only when insulin reserve is exhausted

- **Gestational diabetes (GDM):** [O24.4]

  Def.: Impairment of carbohydrate metabolism recognized for the first time during pregnancy. In most cases disappears after completion of pregnancy, but an increased risk of 50 % for further GDM exists for a subsequent pregnancy. The risk of developing permanent diabetes mellitus is at the moment >50 %/10 years.

  Occ: Approx. 3 % of all pregnancies!

  Co.: 1. For the mother: Increased risk of preclampsia, infections of the urinary tract, polyhydramnios and caesarian section.
  2. For the child: Diabetes is the most common cause of increased intrauterine death and perinatal morbidity of the child: Embryofoetopathy diabetica with increased birthweight > 4.500 g and macrosomia; increased risk of respiratory distress syndrome, postpartal hypoglycaemia, hyperbilirubinaemia, hypocalcaemia, hyperglobulia etc.

Genetics:

Polygenic-multifactorial inheritance; variable penetrance of the diabetogenic genes.
Genetic mutations in type 2 diabetes: ATP-sensitive potassium channel; protein PC-1; PTPN1; GNB3-825T; TCF7L2; SLC30A8 etc.

Inheritance:

- Type 1 diabetes:
  The risk of the child developing type 1 diabetes is approx. 5% if father is affected, 2.5% if mother is affected, 20 % if both affected.
  The disease risk for siblings of a type 1 diabetic is high in identical twins (circa 35 %) and depends, in the remaining cases, on the extent of the HLA identity: HLA identical siblings have a risk of circa 18 %, HLA haplotype identical siblings have a risk of circa 6 %; siblings differing in their HLA types have little risk of developing type 1 diabetes.
- Type 2 diabetes:
  For children with one type 2 diabetic parent the probabiltiy developing type 2 diabetes is up to 50 %. In case of a maternal diabetes the risk is doubled compared to a paternal diabetes. The risk for identical twins is 100 %.

Cl.: Manifestation of diabetes mellitus:

While the development of manifest type 1 diabetes is relatively rapid, type 2 diabetes manifests slowly and often unnoticed, so that diagnosis is often only made on routine examination of blood or urine or during the manifestation of a resulting illness.

- Nonspecific general symptoms:
  Tiredness, lack of energy etc.
- Symptoms due to hyperglycaemia and glycosuria with osmotic diuresis: Polyuria, thirst, polydipsia, weight loss
- Symptoms due to impairment of electrolytes and fluid balance: Nocturnal cramps of the calf muscles, visual disturbances (changing turgor of the crystalline lense)
- Skin appearances:
  - Pruritus (often anogenital localization)
  - Bacterial / fungal skin infections (e.g. furunculosis!, candidiasis!)
  - Rubeosis diabetica (diabetic facial blush)
  - Necrobiosis lipoidica (mostly on both lower legs, brownish red areas, ulcerations possible)
- Impotence, amenorrhoea

Co.: 1. Macro-/microangiopathy:

Diabetic vessel damage is subdivided into non-specific macroangiopathy and a diabetes-specific microangiopathy with thickening of capillary basement membranes. The nonenzymatic glycosylation of proteins in the basement membrane caused by hyperglycaemia seems to play a role in the formation of the microangiopathy. The thickness of the basement membrane correlates with the duration of the diabetes.

1.1. Macroangiopathy with early arteriosclerosis:

- Coronary heart disease: Stenosing arteriosclerosis of the large epicardial coronary arteries: 55 % of diabetics die of myocardial infarction!
  Specific features of CHD in diabetes:
  - Diffuse distribution pattern of CHD with predominant involvement of the distal coronary arteries and of the main trunk
  - Impaired angina perception threshold caused by ADN (see below) with poss. painless infarctions and silent ischaemia
  - Infavourable prognosis
- Peripheral arterial occlusive disease
- Arterial occlusive disease of cerebral arteries and ischaemic cerebral infarction

Remember: Diabetics who also suffer from hypertension have a 20 – 30 % probability of a cardiovascular event (myocardial infarct, cerebral infarct) within the next 10 years (high risk group. If in addition a diabetic nephropathy develops, the cardiovascular risk increases to > 30 %/10 years!
Pain as a premonitory symptom (angina pectoris, pain on exercise in intermittent claudicatio) is often absent due to concominant neuropathy!
These are as well the reasons why on the one hand approx. 75% of all diabetics die due to cardiovascular complications, and on the other hand approx. 75% of patients with cardiovascular diseases suffer from diabetes mellitus or a defect of the glucose tolerance.

1.2. Microangiopathy:

- Glomerulosclerosis (Kimmelstiel-Wilson disease)
- Retinopathy
- Neuropathy
- Microangiopathy of intramural small coronary arteries (small vessel disease)

1.2.1. Diabetic nephropathy (DN) [E14.2]

Def.:- Persistent (micro-)albuminuria (> 20 mg/l)
- Arterial hypertension
- Initially ecreasing glomerular filtration rate
- Increased cardiovascular risk

Ep.: The average progression to DN is circa 2,5 % per year in type 2 diabetes, therefore after 10 years circa 25 % (similar figures are valid for type 1 diabetes). In patients with an increased serum creatinine the mortality rate is around 20 %/year (mainly due to cardiovascular mortality). In manifest DN 75 % of type 1 diabetics and 20 % of type 2 diabetics develop end-stage renal failure within 20 years. In Europa and USA up to 50 % of all dialysis patients are diabetics → main underlying disease which leads to dialysis!

Pa.: Type 1 diabetes: Glomerulosclerosis (Kimmelstiel-Wilson disease)
Type 2 diabetes: Nonspecific vascular and tubulointerstitial renal changes as a consequence of complex risk factors of the metabolic syndrome.

Pg.: Hyperglycaemia γ activation of growth factors in the kidneys (TGF-β and angiotensin II)

- Renal hypertrophy with increase in size of the glomeruli and thickening of the basal membrane
- Increased glomerular permeability with microalbuminuria
- Glomerulosclerosis, interstitial fibrosis
- Renal failure

Risk factors for accelerated progress of DN:
- Arterial hypertension
- Extent of the albuminuria
- Level of diabetic control (HbA1c)
- Hypercholesterinaemia
- Smoking
- possible high protein intake

Remember: Early symptom is a microalbuminuria of 30 - 300 mg/24 h or 20 - 200 mg/l in a random urine (because the microalbuminuria has a range of variation of up to 40 % laboratory testing should be repeated). The risk of renal and cardiovascular complications rises linearly with increasing albuminuria! Temporary/reversible increases in albumin excretion are seen in urinary infections, febrile illnesses, physical effort, uncontrolled blood pressure or blood sugar etc
Frequency and severity of diabetic nephropathy correlates with the duration of the diabetes and the quality of metabolic control. Early antihypertensive therapy (also of a borderline hypertension!), especially with ACE inhibitors delays the progressiom of diabetic nephropathy to end-stage renal failure, and reduces the cardiovascular + total mortality!

Stages of diabetic nephropathy:

Stage	Albumin excretion (mg/l)	Creatinine clearance (ml/min)	Remarks
1. Renal damage with normal renal function a) Microalbuminuria	20 - 200	> 90	Serum creatinine in the normal range Blood pressure increasing in the normal range or hypertension, dyslipidaemia, rapid progress of coronary heart disease, AVD, retinopathy and neuropathy
b) Macroalbuminuria	> 200		
2. Renal damage with renal failure	> 200	60 - 89	Serum creatinine borderline or increased hypertension, dyslipidaemia, tendency to hypoglycaemia, rapid progression of coronary heart disease, AVD, retinopathy and neuropathy, development of anaemia, impairment of the bone metabolism
a) Low grade		30 - 59	
b) Moderate grade	decreasing	15 - 29	
c) High grade		< 15	
d) Terminal			

1.2.2. Diabetic retinopathy : [E14.3+H36.0*]

Occ.: Type 1 diabetes: 90 % after 15 years
Type 2 diabetes: 25 % after 15 years
30 % of all blindness in Europe is due to diabetes! Diabetes is the most common cause of non-traumatic blindness in adults.

Pg.: Microangiopathy; neovascularisation is triggered by an angiogenic growth factor. Poor diabetic control, hypertension and smoking lead to a faster progression of diabetic retinopathy.

■ Nonproliferative retinopathy (background retinopathy):
- Mild: Only microaneurysms
- Moderate: In addition single intraretinal haemorrhages, venous calibre changes with pearlstring-like veins
- Severe: Microaneurysms and intraretinal haemorrhages in all 4 quadrants or veins with pearlstring appearance in at least 2 quadrants or intraretinal microvascular anomalies (IRMA) in at least 1 quadrant (4-2-1-rule)

■ Proliferative retinopathy:
Neovascularisations in vicinity of the optic papilla = NVD (neovascularization disk) or in other parts of the retina = NVE (neovascularization elsewhere) with or without vitreal or epiretinal haemorrhages.
Co.: Retinal detachment (especially in the case of a too rapid reduction of blood sugar or a wide range of blood sugar readings) and secondary neovascular glaucoma

■ Diabetic maculopathy: a) focal b) diffuse c) ischaemic
Macular oedema, hard exudate, intraretinal haemorrhages; central vision endangered!

1.2.3. Diabetic neuropathy: [E14.4] Dependent on duration of diabetes and quality of metabolic control. After 10 years of disease circa 50 % of patients have a neuropathy.
Pg.: Unclear; possible impairment of the microcirculation of the vasa nervorum + metabolic impairment (e.g. nonenzymatic glycosylation of structural proteins etc)

■ Peripheral sensorimotor polyneuropathy (80 %): More pronounced distally, symmetrical, with reduced sensitivity to stimuli and loss of power, especially feet/lower legs (➞ paraesthesia, "burning feet"), areflexia (achilles reflex missing bilaterally), decreased thermosensitivity and algesthesia, later possibly also motor impairment. Determination of superficial sensitivity using Semmes-Weinstein´s monofilament, which is applied onto defined points at the sole with a pressure of 10 g. Determination of temperature sensation e.g. with a "tip-therm tube".

Early symptom: Decreased vibration sense ➞ measuring with 64 Hz tuning fork (128 Hz) according to Rydel-Seiffer with a graduation scale of 0 - 8. The vibrating tuning fork is applied e.g. onto the the medial malleolus and the patient indicates with eyes closed, how long he or she can feel the vibration. A graduation value of < 5 out of a total of 8 is pathological.

Special diagnostic:

- Pedography (= measuring of the dynamic pressure distribution pattern of the plantar soles while walking): Decreased strain on the toes during increased pressure load of the ball of the forefoot.
- Measuring of nerve conduction velocity: In polyneuropathy ↓
  DD: Polyneuropathies of other origin: alcohol abuse, neurotoxic drugs (nitrofurantoin, barbiturates, cytotoxic drugs etc), chemicals (solvents, heavy metals, insecticides etc), paraneoplastic syndrome, malabsorption syndrome, polyarteritis nodosa etc

■ Rarer manifestations of diabetic neuropathy: e.g.

- Pronounced diabetic polyneuropathy:
  Asymmetric proximal diabetic neuropathy with pains in the hip region and at the ventral thigh, reduction of the ipsilateral patellar reflex, poss. paresis of the quadriceps muscle.
- Peripheral facialis paresis; pareses of the ocular muscles (diplopia)
- Diabetic radiculopathy mainly with unilateral segmental pains and sensoric impairments in a region of the trunk.

