Pocket Guide ENDO-DIAB-NET® 2024

"Medicine is a science of uncertainty and an art of probability" William Osler

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Emergencies Addison's (p6), Hypertensive crisis (2, 4); Hyper- & Hypoglycemia (10).
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1. Goals & Manual on how to use it

- Practical & as best as possible evidence-based, weighted guidelines (%Sensitivity / %Specificity), ie.
  Essential, Important, Good-to-know, Helpful, "my Prof told me" a/o controversial, Passed eye test! You never give up, do you? Forget it, there are more important things in life
- Guidelines ⇒ structured "standard of care" ⇒ Optimisation of patient care
- Stepwise (1→2→ 3→4→5) & standardised assessment (possibly by specialist; better by specialist)
- Can be adapted individually, if **well-founded**. Several mosaic pieces are needed to get a medical picture.
- Should cover about 75% of the daily clinical routine. Remaining 25% ⇒ "Meet-the-Professor" & "Gut feeling" & PubMed
- State of error ⇒ will be adjusted "on an ongoing basis" ⇒ constructive input welcome
- Knowledge, learned by and then soon expected of the endo/diab/metabolic ward doctor
- Additional information become visible when clicking on text passages highlighted in yellow
- Consensus **EndoDiabNet™ Aarau - Basel - Lucerne - Winterthur** & associated clinics:
- **Weblinks** **http://www.endo-diab-net.ch/pocketguide/pocketguide.pdf** ; **Lecture archive**
  SWISS ENDO GRAND ROUNDS PW for videos: !endograndRounds23*
- Any changes to the Pocket Guide & suggestions for the seminar can be submitted to the SGED office@sgedssed.ch

Abbreviations: **1°**=primary; **2°**=secondary; **3°**=tertiary; **Δ=**Delta, change; **ABI**=Ankle-Brachial Index; **acc**=according to; **CEI**=angiotensin converting enzyme inhibitor; **AI**=adrenal insufficiency; **Aldo**=aldosterone; **ARR**=aldosterone renin ratio; **AUI**=autoimmune sy; **BP**=2xdaily; **BMD**=bone mineral density (Dexa), **BP** =blood pressure; **BR**=bed rest; **BT**=blood test; **bw**=body weight; **Ca**=carcinoma, calcium; **Carb**=Carbohydrate **CDE**=cert.diabetes educator, **C_2=OH=**alcohol; **cf**=see; **CI**=contraindication; **CIR**=Carbohydrate-to-Insulin-Ration = Resistenzfaktor (**RF**); **cvR**=cardiovascular risk (factors); **CHF**=congestive heart failure; **CKD**=chronic kidney disease; **CL**=clearance; **COC**=combined oral contraceptives; **d**=day; **dly**=daily; **DD**=differential-dg; **Dg**=diagnosis; **Dm**=diabetes mellitus; **E**=Epinephrine; **ED**=erectile dysfunction; **ER**=emergency room; **esp**=especially **FD**=first dg; **F**=female; **FamH**=family history; **fct**=functional; **GW**=Gestation Week; **FAQ**=frequently asked questions; **F/U**=follow up; **fMN**=free metanephrine; **fNMN**=free normetanephrine; **Fx**=fracture; **FNA**=fine needle aspiration; **GD**=Graves' disease; **GP**=general practitioner; **gw**=gestational week; **Has**=hashimoto; **HC**=hydrocortisone; **HCL**=Hybrid Closed Loop; **HRT**=hormonal replacement therapy; **IHT**=insulin hypoglycemia test; **HF**=heart failure; **HR**= heart rate **HRT**=Hormonal Replacement Therapy; **ICM**=ionated contrast media **IR**=insulin resistance; **HI**=health insurance; **LADA**=Late-onset/Latent Autoimmune Dm of Adulthood; **LF**=liver failure; **LSI**=last sexual intercourse **M**=male; **M**=mol/L; **M**=meal; **MD**=physician; **MDI**=Multiple Daily Injections; **Meta**=metastasis; **met Sy**=metabolic Syndrome **MRA**=Mineralocorticoid-Antagonist; **NB**=nota bene!; **NE**=norepinephrine; **NC**=nutrition counseling, **n**=normal/normally; **NAD**=no abnormality detected **NTI**=non thyroidal illness; **fast**=fasting; **OAD**=oral antidiabetic drugs; **OC**=oral contraceptive; **OSAS**=obstructive sleep apnea sy; **P**=plasma; **PG**=pregnancy; **pHpt**=prim. Hyperparathyroidism; **PerH**=personal history **POF**=premature ovarian failure; **PoHI**=permission of health insurance ("PoHI") **pop**=population; **poss**=possibly**; pp**=postprandial; **psb**=please see below **PRL**=prolactin; **qid**=4x/d; **qd**=1x/d; **q6h**=6 hourly; **sa**=see above; **sb**=see below; **S**=serum; **SE**=side effect, **SGA:** Small for Gestational Age; **SOP**=standard operating procedure; **Subst**=substitution; **Susp of**=suspicion of, **Stx**=strumectomy; **Sx**=surgery **Sy**=syndrome, symptom, **TC**=total cholesterol, **TG**=triglycerides; **Tg**=thyroglobulin; **Thy**=thyroid; **tid**=3x/d; TIR= Time In Range **TMNG**=Toxic multinodular goiter; **TPN**=total parenteral nutrition; **Tu**=tumor; **Tx**=therapy, **TMNG**=toxic adenoma; **U**=urine; **US**=ultrasonography; **VF**=visual field; **VP**=venipuncture; **wt**=weight; **WHR** =waist (aBPominal ø)-Hip (Troch. major)-ratio; **wkly**=weekly, **AbküFi KSA**

Disclaimer: Half of what we teach you is wrong, but we don't know which half…support research to find out !
Protection fee (= a little funding for our research…): € 45.-, $ 50.-, **CHF 45.-** („was nichts kostet, ist nichts wert…")
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2. Art. Hypertension & adrenal Incidentaloma

„When you hear hoof clapper in the central park, first think of horses, then look for zebras“

SMF 05; 5: 317-21 & 341-4; JCEM 2010; 95:4106-13; Endo Rev 04: 25: 309-40, NEJM 07; 356: 2372-80, EJE 09; 161: 513-27, Lancet 2010; 376: 1903-09

Arterial Hypertension

”Office BP” > 140 / 90mmHg (“Autom. BP” >130 / 80 mmHg), ≈20-30% of adults

>90% „essential“, cost/benefit of further diagnostics is debated -> selection based on cvR; verify increased BP with **24h-BP** (mean 24h-BP <120 / 80 mmHg, nocturnal BP-drop <10% ⇒ risk for end organ damage, OSAS, neuropathy) or **patient self-measurement** (automatic machine measurements (3x))

When to think of 2° hypertension?

- **Suggestive history & findings: sudden onset, <25-40Yrs, BP>160/100mmHg, "Spills", pos FamHx**
- **Resistance to tx:** BP>140/90 despite **quadrupple-therapy for several wks** (incl diuretics), BP↑ under Tx (**Compliance?**)
- **End organ damage: left ventricular hypertrophy** (Echo, BNP & EKG (insensitiv)), **atherosklerosis** (Makroangiopathy (CHD, CVI<50Yrs, aortic aneurysm, CKD, Microalbuminuria (Alb/Crea iU↑), macular edema **cvR:** met. Sy, smoking, age, pos FamHx, no nocturnal dipping

Stepwise diagnosis of 2° hypertonsion

1) "Stress/life-style", 30%. „white-coat“(⇒ 24h-BP), intracranial pressure, **NaCl-diet >9g/d?** (Na >180mmol/24hUrin)

2) Met Sy? (p7ff), **OSAS** Score D, F: snoring, day-time sleepiness, headache ⇒pulsoxymetry

3) Vascular: Renal (>70% renal artery stenosis, often atheroscl.): flow murmurs, >30% Crea ↑ after ACEI
⇒ duplex-US (90%/80%) & active plasma renin (aPR) recumbent ↑ (p3) urine sediment, MRI-angio (97%/93%)
Aortic insufficiency or stenosis (atheroscl./coarctatio)? Radial-Femoral Pulse Delay or BP BPs: righ>left arm or BP right Arm>Bein ⇒ angiography

4) Drugs compliance? NSAID, steroids, anabolics, cyclosporin, antidepressiants, COC (e2), alkocol(-withdrawal), cokain, licorice

5) Pregnancy (EPH-gestosis, p12: LMP? (HCG-test), **polyglobulia**, porphyria

6) "Dessert" Endocrine cause (10-20%) — **Screening-Test** (clinical pretest-probability → laboratory test → Imaging!)

- **Hyperaldosteronism** (2-10%, p3) ⇒ **S-K<4mM?** (on diuretiks <3.5mM? OSAS?) →**aldosterone/renin-ratio (ARR)**
- **Cushing syndrome** (p5) ⇒ **Signs & Symptoms? → free urine cortisol (FUC)**
- **Pheochromocytoma /Paraganglioma** (p4) ⇒ **Trias? → plasma metanephrines & normetanephrines**
- Dysthyroidism (Hyper→BP_{syst}↑; Hypo→$BP_{diastole}$↑) (p19f) ⇒ TSH
- pHpt, acromegaly (signs & symptoms?) (p16, 23) ⇒ Ca^{2+}, IgF1
- Deoxycortisol (DOC)-excess ⇒ K & Aldo & Renin low → HPLC steroid profile i 24h-urine Inselspital Bern
- Monogenetic variants (e.g. mutations of mineralocorticoid-receptors) ⇒ pos. FamHx, poss. K, Mg low, Aldo & Renin “normal”, worseninf in pregnancy or cyklus, → genetics A. Lauber, Fribourg

Tx: Δ Lifestyle! Nicotine↓, Excercise↑ (>5x30’/wk), **wt↓** (Δ5kg≈Δ10mmHg, vegetable & fruits↑, saturated fattyacids↓), **NaCl↓** (2g/d↓ ideally <5g/d, 24h-urine Na<80mM/d, avoid premanufactured food, use Na-depleted salt (e.g. magdi sol), fresh herbs). **Drug choice & BP-target depend of cvR**: **ACEI** & **diuretics**, **Ca-Antag** (P-Ca↑), βBlocker (KHK), **AT-II Antagon.** (ATA), poss. with Neprilysin-inhib. (Entresto ® in CHF), **Renin-inhib.** aliskiren (Rasilez® Tbl. 150, 300mg qd) **MRA** (KI: K↑): spironolactone (Aldactrone ® Tbl. 25-100mg) / eplerenone (Inspra ® Tbl. 25mg BP; Ind: CHF) / finerenone (Kerendia ® Tbl. 10-20mg qd, **Ind:** Dm2 to delay CKD, PoHI); **α-Blocker** monoxidine Physiotens® Tbl. 0.4mg qd; **aldosterone synthase inh** baxdrostat, lorundostat