■ Autonomic neuropathy (AN): (second most common!)
Def.: Neuropathy of the autonomic nervous system (sympathetic and parasympathetic nervous system)

- Cardiovascular AN:
  Occ.: 15 % of diabetics at time of diagnosis, > 50 % of diabetics after 20 years of disease duration; mortality increased circa 4fold due to ventricular arrhythmias leading to ventricular fibrillation (sudden cardiac death).
  - ■ Silent myocardial ischaemia and painless myocardial infarctions with increased mortality
  - ■ Reduced variability of heart rate with fixed frequency
    a) In an ECG at rest and in a 24 h-ECG
    b) During maximum inspiration and expiration (difference of the heart rate < 9/min)
    c) During a Valsalva manoeuvre
    d) During an orthostatic test
  - ■ Resting tachycardia (vagus damage)
  - ■ Asympathetic postural hypotension (sympathic damage): Reduced systolic/diastolic blood pressure and absent reflex tachycardia when moving to a standing position.
  - ■ Poss. flattened or inverted circadian blood pressure curve with elevated nocturnal blood pressure readings
    Special diagnostic: Detection of a cardial sympathic dysinnervation (predominantly of the posterior cardiac wall) by ^{123}J-MIBG scan.
- AN of the gastrointestinal tract (parasympathetic damage)
  - ■ Impairment of oesophageal motility, poss. with dysphagia (rare)
  - ■ Gastroparesis with epigastric fullness/pressure feeling, poss. postprandial hypoglycaemia
    Di.: Ultrasound (detection of reduced peristaltic and delayed gastric emptying), poss. special diagnostic: C^{13}-octan acid breath test or scan of gastric emptying
  - ■ AN of the intestines with postprandial diarrhoea alternating with constipation
  - ■ Anorectal dysfunction (incontinence)
- AN of the urogenital tract (damage to the parasympathetic system)
  - ■ Atonic bladder and disturbance of micturation poss. with residual urine and predisposition to urinary tract infections
  - ■ Erectile dysfunction and absence of the spontaneous nocturnal tumescence (circa 50 % of all diabetics, depending on patient´s age and length of the disease)
- AN of the neuroendocrine system:
  Reduction/absence of the hormonal contraregulation in hypoglycaemia (decreased perception of hypoglycaemia !)
  Reduced release of catecholamines during orthostatic and physical strain
- AN of thermoregulation:
  Reduced sweating, vasodilatation (warm and dry diabetic foot!)

- AN of the pupils: Decreased pupillary reflexes (special diagnostic by means of pupillometry: slow mydriasis)

1.2.4. Diabetic foot syndrome (DFS, 25 % of older diabetics): [E14.7]

Def.: Syndrome of variable clinical picture with differing aetiologies, which in case of injury to the foot can result in infected ulcers and complications as serious as amputation of the limb. The diabetic foot syndrome is the most common complication of the diabetic patient.

Grades of severity of the foot lesions: Classification according to Wagner (grade 1 - 5 ➞ depth of the lesion) and Armstrong (A - D ➞ pre-disposing factors)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
A	Foot at risk without any lesion	Superficial wound	Wound reaches to tendon or capsule	Wound reaches to bone or joint	Necrosis lilimited to forefoot or heel	Necrosis of the whole foot
B	with infection (most common pathogens: staphylococci, enterococci, pseudomonas aeruginosa; often mixed infections)					
C	with ischaemia					
D	with infection and ischaemia					

■ Neuropathic diabetic foot (50 % of all DFS):
- Warm foot with very dry skin (no foot odour !) and hyperkeratoses
- Impaired sensitivity (sensitivity to vibration and/or touch ↓), reduced or completely vanished sensation of pain and temperature (with danger of unnoticed trauma!)
- Palpable foot pulses
- Doppler index (ankle pressure/arm pressure) normal (impairment through media sclerosis)
- Transcutaneous pO_2 normal
- Impairment of the unrolling-motion of the foot with increased pressure load beneath the head of the metatarsal bones and the big toe
- Co.: Infections; painless neuropathic ulcers (= malum perforans) at pressure points (heel, ball of foot), often triggered by missing or incorrect foot care, incorrect foot wear, (micro-)trauma, limited joint mobility

Diabetic-neuropathic osteoarthropathy (DNOAP)with necroses in the region of the metatarsophalangeal joints, tarsometatarsal joints or other foot joints (Charcot´s foot). Early symptom: Inflamed lymphedema of the foot and osteo-oedema (MRI)

■ Ischaemic foot in peripheral vascular disease (PVD), esp. of the arteries of the lower legs (circa 50 % of all DFS):

- Medical Hx:
  - Diabetes mellitus
  - Arterial hypertension
  - Intermittent claudication
  - Hypercholesterinaemia
  - Smoking
- Clinical signs:
  - Cool, pale foot with poss. livid discolouration
  - No palpable foot pulses
  - Doppler index (RR ankle : RR arm) < 0,9; transcutaneous pO_2 ↓
  - Sensation intact = pain
  - Acral necrosis/gangrene, threat of amputation (Germany: more than 60.000 amputations/y. →2/3 of diabetics)

Di.: Pulse status, ankle-arm pressure index, coloured duplex ultrasonography, MR angiography; consultation with vascular surgeon

• Combined form of neuropathic and ischaemic diabetic foot
(circa 35 % of all DFS)
Claudication and pain at rest can be reduced or absent because of the neuropathy! Prognosis unfavourable!

Remember: As long as a PVD is missing, the foot pulses are well palpable !

2. Diabetic cardiomyopathy

Remember: CHD, arterial hypertension and diabetic cardiomyopathy are the 3 risk factors for the development of heart failure in diabetics. The mortality of diabetics with heart failure is circirca 15 %/year.

3. Reduction of immune resistance with tendency to bacterial skin and urinary tract infections
4. Deficiency of lipid metabolism: Triglycerides ↑, LDL cholesterin ↑, HDL cholesterin ↓
5. Fatty liver

6. Diabetic coma, hypoglycaemic shock
7. Hyporeninaemic hypoaldosteronism with hyperkalaemia, hyponatraemia, hyperchloraemic metabolic acidosis and poss. hypotension (see there for details)

Di.:

- **Medical history** (family history, pregnancy complications etc)
- **Clinical picture:** Fatigue, polyuria, polydipsia
- **Laboratory findings:**
  - **Determination of blood glucose:**
    Specific according to the hexokinase ferment method:
    The largely identical intermediate stages of impaired glucose homeostasis (impaired fasting glucose = IFG) and the pathological glucose tolerance are risk factors for future diabetes mellitus and cardiovascular disease.

Diagnostic reference values for the determination of diabetes mellitus (American Diabetes Association and guidelines of the German Diabetic Association):

Stage	Fasting venous plasma glucose	Random blood sugar	Oral glucose tolerance test (OGTT)
Diabetes	≥ 126 mg/dl (≥ 7,0 mmol/l) *)	≥ 200 mg/dl (≥ 11,1 mmol/l) and symptoms of a diabetes	2 h value ≥ 200 mg/dl (≥ 11,1 mmol/l)
Impaired fasting glucose = IFG	≥ 100 - 125 mg/dl (≥ 5,6 – 6,9 mmol/l)		Pathologic glucose tolerance („impaired glucose tolerance = IGT“) 2 h value ≥ 140 - 199 mg/dl (≥ 7,8 < 11,0 mmol/l)
Normal	< 100 mg/dl (< 5,6 mmol/l)		2 h value < 140 mg/dl (< 7,8 mmol/l)

Note: The glucose concentration in the plasma (with a haematocrit of 43%) are on average around 11% higher, because of the different water concentration in blood and plasma. Therefore the International Federation of Clinical Chemistry proposed to state glucose results only as plasma readings – independent of the type of sample or the method of reading.

Explanations:
Fasting blood sugar (= FBS) is the crucial test for the diagnosis of a diabetes mellitus and for the monitoring of its therapy. It is just as accurate as the OGTT´s 2 hour value in predicting the risk of developing a microangiopathy. It is simple, efficient and cheap. The reading should be verified by a quality controlled repeated value.
Fasting is defined as a period of 8 hours without nutrition.
Random blood sugar = at any time of the day, without relation to meals; symptoms are diabetes associated symptoms such as polyuria, polydipsia and weight loss.
Blood glucose levels measured by instruments using strips can vary up to 15 % from the actual value and should therefore not be used for a diagnosis.

Note:
- Normal blood glucose values at the moment are defined as ≤ 100 mg/dl (≤ 5,6 mmol/l) in the venous plasma.
- The possibility of incorrect low blood sugar levels has to be taken into consideration when measuring serum glucose, because of the in vitro glycolysis (break down circa 10 % per hour!). Serum samplings without addition of glycolysis inhibiting agents (e.g. sodium fluoride) must not be used for glucose testing.

DD: Temporary hyperglycaemia in myocardial infarction, stroke, infections, increased intracranial pressure, acute intoxications (CO), after ingestion of thiazide diuretics etc

- **Determination of glucose in the urine** (in the morning urine, in day portions and in the 24 h urine):
  Repeated findings of glucose in the urine indicate apart from few exceptions (s.b.), the existence of diabetes mellitus. Every diabetic should analyze his or her individual renal threshold (blood glucose level, at which glycosuria appears for the first time).
  The normal renal threshold level for glucose is around 180 mg/dl glucose in the blood (lower in pregnancy around < 150 mg/dl → poss. physiological glycosuria in pregnancy). The physiological glucosuria can be up to 15 mg/dl. The lower detection level of the test strips is circa 30 mg/dl.

Consider: In cases of diabetic nephropathy the renal threshold for glucose can be increased (to up to 300 mg/dl), meaning that in these cases no glycosuria is observed despite hyperglycaemias of e.g. 200 mg/dl. Therefore the absence of glucose in the urine does not exclude a manifest diabetes (early diagnosis of diabetes with FBS)! Therefore the self monitoring of glucose in the urine is not a suitable way to achieve a normoglycaemic therapy target.

The exceptional case of glycosuria despite normoglycaemia is found in renal diabetes due to tubular partial functional deficiency. Hereditary defects of the glycometabolism (pentosuria, lactosuria, galactosuria, fructosuria) are excluded by the specificity of the enzymatic determination method.

- **Determination of ketones** (β-hydroxybutyrate, acetoacetate, aceton) in the blood. Fast testing instruments detect the leading agent β-hydroxybutyrate. In diabetic ketoacidosis (DKA) levels of > 3,0 mmol/l β-hydroxybutyrate are found.
- **Oral glucose tolerance test (OGTT):**
  Ind: The OGTT is not recommended for routine clinical examination (significance in unclear cases).
  Conditions:
  - Avoidance of a state of hunger (at least 3 days ≥ 150 g CH/d)
  - Need to remain nil by mouth 10 h before the test
  - No febrile illnesses
  - In women not during menstruation

  Causes of abnormal OGTT: Various physical factors (e.g. myocardial infarction, long confinement in bed etc) and also drugs (diuretics, corticosteroids, oestrogens etc) lead to elevated blood sugar levels. Therefore the OGTT should not be performed in these circumstances.
  In patients after a partial gastric or upper intestinal resection and also in patients with the malabsorption syndrome, the intravenous glucose tolerance test should be performed.