Tx-resistant hypertension: „drug rotation“, orthostasis? **Compliance?** poss. efore bedtime (nächtl. Dipping!), individualised Tx
(rel) CI: thiazide: CKD, gout, pHpt; **βB**: Asthma; **Cyp3A4↓** (verapamil / diltiazem, Plendil): grapefruit; **NSAID** ⇒ antihypertensive-effect↓, **pregnancy:** p12

Hypertensive urgency BP > 180/110mmHg & headache, epistaxis, psychomot. agitation & NO acute end organ damage; **Tx:** po & ambulatory, **nifedipine** (adalat ret® 20mg⇒CR 60po, **CI**: SS, aortic stenosis), **captopril** (Lopirin® 12.5-25mg po tid (-100mg/d), **CI:** SS, bilat NAS, CKD), **labetalol** (Trandate® 200-400mg po tid, **CI:** asthma, AV-block, acute CHF, low T1/2 3-6h), **clonidine** (Catapresan®, OH-delirium, 0.15mg po, **CI:** CHD, AV-block)

Hypertensive emergency DG: BP +/- > 200/**120mmHg & acute end organ damage** (Neurol Sy (enzephalopathy, bleeding), acute pulm. edema, ACS, eye sy (papillary edema, bleeings, exsudates)), **TH:** iv & inpatient (ICU), immediate BP↓, **labetalol** (Trandate®, CHD, 10-20-80mg iv q15’, **CI:** sa), **urapidil** (Ebrantil® 10mg weise iv; **phentolamin** (Regitin®, pheochromocytoma, 5-10mg iv q10’); **ICU: Nitroprussid** (CHD w CHF, 0.25-10ug/kg/’); nitroglycerin (Perlinganit®, CHD w acute HF, 5-100 ug/‘ iv); **esmolol** (Brevibloc®, CHD, 200-500 x 4min⇒50-300 mg/kg/’ kont. iv), **furosemide** (Lasix®, acute HF, 40-250mg iv)

Adrenal incidentaloma

DEF: Incidentally detected adrenal mass >1cm; ENS@T-biobank

Prevalence: ≈2% (20y) -7% (70y, Tu-Pat), 10% bilateral **2 questions: hormonally active?** (typ. <2cm & <10-20HU, 25% hormonally active (cortisol>catechol.), 30% of these asymptomatic); **malignancy (ACC)?** (4%, 99% metastases, size (<4cm 5%, >6cm 25%), course in F/U, peak 1-10 & 50-60y)

SY: Hypertension? S-K<4mM? signs of Cushing (p5, incl. met. Sy, osteopenia/porosis)? Pheo-Triad? Virilisation?

DD „bilat. big adrenals": CAH/AGS (p17), Conn, Cushing (incl. BMAH p. 5); MEN, metastasis, infection (tbc), **assess adrenal insuff.**

DG: Na, **K, Crea**, Urea, **ARR** (p3), FUC (p5), ACTH, **fMN, fNMN** (CHUV, if >10HU i CT), DHEA-S; Testosteron, 17OH-Prog n 250ug ACTH (p 17)
- **& metabol. Sy a/o osteopenia/porosis → autonomous cortisol-secretion? 1mg DST <50nM no, >138nM → Sx;**
50-138nM: mild autonomous cortisol secreation (**MACS**); individually based on RF (f>m, low-normal ACTH) 6-12mtl. follow-up vs Sx. 2mg DST?

P-DHEA-S <3mM (wg part. suppr. ACTH) ⇒ ad Sx, poss. 3x **salivary cortisol a/o 24h-urine (20ml 6M HCl):** K, Aldost, **Cortisol,** MN, NMN
suspected ACC ⇒ steroidprofile 24h-urine to measure precursors with mineralocorticoid action, e.g., 11-DOC

Imaging: Benign: **noncontrast CT < 10HU and homogenous** (myelolipoma: heterogenous, <-40HU in lipid rich areas) →No F/U (> 40 yrs)
CT w contrast: relative washout: > 58% (> 40%?), absolute > 60%, **MRI:** loss of signal in/out phase; **FDG PET-CT:** Absence of FDG uptake or uptake less than liver;. Indeterminate **noncontrast CT** HU > 10 (> 20) and / or heterogenous and / or size > 4cm (illustration), **MRI:** no loss of signal, **PET-CT:** high uptake, **CT with contrast:** washout slow; **further action dependent on est. malignancy risk → tumor board**; immediate additional imaging, interval imaging 6-12 months or surgery (with prior tumor staging: CT Thorax;PET-CT). Earlier surgery in pat < 40 yrs

F/U no F/U if >10HU in CT & homogenous; else 6-12 mthly, if no surgery, if no change in size in non-contrast CT /MRI:no further F/U; if significant growth with largest diameter > 20% (and > 5mm) or hormonally active → Sx. if growth < 20%: poss. additional F/U imaging 6-12 months
Adrenal biopsy: limited indication, e.g.extra-adrenal malignancy if change of management. Lesion must be hormonally inactive and indeterminate. NOT in suspected ACC

NNR-Ca “ACC” **resectable:** individualized (depending on ENSAT staging, degree of resection, Ki67 index): Surgery, **mitotane** (Lysodren tab 0.5-1g QID, blood level 14-20mg/L, side effects: adrenal insufficiency, GIT, neuro), chemotherapy, local radiotherapy; **unresectable:** mitotane (s.a.), chemotherapy, local therapies (RT, SIRT, RFA).

***Validation Crea i 24h-U:** 100 (Twiggy) - 250 (A. Schwarzenegger) umol Crea/kg/d; **M** 11.7 – 17.6 mmol/d; **F** 7.0 – 9.5 mmol/d

GFR: Cl_{Crea} (ml/’) = U_{Crea} x U_{Vol} / (S_{Crea} x 1440’) ≈ (140-Age) x kg x 1.23 / $S_{Crea\ [uM]}$; **F** x 0.85; **reference range:** M 97-140; F 75 -125ml/’

3. Hyperaldosteronism

"Conn-Syndrome has generated a number of publications that equals the number of patients in whom it is the cause of hypertension"
Curr Opin Endo Diab 01; 8: 124-9, Lancet 99; 353: 1341-7, Clin Endo 02; 57: 457-65 & 07 ; 66 :607-18, JCEM 08; 93: 3266-81 & 09; 94: 3623-30 & 11; 96: 2771-8, EJCI 03: 33:787-93

Physiology: angiotensinogen (renin) ⇒ angiotensin I (ACE) ⇒ angiotensin II ⇒ aldosterone ↑⇒ renal K^+/H^+-excretion ↑; metabolic alkalosis (VBGA: HCO_3^-↑, Cl^-↓), S-Na(↑),P-Ca↑, P-Mg↓; **Hyperaldo = cvR** (CVI <50J (OR 2.5), CHD & CHF (OR 2), AFib, OSAS)
Na-deficiency→ P-aldosterone ↑; K-deficiency→ P-aldosterone↓, typ. salt in CH wholefood NaCl/d ≈ 12.5g (=5g Na+) ≈ 215mmol (1g Na = 43mmol); K/d ≈ 50-140mmol; K-losses: urine ≈ 40-120mmol > stool, sweat ≈ 0-10mmol each

1) Screening (debated! Cut-offs depend on context „functional vs hyperplasia vs adenoma"-**continuum**)

- art. Hypertension & P-Kalium↓ (spontaneous < 4 or <3.5 mM with „low-dose diuretics"), **a/o incidentaloma, OSAS, pos FamH**

2) Initial Dx **intraindividual variation**, **algorithms,** stop aldactone/eplerenone & aliskiren for 4 wks. β-Blocker, ACE-H/ATA (+/-Thiazid) ok, if aPR↓.

"AaRR" (P-Aldo / aktive P-Renin (aPR)-Ratio) n <30 (Sens. 98%, Spez. 82%) **bzw. >35** (90%/ 86%) **pM/mU/L, cave:**

a) BT 08h, fasting, seated for 10', **analytics (KSA):** EDTA-plasma, aktive tenin LIAISON direct renin assay, aldosterone LIAISON

b) **AaRR validated for euvolemia & K>3.5mM & S-aldosterone >420pM**, poss. repeat (hypo-Na a/o hypovol. -> Renin↑ & Aldo↑)
⇒ **K-enriched diet** a/o **KCl Hausmann 2 drg tid** (745.5mg=10mmol K/Drg) poss w ACEI/ATA (aPR only (↑) → demasks hyperaldo & art. hypertension↑

c) **AaRR↑** βBlocker, NSAID, methyldopa, clonidine, drospirenon / luteal phase & OC, CKD, Age; 8am, aliskiren (<2Wo (PRA↓ →ARR↑)
AaRR↓ aldactone & licorice (4wks); aliskiren (2 wks (aPR↑), **P-K↓, amilorid**(aldo↑/aPR↑↑)/thiazide/saluretic., ACEI & ARB (2wks), amlodipin, diltiazem, Dm, coffee, 11am

3) Confirmation Dx ideally with **"normal" NaCl-diet)** (dh, mMol/d 120 Na, 60 K), **poss. K-enriched diet,** women 1. half of mens. cycle

I) AaRR adapted BP-Tx doxazosin (Cardura CR ® 4-8mg qd), amlodipin (Norvasc ® 5-10mg qd), verapamil (Isoptin RR ® 240 qd-BP), minoxidil (Loniten ® 10-20mg bid) & orienting **spot urine** K-U/P ↑>10

II) 24h-urine stop KCl-Tbl. 2d pre-collection! **Aldosterone** (n<33nmol/d; >42), **K** (>30 (40) mmol/d,), **Na** >100 (200) mmol/d

III) Aldosterone-suppression tests S-aldo <140 pM ("exclusion") **>280 pM** ("diagnostic"), poss. Suppression >50% if basal value ↑↑ & aPR <5mU/L
a) oral NaCl-load NaCl 1-2Tbl 1g=17mmol (U_{Na}>200mM/d) & KCl 1-3 Tbl 745 mg (10mmol) or KCitrat effevescents (30mmol) tid or amilorid (due to S-K↓)
b) NaCl stress test D F outpatient: 2l 0.9% NaCl x 4h, supine, VP 0&2h m Na, K, crea, urea, aldosterone, cortisol f. a/c ratio (sens >90% (seated pat.))
c) Florinef-test inpatient; Tbl 0.2mg BP x3d & 1-3 KCl Drg tid/iv ⇒ VP 09h n. 60' upright (K-Kontrolle 2x/d; rel. CI: CHF, BP↑↑)
d)**Captopril-test** 2h n 25mg lopirin ® po, (normal: renin↑; Aldo 30%↓, ARR 20%↓, spec↑ f APA, diagnostic performance limited if low salt intake