  Performing the test: After determinating the FBS, adults drink a solution of 75 g of glucose. Blood glucose dtermination 120 minutes after glucose uptake. The OGTT is contraindicated if the fasting blood glucose levels are already clearly pathological (see above).
- **Continuous BS measuring over 24 h** (sensor method or microdialysis): Special diagnostic test in specific circumstances (e.g. clarification of unexplained hypo- or hyperglycaemias)
- **Diagnosis of gestational diabetes:**
  Because of the absence of clinical symptoms, screening of pregnant women with increased diabetic risk at 24 - 28 weeks gestation. Determination of blood glucose 60 min. after 50 g glucose (or oligosaccharide mixture; no preparation required, not fasting). A blood sugar > 140 mg/dl (> 7,8 mmol/l) is suspicious of gestational diabetes; further clarification by means of standardized OGTT.
- **Screening examination for diabetes mellitus:**
  Fasting BS for individuals > 45 y. every 3 y. For risk groups earlier:
  - Overweight, hypertension, dyslipidaemia
  - Positive family history (relative of 1. degree)
  - Members of ethnic groups with high diabetic risk (e.g. Pima indians)
  - After delivery of a child with a birth weight of > 4.500 g
  - History of gestational diabetes
  - History of pathological glucose tolerance or impaired glucose homeostasis
- **HbA1c**
  Glycosylation of the haemoglobin leads via an instable form of aldimine (unstable HbA1) to the stable form of ketoamine (stable HbA1), which consists of the 3 sub-fractions a,b and c. Both parameters reflect the same, because most of the c subtype (HbA1c) corresponds to 70% of the HbA1. HbA1c reflects as blood glucose memory the patient´s blood glucose level in the preceding last 8 weeks.
  False low concentrations are measured if the lifespan of the erythrocytes is reduced (i.e. in haemolytic anaemia) or in the first half of pregnancy.
  False high concentrations can be found in renal insufficiency, hyperlipoproteinaemia, chronic alcohol abuse, second half of pregnancy and lactation period, high dose salicylate therapy. Refernce range for HbA1c: < 6.2 % (45mmol/mol)
  Remember: The risk of an infarct is 40% increased if the HbA1c is 7% = 53 mmol/mol, in readings around 8% = 64 mmol/mol the risk is 80% increased. (UKPD-study).
  The diabetic complications are reduced by 20% (UKPD-study) per a reduction of 1 % of the HbA1c value. The risk of hypoglycaemia is 3fold increased!
- **Screening for further risk factors** such as premature arteriosclerosis (hypertension, hyperlipoproteinaemia, smoking etc)
- **Test for microalbuminuria** (at least 1 x/year in diabetics)

Th.: 1. Diet, normalisation of weight
2. Physical activity increases on the one hand the sensitivity of the muscles to insulin, but also the non-insulin mediated glucose absorption.
3. Drugs: a) oral antidiabetics , b) insulin, [c) GLP1-analogues]
4. Patient education and monitoring
5. Exclusion of or therapy for poss. further risk factors for premature arteriosclerosis
6. Prophylaxis of, and therapy for, complications

To 1 - DIET:

In type 2 diabetes therapy must always start at the onset of impaired glucose tolerance, to avoid vascular complications! In this respect normalizing weight is of highest priority (target value: BMI < 25). If this is successfull drug therapy is often unnecessary and progression to diabetes can be avoided or delayed. In times of hunger the number of manifest type 2 diabetics is at its lowest.

In the mostly normal weight type 1 diabetic, food and insulin supply must be optimally coordinated, in order to achieve a normoglycaemic metabolic state: In conventional insulin therapy meals must be adapted to a strict pre-set insulin therapy system. In the intensified insulin therapy the insulin supply is adapted to a relatively free calculable nutrition uptake as required! (see below)

Daily energy requirement (in kcal):
Normal weight x 32 in mild physical activity (most frequent case)
Normal weight x 40 in moderate physical activity
Normal weight x 48 in heavy physical activity
Normal weight (according to Broca) in kg: Height in cm - 100 (women - 10 %)
Body mass-Index:

$$\frac{\text{Body weight (kg)}}{\text{Height (m)}^2} \rightarrow \text{Normal index: } 18{,}5 - 24{,}9 \text{ kg/m}^2$$

1 kcal = 4,2 kilojoules	
1 g carbohydrate	= 4,1 kcal = 17,2 kJ
1 g protein	= 4,1 kcal = 17,2 kJ
1 g fat	= 9,3 kcal = 38,9 kJ
1 g alcohol	= 7,1 kcal = 30 kJ

- No large meals, several small ones instead.
- Composition of the diet:
  - Proteins 10 - 15 % of total calories (low fat meat, fish, vegetable proteins). In diabetic nephropathy low protein diet.
  - Fat: 30 % of total calories, possibly with a high proportion of unsaturated fatty acids. If additional disorder of the lipid metabolism is present, the proportion of fat of the total calories should be reduced to< 25 %.
  - Carbohydrates: According to the remaining calorie requirement, 50 - 60 % → calculation according to bread units (BU) 1 BU = 10 g CH (corresponds to approx. half a roll). The Langerhans' islets excrete for every BU circa 1 IU insulin. The amount of BU can be determined from exchange tables. In conventional insulin therapy the BU are distributed in a ratio of 2 : 1 with meals and between meals, to avoid a hypoglycaemia between 2 main meals. This is not valid for the intensified insulin therapy.

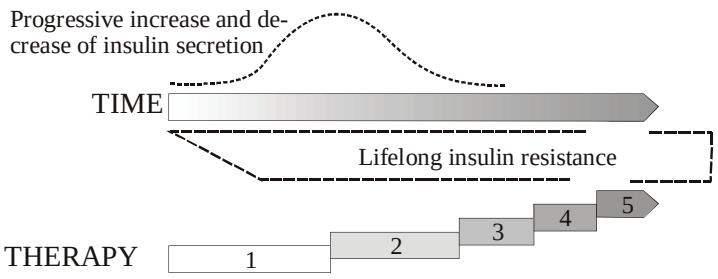
    Fast resorbable monosaccharides (glucose) and disaccharides are unfavourable (saccharose = cane sugar, lactose = milk sugar). Allowed sweeteners are saccharine, cyclamate, aspartame (note: aspartame is carcinogenic in animal studies). Sugar exchange products (fructose, xylitol) undergo glycolysis independently of insulin and therefore have only a minor glycaemic effect. But also fructose should be used with care, because it has a more negative effect on lipids and body weight than other saccharids.
    The maximal allowed amount of carbohydrates (carbohydrate tolerance) corresponds to the daily amount of carbohydrates at which no essential glucosuria occurs and at which the blood glucose levels after a meal remain < 140 mg/dl.
  - Large amounts of high-fibre roughage lead to a delay of the carbohydrate absorption and a decrease of the blood glucose levels in type 2 diabetics.
  - Alcohol only occasionally up to a max. of 20 g, always together with carbohydrates (alcohol inhibits gluconeogenesis in the liver → danger of hypoglycaemia).

to 3.:

- **TREATMENT OF TYPE 1 DIABETES:**

  INSULIN SUPPLY - diet - physical activity - education

- **STEPWISE TREATMENT OF TYPE 2 DIABETES ACCORDING TO PHASES**



1. **WEIGHT NORMALIZATION** – diabetic diet – physical activity – education

   Remember: Trials show, that the progression of type 2 diabetes can be halted by normalization of weight and regular physical activity!

2. Oral antidiabetic: Metformin is the drug of choice in overweight type-2 diabetics.
3. Metformin + 2. oral antidiabetic respectively incretin mimetic
4. Basal insulin + oral antidiabetic : Secondary failure of SU therapy (= exhaustion of the B cells) is observed on average after 10 y., then combination of SU and injection of an intermediate insulin in the evening (bedtime insulin).
5. Basal insulin + bolus insulin + oral antidiabetic: With exhaustion of endogenous insulin production, SU lose their effect → conventional or intensified insulin therapy is commenced.

Drugs:

Oral antidiabetics (OAD):

Insulinotropic and noninsulinotropic drugs:

Insulinotropic = β-cytotropic	**Noninsulinotropic = nonβ-cytotropic**
Sulphonylureas, meglitinides, DPP-4-inhibitors, incretin mimetics	Biguanides (metformin), α-glucosidase inhibitors, glitazones
Effect on the β-cell Treatment of the secretion deficit Effect also in later stages of disease Danger of hypoglycaemia (SU, glinides) Danger of weight gain (SU, glinides)	Peripheral effect Treatment of the insulin resistance Effect mainly in earlier stages of disease No danger of hypoglycaemia Suitable for obese patients

■ **Biguanides:** Metformin

Ef.: - Delayed intestinal glucose absorption
- Inhibition of hepatic gluconeogenesis
- Increased glucose uptake in muscles
} extrapancreatic effects
- Small appetite lowering effect (→ poss. weight rediction)

Considering all those effects Metformin is (in absence of contraindications) the first line drug according to the guidelines in the therapy of the obese type-2 diabetic.

Remember: In the UKPD study metformin performed in all areas (micro- and macroangiopathy, lethal outcome) better than all other forms of therapy and is therapy of 1. choice in overweight type 2 diabetics with respect to their CI.

SE: Very rarely lactic acidotic coma (with high mortality) only if disregarding the contraindications; often gastrointestinal complaints etc

CI: Renal insufficiency!, decompensated cardiac failure, respiratory impairment, severe hepatic impairment, conditions which predispose to hypoxia of tissue, wasting, slimming diet, fasting, acute concommitant illness, pregnancy, before and after surgery, 48 h before and after intravenous urography (danger of lactic acidosis!), alcoholism; old age is a relative CI and others

Dose: 1 - 2 x 500 – 1.000 mg/d after the meals; to start with smallest dose and increase slowly.

■ **α-glucosidase inhibitors:** Acarbose (glucobay®), miglitol (Diastabol®)

Eff.: Competitive inhibition of glucoamylase, saccharase, maltase in the intestinal mucosa. Postprandial blood glucose peaks are flattened. The unfissured carbohydrates stimulate the enterohormone GLP-1 (glucagon like peptide) in the lower small intestine. This sensitizes the β-cells to glucose stimulus.

Similar effects of α-glucosidase inhibitors can be achieved with a high-fibre diet.

SE: At higher doses symptoms of carbohydrate malabsorption can occur (flatulence, bloating, abdominal pain, diarrhoea), increase in liver enzymes etc

CI: Pregnancy, age < 18 y., severe renal insufficiency, chronic intestinal disease

Dose: Careful adjustment of dose: Initially 50 mg/d at beginning of a meal. If tolerated slowly increase the dose to 3 x 50 mg/d (higher doses cause more side effects.

■ **Glitazones (thiazolidinediones):** In the ProActive study mild decrease of clinical end points with pioglitazone.

- Pioglitazone (Actos®), pioglitazone + metformin (Competact®)
- Rosiglitazone (Avandia®); rosiglitazone + metformin (Avandamet®)

Eff.: „Insulin-sensitizer", improves the sensitivity of the peripheral cells for insulin (decrease of the insulin resistance). Redistribution of the visceral (hormone-active) adipose tissue into the periphery.

SE: e.g. weight gain, oedema → poss. deterioration of cardiac impairment; rarely hepatic damage. Suspicion of increased risk of fractures in women.

Ind: For combination therapy in type 2 diabetes with metformin or SU

CI: Liver diseases, cardiac failure > NYHA I, severe renal impairment, pregnancy, lactation etc.
Rosiglitazone is contraindicated also in the acute coronary syndrome and after myocardial infarction, because it seems to increase the cardiovascular risk.

Dose: e.g. pioglitazone 15 - 45 mg/d, rosiglitazone 4 - 8 mg/d; monitoring of liver enzymes and body weight

■ **Insulinsecretagogues (insulinotropic substances):**

1. Sulphonylureas (SU):

Eff.: Stimulation of insulin secretion by increasing sensitivity of B-cells to glucose. Proof of efficacy for risk reduction of clinical end points exist for glibenclamide (UKPDS).

Ind: Type 2 diabetes with sufficient remaining intrinsic insulin production - provided that dietetic therapy alone (weight normalization!) is not enough (step 3 of the graduated therapy plan).