4) Localisation & Classification

MRI (incl. Picture of NN-veins), poss. **CT-Abd cave:** Incidentaloma w contralat. Conn? → >35Yrs. & aldo<550pM →
- **adrenal-catheter (USB) SE:** NNR-thrombosis (radiol. expertise!) cortisol(C), aldo (A) of v.cava inf & adrenal both sides w 50ug/h ACTH-infusion.
a) catheter close to adrenal? $C_{NNR}/C_{V.cava\ inf}$ >5-10; **b) Lateralisation ?** $(A/C)_{side}/(A/C)_{control}$–ratio ≥4 & $A/C_{V.cava\ inf}$ > $(A/C)_{control}$)
c) contralaterale suppression $A_{NNR\ diseased\ side}$ >> $A_{V.cava\ inf}$ > $A_{NNR\ healthy\ side}$ ⇒ APA ad Op

Additional tests, if still ambiguous DD adenoma to hyperplasia
- Dex-ACTH-test: 1mg dexamethason (Milicorten®) 11pm; 250ug ACTH test 08h, BE n 0, 30, 60, **90** min, Conn-Sy: S-aldo >1050nM or >4x-increase 90 min / 0 min
- Orthostasistest: adenoma: 8am supine **S-aldo>700pM** (>400) (60%/100%), ↓ 2h upright (40%/100%);
- if S-aldo 400-700 ⇒ **aldactone-trial** (100→300mg/d spironolactone®x 4/52 ⇒ if BP ↓↓ ⇒ poss adrenalectomy
- **1.25l NaCl 0.9% iv x 2h** ⇒ aldosterone ("A", pM); cortisol ("C", nM); Adenom: $A/C_{after\ NaCl}$>2(>$A/C_{before\ NaCl}$)
- > 131-Iodine-cholesterol-szintigraphy under prednisone (ACTH↓↓; **Ind:** side-localisation of bilaterally enlarged adrenals

A) 1° Hyperaldosteronism: aldo↑ (typ. >450pM) & renin↓ (typ. <1mU/L) ⇒ ARR↑

Mostly caused by multiple microscopic aldosterone- producing foci with somatic driver mutations, formally divided into:

a) Conn-Sy ("dominant unilateral nodule or adenoma (APA/APN) present"): 50-70%, typ. 0.5-2.5cm, P-Aldo >550pM (90%/90%), Ca <2%
TH: lapr. adenomectomy → aldactone 1wk preop prevents postop aldo↓ (K↑, BP↓) **Tx:** NaCl po↑; Florinef Tbl. 0.05-0.1mg qd, if not possible/rejected → MRA & NaCL 5g/d
50% persist. hypertension (**RF:** >2 antihypertensive drugs; BMI >25mg/kg2; >6yrs hypertension; male), nevertheless **cvR↓**

b) Bilateral hyperplasia ("multiple aldosterone producing micronodules or diffuse hyperplasia"): 30-50%, DD: CAH (psb)
Tx: MRA (Mineralocorticoid-Receptor Antagonist): aldactone (Spironolactone® 50-200mg/d), **SE:** gynecomastia→eplerenone (Inspra® 25-100mg/d), less SE, PoHI (Ind f CHF); firenerone; **aldosterone synthase inh** baxdrostat, lorundostat **Alternative BP-Tx:** Norvasc ® 10mg/d, Reniten ® 20mg/d, Midamor ®(Amilorid) 5-30mg/d b K↓; if nodular poss. Op «debulking»

c) Familiar Glucocorticoid-remediable aldosteronism (GRA, <5%)
aut.-dom, pos FamH, promotor 11-β-hydroxyl. on aldo-synthase⇒ACTH-dependt, often only mild Sy K ↓ (50%, thiazids), and BP (↑⇒CVI)
DG Dex-suppressions-test 0.5mg po 6h x 3d ⇒ S-aldo <55pM (2ng/dl), 24h-U-aldo<5.4nmol/d (2ug/d) ⇒ PCR f mutation**; 250ug ACTH-Test** ⇒ aldo 30'&60'↑↑, **TH:** Amilorid (Midamor® 5-30mg/d; Dex 0.5mg/d (adrenal-suppr, stressprophyl.), aldactone (Antiandrogen, irregularities of mens. cycle), nifedipin
D) Urinary 18-oxy-cortisol ↑ (steroidprofiling of 24h-urine @ Inselspital Bern)

B) 2° Hyperaldosteronism: typical: S-K↓, alkalosis, but S-Na (↓) & aldo↑ & renin↑ ⇒ ARR↓

a) BP n/↓: cirrhosis, CHF, hypovol., GIT (vomitus, diarrhoa, Laxativa), hereditary or acquired (diuretics!) nephropathys
- **Thiazids ≈ Gitelman-Sy** (Mut. Na/Cl transporter in distal tubule ⇒ Na-reabsorption↓, K↓, Mg↓; **Tx:** amilorid (Midamor ®), E'lyt Subst.
- **Loop-diuretics** (furosemide, torasemide, "Pseudo-Bartter"-Sy), **≈ Bartter-Sy** (Mut. Na/K/Cl2 trsp in Henle-loop, K↓, Mg↓↓, Ca↓) **Tx:** NSAID, substitution of electrolytes, K-sparing diuretics

b) BP↑: renovascular hypertension (renal artery stenois > renal insufficiency >> renin-prod Tu ⇒ crea, US/Duplex)

C) Aldosterone-independent mineralocorticoid-exzess: Aldo(↓) & Renin(↓) ⇒ ARR(↓)

a) Familial (<2%, renal 11-HSD2 ↓: pos FamH, **DD:** licorice, chew tabac; **DG:** S-aldo↓; urin: cortisol (mineralcort. activity)↑ / cortisone↓ (>10, n <1), **Tx:** amilorid, eplerenone (poss aldactone), if no effect or SE: cortisone 10mg/d

b) CAH/AGS (p17)**:** 11β- (virilisation) >> 17α-hydroxylase↓ (androgen↓), corticosterone (DOC) & compound S↑, urine steroid profile (Inselspital)

c) abnormal steroid production (e.g., DOC) b incidentaloma (p 2), Cushing Sy (ectopic ACTH)

d) Liddle-Sy: aut-dom mutation of tubular Na-canal ⇒ Na-reabs & K-excr ↑ **TH:** amilorid (Midamor®), typical improvement to Bactrim ® (UTI)

e) K↑ (fct. hypoaldosteronism) **DD:** interstitial nephritis; renal-tubular acidosis, hypovolemia, CHF, Dm, drugs: ACEH / ATR-blocker; spironolactone, NSAID; pos. FamH: **Gordon-Sy** K&BP↑, renin ↓, aldo →↑; "pseudohypoaldo type 2", mut. KLHL3-gene thiazide-sens NaCl channel **Tx:** thiazide & NaCOH 1.2g

f) Monogenetic variants (e.g.,. mut. mineralocorticoid-receptors) ⇒ pos. FamH, poss. K, Mg low, aldo & renin "normal", exacerabtion pregnancy, mens. cycle, → for genetics A.. Lauber (Fribourg)

4. Pheochromocytoma & Paraganglioma (PPGL)

"The "great mimic": often sought, rarely found (Prävalenz 5/Mio)…yet, mostly discovered when it is too late… in autopsies
Endocrine Reviews 2021; NEJM 19; 381: 552-65, JCEM 10; 95; Lancet 05; 366: 665-75, SMF 12: 12: 66-71, Clin Endo 2022

10%(-40%) rule? children, extraadr. (symp od parasymp [=Glomustu]), bilat., multiple, maligne, rezdiv., familial (35% Keimbahn- Mut (va <20J), 35% Somat. Mut.)

1) SY Pressure elevation (BP↑, only 50% paroxysmal, typ. palpation/biopsy puncture BP↑, less psych. stress, **≈10% normoton**)
& Paroxysmal trias ("spells") a) Pain (headache), b) Perspiration / Pallor (trunk) c) Palpitationen (90%"or"/94%"and")
Plethora other Sy: dizziness, constipation, wt↓, PG↑↓, BP↑↓ (shock), orthostasis (Dopamin?), micturition-dependent crises (bladder tu), flush („menopause"), T↑, „psychosis", „spells" after metoclopramid, **50% „incidentaloma"!**
Polyendo Sy? MTC (MEN-2; 50% symptomatic, 30% BP↑); cerebral/retinal angioma or stroke (VHL) neck tu (glomustu), neurofibromas

2) DD sweating & flushing, panic attacks (>3/13 Sy; acute & max. within 10': palpitations, angina, dyspnoea, paresthesia, trembling, chills/flushing, sweating, nausea, drowsiness, fear of suffocation, derealisation/depersonalisation, feeling loss of control / going crazy, fear of death), **carcinoid** (red head, BP↓), **drugs / toxins** (cannabis, cocaine, ephedrine, "fashion drugs & pills")

3) „Before you start" assure specificity (avoid false positives)
Drugs? carbidopa – u levodopa (Madopar®) ⇒ Dopa↑ (→ Methoxytyramin↑)
Stop ≥2wk antidepressants (↑, tricyclics >SSRI (Venlafaxin)), clonidine (↓), **≥48h** Extasy ®, paracetamole (peak NMN in old assays without mass.spec), α & β blocker (labetalol & dibenzyrane ↑), C2; **BP-Th** w **Norvasc ®, Co-Reniten ®**, Loniten ®
Stress, exercise, hypoglycemia, OSAS, acute illness, **renal insuff.** (15-50%↑, renal clearance of free "conjugeated" sulfated (nor)metanephrines)
Diet? Effects on catecholamine & tyrosine (va false pos): avoid coffee (inkl. decaf), tea, cocaine & coke, nicotine, banana, chocolate

4) Screening; „**reference values**" dependent, if „healthy" („incidental.") or DD of arterial hypertension („hypert."), cave: CKD & HD
- Plasma Pat. Info D, F, morning, fasting, **30' supine,** "no stress" wait 30' after insertion of canula, centrifuge within 30', transport on ice
Metanephrine (MN) (95%/93%, adrenal, MEN2), **Free:** "incidental." >0.56nM; "hypert." >0.85nM, **Total:** "incidental." >7.5nM; "hypert." >11nM
Normetanephrine (NMN) (extra-adrenal, VHL) **free:** "incidental." >0.7nM, **total:** "incidental." >13nM; "hypert." >30nM; "Hypert." >1.3nM
Dopamin → **3-Methoxytyramin** if >0.2nM -> **paraganglioma?** neck → SDHB mut. & **metastasia,** false pos b CKD & nutrition ("total", sa),
if unclear: A (n 0.02-1.23nM, "adrenal"), **NA** (n 0.64-6.55nM, "extraadrenal") "Pheo" A+NA>12nM (2000ng/l); "Vd. a" >5nM (70%/86% wg "Stress", Sport)
- 24h-Urin (ohne(!) HCl-Säure, auf Sammelzeit & Lagerung (**4°C**) achten→ Pat. instruction for correct sampling ; **poss „postictale" urine** (event ⇒ discard unirne ⇒ collect next spoturine)
MN „Incidental." > 653nM/25h; „Hypertensiv" >1490nM/24h), **NMN** „Incidental." >1759nM/24h; „hypertensiv" >3800nM/24h)
nur noch selten nötig: **A** (n<15nmol/mmol Crea; <110nmol/d); **NA** (<75/<472) (90%/**90%**), VanillinMandelSäure (VMS) (<5/<33) (42%/ 95%) → obsolet!, maligne:Dopamin u. HVMS↑
Chromogranin A? (<5% nonsecretinng, cave PPI)

5) Further testing (if basal MN & NMN ↑↑(>4x))
Clonidin-suppression (80%/98%) drugs to stop sa (spec↓); 08-09h, fasting, recumbend ⇒ 300 ug Catapresan po 60-80 kg bw (4.2ug/kg bw).
⇒ BT -5', 0, 2h, **3h** (+BP +HR) ⇒ **Minimum NMN >0.6nM** & **Abnahme** v initial erhöhten **NMN** um **<40%**

6) Local. typ. >3cm, cystic-vaskular/hemorrhagic, 95% intraaabdominal, >10cm u/o Vd. a (fam.) paraganglioma screen skull base to pelvis **CT** (skull base to pélvis, typ. density >10HU nativ or **MRI** (cystic, signal T2↑), **^{18}F-DOPA-PET-CT** (adrenal Pheo) **^{68}Ga-DOTATATE-PET-CT** (extraadrenal paraganglioma)>**^{18}F-FDG-PET-CT** (93%/89%) >^{123}J-metaiodbenzylguanidin (MIBG)-scinti (60%(cave: βB, Ca-Antag., extraadr od NA prod pheo)/64%) > Octreotid-Scintigraphy
2-10% paraganglioma (PGL) along back trunk (head, neck (parasympathetic) bzw. thorcic-abdomen (sympathetic), typ NA>A & 3-methoxytyramin↑; 30% malign, & GIST (**Carney-diad** → genet w. FamH (SHD-B/C/D Mut)); & GIST & pulm. chordoma (**Carney-triad** → genet. but neg. FamH (spontaneous mut 1q loss)), **Tx:** Sx vs radioth **a/o metastasis** (10% pheo, 40% araganglioma) **⇒ US/CT/MRI-neck/skull base** (MTC, Paraganglioma / Glomustu); **ophthalm. consult** (retinal angioma ⇒ VHL?)

7) Genetics (**p22, esp. PGL,** CH gene experts, **PoHI,** 2x5ml EDTA plasma & informed consent) PPGL 30% germline mut., 40% somatic driver mut. **consult pro/con to patient** (incl. screen of family (family tree template)), nudge <60y, pos FamH, NMN>MN, paraganglioma/glomustu (SDHD/B, Krebs cycle-enzymes) / bilat / extraadren. / malign Pheo / MTC / Angioma / CVI (VHL) / GIST / RCC, **RET/MEN II** (p22; MTC, pHpt, 50% pheo, adrenal-bilat, typ MN>NMN), **VHL** (50% Pheo=Typ2, typ NMN>MN, (retinal) Hemangio-blastoma, visc. Tu), **SDH-(AF2)/B/C/D** (paraganglioma (psb), "3PA-Sy" (pheo, paragangl., Pit. Tu, GIST, RCC), Carney-Dyade/triad/complex?, **NF 1** (neurofibromatosis typ e 1, 2% pheo., typ. A>NA), **FH** (leiomyomatosis & renal cancer), **EPAS 1** (polycythemiea somatostatinoma);**TMEM-127, MAX** (30% malign), **3PA's** (comb. pheo & paragangliome & pituitary Tu), poss. complex genetics (Incomplete penetrance, "maternal imprinting" SDHD, i.e., mut only manif. a father -> paternal inheritence)

7) Tx
Hypertens. crisis (p2) **Tx: uradipil** (Ebrantil® 10→25→50mg iv Every 15-30', poss. Inf 2mg/min -> 9mg/h)
cardial arrhythmias Tx: esmolole (Brevibloc® 50-200ug/kg/' iv), lidocain (50-100mg iv)
preop. preparation debatable 7 - 14d outpatient (secreting paraganglioma, no need for orthostasis, intraop initial venoligation → complications ↓)
Phenoxybenzamine (Dibenzyrane ®, irrevers. α1/α2-block, cave: postop hypotension) Cps: 10→30mg BID/TID), **doxazosine** (Cardura ®, revers. α1-Block.) Tbl 2→16mg QD) gradual dosing, increase 2-3daily, cumulation! **SE**: orthostasis ⇒ check euvolomia ⇒ >5-6g NaCl po (1L /d Bouillon or Isostar ®),
cave:, no "unopposed" β-blocker! (⇒ vaskovonstr. ⇒BP↑); **tachykardia** ⇒ & β blocker needed in 30% (metoprolole (Beloc Zok ® 100-200mg QD-BP, Inderal ® 10-20mg QID)
consider: nifedipine (**Adalat ret ® Tbl 20mg QID→CR60**), Duramipress® (D) 2-5mg TID; Hytrin BPH ® (starter pack→ 20mg);
Sx: laparoscopic vs open (>6cm, susp. of invasive) **SE:** intraop. BP peak ⇒ nitroprusside 0.5-10mg/kg/' / phentolamine
Postop.: enough fluid e.g., 4-7l/24h **Glc 5%** until BP stable and cessation of polyuria
look out for hypoglycemia with rebound-hyperinsulinemia, postop. hypotension: adrenaline, poss. Vasopressin iv)
F/U: 25% essential / fixed Hypertension
Follow-up: recurrence 10%, min 10yrs to live-long for high-risk patients, (6-mthly SDHB mut.; Yearly: young., germeline mutationen, tu-size, paraganglioma; → biomarker (MN & 3 methoxythyramine, chromogranin A if low-metanenephrine neg. tu, cave: PPI u CKD) resp. imaging (Dopa-PET, Sandostatin PET)
Malignant (rare) dg by follow-up not histology (infiltration in capsule a/o vessels not dg!), **Sunitinib** (onco. consult), poss. chemoebolisation, ablation w radiofrequency, radioth, polychemoth (cyclophsophamid?, Vincristin?, dacarbacin?) → **inclusion in clinical studies**

5. Cushing Syndrome & Hypercorticism

"If you think Cushing is easy, you have not seen enough cases to do it yourself." Besserism

JCEM 04;89: 3752-63, 05; 90:5730-6, 06; 91:7-13 & 3746-53, 08:93:1526-40 & 2454-62, NEJM 17; 376:1451-1459, Lancet Diab Endo 2021;12:847-875

Exogenous (tx with steroids incl topical (e.g., fluticasone, if combined with CYP3A4-inhibotor (e.g., ritonavir ® (Norvir ®, Kaletra ®)), "pseudo") **> ACTH-dependent** (2 pat./mio/yr, f>m, M Cushing, ectopic) >> **ACTH-independent** (adrenal-adenoma >> Ca)

1) SY Photo history! rapid weight gain w typ. fat distribution (>3kg↑, trunk, full-moon face, buffalo hump, filled fossae supraclaviculares, poss. edema), muscle weakness (squads, "signe du tabouret"), **metabolix sy**, **osteopenia/-porosis**, **skin** (parchment thin, ≥3 ekchymosis ≥1cm, stria rubrae, plethora, acne), amenorrhoa & hirsutism (virilisation ⇒ Ca?), **psych. Sy** (depression, manic, anxiety disorders, psychosus), **thromboembolism, infections↑,** Lc↑, Eos↓, Ly↓ Tc↑, P-Na↑, P-K↓, HGH↓, TSH↓ **cave:** signs can be masked, e.g. ectopic Cushing Sy with cachectic tu od young patients, **drug history!**

2) Outpatient Screening repeat 2-3x (DD cyclical Cushing-Sy), poss. follow-up after 3-6 mo

- **24h-FUC** (free urine cortisol) no<500 nmol/24h (Cu>700; assay-dependent, 95% (false low Cl_{Crea}<30ml/') / 98% (false high m HPLC: carbamazepine (cross reaction), pseudo-Cu, PCO, stress, >4l urine volume, pregnancy 2. &. 3. trim., fibrates, digoxine, HAART (hepat. degratation↓)
  FUC/Crea <70 nM/mM (24h urine), <21 nM/mM (overnight = 22-8h; 87% (CKD) / 95%)
- **1mg DST** (Dexamethasone Suppression Test) **Ind:** Susp of subklin. Cushing-Sy ("autonomous cortisole secretion")? dexamethasone Tbl. 1mg 24h po ⇒ cortisol 08h no<50 (<140) nM; Cu>280) (90%(CKD, LF, M. Cu) / 75% (pseudo-Cu, HAART)), **"Pitfalls":** CBG↑(SS, E2), dex-metabol↑(CYT P450↑:phenytoine, carbamazepine, rifampicine, phenobarbital, pioglitazone), compliance?⇒P-dex 8h 5-17nM, poss. 2mg DST;
- **SC 23:30h** (Salivary Cortisol) no< 1 - 2.5 nM (HPLC, 95%/80%): **NB:** 4h prior NO teeth brushing, false high "jet-lag" & "life-lag" (sex, drugs, rock'n'roll, thriller...be relaxed), soak the tampon well (1-2 min f 1-2ml)

3) DD «Pseudo-Cushing» = increased cortisol levels **depression, stress, C2, anorexia, obesity** (PCO, WHR↑)