Note: At the time, when diabetes manifests itself, the majority of diabetics still have exaggerated levels of insulin in the blood. Here sulphonylureas lead to normoglycaemia, but the metabolic syndrome deteriorates through the additional hyperinsulinaemia! Therefore weight normalization and physical activity are an indispensable part of therapy! Overweight type 2 diabetics are treated initially with metformin.

CI: - Type 1 diabetes
- Pregnancy (change to insulin)
- Severe renal impairment, hepatic impairment
- Diabetic metabolic imbalances (precoma/coma, acidosis/ketoacidosis)
- Reduced cognitive states (e.g. accidents, operations)
- Diabetic gangrene
- Allergy to sulphonylureas

SE: - Hypoglycaemia - causes:
- ■ Overdosage
- ■ Reduced nutritional intake
- ■ Physical exertion
- ■ Alcohol consumption
- ■ Renal impairment (delayed renal elimination)

- Gastro-intestinal irritation
- Allergic reactions (sulphonamide allergy)
- Rarely blood disorders (agranulocytosis, haemolytic anaemia)

Interaction of sulphonylureas with other substances:
(which can predispose to hypoglycaemia or to inhibition of its efficacy), e.g.:

Increase (risk of hypoglycaemia)	**Reduction**	**Risk factors for the occurrence of severe hypoglycaemias under SU therapy**
Beta-adrenoreceptor blockers	Glucagon	Age > 70 years
ACE inhibitors	Öestrogens, gestagens	Cerebrovascular or cardiac diseases
Coumarin derivates	Corticosteroids	Renal or liver impairment
ASA	Phenothiazine derivates	Alcohol
Nonsteroidal antiinflammatories	Saluretics	Erratic food intake
Sulphonamides	Thyroid hormones	Diarrhoea
Clarithromycin	Sympathomimetics	Physical exertion
Gatifloxacin	Diazoxide	
Alcohol (be careful !)	Nicotinic acid derivates	

Examples of preparations:

■ Glibenclamide has the greatest hypoglycaemic effect. Decreased risk of microvascular complications shown (UKPD study)
Dose: 1,75 - 10,5 mg/d

■ Glimepiride (Amaryl®): Is given as a single dose immediately before breakfast.
Dose: 1 - 3 (6) mg/d

All SU are commenced at the smallest dose, slowly increasing. Attention has to be paid to the danger of nocturnal hypoglycaemia! In the first 4 weeks tight blood glucose monitoring is necessary, as after 2 - 3 weeks the metabolic status often improves and then poss. dose reductions can be indicated! At maximum dose of glibenclamide 2/3 are given in the morning and 1/3 of the dose in the evening. A dose at midday is unnecessary, as the islet cells remain stimulated by the morning dose. Regular blood glucose measurement is necessary; in weight reduction dose reduction. Caution in older patients with irregular mealtimes! Mild renal impairment can prolong the duration of action → in hypoglycaemias of renal patients on SUs frequent monitoring and poss. change to other antidiabetic agents.

2. Sulphonylurea analogues: Meglitinides: Evidence of efficiency regarding the risk reduction of clinical endpoints is not available.
Repaglinide (Prandin®), nateglinide (Starlix®)
Eff: Meglitinides are so-called postprandial glucose regulators. The effect on FBG is less noticable. They lead to short term insulin secretion from the B-cells via a blockage of the ATP-sensitive potassium channels. Similar to an intensified insulin therapy they are taken with meals. The risk of hypoglycaemia is thought to be less than with SU. Precondition: Good patient education + compliance

Ind: Type 2 diabetes, step 3: Alternative to SU (esp. in renal insufficiency)
CI: Similar to SU, repaglinides in combination with gemfibrozil
SE: Hypoglycaemias, gastrointestinal SE, rarely increase in liver enzymes, visual disturbances, allergy
Interactions: No combination between repaglinides and gemfibrozil (see above), careful regarding combinations with drugs which interfere with CYP3A4 (e.g. clarithromycin, ketoconazol, itraconazol)
Dose: e.g. repaglinide (Prandin®) 0,5 - 2,0 mg before meals; start with lowest dose!

Failure of the SU therapy:

Primary failure of the SU:
Relatively rare occurrence in IDD = late manifestation type 1 diabetics

Secondary failure of the SU:

a) Supposed (reversible) secondary failures:
- "Diet failure": Overweight type 2 diabetics, in which the possibility of dietary manipulation is not yet exhausted.
- Transient deterioration of glucose homeostasis through stress situations or infections

b) Genuine secondary failure in optimal diet and weight normalization:
A secondary failure rate of circa 5 % annually is estimated. Secondary failure occurs after an average of 10 years of diabetes duration and is a consequence of exhaustion of the B-cells causing insulin deficiency . As a result the genetically pre-set insulin resistance can no longer be compensated. No other therapy seems to develop a secondary failure as quick as the therapy with SUs. The cardinal symptom is hyperglycaemia despite maximal therapy with SU.
Note: Determination of the C-peptide in relation to the fasting blood glucose (FBG) allows an orientation, whether insulin is required, but it is not a routine diagnostic test:

Th.: Combined therapy OAD + insulin:

■ **Basal insulin supported oral therapy (BOT)**
- Continuation with OAD.
- Additional dose of a delayed insulin (NPH-insulin or long-acting analogue insulin) in lowest dose possible before bedtime. Starting with a small dose (6 IU) and increasing if required very slowly and in small steps. Usually 8 - 16 IU is sufficient! FBG should be in the normal range.

Advantages:
- Only 1/3 of the insulin dose is needed compared to monotherapy with insulin alone.
- A relatively good adjustment is achieved with one insulin.

→ If the HbA1c remains too high with BOT a short acting insulin for breakfast or the main meal can be added daily = BOT-plus

■ **Prandial or supplementary insulin therapy (SIT):**
Precondition: Insulin production is still sufficient for the basic supply; only increased insulin requirement at meals is supplemented by ´fixed´ doses.
Continuing oral antidiabetics + additional injection of a small preprandial dose of normal insulin. Starting dose: FBG (mg/dl) x 0,2 = daily insulin dose. Dividing of this dose in the ratio 3 : 1 : 2 (breakfast/lunch/dinner).
Advantage: Better controls of the postprandial blood glucose peaks

3. GLP-1-based therapy:

GLP-1 = glucagon-like peptide 1, it is formed out of proglucagon by the neuroendocrine L-cells of the small bowels in relation to food intake and inactivated within minutes by the enzyme dipeptidyl peptidase 4 (DPP-Together with the gastric inhibitory polypeptide (GIP → became ineffective in type-2 diabetics) they are incretins = hormonal stimulation factors of the insulin secretion released by the intestines.
Eff.: Stimulation of insulin secretion, inhibition of glucagon release, reduction of appetite, delay of the emptying of the stomach.

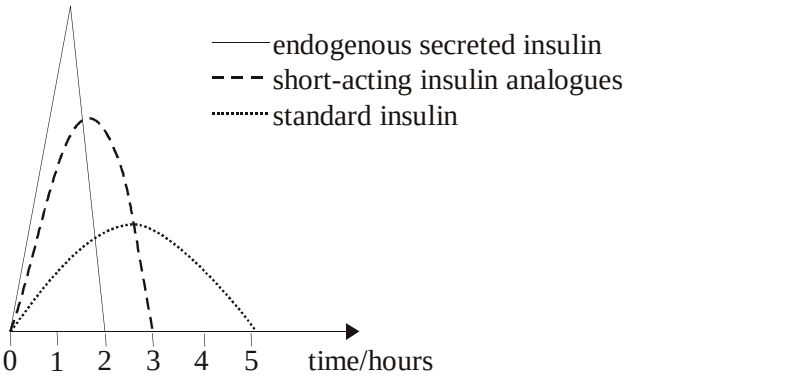
■ **DPP-4-inhibitors (gliptins):** Sitagliptin (Januvia®, Xelevia®), Vildagliptin (Galvus®), Saxagliptin (Onglyza®), Linagliptin.
Eff.: Inhibition of DPP-4, which is responsible for the break down of the glucagon-like-peptide 1. This leads to an increase of GLP-1, which stimulates the insulin secretion and inhibits the glucagon secretion.
Hypoglycaemias are rarely expected, because the incretin effect is glucose dependent. Long-term data are still awaited.
SE: Rare → gastrointestinal and hepatic disturbances, pancreatitis, only rarely hypoglycaemias, etc.
Ind.: Type 2 diabetes, in addition to metformin and/or SU, if these alone have an inadequate effect.
CI: Renal insufficiency, liver insufficiency.
Dose.: Sitagliptin: 1 x 100 mg/d; vildagliptin: 2 x 50 mg/d; saxagliptin: 1 x 5 mg/d

■ **Incretin mimetics:** Exenatide(Byetta®), Liraglutide (Victoza®)
Eff: Incretin-mimetics are GLP-1-analogues, which bind on the GLP-1-receptors with high affinity and are not inactivated by DPP-4. They lead to an increase of the insulin secretion and an inhibition of the glucagon

secretion. No hypoglycaemias occur, because insulin secretion only is increased in the presence of an elevated glucose level. Long-term data still are awaited.
Ind: Type 2 diabetes in combination with metformin and/or SU, if they alone have an inadequate effect.
SE: Frequently nausea, vomiting, diarrhoea; very rare pancreatitis; AB formation against exenatide with occassional reduction of its effect etc.
CI: pancreatitis and others (→ by-pack leaflet)
Dose: Exenatide: initially 2 x 5 µg/d s.c. circa 30 minutes before the main meals. Increase of dose after 4 weeks possible to 2 x 10 µg/d s.c.
Liraglutide is effective over 24 h and needs only to be given 1 x/d s.c.: slow increasing dose 0,6 → 1,2 (→ poss. 1,8 mg/d).

INSULIN

Insulin is synthesized in the B-cells of the Langerhans islets from the precursors pre-proinsulin and proinsulin; the C-peptide (connecting peptide) is segregated from the centre of the molecule chain of the proinsulin. Since insulin and C-peptide are secreted equimolarly and simultaneously into blood, measuring C-peptide allows an assessment of B-cell pancreatic function. Compared to insulin determination in serum, C-peptide measurement in serum has the advantage that no cross reaction is possible with insulin antibodies, and measurement of the exogenic insulin dose remains unaffected. Furthermore the determination of C-peptide is less likely to be influenced by short-term fluctuations of insulin synthesis, due to its longer biological half-life (circa 25 minutes).
In patients with insulin dependent diabetes, C-peptide is lowered.
The secretion of insulin, which is stored in the granula of the B-cells, is proportional to the blood glucose level. Due to rapid inactivation of circulating insulin through insulinases, the plasma half-life is short (5 minutes). An excess of contrainsulinergic hormones (STH, ACTH, corticosteroids, glucagon, adrenalin, thyroxine) can lead to a diabetic metabolic status (WHO classification III D).



Action mechanisms of the insulin:

1. Membrane effect: Stimulation of the transport of glucose, amino acids and potassium into the muscle and fat cells.
2. Metabolic effects: Stimulation of the anabolic metabolic processes (glycogen synthesis, lipid synthesis, protein synthesis) and inhibition of the catabolic processes (glycogenolysis, lipolysis, proteolysis).

In diabetics the uptake of glucose into the cells is more difficult (insulin resistance a./o. insulin deficiency). Only higher blood glucose levels can sufficient glucose get into the cells. The deficiency in glucose in the cells of the adipose tissue storage leads to a reduced production of glycerin phosphate, so that fatty acids are not synthesized to triglycerides and leave the fat tissue. In the liver they are broken down via acetyl-CoA to ketone bodies (diacetic acid, β-hydroxybutyric acid, acetone). The ketone bodies, which are also used by the muscle cells as a source of energy, reduce the cell´s permeability for glucose, so that the situation is worsened further (insulin antagonistic effect of the ketone bodies).