- **Cortisol-day-profile:** VP 8h,16h (>50% v.8h) u. 24h (>47% v.8h od absol. n<150nM, venflon 10pm, hosp, "sleeping", VP within 2': no<50 (>70)nM)
- **Dex-CRH-test:** 0.5mg Dex 6hx2d (8x; $D1_{12h}$ - $D3_{6h}$), $D3_{8h}$ 1ug/kg CRH iv ⇒ ACTH & cortisol 0' & 15'
  DD: Cortisol Cu>38 (>70)nM (0': 80/90%; 15': 90/90%) & ACTH 15' >15 (>27)ng/L (n<10ng/L, cave: literature w ovine CRH = stronger stimulus than hrCRH)
- **Desmopressine-test**: M. Cu: basal cortisol >331 nM UND Δ-ACTH 0-30' >18ng/L (>4 pM) n 10ug desmopressine iv (Minirin ®) **DD:** Pseudo-Cu
- **Liddle test:** Sens/Spez. only 70-80%) 0.5mg dex 6+12+18+24h on day 2&3; day 1&3 FUC each (n <27 (>50)nmol/d; Tag1/3 n >2; 79%/74%), day 1 & 3 S-Cortisol (day 3< 50 (138) nM) u. P-ACTH 08am (no suppr>50%)

4) DD ACTH–dependent

- **2x P-ACTH 08h** on ice: <5ng/L⇒adr; 5-15⇒CRH-Test >15⇒central or ectopic (typ >80)
- **hrCRH-Test** (ideal b IPSS (psb), 1ug/kg iv, VP: 0', 15', 30' (peak) M Cu: P-ACTH >20ng/L bzw **≥35%↑** (90%/95%) od S-Cort. >20%↑ (90%/95%)
  - Grenzwert ⇒ 8mg high DST? (8mg@24Uhr po/iv⇒S-Cort+P-ACTH v & n. Dex@8h; M.Cu: Cort. n. Dex <32% of basal (<140), P-ACTH>50%↓; ektop: Cort.n.Dex >140, P-ACTH<50%↓ (80%/95%)

5) Lokalisation

a) M Cushing MRI-Sella (1.5-3T, with & without contrast i coronary u sagittal fine layering; resolution 3mm)
cave: falsch neg da 95% d. Adenome<1cm ⇒ b neg MRI od Befund <5mm ⇒ 18F-FET-PET-CT (O-(2-[18F] fluoroethyl)-l-tyrosine) or **Methionin-PET-CT** (PoHI (or hospitalization in consult. with dept. of nuclear medicine!) & IPSS; 10% false pos (incidentaloma!)

"IPSS" (Inferior Petrosal Sinus Sampling; in consultation with dept. of neuroradiology, 4 assistants, check catheter positioning regularly!)
VP -10', -5', 0, 3, 6, 10, 15' SP left & right, peripheral (+ 30', 60'); ACTH, TSH; PRL, 100ug CRH or 10ug Desmopressin i.v.
Dg: I) M. Cushing? ACTH central/peripheral >2 (1.6) ⇒ post-CRH >3 & early peak ⇒ peripheral ACTH >35%↑, Cortisol>20%↑ (sa)
II) ectopic? <2 resp. <3 ⇒ ad b); **III) side localisation?** ratio ACTH right/left >1.4, pre- & post-CRH (relative to PRL resp. TSH)

b) Ectopic «whole body»-CT/MRI (neck>thorax>abdomen), if neg. **68Ga-SSA-PET-CT**, mammography, "whole body-catheter"
DD: NET (p22); Ca (lungs, MTC, thymoma, pancreatic, other) ⇒ rapid progress, ACTH & FUC↑↑, S-K↓

c) Adrenal MRI adrenal / CT-abdomen ⇒ adenoma > Ca (>10HU & inhomogenous; Pregnenolone u. Compound S↑↑) **> BMAH** (Bilateral Macronodular Adrenal Hyperplasia (prev. „AIMAH", but in part ACTH-dependent. resp. other aberrant receptoren on hyperplast. adrenal cortex !-> comb. stimulations-test, e.g.): sporadic hypercort & hyperandrog (17-OH-progesteron after ACTH (↑)), **> ACTH-dependent McCune Albright, MEN 1, Carney Complex** (p22)

6) Therapie:

5yr mortality untreated 50% or 4x>norm (cvR & infections), **diet under steroids,** thromboembolic prophylaxis from Dg to 6Wk postop

a) M Cushing: Transsphenoidal resection remission ≈80%, preop metopirone/ketoconazole (psb) &HC); postop. T+1, +2, +3 +5d: S-Cortisol 08h <50 (50-200) nM ⇒ „cure";20% recurrence in 5yrs → **pasireotide** (Signifor® 0.6 – 1.8mg bd sc; Signifor LAR® 10 – 30mg mg/Mon im., 50% response, PoHI with evidence of FUC-decrease needed, **SE:** hyperglycemia (75%), Pat. info D, F) **u/o carbegoline** (Dostinex®) Tbl. 0.5 – 6mg/Wo⇒ titration w FUC, 30% response; **a/o Osilodrostat** (Isturisa®,Tbl. 2-30mg bid 50% response) **a/o** other **adrenostatics** (sb)
F/U & exclude recurrence? ⇒ 24h-FUC (& DST & SC 23:30) 3-6mthly; → Re-Sx od bilat. adrenalectomy (30% Nelson-Sy (dark skin, pituitary adenoma) → preop. γ-knife or adrenostatics; postop HC +50-100ug florinef/d
- MRI follow-up → Tu visible → **γ-knife** ≈50% remission in 6-60Mon, **SE** hypopit., adrenostatics until effect occurs
Normalization of HPA-function within 1 – 2.5 yrs (adrenale > M. Cushing), offer psychological support and consultation screening of psychologic Veränderung anbieten. **Dose control?** signs & symptoms, 24h-FUC (target 250-500nM), Cortisol fasting (n), Cortisol 12.30-17.30 >100nmol/ol, stop 2 wks pre-op

b) ectopic Cushing-Sy: 50% pulmonary (NET & SCLC)>MTC>thymoma>Pheo, MRI or Ga-SSTR-PET/CT, rapid Op a/o adrenostatics (monitor P-K+↓)

c) Adrenal Cushing-Sy: Adrenalectomy, life-long follow-up 1x/yr: cvRF / psycholog. sy /vaccination, poss. DXA, DST/SC 23:30 if HU > 10, MRI/CT follow-up, HC 15-30mg/d (initial -60mg/d) & stressprophylaxis (sa)

Adrenostatics (e.g., inoperable/ectopic Cushing, recurrence or drugs preop, adrenal-Ca p2), PoHI, **«block & replace w stressprophylaxis»**
- **ketoconazole** (Cps 200mg, 1-2tbl bd-tid (magistralrp hospital-pharmacy, PPI stop), **SE:** LFT↑, hypogonad. & gynecom., QT↑, Cyt3A4↓⇒ drug-interaction
Ind: 4wk preop. od palliative **a/o metyrapone** (Metopiron® Tbl. 250-1000mg tid-qid, initial tx, fast response, titration m 24h-FUC & SC 23:30? not teratogenic **SE:** GI-Sy & vertigo, hypertension & K-loss due to 11-DOC↑ (→ FUC by massspec Lab KiSpi USZ), acne, hirsutism, **osilodrostat** (Isturisa®, start 2mg bd, max. 20mg bd, 80% remission within 3mo long-term tx, **SE:** arthralgias, nausea, diarrhea, cortisol-withdrawal, Cyp3A4 interaction & QT-prolongation **etomidate infusion** (IPS, init. 5mg bolus + 0.02mg/kg/h, qd. cortisol), **mitotane** (Lysodren ® 3-5g/24h, derivate of DDT); Ca: **Doxorubizin** (Onkolgie, delayed effect, **SE:** GIT & neuroogical, hypercholest., hypogonadismus, hypothyroidism; trilostane; **Mifepristone** (Rez-blockade, va b Psych.stör 10-30mg/kg/d **SE:** Nausea, Fatigue, Kopf u Gelensz, Oedem),
→ **Stress prophylaxis! Withdrawal!** (p6) → **cortisone base tx.** e.g., **HC** initial 20-10-5mg ⇒ 15-5-0 od **Plenadren ®** bedtime, thromboprophylaxis

6. Addison Syndrome & Therapy with Steroids

"Addison's disease represents, as Syphillis, the Cameleon of Medicine"

Becker 01; JCEM 06; 91: 3954-61; Lancet 14; 383: 2152-67, Ann Int Med 03; 139: 194-204, JCEM 09; 94:1059-67, **www.adrenals.eu/de**

Prod: DHEA(S) 25mg/d > Cortisol: 5 (-15) mg/d, "Stress" max 6x↑≈100mg/d > Corticosterone 4mg/d > Aldosterone 0.1mg/d

DX: Typically an atypical clinical presentation (SE/SP <50% ⇒ coin flip is superior),

- e.g. **fatigue**, sleep disturbances, driveless, weakness, **muscle/joint pain**, nausea, vomiting, aBPominal pain, loss of appetite, weight loss: ≥3kg, orthostasis, reduced stress resistance, salt cravings, neuropsychiatric symptoms ("hypo"), hypoglycemia
- U-Na^+/K^+ <30 (Renin↑ in primary Adrenal Insufficiency (AI), after Hyponatremia stimulus due to "SAAD"), BG <3.3mM (or "new" hypos under Insulin), HCO_3^-↓; urea↑, Ca↑, Eosinophilia >3%, Leucopenia, lymphocytosis
- **Blood cortisol (fasting, 8am):** <100 (<80) nM (& ACTH↑) ⇒ Dx; >500 (415) nM ⇒ Exclusion, 100-500nM ⇒ Synacthen test !
- Salivary Cortisol 8 a.m. (≈free Cortisol) <5nM (& ACTH↑) ⇒ Dx; >16nM ⇒ Exclusion, 5-16nM ⇒ Synacthen test !

1° DD Addison's disease: autoimmune polyglandular sy. (APS; 75% p.22) > **Mets**(lung)/ Hemorr./HIV&TB/Hemochrom.>**Medi** Immune-checkpoint-Inhibitors (ICI, poss. Assess 8am Cortisol monthly with every cycle of ICI-th up to one 1yr after discontinuation, cut-off <140nm?, 141-274nm? Refer to endocrinologist), Metopirone, Ketokonazole, **Opiate,** Etomidate, Rifampicin, Phenytoin, Imipramine, Chlorpromazine) >Congenital adrenal hyperplasia (CAH)> Adrenoleukodystrophy (X-chrom **Sx**: can be oligosy, hypogonadism, dementia, spasticity, blindness, Dx: screening of male patients if autoantibodies neg & no other causes,; genetics ABCD1-mutation very long fatty acids ↑ (> C24; C26:0, C26:C22; C24:C22) KisSpi ZH, **Tx:** Bone marrow transplantation, gene tx?)

Sx: ↑Pigmentation (mucous membranes, areolae, hand lines, pressure points), "salt craving" orthostasis, ♀: ↓ Libido, dry itchy skin

- **250ug iv Synacthen Test D F** iv cortisol p̄ 60'>550 (>415-600) nM; **lying Renin p̄ 30' ↑** (esp. w/ RF e.g. pos. 21OH-Ab)
- Synacthen depot test (1mg/d im over 1d or 3d: ⇒ iv Cortisol p̄ 8h or 80h. >1000nM in secondary AI or healthy subjects. <1000nM in primary AI.
- **P-ACTH↑ 08 a.m.** >50 (>100) pg/ml), **21OH-Ab** (80%/95%), **DHEA↓**

2° DD: S/P **Steroid** (±independent from duration [5-30d] & dose [30-250mg]) > Hypophysitis / Pituitary tumors (Other axes? p23)

- **Short Synacthen test** 1ug (250ug) ACTH iv Cortisol p̄ 25' >500 nM (>550nM w/ HRT&Pregnancy, >700 w/ Extreme Stress e.g. shock)

  Salivary cortisol 30' post ACTH >40nM (free cortisol, i.e. indep. HRT/Pregancy); **cave:** in acute pituitary insult: Synacthen test **falsely negative 2-4 wk!**
- **Standard (250ug) Synacthen Test:** cortisol >550 nM (>600 HRT&Pregnancy) p̄ 30' (pituitary), p̄ 60' (adrenal)
- **Insulin hypoglycemia test (IHT)** 0.05-0.15U/kg Insulin iv (poss. 2x); **Goal: BG <2mM & Hypoglycemia Sx** nadir gen. p̄ 15'-45'
  CI: CHD/Arrhythmia (ECG), Epilepsy, > 65y.o. Info: last hydrocortisone dose to be taken at midday the day before;
  VP -30', 0', 20', 30', 45', 60', 90'; cortisol norm. peak >550nM; ACTH norm. peak >150ng/L, BG: 3-5x↑; GH norm. peak >5 ng/ml; if <2.66 ng/ml ⇒Tx (p23)
  can be combined w/ **GnRH-Test** (no mens. p̄ 3 months HRT-stop. p18) or **TRH-Test** (200ug iv): 30' TSH norm. 2-25mU/L; PRL norm. >2x↑ (Info: 2months stop T4, 10-days stop T3)
- **Metyrapone test Ind:** when IHT not poss. **Proc:** 8 caps. of 250mg at 12 a.m. p̄ late snack (↓S/E GI) ⇒ VP 7:30 a.m. Cortisol (<140nM (<276)) & ACTH (>150ng/L) or Compound S (CS) +Cortisol (>450nM, 71%/69%) or CS alone (>260nM, 67%/68%, unstimulated CS<12)
- **CRH-Test:** DD sec./ter., **Proc:** 100ug iv; VP 0', 30', 60'; ACTH p̄ 30' norm. >6,6-8,8 pM (30-40pg/ml) / 2-4x↑, Cortisol norm. peak>500nM (CRH weaker stimulus)

Tx "Crisis" (Asthenia, Hypotension, GI-Sx) w/ **"Stress"** (INF, Trauma, SX) ⇒ **VP Cortisol & ACTH ⇒ Solucortef** 100mg iv Bolus & 2L [5% Glucose] or [0.9% NaCl] over 1h ⇒ 50mg q6h → q1d; if need be Rectodelt ® (D) Notfallset (KSA Ambi Med

Daily (LT) Replacement: Cortisol 10-15mg mornings, 5-10mg afternoons, (HC Galepharm® 500 caps 10mg, cost ≈ 50.-/mo) ≈ 10mg/m^2/d, **w/ more symptomatic or infection-prone patients** -> HC-dual-release-retard **Plenadren®** caps. 5&20mg 1-0-0 (CHF ≈700.-/mo., mimics circadian rhythm, weight benefit!), Chronocort® (EU) or Prednison MR (**Lodotra®** cap. 1, 2, 5mg at 22p.m.), both w/ insurance's cost approv., (p̄ 6 mo. of HC Tx w/o response)) **cave: Stress prophylaxis w/ „norm." HC or Pred !**

Increased requirement: Pregnancy: +50% in 3rd trimester, **„Stress"** (subj, physical >> psychological), **1°**>2°, CYP450 Induction, T4↑,

Stress prophylaxis "Minor" (common cold): 2-3x[dos]x 2-3d; **"Major"** (Trauma, SX, «Men's cold») 100-200mg/d HC (Solucortef®), e.g. uncomplicated Sx: (T0) 50mg i.v. q8h; T1 50mg i.v. q12H, T2 50mg iv morning, T3 HC po 30-10-0; T4 HC po 20-5-0; Patient training KSA

Emergency sheet & set, Emergency-Sheet «mild», Pat Brochure (KSA D/F/I/E; SGED D / F / I); Self Help Groups (also for relatives)

1°: Florinef Tab 0.1mg ¼- ½ Tab/d in 80% of cases (Orthostasis? K^+, Renin? ↑ dosage in pregnancy, ↓ dosage in Hypertension & HF); **Hypertonie:** Prednisom instead of HC? ♀: DHEA: 25-100mg/d, Pilger Apotheke, BS

Tx-Control: clinical (ask suggestive signs for under- (see above) and over-substitution (p5, Tips on **Nutrition w/ Steroid tx**.)

„Corticotroph Insufficiency Related to Critical Illness» („CIRCI") HPA-Axis "Exhaustion" after several weeks of ICU stay w/ initially normal HPA function : DD: steroids, etomidate, opiate, etc. Dx: persistent vasoactive requirement, delirium, basal cortisol or 30' p̄ 250ug ACTH <550nM↑ ACTH (slight) increase ⇒ Tx: 60mg Hydrocortison p.o. Solucortef iv (tid?)

Pharmacology „Steroids, misused, enable a patient to walk to his autopsy room"

Substance	Trade Name® e.g.	Biol. $T_{1/2}$ [*Plasma $T_{1/2}$*]	Glucocort. & Antiinfl.Potency	Mineralocort. Potency	Cushing Dose (mg)
Hydrocortison = Cortisol	Hydrocortisone Solu-Cortef	**8-12h** *[2-4h]*	1	1	≈ **20**
Prednison ≈ Prednisolon	Prednison, (Lodotra) Spiricort	**12-36h** *[4-6h]*	≈ 3.5 ≈ 4	≈ 0.6	≈ **5**
Methylprednisolon	Solu-Medrol	12-36h *[2-4h]*	≈ 5		≈ **4**
Dexamethason ≈ Triamcinolon	Fortecortin Kenacort	**36-72h** *[3-5h; no crossreaction with cortisolassay]*	≈ 30-150	0	≈ **0.1**-1
Betamethason	Celestone Betnesol	36-72h *[5-8h]*	≈ 30-150		≈ **0.1**-1
Fludrocortison Aldosterone	Florinef Tbl	18-36h *[3-4h]*	≈ 10	≈ 125 ≈ 700	(≈ 2-3)

7. Diabetes mellitus (Dm) – General Aspects

"There is no disease that requires of its sufferer such discipline and decision-making each day."
ua Ann Intern Med 01; 135:1079-83, Diabet Med 03; 20: 175-81; JAMA 01; 185: 2486-97; Diab Care 10; 33 (S1): 11-61, SMF 11; 11: 233

DEF (ADA): venous Plasma-Glucose (**PG**) **2x ≥7** (fasting =8h no food) or **≥11.1 mM** (random) or **HbA1c ≥6.5%**
„Prediabetes"= Impaired Fasting Glucose (IFG: PG 5.6-6.9mM, random 7.8-11mM or HbA1C 5.7-6.4% ⇒ risk↑ f death, cvR, Dm (5x) → control i 6-12Mt, incl cvR, prevention, (**75g oGTT (old & lean)**: Dm = PG fast 2h >11mM; 7.8-11mM =impaired Glc Tolerance IGT)
Evaluation PG: **Diabass Pro, cont. PG-measurement** (p13); **HbA1c-pitfalls**: falsely low ↓: in uremia (ca -0.5%); asians with HbE (->Immunoassay) → **Fructosamin estimated HbA1c**: HbA1c = 0.017 * Fructosamin (uM) + 1.61

DD: Type 1 (10%, p8), **Type 2** (80%, p9, unofficially **"Dm Typ 1.5"**; overweight. Dm 1 / initial Dm 2 with secondary failure), **Gestational diabetes** (p12), **«Type 3»** (3a) **Monogenetic Dm (alt "MODY", S. 8** genetically defective β-cell function; diabetesgenes.org) 3b) insulin effect ↓, **3c) pancreatoprive**/hemochromatosis (p8),3d) impaired hormone product.; 3e) Drug-induced (**Steroids** (p9), Immunosuppressants (CNI, mTORi) Neuroleptics), 3f) Viral; 3g) Autoimmune; 3h) genet. Syndrome; others: Stress/SIRS/Sepsis (p11 & 27), Posttransplant Dm, Endocrinopathies (p 22)
PG-screening (every 3y after ADA): **BMI>25kg/m², >45y, FA/GDM/PCO/Ethnia, ≥2 Sy metabol Sy, Atheroscl.,**
Dm most common reason for **Blindness worldwide resp. dialysis & amputation in CH**

DG-scheme (discharge report/diagnosis list)
Diabetes mellitus Typ 1, 2 (insulin-dependent mon/year) **or „DD"** (steroid, type 3c pancreas, haemochrome, etc) **(ED mon/year)**
- **currently out of target range** (= ≥3xdaily. gluc measured & daily correction or Gluc fluctuations ≥5mM or 3x>15mM or 1x<3mM or HbA1c>9%)
- **cvR** (cardiovasc. riskfactors)**: Nicotine, metabol. syndr.** (BMI, BP, lipids), FA?, GDM?, OSAS?, hyperuricemia?
- **followup complications**: Angiopathy (macro: CHD, PAVK, CVI; micro: retino-& nephropathy); polyneuropathy (PNP); feet (see below)
- **HbA1c** good (6-7%), satisfactory (7-8%), unsatisfactory (8-9%), poor (>9%); **false low:** transfusion., hemolysis, Hb-pathies, anemia ⇒ Fructosamin
- **Hypoglycemia:** none / rarely / frequently; mild / severe (Perception threshold?)
- **current therapy:** dietary, orale antidiabetics, insulin (basal/"Bedtime", Basis-Bolus, FIT)