Rule of 40s:

- The daily insulin requirement for a ´normal individual` is 40 IU of insulin (more in the obese): 20 IU of insulin for the ingestion and 20 IU of insulin for the basal metabolism.
- 1 IU of insulin lowers the blood glucose level by 30 - 40 mg/dl (in the absence of resistance)
- 1 BU (bread unit) = 10 g of carbohydrates increases the blood glucose level by 30 - 40 mg/dl (in the absence of resistance).
- Conclusion: 1 IU of insulin neutralizes on average 1 BU.

Insulin secretion can be divided into two components:
1. Basal insulin secretion
2. Insulin secretion dependent on meals.

The basal insulin secretion with low insulin concentrations in the blood (5 - 25 µU/ml) suppresses the release of glucose from the liver. Therefore in insulin deficiency increased blood glucose levels occur as well in the fasting period. On the other hand, meal dependent insulin secretion is required for the utilization and storage of glucose from the nutrition.

Indications for an insulin therapy:

1. Type 1 (insulin dependent) diabetes
2. Type 2 diabetes: Insulin therapy in time, if diet + oral antidiabetics no longer lead to good control.
3. Pregnancy, if diet alone does not lead to normoglycaemia.
4. Diabetic complications (microangiopathies, [pre-]coma diabeticum)
5. Poss. perioperative conditions or those diabetics requiring intensive medical care

Insulin preparations:

Human insulins and insulin analogues are in current use.

Insulin is available in Germany in two different concentrations. As **U40** (40 IU/ml) for the conventional injection with insulin injection devices, and as **U100** (100 IU/ml) in cartridges for insulin pumps and injection aids (pen). **Attention:** The matching calibrated syringe must be used. In Germany U 40 insulins are only offered by Braun®.

1. Short-acting insulins

a) Standard insulin: Onset of action after 30 - 60 min.; duration of action circa 5 h
- Insuman Rapid
- Actrapid®
- Huminsulin®

Ind: - In metabolic imbalances and when used for first time
- For intermittent therapy (e.g. perioperatively)
- For intensified conventional therapy (ICT) and for insulin pump therapy

Administration: Subcutaneous; in patients in coma intravenous
In s.c. administration duration between injection and meal circa 15 - 20 min.

b) Short-acting insulin analogues: Variation of the amino-acid sequence avoids subcutaneous hexamer synthesis, thus more rapid resorption; onset of action circa 10 min., duration of action circa 3,5 h.

Insulin Lispro (Humalog®)
Insulin Aspart (NovoRapid®)
Insulin Glulisin (Apidra®)

Advantage: No delay of meal after injection, fewer postprandial hypoglycaemias; insulin between meals may possibly no longer be necessary. Possible postprandial injection.

Disadvantage: Its effects may be too short for acting on slowly resorbable carbohydrates; basal insulin supply must be dosed exactly;

CI: Disorders affecting gastric emptying, e.g. in AN with gastroparesis (→ danger of hypoglycaemia!) etc

2. Depot insulins:

By combining insulin with protamine, zinc, insulin preparations with longer duration of effect are achieved.
Administration: Subcutaneous; depot insulins must not be given intravenously!

a) Intermediate insulins:

NPH insulins (neutral protamine hagedorn insulins)
Principle: Insulin protamine cristals; onset of action after circa 60 min., duration of action 9 - 18 h
Examples of human insulins:
- Insuman® Basal
- Huminsulin® Basal

Ind: Combination therapy insulin + oral antidiabetics (SU, metformin); conventional and intensified conventional insulin therapy (ICT)

b) Long-acting insulins:

Onset of action after circa 60 min., duration of action up to 24 h
Ind.: Coverage of basal insulin demand in the intensified conventional insulin therapy (ICT).
Example of human insulin: Ultratard® HM (insulin zinc cristals)
Steady-state conditions are only achieved after 3 - 5 days, due to their long duration of effect.
Long-acting insulin analogues:
Insulin Glargine (Lantus®), Detemir (Levemir®)Insulin

3. Insulin mixtures from standard insulin (or short acting insulin analogues) + NPH insulin:

NPH insulins can be freely mixed with standard insulin (not possible with zinc insulins). For virtually all needs corresponding trade preparations are available.
Ind: Conventional insulin therapy with 2 (- 3) daily injections, division of doses: 2/3 in the morning, 1/3 in the evening
Time between injection and meal with standard insulin approx. 30 minutes (insulin analogues without delay between injection and meal); administration s.c.
Examples:
- Actraphane® 30 with 30% proportion of standard insulin (and 70% of NPH insulin).
- Huminsulin® Profil III with 30 % of standard insulin (and 70% of NPH insulin)
- Insuman® Comb 25 with 25 % of standard insulin (and 75% of NPH insulin)
- Humalog Mix® 25, with 25% of insulin-lispro (and 75% of Lispro-NPH)
- NovoMix® 30 with 30% of insulin-aspartat (and 70 % Aspart NPH)

Remember:

1. Intermediate and longterm insulins are also called depot insulins. They must not be given i.v.!
2. All intermediate and NPH-insulins must be tilted from side to side at least 10 times in order to achieve a homogeneous mixture. But only circa 10-20% of the patients are doing this sufficiently, so that the insulin application varies enormously (circa 10 – 200%)
3. Insulin analogues are relatively expensive, clear artificial insulins, which do not need to be mixed thoroughly. Clinically relevant advantages or disadvantages compared to human insulins are not proven.

Complications of insulin therapy:

1. Hypoglycaemia
   Cause: Overdosage (rare due to suicidal attempts), missing or inadequate food intake, increased physical activity, weight reduction, interaction with drugs (e.g. beta-blockers) and alcohol (life-threatening hypoglycaemias in drying-out cells!).

   Note: When change from animal to human insulin a 10 - 20 % decreased insulin demand has to be expected (danger of hypoglycaemia !).

2. Lipodystrophy of the fat tissue at the injection sites

   Pro.: Systematic alteration of injection sites (whole abdominal area and lateral thigh - not on upper arm)

3. AB related complications are extremely rare when human insulin is used.

4. Insulin resistance:
   Additional requirement of insulin due to impairment of the interaction between insulin and its receptor on the cell surface a./o. due to glucose utilization in the cell → Causes:
   - Overweight (most common)
   - Hypertriglyceridaemia
   - Infections (common)
   - Increase of insulin antagonizing hormones (s.a.)
   - Stress / trauma
   - Ketoacidosis (Pre-/coma diabeticum)
   - AB against insulin (extremely rare for human insulin)

   Note: Pseudoresistance occurs in hyperinsulism (due to too high insulin doses: Hypoglycaemias and afterwards reactive hyperglycaemias): in this circumstance only a gradual reduction (!) of the insulin dose helps (see below: Somogyi effect).

A) Conventional insulin therapy (CT)

with intermediate insulin or insulin mixtures with intermediate insulin + standard insulin: Satisfactory stabilization can only be achieved with at least 2 injections/d. 2/3 to 3/4 of the daily dose is injected before breakfast, the rest before dinner (time between injection and meal = 30 minutes with standard insulin - with insulin analogoues no time difference). Better stabilization is possible with 3 injections
In the morning: mixed insulin – at lunch time: standard insulin – in the evening: mixed insulin
Disadvantage: A fixed pre-set dose of a depot insulin without addition of standard insulin is not sufficient to neutralize the blood glucose increase after nutrition. On the other hand, the insulin level is unphysiological high between meals, so that inbetween meals are necessary to avoid hypoglycaemia: As a result the patient must obey a fixed meal schedule: If the patient does not eat enough his insulin dose will be too excessive and vice versa.

Remember: Conventional insulin therapy = The patient must eat, because he injected insulin!

Note: Morning hyperglycaemia can have 3 causes:

1. The duration of action of a single morning dose of a depot insulin is too short, so that the blood glucose level increases during the night and esp. in the morning.
   Th.: A second dose of insulin in the evening (morning/evening ratio: 2 - 3 to 1).
2. Somogyi effect: The patient receives an insulin dose in the evening, which is too excessive: This causes nocturnal hypoglycaemia (nocturnal blood glucose testing around 3 - 4 o`clock) and reactive hyperglycaemia in the morning.
   Patients who tend to have nocturnal hypoglycaemias should not go to bed with a blood glucose level < 120 mg/dl, because by 3 am it will have decreased by 30 - 40 mg/dl, only increasing again after 3 am through to morning time. If patients are below 120 mg/dl at 23.00 they should eat one or two BU. Nocturnal testing around 3 h is only necessary if hypoglycaemia is suspected, for example if the patient undertook a lot of sport, or after alcohol consumption.
   Th.: Decrease of the insulin dose in the evening!
3. Dawn phenomenon: Despite constant insulin supply hyperglycaemia occurs in some patients in the early morning (after 6 o´clock). The cause is increased insulin demand in the second half of the night, due to increased growth hormone (GH) secretion (esp. type 1 diabetes).
   Di./Th.: Blood glucose testing in the night (e.g. 22 / 2 / 4 o´clock) and adaption of the insulin dose in the evening(intermediate- or long-acting insulin), or use of an insulin pump → supply of an elevated basal rate in the early morning hours.

Additional remarks

- Readjustment of poorly controlled diabetes:
  Never change diet and insulin simultaneously, otherwise the overview is lost. The patient remains on his old routine system for 2 days, frequent blood glucose measurements are performed, and only then is the insulin therapy changed.
- If adjustment carries a danger of hypoglycaemia (which the patient must be educated about → ***attention***: driving!) dextrose should be at hand. Relatives should be familiar with the emergency treatment of hypoglycaemia in case of hypoglycaemic shock (1 mg glucagon i.m. or s.c.).
- During longer lasting unusual muscle exercise (e.g. sport on weekends) the insulin demand decreases, so that on that corresponding (and poss. also following) day only a reduced insulin dose (e.g. 50 %) should be injected.

B) Intensified insulin therapy

Basis /bolus concept:

Dividing the insulin level of a healthy individual into a basal rate and additional meal dependent (prandial) rate, insulin peaks can be imitated in an insulin dependent diabetic in 2 ways:

a) Intensified conventional insulin therapy (ICT):

The basal insulin demand is covered by at least two injections of an intermediate-acting insulin (poss. single dose of a long-acting insulin). In cases of normal daily routine, sometimes a single dose of a depot insulin in the evening is sufficient. The injection in the evening is based on the daily routine of the patient and on the nocturnal blood glucose curve. Usually it is applied between 22 - 24 o´clock.

Around 40 - 50 % of the total daily insulin dose falls into the basal insulin supply. The other 50 - 60 % of the daily dose is divided between the meal dependent (prandial) bolus doses of standard insulin or short-acting insulin analogues. The individual dose depends on the size of the meal, the preprandial tested blood glucose level, the time of the day and on any planned physical activity. An interval between injection and meal is not absolutely necessary in this case, but circa 15 min. is desirable.

There is a circadian insulin sensitivity, and therefore the insulin demand per carbohydrate unit (CU) varies at different times (ratio normally 3:1:2)

Insulin demand per CU: In the morning circa 2 IU, at noon 1,0 IU, in the evening 1,5 IU (in the absence of resistance)

The adjustment of the dose of the standard insulin in levels which differ from the target blood glucose (90 - 120 mg/dl) is based on the experience, that 1 IU of standard insulin lowers blood glucose by circa 30 mg/dl (in blood glucose levels ≤ 300 mg/dl). In blood glucose levels > 300 mg/dl 1 IU of standard insulin lowers the blood glucose by circa 60 mg/dl.

Examples of injection patterns of the ICT (S = standard insulin, D = depot insulin)

Breakfast	Lunch	Dinner	At night (23 h)
S	S	S	D
S + D	S	S	D
S + D		S	D
S	S + D	S	D

In patients with sufficient basal insulin secretion a trial can be done with a supplementary insulin therapy (bolus of a rapidly acting insulin at the main meals without basal insulin).

b) Insulin pump therapy:

Here standard insulin is used exclusively. Continuous subcutaneous insulin infusion (CSII) is achieved by means of an external pump. In modern instruments the basal rate can be programmed separately for each hour, so that e.g. a Dawn phenomenon can be counteracted in an optimum way. At mealtimes the patient releases – dependent on the preprandial blood glucose level and the desired amount of food – bolus insulin doses via the insulin dosing instrument. In this case they are insulin pumps without an automatic glucose sensor (the blood glucose testing is done manually by the patient) = "open-loop-system". The ideal instrument would be an insulin pump with continuously working glucose sensor (e.g. the Ulm "glucose clock"), in which the insulin supply is regulated = feedback-regulated pumps = "closed-loop-system". With insulin pump therapy the insulin demand is usually lower!

Co.: 1. Local infections
2. Decompensation into coma if insulin flow is blocked
3. Danger of hypoglycaemia in case of insufficient self control of blood glucose

Ind.: - Pregnancy
- Severe Dawn phenomenon
- Threatened late complications of diabetes etc

Preconditions for an intensified insulin therapy:

- Cooperative patients with the ability to decide therapeutic options
- Intensive diabetes education
- Daily self monitoring of the metabolic status (at least 4 self testings of blood glucose)
- Supervision of patients by experienced diabetic physicians

Advantages of the therapy:

- Ideal control of metabolism

- Individual synchronized arrangement of food intake (the patient injects insulin, when he wants to eat) and physical strain (rapid adaption of the insulin dose is possible). The results of the Diabetes Control and Complication Trial (DCCT) in type 1 diabetics show, that the rate of diabetic late complications (retinopathy, nephropathy, neuropathy) is reduced by 50 % with intensified insulin therapy. Optimising the metabolic state prevents further progress of existing complications. However, this therapy causes a threefold increased risk of hypoglycaemia.

Therapeutic target:

Prevention of diabetic late complications by targeting an almost normoglycaemic metabolic status:

1. ● Fasting blood glucose and preprandial 80 - 110 mg/dl (4,4 - 6,1 mmol/l)
   Blood glucose postprandial ≤ 140 mg/dl (≤ 7,8 mmol/l)
   Blood glucose self monitoring by the educated patient
   ● Urine free of glucose
   ● Negative for ketones
   ● Albuminuria < 20 mg/l
2. Avoidance of hypoglycaemic reactions
3. Normalization of body weight and blood lipids ● Target values:
   LDL cholesterol < 100 mg/dl (< 2,6 mmol/l)
   HDL cholesterol > 45 mg/dl (> 1,1 mmol/l)
   Triglycerides < 150 mg/dl (< 1,7 mmol/l)
4. Normalization of the glycosylation long-term parameter HBA1c (monitoring every 3 months):
   Therapy target:
   - In type-1 diabetics blood glucose and HbA1c target should be as close to normal values as possible in order to avoid late complications
   - In type-2 diabetics the therapy target is still in discussion. An HbA1c < 6,5 = 48 mmol/mol (Germany) respectively <7,0% = 53 mmol/mol (USA) is recommended. It is important, that the blood glucose and the HbA1c is not lowered too rapidly in cardiovascular risk patients and as well in diabetic retinopathy.
   Note: The ACCORD-study showed, that older type-2 diabetic patients with a high cardiovascular risk did not benefit from an intensive blood glucose reduction with HbA1c results < 6,5% = 48 mmol/mol; on the contrary a higher mortality was found compared to patients with HbA1c results around 7,5% = 58 mmol/mol. This was not verified in the group of well adjusted type-2 diabetic patients of the ADVANCE-study.

   Interpretation of blood glucose and HbA1c:
   ● Normal blood glucose, high HbA1c:
   - Pretending of having a good diet discipline only for a short period before the ambulant testing is performed
   - In unstable metabolic status high HbA1c values indicate metabolic decompensation in the preceding weeks despite normal blood glucose.
   ● Elevated blood glucose, satisfactory HbA1c values: Only temporary increase of blood glucose (e.g. stress related high glucose during visit at the doctor) in otherwise satisfactory stabilization
   ● Normal blood glucose and HbA1c values: Good metabolic status in the last 4 - 8 weeks
   ● Elevated blood glucose and HbA1c values: Bad metabolic status in the last 4 - 8 weeks
5. Eliminating of poss. further risk factors for premature arteriosclerosis:
   ● Smoking cessation
   ● BP < 130/< 80 mm Hg
   ● With proteinuria ≥ 1 g/d the target RR is < 125/< 75 mm Hg

   Remember: For every 10 mm Hg lowering of systolic BP, diabetic complications decrease by 12 % (UKPD study).
6. Regular examination to detect poss. late complications (documenting in the health record)
   - Screening for (micro-)albuminuria, urea, creatinine in serum
   - Inspection of the feet by the doctor
   - Patient education concerning prevention of foot complications (self inspection of the feet, professional foot care and adaequate shoes, protection from injuries etc)
   - Pulse status, neurological status
   - Ophtalmological examination with ophthalmoscopy, poss. fluorescence angiography
7. Early prevention and treatment of complications:

   Basis: Best possible blood glucose control and treatment/elimination of other vascular risk factors

   ▶ Diabetic foot syndrome (DFS)
   Precondition: Interdisciplinary collaboration in diabetic foot clinics: Differentiating between neuropathic foot (neurologic diagnostic) and/ or peripheral vascular disease (PVD) (vascular investigation)
   Therapy points:
   Foot care (patient education !) - relief of pressure – diabetes shoes for relief – avoidance of trauma and infections – cleaning of wounds/débridement of necrotic coating + treatment of infections – revascularisation therapy in PVD. Bypass grafting of peripheral vascular occlusion, as well as interventional measures in patients with DFS prevent, in the majority of cases, amputation of the endangered leg. Poss. additional hyperbar oxygenation (HBO).

Frequency of bacterial infections in chronic wounds in the DFS: Staph. aureus (50 %) alone or combined with enterobacter (40 %), streptococci (30 %), staph. epidermidis (25 %) etc. After taking culture swabs, initial treatment with broad-spectrum antibiotics, changing according to culture results

Remember: Unsuitable footwear is the most common cause of pressure sores/ulcerations/necrosis. No amputations before vascular + diabetic specialist consultation! Revascularisation therapy in vascular surgical centres can reduce the high number of major amputations (= amputations above the ankle)!

Prg.: Without good prevention and therapy high risk of amputation. After amputation 50 % of the patients die within 3 years (caused by further complications of diabetes).

▶ Diabetic retinopathy - annual ophtalmological examination !

Nonproliferative (background-) retinopathy		**Proliferative retinopathy**	
Microaneurysms intraretinal haemorrhages	IRMA `pearlstring` veins	Proliferations of vessels	Preretinal haemorrh. retinal detachment
↑	↑	↑	↑
Panretinal laser coagulation			Surgery of vitreous body (vitrectomy)

Remember: Intensified insulin therapy in type 1 diabetes can reduce the risk of diabetic retinopathy by circa 75 % (DCCT study). The HbA1c should not be lowered too rapidly

▶ Diabetic macula oedema (can occur in every stage of the diabetic retinopathy):
Focal laser coagulation, infiltrative injection of glucocorticosteroids or VEGF-antagonists (off-label use)

▶ Diabetic polyneuropathy:
- Only optimum blood glucose stabilization can lead to improvement! HbA1c target of < 6,5 – 7%.
- In order to ease symptoms various pharmacological substances are recommended: Antidepressants (i.e. amitryptyline or duloxetine), anticonvulsants (i.e. carbamazepine, pregabalin), antioxidants (i.e. α-lipoic acid) and analgetics.

▶ ADN with gastroparesis: Metoclopramide often loses its action after few weeks. Attention has to be paid to postprandial hypoglycaemias in insulin therapy poss. adjustment of injection-meal interval! In therapy resistent gastroparesis poss. implantation of a gastric pacemaker.

▶ Diabetic nephropathy (DN): Annual screening for micro- and\or macroalbuminuria!
- Aim for BP readings in the normal lower range! (see above), preferably with ACE inhibitors or AT1 blockers, which act renoprotectively.
- Avoidance of nephrotoxic substances
- In persisting proteinuria: Protein restriction (0,8 g/kg BW/d), preferably fish and vegetarian proteins, diet low in sodium chloride (limit NaCl supply to 6 g/d).

▶ Erectile dysfunction:
- Urological history + diagnostic (exclusion of a deficiency in testosterone and of a hyperprolactinaemia; drug history; SKAT test, diagnostic of arterial + venous vessels)
- Therapeutic options:
  - Phosphodiesterase-5-inhibitors: Sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®)
    SE: e.g. headaches, facial flushing, drop in BP, esp. In combination with nitrates, molsidomin or alpha-blockers; rare visual disturbances or loss of eyesight
    CI: CHD, after myocardial infarction or stroke; simultaneous therapy with nitrates or molsidomin; arterial hypotonia, cardiac insufficiency among others
  - MUSE (pharmacologic urethral system for the erection) with prostaglandin E1 analogues, e.g. alprostadil is more comfortable for the patient than the selfinjection therapy into the cavernous body of the penis.
  - Vacuum pump if venous flow is too rapid

▶ **Diabetes therapy in pregnancy (incl. gestational diabetes):**
- Close cooperation between physician and obstetrician
- Extensive patient education
- If therapy with diet alone not possible, intensified conventional insulin therapy or insulin pump. Oral antidiabetics contraindicated. In known diabetes optimization of the metabolic control preconception.

Therapeutic targets: Preprandial blood glucose 60 - 90 mg/dl, 1 h postprandial < 140 mg/dl, 2 h postprandial < 120 mg/dl, median blood glucose < 100 mg/dl, normal HbA1c. If control is optimal, infant mortality is comparable with nondiabetics (< 1 %).
Gestational diabetes usually resolves post partum, but a high risk remains for later development of diabetes.

Consider an alteration of the insulin sensitivity in pregnancy:
1. Increasing insulin sensitivity with higher risk of hypoglycaemia in the 8. - 12. week of gestation
2. Decreasing insulin sensitivity during the 2. half of pregnancy ➞ increase dose.
3. Returning insulin sensitivity immediately after delivery ➞ reduce dose.
4. Breast-feeding reduces the insulin requirements by circa 5 IU.

▶ **Diabetes and surgical procedures:**

- Circumstances: Insulin patient:

Preoperative minimum requirement: circulation stable, normal water and electrolyte balance, constant pH, blood glucose < 200 mg/dl.

Perioperative separate infusion of glucose 5 % plus necessary electrolytes (100 - 200 ml/h) + standard insulin i.v. via pump. Regulate insulin supply depending on blood glucose level (hourly controls). Check serum potassium every 4 h.

Alternative: appropriate insulin supply by application of insulin pumps.

Current blood glucose (mg/dl)	Insulin dose (IU/h)
120 - 180	1,0 if preoperative daily requirement < 40 IU 1,5 if preoperative daily requirement 40 - 80 IU 2,0 if preoperative daily requirement > 80 IU
> 180	each time 0,5 IU more
< 120	each time 0,5 IU less
≤ 100	reduce insulin supply or stop, increase glucose supply, blood glucose controls every 15 - 30 min.