Insulin prescription **PG Documentation KISIM-KSA** (Quickguide, Carb-to-Insulin-Ratio (CIR) & Carb. Amount), Pat. Info, indiv. Diabetes diet

Staging (**Flow-sheet**, usually annually., b overt complications 3-6mthly, see. Pat. Info, Tax deduction leaflet)
- **Not disabling!** With DM generally normal «working & living» is possible. Basic-health-ins., SUVA, IV without restrictions; everything else (extra-mandatory insurance & daily allowance ins.) with reservations ⇒ change of job difficult, self-employment difficult. Tips for allegedly „**challening Dm**", **Empowerment**, e.g. „**Diabetes Pass**" or „Evivo", **DIAfit**, **"yellow card" for "no shows" to appointments**
- **Travel** & **Driving** (esp. with Th. hypoglycemia-risk: Sulfonylharnstoffe, Glinide, Insulin), **«Clarke Score»** to estimate risk for hypoglycemia
Target: PG 5-10mM & > 6 Mth no sympt. Hypo **Pat. Info SGEDSSED** bzw. **Leaflet** ((sign & document in patient chart)
⇒ **before EVERY car-ride measure PG! <7mM** ⇒ 10g CH; **<5**⇒20g CH & PG n 20'; **<3.5**⇒ 45' n CH PG; **if nec. check fitness to drive acc. guidelines SGEDSSED; Reporting** (right to report to GP / Mandatory report to medical consultant insurance, policies (BGU 1C_391/2019), **form AG, BS.**
Dm on Insulin a/o tx with hyporisk: impossible to pilot airplane, tram, train („commercial" transport. of passeng., Kat. D), Taxi/Uber ok with «good compliance»
- **Nutritional counselling (USB, KSA):** Carbs (g & distribution), calories, „24-h recall", Alcohol, **beware of nutritional dogmas**
- **Diabetes counselling** (p13), hypoglycemia symptomes, PG-measuring, insulin inj. (p13f), Th-refractory? → **in-hospital PG adjustment**
- **cvR: FamH** (F<65y, M<55y) **& PerH** (PAVK/ CVI/MI), **>65y, nicotine, met Sy** (p9), Alb/Crea iU↑, **susp. KHK: MPS/Ergometry**
- **Status: Weight** (kg/m2), **aBPominal circ., HR, BP** (Orthostasis), „ankle-brachial-index" PAVK <0.9, severe <0.4; Mediacalcinosis>1.3), **vessels** (murmurs, Aa. carot., renalis, aBP., ing), **Injection sites; Potency**; **Hands** (Cheiropathy, Dupuyten); **dental status, feet** (Pulse, ASR, Vibration x/8, 10g Monofilament, Arch↓, Hyperkeratosis, Skinlesion, funghi, nails, Charcot), **Shoes** (Sole > Foot!)

follow-complic.: „Legacy" (initial) good HbA1c! Labor Crea (Clearance), **Lipids, Liverenzymes** (NAFLD / NASH, p9), uric acid
- **Microangiop.: Retinop.: Ophtalmology (priv., consult)** after 20y 90% Dm1 (prolif) & 70% Dm2 (exsudative) ⇒Makulaedema -> **Lucentis (VGEF)**

Nephropathy **Alb/Crea iU** 2. morning urine, falls 2x ↑ ⇒ **ACEH**, GFR_{calc}<40ml/'⇒ad Nephro (treat cvR incl. BP, Dietary protein <0.8g/kg/d, Hkt 34-36%, uric acid <300uM; no NSAID), **Ctrl:** Dm 2 6mthly, Dm 1 after 5y disease;
Alb/krea↑ without Dm (in adip. M >50y, smoker ⇒ independent of cvR; DD: UTI, Orthostasis, work, amyloidosis)
- **Macroangiopathy (esp. in Dm2): Atherosclerosis with clin sy** PAVK (Pulse?) / CHD ⇒ **Angio / cardio consultation**

Polyneuropathy (PNP): sensory: symm. "socks&gloves" ;**Tinel's sign pos** -> ad Plast.surgery for Nerve decompress.; **autonom:** cv (Orthostasis, fixed RR, tachycardia at rest, silent CHD), GIT, UGT; **mot:** III, IV, VI, VII, Amyotrophy **TH: euglycemia!** (Hosp. w. Insulin/Thioctazid iv?); **Vit B12?** (poss. Meformin stop) **Pain**: **Panadol** ⇒ **(&) Saroten**(10→75mg/d)/Tolvon ⇒ **(&) Pregabalin** (Lyrica® Cps 75, 150, 300mg, **Duloxetin** (Cymbalta® pill 30-60(-120)mg qd), poss. **SSRI** ⇒ **(&)Tramal** („start low, go slow") ⇒ **Lidocain** (Neurodol) dermal plaster **or Capsaicin** Magistral-Rp Creme0.075% tid-qid x8/52; **Orthostasis & P-K↑** with Vasodysregulation & hyporeninäm. Hypoaldosteron **TH:** Fludrocortison Florinef® pill. 0.05 – 0.1mg mornings;Midodrin (Gutron® pill. 2.5-10mg qid) **Gastroparesis**: Th-trial dep. on Sy w. Metoclopramid (Paspertin), Domperidon (Motilium), Erythromycin; Immodium, Transipeg
Sexual dysfct: (couples) therapy **F:** address it! -> https://www.fsfiquestionnaire.com/ **M: Erect. dysfct (ED) / Impotence DD:** cvR (-> exerc-EKG?) Urology / Angio? Hypogonadism? β-Blocker? **TH:** success in 40-50% w. DM , not subj, to insurance! Viagra (25-100mg po/sl), Cialis (5mg qd po ED&BPH), Levitra **KI:** Nitrate
Paradontosis ⇒ dental state, **sleep-apnea Syndrome ?** (Screening Epworth Score), **fatty liver (ASH, NASH) ?**
CHF? Screening Resting Tachycardia, NT-ProBNP (?) >500 –1000ng/L → Echo, if nec. Optimize Th (ACE-I, diuretics, βBlocker, Aldo-Antagon.)

Diabetic Foot **Exam KO:** acc. **SGED**, Sens. ↓ (Vibr. <4/8, Finger, Monofilament) PNP 3 mthl ⇒ **Pat-Info, Footconsultation**, **Risk groups, Podology** (PoHI, Verordnung) no barefoot walking, PNP: no hot water bottle, dly. Selfinspect., poss. w. mirror incl. between toes (→ **Onychomykosis?** swab?,**TH: Loceryl/Lamisil** pill 250mg x 3 (-6) Mon Interdigital: **Imazol-Paste/Lamisil-crème**), **Hyperceratosis Th.** (Allpresan foam Nr. 3 (in DFB available) or 20% Urea Footcreme (Eubos® BP)), **Perfusion / Footpulse? →Angio-consult, Deformities? TH: Podology** (www.podologie.ch, only subj. to ins. w. Diploma) & **Orthoped. shoemaker** www.osm-schuhtechnik.ch (e.g., Härdi Schöftland, Malgaroli Aarau&Baden, Villiger Niederlenz): **local pressure relief** with **Orthosis / bandage shoe** /. Recipe for 2 Pairs „**orthoped.series shoe w diabetesadapt. footbedding**" / **orthoped. Customized shoe** (cave: **PoHI** <65y (IV) better than >65y (AHV) → **Orthopedics: Gait analysis** → OPED"/Vacu-Diaped shoe → immobilization & "Total Contact Cast", **Charcot-foot:** pressure release! NSAID (as Sudeck?, p16), anti-TNFα? **Malum perforans? Wound therapy SOP**; **Edema th** (compression socks, Angio), **Debridement** (scalpel, Derma), **Creams** (e.g. Regranex®, Apligraf® if Th-resisntecy), **Infection? DG: Pus or inf. Sy** (≥2 local [cave: in PAVK underestim. Rubor, Calor, Tumor, Dolor] or systemic) Lc, Cellulitis, **Plantar fasciitis** (**Sy:** blisters, plantar pressure point ⇒emergeny SX!; **Biopsy** (most. Mixed Inf.. acute: *S. aur., Strept. Grp BACG* / Anerobians (ischemia&gangrene) / Gram-neg (AB-pretreated); **Osteomyelitis? DG: "Probe to bone"** (50%/85%, "scratch"), Rx, MRI; Szinti **TH:** Orthop. cleanout / Debridement & antibiotics, e.g. Clindamycin (Dalacin) pill 2x300mg tid (alt. Rifampicin (Rimactan) pill. 600mg) & Augmentin pill. 625mg tid (alt. Tavanic Tbl. 500mg BP); x 2/52 (tissue infection) up to 6-12/52 (Osteomyelitis); if recurrent a/or pretreated & Ciproxin pill 2x750mg (Gram neg), GCSF/sytem. hyperbaric O2 (anaerobians)

Vaccinations: see www.bag.admin.ch: yearly: **Influenza**, > 65y: **pneumococci** (1x Prevenar13 Konjugat, CHF 90.-, not ins. obligat); 10-yearl.: DiTePer, if nec. HBV, HPV, HZV

8. Dm Type 1

„Tell me and I'll forget. Show me, and I may not remember. Involve me, and I'll understand."

typical: young, slim, acute, ketonemia (Freestyle β-ketone-strips!)**, wt↓,** HDL-C no, inheritance risk 4%(father>mother), Twin≤50%;
Prg f honey moon: **GAD-II Ab** (90% Sens, poss. IA-2, ZnT8-Ab), **random C-peptid e<200pM b PG>6mM** (glucagon-stimul. <600pM),
LADA (Late Autoimmune Dm in Adults): >35yrs, pos GAD-II and other-Ab; check for polyglandular autoimmune syndrome (p22)

DD: a) Hemochromatosis: transferrin saturation >45%, Ferritin >1000 ⇒ (gene-analysis ⇒ consult gastroentorology)
b) pankreatopriv / C2, CF (typ. ASAT/ALAT>1). **Arginin stimulation test** Proc: 0.5g/kg Arginin x30'; VP 0', 15', 30', 45', 60' m PG, Glucagon, Insulin, C-Peptid. **Dg:** Glucagon n≈100%↑, Dm 1 ≈ 200%↑ (i. Ggs zu flachem Insulin), pankreatopriv/C2<50%↑
c) Monogenetic (old "MODY"): most common: HNF1A, HNF4A, and GCK etiologies **RF:** aut.-dom! → **Pedigree** http://www.diabetesgenes.org/content/mody-probability-calculator -> risk >25%: PoHI EDM gene experts in CH (USZ, HUG, Munic), **Tx:** OAD,; **mitochondrial Dm:** w sensorineural hearing loss; CI f metformin; **Tx:** OAD, rarely need for insulin
d) „ketose-prone" Dm type: (typ. in colords): severe insular glucose toxicity and ketoacidosis