In the following procedures a reduction in insulin requirement has to be taken into account postoperatively, with the danger of hypoglycaemias:

- Amputation of an extremity because of gangrene
- Excision of an infected organ (e.g. gallbladder)
- Drainage of an abscess or of a phlegmon
- Hypophysectomy, adrenalectomy, pheochromocytoma surgery
- Delivery via caesarian section

- Circumstances: Type 2 diabetes/patient on oral antidiabetics:

Metformin is to be stopped 48 h before surgery, no sulphonylureas on the day of surgery!

Minor and medium surgery: Infusion with 5 % of glucose (adding necessary electrolytes), to check blood glucose hourly.

Blood glucose < 200 mg/dl → surgery.

Blood glucose > 200 mg/dl → Insulin supply (see above)

SU with first postoperative meal, blood glucose monitoring

Major surgery: Preoperative change to insulin

Remember: Blood sugar normalization through insulin therapy can reduce the mortality in surgical intensive care patients by 30 % and septic complications by nearly 50 %!

▶ **Pancreas transplantation:**

Ind.: Secondary diabetic complications (i.e. nephropathy, retinopathy and neuropathy) or life threatening hypoglycaemias. No age restriction. Islet cell transplantation in very high surgical risks. A kidney in vivo donation should be considered in time before dialysis is required.

Procedures: Simultaneous pancreas/kidney transplantation (SPK), isolated pancreas transplantation (PTA) or pancreas transplantation after successful kidney transplantation (PAK)

The pancreas is transplanted heterotropic and it is drained either systemic (vena cava), portal venous, exocrine or cystic.

Immune suppression according to different protocols

Prg.: The 10 y. survival of diabetic patients with pancreas and kidney transplantation is 60% higher than of those patients who only had a kindney transplantation. Life expectancy of the diabetic dialysis patients increases from 8 years to 23 years after a successful transplantation. SPK is the most cost effective therapeutic option.

Conditions:

1. Detection of auto-antibodies against cytoplasmatic islet cell antibodies (ICA), insulin antibodies (IAA) or GAD-antibodies (glutamic acid decarboxylase) and/or decreased C-peptide.
2. Exclusion of severe cardio vascular impairment, malignancies and acute infections
3. Blood group compability and negative cross-match (mixed lymphocyte culture = MLC)

Co.: Haemorrhage, thrombosis, transplantation pancreatitis, rejection, infection, abscess

Rejection rate is dependent on the procedure and the immune suppression protocol, it varies between 5-20%. 90 day mortality up to 3.5%.

▶ **Therapy forms/diagnostic under clinical trials:**

- Development of an artificial endocrine pancreas = "Closed-Loop-System", consisting of continuous working glucose sensor, micro computer and insulin pump (e.g. `Ulm glucose clock´). Here the insulin supply is regulated via glucose controls (feedback regulated).
- Gene therapy of the type 1 diabetes (reprogramming of liver cells for insulin production)

Prg.: While the mortality from coma in diabetes has dropped from > 60 % (around 1900) to approx. 1 % (insulin, oral antidiabetics), nowadays diabetic mortality is determined by the extent of vascular damage: Vascular related causes of death in diabetes mellitus nowadays approach 80 %! Therefore every diabetic with a vascular risk factor (e.g. hypertension) should receive prophylactically ASA (100 mg/d). Reduce LDL cholesterol with statins to 100 mg/dl (in very high risk to 70 mg/dl).

With early aggressive treatment of diabetes and hypertension the prognosis is good; in cases of unsatisfactory control of diabetes life expectancy and quality are reduced.

The prognosis of type 2 diabetes can be improved substantially, by early normalisation of weight and central obesity!
Most common cause of death: Myocardial infarction (55 %) and/or renal failure (> 40 %). In former times almost 10 % of type 1 diabetics became blind due to retinopathy!
Poor metabolic control further increases the danger of late complications such as autonomic diabetic neuropathy and diabetic foot syndrome.

Pro.: Various intervention trials for prophylaxis of type 1 diabetes:
- Primary prevention: The risk for type 1 diabetes could be reduced by 80 % in Finland due to vitamin D prophylaxis.
- Secondary prevention → target group: antibody +, but no manifest diabetes mellitus yet (until now without success)

COMA DIABETICUM = HYPERGLYCAEMIC COMA [E14.0]

Def.: The coma diabeticum is a severe metabolic imbalance with a severe defect of the sensorium, caused by a relative or absolute insulin deficiency. Only 10 % of the patients are in fact unconscious according to neurological definition.

Causative factors:

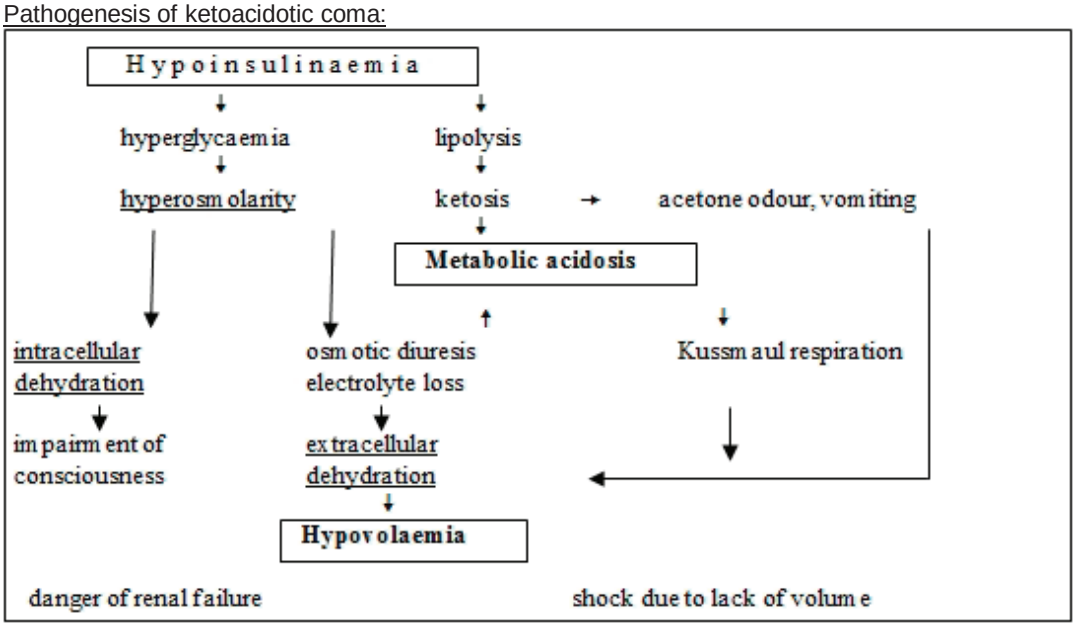
Absolute or relative insulin deficiency
- Absent exogenic insulin supply:
  - First manifestation of previously unrecognized diabetes
  - Omitted injection; interrupted insulin supply in insulin pumps
  - Oral medication instead of insulin (in insulin dependence)
- Insufficient exogenic insulin supply:
  - Insufficient dose prescribed
  - Technical error in the calculation of dose and injection
- Increased insulin demand:
  - Infection (pneumonia, UTI etc)
  - Dietary error
  - Surgery, accident, pregnancy
  - Gastrointestinal disorders
  - Myocardial infarction
  - Hyperthyreosis
  - Therapy with saluretics, corticosteroids

In 25 % of cases it is a so-called manifestation coma, meaning that diabetes mellitus is diagnosed for the first time in the state of the coma. Infections represent the most common triggering cause (circa 40 %)!

Pg.: The ketoacidotic coma if typical of type 1 diabetes, the hyperosmolar coma of type 2 diabetes.

Remember: Absence of a diabetic ketoacidosis (DKA)does not exclude a coma diabeticum!

Pathogenesis of ketoacidotic coma:



- Pathogenesis of hyperosmolar coma:
  A relative insulin deficiency leads to decreased peripheral glucose utilization, while at the same time there is an increased hepatic release of glucose. In this case small amounts of insulin prevent the ketosis through inhibition of the lipolysis in the fat tissue.

Cl.: 3 clinical forms of the diabetic decompensation:

- Cardio vascular form (lack of volume, shock)
- Renal form (acute renal failure)
- Pseudoperitonitic form: Signs of peritoneal irritation, atonia of stomach and intestines, esp. gastric wind (→ aspiration tube!)
  DD: Acute abdomen

Assessment of the severity of an impairment of consciousness using the Glasgow coma scale:

		Points
eye opening	spontaneous	4
	in response to speech	3
	to response to pain	2
	no eye opening	1
verbal reaction	oriented	5
	confused	4
	random words	3
	moaning, no words	2
	none	1
motor response	carrying out requests	6
	localizing response to pain	5
	withdraws to pain	4
	flexor response to pain	3
	extensor posturing to pain	2
	no response to pain	1
maximum score		15
minimum score		3

	Hyperosmolar coma (typical of type 2 diabetes)	**Ketoacidotic coma (typical of type 1 diabetes)**
Precoma	– loss of appetite, vomiting – thirst, polydipsia, polyuria – weakness, tachypnoea – signs of the dehydration with tendency to collapse (strongest in the hyperosmolar coma)	
	Insidious onset !	poss. pseudoperitonitis (abdominal pain) poss. acidotic (deep) respiration
Coma	2. Dehydration and development of shock (pulse ↑, RR and CVP ↓) 3. Oligo-anuria, reduced reflexes 4. ECG: signs of hypokalaemia and poss. arrhythmias laboratory: 5. Hyperglycaemia 6. Glucosuria 7. Serum Na^+ normal or mild decreased 8. Serum K^+ variable: despite loss of potassium the K^+ levels in the serum can be normal or elevated due to acidosis before the start of the insulin therapy. 9. HCT + Hb ↑, leucocytosis	
	hyperglycaemia > 600 mg/dl hyperosmolality > 300 mosmol/kg H2O minimal acetonuria	hyperglycaemia > 350 mg/dl ketonuria: in urine stix acetone +++ ketonaemia: β-hydroxybutyrate > 5 mmol/l metabolic acidosis with standard bicarbonate 8 - 10 mmol/l anion gap increased through ketone bodies

Serum osmolality (in mosmol/kg H_2O) = 1,86 x Na^+ + glucose + urea + 9
(all in mmol/l; if quoted in mg/dl → to divide glucose by factor 18 and urea by factor 6)

Gap of anions (in mmol/l) = (Na^+) – (Cl^-) – ($HCO3^-$)
Reference value: 8 - 16 mmol/l

DD: Causes of a loss of consciousness:

1. Toxic:
   - Exogenous intoxication (esp. alcohol, heroin, sedatives, psychopharmaceutical drugs)
   - Endogenous intoxication (uraemia, coma hepaticum)

2. Cardiovascular:
   - Collapse
   - Shock
   - Stokes-Adams syncope, circulatory arrest
3. Endocrine disorders:
   - Hypoglycaemic shock, coma diabeticum
   - Addison´s disease
   - Thyrotoxic crisis and myxoedematous coma
   - Hypophyseal coma
   - Hypercalcaemic crisis
   - Diabetes insipidus
4) Cerebral diseases (***Note:*** Often with reactive hyperglycaemia!)
   Hypertonic massive haemorrhage, encephalomalacia, subarachnoid haemorrhage, sub-/epidural haematoma, head-brain injury, epilepsy, meningitis, encephalitis, sinus thrombosis, generalised seizure etc
5) Psychological: Hysteria
6) Anoxaemic: Suffocation, hypercapnia in respiratory failure
7) Lactoacidotic coma
   Cause: Severe hypoxia, following fructose infusion in fructose intolerance, very rarely SE of biguanide therapy (di.: blood lactate ↑)

DD	**Coma diabeticum**	**Hypoglycaemic shock** [E15]
development	slowly, days	sudden, minutes
Hunger		+ + +
Thirst	+ + +	
muscular system	hypotonic **never convulsions**	hypertonic, tremor
Skin	dry !!!	Sweating
breathing	Deep respiration,* ketotic odour	Normal
Eye balls	soft	Normal
	fever, abdominal pain	delirium prodrome (incorrect diagnosis: alcohol abuse!); poss. picture of a cerebral infarction with neurological deficit; Babinski positive, poss. epileptic seizures

* In hyperosmolar coma normal breathing, because no ketoacidosis (→ and no ketotic odour!).

The DD between coma diabeticum and hypoglycaemia is easily made with capillary finger glucose testing.
Should there be the slightest doubt in the differential diagnosis (emergency service, blood glucose meter not available), insulin should never be administered, as it can quickly cause death!

Di.: History/clinical picture - laboratory (blood glucose ↑, in diabetic ketoacidosis (DKA) β-hydroxybutyrate ↑)

Th.: Intensive therapy unit

A) General measures:
- Control of respiration, circulation, fluid/electrolyte balance
- Insertion of urinary catheter for fluid balance monitoring (+ antibiotic prophylaxis)
- Central venous catheter for measurement of CVP
- Gastric tube (because of gastric atonia and pyloric spasm with nausea)
- Close laboratory monitoring (blood glucose hourly, potassium + blood gases every 2 h)
- Ulcer and thromboembolic prophylaxis (low-dose heparin)

B) Specific therapy:

1. Treatment of dehydration and hyperosmolality:
   In untreated diabetic coma hypernatraemia due to dehydration occurs, but there is also a concomitant sodium renal loss. With normal urine output and a moderate hypernatraemia (< 150 mmol/l) rehydration with normal saline (0,9 % NaCl) is indicated. The use of semi-isotonic NaCl solutions or hypoosmolar full electrolyte solutions can be indicated in severe hypernatraemia (> 150 mmol/l) or severe hyperosmolality (> 320 mosmol/kg H2O).
   Dose in relation to time: In the 1. hour 1000 ml, after that depending on the CVP: 0 cm → 1.000 ml/h, 1 - 3 cm → 500 ml/h, 4 - 8 cm → 250 ml/h, 9 – 12 cm → 100 ml/h. In the first 8 hours the average fluid requirement totals 5 - 6 l. After the 8. hour 250 ml/h is often sufficient.
   Dose adjustment depends on diuresis and clinical picture (in patients with cardiac impairment avoid too rapid infusion → danger of pulmonary oedema!).
2. Insulin therapy:
   Use only standard insulin! Plasma half-life of insulin circa 5 minutes. Various dose patterns are recommended. The „low-dose“ insulin therapy with an initial bolus of 20 U i.v., followed by 5 U of standard insulin/h i.v. via dosage pump has proved successful in most patients.

If hypokalaemia exists before insulin therapy (which rarely is the case), it should be balanced first. No insulin therapy without accompanying volume supply (point 1).
The blood glucose should not be lowered faster than 100 mg/dl per hour and initially not < 250 mg/dl (too rapid lowering of the blood glucose can lead to damages to the retina).
Advantage of the „low-dose" insulin therapy: Smaller incidence of hypokalaemia and hypoglycaemia in the course of the therapy as well as lower risk of cerebral oedema.
Disadvantage: Some patients require higher doses: If blood glucose does not come down within 2 h with the initial dose, the dose must be doubled (in rare cases far higher amounts of insulin are necessary in order to break an insulin resistance). When the blood glucose is reduced to circa 250 mg/dl, the supply of standard insulin is reduced to 2 U/h with simultaneous infusion of 5 % glucose solution.

3. Correction of acidosis:
Through the effects of insulin, the acidosis is counteracted efficiently by inhibition of the lipolysis. A mild acidosis therefore does not require correction! Cautious administration of bicarbonate only if the pH drops to < 7,1, and give only 1/3 of the calculated requirement to avoid provoking a dangerous hypokalaemia!

4. Electrolyte balance:
- Sodium replacement with the fluid substitution
- Potassium replacement:
  Ind: After start of the insulin therapy, as soon as the blood glucose decreases
  CI: Anuria, hyperkalaemia
  Dose: Depending on the serum K^+ level and on the pH. In pH > 7,1 the following standard values are to be used:

Serum K^+ (mmol/l)	K^+ substitution (mmol/h)
< 3	20 - 25
3 - 4	15 - 20
> 4 - 5	10 - 15

  In this phase avoid cardiac glycosides (danger of digoxin toxity!). In cases of significant hypokalaemia (< 3 mmol/l) poss. interruption of the insulin supply.
- Phosphate replacement:
  Ind: Poss. in serum phosphate < 0,5 mmol/l
  CI: Renal insufficiency
  Dose: Circa 50 mmol/24 h

Remember: Low dose insulin therapy and slow correction of the metabolic imbalance reduces complication rate! Fluid shifts in the CNS during diabetic coma take time to normalise. It is to be expected that the patient may not regain consciousness immediately, following correction of blood glucose, pH and volume/electrolyte imbalances.

Transition from coma therapy to oral nutrition:
Build up with light diet, e.g. initial gruel diet, while before every meal a small administration of standard insulin is given s.c.. After that readjustment of the diabetes.

HYPOGLYCAEMIA [E 16.2] and HYPOGLYCAEMIC SHOCK [E 15]

Syn.: Hypoglycaemic shock, coma hypoglycaemicum

Def.: Blood glucose < 40 mg/dl (< 2,2 mmol/l) or
Whipple Trias: BG < 45 mg/dl (< 2,5 mmol/l) + hypoglycaemic symptoms + disappearance of these symptoms after administration of glucose

Aet.: A) Fasting hypoglycaemia:
- Insulinomas, Extrapancreatic tumours (e.g. hepatocellular carcinoma)
- Very rarely paraneoplastic secretion of insulin-like peptides (e.g. IGF II)
- Severe liver disease (reduced gluconeogenesis and glucose release), uraemia (substrate deficiency for gluconeogenesis)
- Insufficiency of the adrenal cortex or anterior pituitary (failure of contrainsulin working hormones)
- Very rare β-cell hyperplasia in the first years of life (nesidioblastosis) through mutation of the sulfonylurea receptor
- Glycogenoses
- Renal hypoglycaemia (renal diabetes mellitus)
- Hypoglycaemia of the newborn of a diabetic mother

B) Reactive (postprandial) hypoglycaemia:
- Early stages of diabetes mellitus
- Gastric emptying disorder due to autonomous neuropathy (diabetic gastroparesis)
- Dumping syndrome after gastric resection

- Reactive postprandial or adrenergic postprandial syndrome in an increased vegetative sensitivity towards and adrenergic contra-regulation.
- Rare hereditary defects (e.g. leucin hypersensitivity, fructose intolerance)

C) Exogenous hypoglycaemia:
- Overdosage of insulin or sulphonylureas (most common cause)
- Hypoglycaemia factitia: Nonaccidental due to insulin injections or ingestion of sulfonylureas (psychotic, suicidal or criminal)

Characteristics: Hypoglycaemia occurs erratically and independently of meals. Affected individuals are often health professionals or relatives of diabetics.
- Excessive alcohol consumption while fasting
- Interactions of drugs with antidiabetic agents (e.g. sulfonamides, nonsteroidal antirheumatics, beta-blockers, ACE inhibitors)

Causes of a hypoglycaemia in diabetes mellitus:

1. Most common, relative overdosage of insulin or sulphonylureas, e.g. if a patient omits usual food intake during an intercurrent illness, while continuing to take the hypoglycaemic agent in the usual dose! Following new adjustment of sulphonylureas the metabolic state can improve after approx. 3 weeks, when hypoglycaemia can occur unless dose reduction is instituted. During intensified insulin therapy with optimum blood glucose and HBA1c levels, hypoglycaemia can easily be induced. In the event of frequent hypoglycaemias, the perception of hypoglycaemia isreduced, so that autonomous warning symptoms are frequently not perceived in time.
2. Interference with blood glucose lowering drugs
3. Absolute overdose (accidental, suicidal, criminal)
4. Heavy physical strain
5. Alcohol consumption (alcohol inhibits gluconeogenesis)

Cl.:

Phases	Symptoms and clinical signs
c) Autonomous symptoms: a) Parasympathetic reactions b) Sympathic reactions	 Very intensive hunger, nausea, vomiting, weakness Agitation, sweating, tachycardia, tremor, mydriasis, hypertension
4. Central nervous = neuroglucopaenic symptoms	Headaches, endocrine mental syndrome (mood swings, irritability, poor concentration, confusion), impaired coordination, primitive automatisms (grimacing, grasping, smacking), convulsions, focal signs (hemiplegia, aphasia, diplopia), somnolence. Hypoglycaemic shock = hypoglycaemic coma, central impairment of respiration and circulation

In severe autonomic neuropathy the symptoms under 1 can be reduced or absent!
Glucose is the only source of energy used in cerebral metabolism → high sensitivity of the brain to hypoglycaemia.

DD: Coma diabeticum (DD-chart: see there), psychoses, epilepsy, CVA etc

Remember: In suddenly occurring, aetiologically unclear neurological or psychiatric symptoms, always think of hypoglycaemia and check blood glucose!

Di.: Determination of blood glucose concentration in every emergency! Hypoglycaemic symptoms occur in most cases only with values < 50 mg/dl (in diabetics they can occur above that value).

In spontaneous hypoglycaemia in nondiabetics the cause must be clarified by further investigations:
Determination of blood glucose, serum insulin and C-peptide during a spontaneous hypoglycaemia or in the 72 h fasting test (= fasting test with initial OGTT) with determination of the insulin/glucose ratio during a hypoglycaemia (see chap. insulinoma).
Insulin and C-peptide show a parallel increase in endogenous secretion; in hypoglycaemia due to exogenous insulin supply (hypoglycaemia factitia) the C-peptide is reduced! After taking sulfonyl-ureas (e.g. in a suicidal attempt) insulin and C-peptide are increased. Detection of glibenclamide in serum or proinsulin in serum (high in insulinoma, normal after having taken sulfonylureas) are in this instance of diagnostic help.
Delayed hypoglycaemia can be assessed by an OGTT over 5 h.

Th.: A) Causal:

As far as possible elimination of the triggering cause, poss. preserving a blood sample for further diagnostic evaluation

B) Symptomatic:

Mild hypoglycaemia (still conscious): 5 - 20 g of glucose = dextrose = grape sugar (poss. as well saccharose = cane and beet sugar) orally. Oligosaccharide drink (fruit juices, cola) are also suitable, as long as no therapy with acarbose (α-glucosidase inhibitor) took place.

Severe hypoglycaemia: 40 - 100 ml of 40 % glucose i.v. under blood glucose monitoring, subsequently 5 % glucose per infusion (until blood glucose circa 200 mg/dl).

Glucagon:

If no venous access possible, the patient is aggressive or first aid has been unprofessional: 1 mg of glucagon i.m. or s.c. (e.g. GlucaGen Hypokit®): Increase of endogenous glucose production. Glucagon has no effect if glycogen reserve is exhausted.
After regaining consciousness immediately continue administration of glucose orally or i.v. while monitoring the blood glucose.

Therapy of reactive hypoglycaemias in vegetative instability: Diet poor in carbohydrates, rich in fat and proteins in form of many small meals, application of parasympatholytics or poss. also non-cardioselective Betablocker.

Therapy of dumping-syndrome: See chapter

Therapy of insulinoma: See there

Pro.: Education of diabetics to enable them to be aware of early symptoms of a hypoglycaemia (increase of the "hypoglycaemia awareness").

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