Screening for late complications (p7): dep. of cvR & initial dg <10y after 1-5yrs, diabetes-pass to set common goals
TH: to be supervise by specialist, care concept for newly dg Dm type 1, concept for inpatient PG adjustment
Experimental / immunosuppressive: Teplizumab preventative in patients with genetic risk a/o increase of lag-time of C-peptide decline → screening prg ?
Nutrition & diabetes counselling: yrly, esp recurrent Hypo., wt↑↓ >5kg, problems CH-estimation ("Nutri-Lernbuffet")
Initial base-bolus insulin regimen: during honeymoon ⇒ reduce or pause insulin, verapamil ? (p9), multiple daily injections ("MDI")
- **Base:** rule of thumb: units (U) = kg / 4; Lantus / Levemir / Insulatard
- **Bolus:** Fiasp/Humalog/NovoRapid/Apidra, Actrapid; regimen to meals dep. on ch (30-100g)
  e.g., before meals f 40gKH: 2U (PG<5mM), 3U (5-7) 4U (7-9), 5U (9-12), 6U (12-15), 8U (>15), 10U (>20)
- **Insulinpump** (**p13**) **Ind:** unstable PG (e.g., comfort, pregnancy, sports, hypglycemia, -perception↓, dawn-phenomon) & good compliance
  Checklist high PG: change catheter?, adapt injection site? (incl. abdomen, leg, buttocks), estimation error? (⇒ weigh food !),
  protein a/o fat-rich meal (⇒ set pumpt to mulitwave bolus mode, i.e., 50% rapid, 50% over 5h)
- **Dm & terminal CKD:** systematic evaluation of a combined kidney-pankreas- or kidney-islet cell-**transplantation**
- **address issues of disease acceptance**, poss. psychosomatic a/o psychiatric consult, , military service ? **pregnancy ?** (p12)
- **Obese Dm1:** empower diet & exercise, **GLP-1 Agon.** (semaglutide (p9) HbA1c 0.2%↓, insulin need 5-10%↓), **metformin** (weight -1%), **SGLT-2 Inh.** (HbA1c 0.5%↓, less hypoglycemias, ,cave: DKA 5%,

Basic rules (of thumb) of functional insulin tx ("FIT") manual, to be learned in a course, control booklet
- **Total requirement: bw x (0.5 - 0.7) ≈ U Insulin/d**; insulin action time p13; insulin degradation: ca 2/3 hepatic, 1/3 renal
- **Carbohydrate to Insulin Ratio (CIR) = Resistance Factor (RF): 1 U insulin for 10g CH or for lowering PG 2mM**
  Insulin requirement min around 2am (≈0.5U/h), max around 06am (≈1.5U/h dawn phenomenon); during menses↓ & luteal phase↑

A) Basic depot insulin (dose finding **fasting day or skip meal tests),** poss CGM, **40-50% of daily requirement**;
.e.g., **Tresiba ®** (qd), **Lantus ®** (BP) - qd, **Levemir ®** BP – qd, **Insulatard ®** BP - tid**, reduce dosing starting pump 10-20%**
PG>8mM⇒1U NovoRapid ® / Humalog ® sc; <4mM⇒10 g dextrose po (e.g., 3 Dextro-Energen ®),
measure PG 2hrly (at night 22, 02, 06h):if PG>8 bzw <4mM check 1hrly

B) Fast acting meal insulin Fiasp ®, NovoRapid ®, Humalog ®, Apidra ®, Actrapid ® (inject 15-30min before meals)
Correct **estimation of CH** essential ⇒ **meals test**, "Nutri-Lernbuffet", poss **nutr. counsil refresher cours**, individualized diabetes diet KISIM
45-55% of daily requirement, usually **0.5-2E/10g KH** (dep. on bw & RF = CIR),
F/U 2h pp PG (ideally pp = fasting PG); nutritional table
e.g., 200g CH & 20U Tag = 1U/10g CH; typ breakfast 20-60g; lunch 60-90g; diner: 60-90g. snacks not necessary;
>10g CH ⇒ insulin required, fat- (or protein od extremely rich on CH (>100g)) → delays gastric emptying & CH resorption
poss. improved pp PG & less hypo with CH w lower glycemic index (high fiber like apple, oranges, pears, artichocks, broccoli; vs low fiber like bananas, fruit juices, tomatoes)

C) Correction insulin 1U lowers PG ca 2 (1.5-6)mM (fasting day), usually to be added to meals bolus
Goal preprandial 5-7 mM; **cave:** lower insulin dosing for corrections at night (23-05h), F/U 2hrly

D) Excercise & sport (g CH/h; e.g., 70kg): **20**≅hiking (5km/h), cleaning; **50**≅ running (10km/h), soccer; **100**≅ racing (15km/h), cross-country skiing ⇒ add CH or reduce insulin (apply only ½ insulin dose before sports a/o basal insulin afterward (poss before) 10-50%↓), typically **Hypo abends/nachts** after extensive & prolonged (>4h) excercise in the afternoon (max. n 8-16h, can be reduced by 10sec „final sprint").
Individual differences! Poss recommend **DIAfit**. leaflet Diamon

E) Illness Depot-Insulin↑ (10-50%), PG 2-4h ⇒ correction-Ds↑, if PG not↓, Ketodiabur ® test if PG>15mM

F) Travel **E→W (USA)**: "long day "; correct with fast acting or depot↑ (1/10 d Ds x Std. ZZ); **W→E (Asien):** "shortened Tag"; Basal↓ or skip
Driving (p7) **Risk for accident: Dm1:** ↑, esp. if poorly controlled, **Dm2**: not increased (also not if on (basal) insulin)

G) Hypoglycemia also seep 10 & 22; in a „well controlle" diabetic patient a Hypoglyemia grade II – III per yr is expected
- **Grading: I** (PG <3.5mM w/o sy, manageable by patient), **II** (PG<2.5, extermal help required), **III** (unconscious, seizure)
- **Signs & symptoms: multiple**, e.g., „stressed", hunger, **neuroglykopenia** (confusion, behavioral abnormalities, visual disturbances)
- **Tx: Glucose in pocket** PG < 4mM⇒10g CH, < 3mM ⇒ 20g CH, check PG after 1h
a) Acute PG increase: 10g CH = 3 sugar cubes, Dextro Energy ®, Insta Glucose ® Gel, 1dl Cola or fruit (orange) juice
b) PG stabilization: 10g CH = 3 Darvida ®, ½ slice of Swiss whole wheat bread, 1 apple, 1 yogurt light, 2dl milk,
c) Unconscious: **Glc iv:** 10g CH = 100ml 10% = 50ml 20% = 25ml 40% = 20ml 50% Glc, glucagon (Baqsimi ® nasal PoHI; GlucaGe ® Hypokit (1mg sc) **&** 20g CH), if desperate CH in cheek pouch
- **search for causes, check PG goals** ⇒ Pat.-education, evaluate CGMS (with alarm) or CSII, try coffee
- **Unnoticed a/o severe hypoglyemias? «Clarke-Score»** for hypoglycemia awareness

9. Dm Type 2 & Metabolic Syndrome

"An ounce of prevention is worth a pound of cure"

Lancet 05; 365: 1415-28; Ann Int Med 2010 ; 152:307-14; Diabetes Care 2010;33 1647-1651, Diab Care 2011; 34: 789-94, SMF 12; 12: 562-6

„typical“: pos FamH a/o GDM, hyperuricemia, **metabolic Sy = cluster of metabolic cvR**

DEF (>2): **PG fasting** ≥5.6mM, **BP**≥130/85mmHg, **waist circumference** (belly button equator) M≥102, F≥88 cm (M≥94, F≥80 cm)

TG ≥1.7mM; **HDL-C** M<1, F<1.3mM (ATP III) **DD: LADA** (p8): no metabol. Sy, hypoglycemia under Tx, "slim" dm type 2 ⇒ low C-peptide, GAD II-Ab; if neg ⇒ MODY, mitochondr. Dm, hemochromatosis?, **pancreatoprive** (p8), **steroids** (drugs, Cushing-Sy, “stress”), **other diabetogeic durg:** atyp. neuroleptic, cyclosporin A, tacrolimus, thiazides, HAART, dopamine

TH Empower the patient to treat all cv-risk factors (AGLA guidelines) (i.e. pat can support tx & reach goals independently)

1) Nutritional counselling PoHI, (USB, KSA) to instruct calory-reduced diet, **Goal: wt >10%↓ resp. not↑**. **Special diets** Obesity, Dm (KSA), CH-adapted aso, p14 &15, low carb? (p23), «Villger's Oat days»), Snacks if tendency for hypoglycemia (10gKH) → **bariatric surgery ?**

2) Exercise↑ 1-2h/d „walking“ (dog a/o pedometer), >30Min/d «sweaty» exercise, Fitness-Myths, Pat. info

3) Diabetes counselling: baseline & follow-up; wt u/o HbA1c↑, switch to/from Insulin resp. OAD

4) Nicotine↓ Nikotinell® TTS / chewing gum, www.nicotinell.ch, varenicline (Champix®), Zyban®, Cymbalta®, **Smoking counselling** (Pulmology, OSAS ?)

5) Polypharmacy! SGED-SSED Guidelines, compliance? cost / benefit? **Metabolic Surgery ?** (p15)

- Statins independent of LDL-C level, >40Y a/o ApoB >65-100mg/dl.; **2° prophylaxis, «polypill»** (statins, HTZ, atenolole, ramipril, ASS) already for 1° prophylaxis ?

6) Target-PG: fasting 5-7, pp <10 mM (2h n Essensbeginn), **no hypoglycemia** (CHD w Insulintx), Th-resistance?--> **inpatient PG control**

HbA1c individually 6 - <8% (HbA1c x 2)-4 ≈ mean PG past 6-8wks. analysis of PG control, e.g. with **DIABASS**.

Antidiabetics: Comb. metformin & SGLT-2 Inh → ≈ 20 E Insulin↑ → HbA1c ≈ 1-2% ↓ initially). **PoHI for «high cvR» w comb SGLT-2 & GLP-1 Agon**

- **Metformin** (Glucophage®, Metfin®) 1g 0-0-½⇒1-0-1, **SE:** GIT, **Vit B12-Mangel**-> check yarly **Tx:** Vitarubin oral po qd or Vit.B12 Amino®1000ug 3-1mtl.sc, malabsorption **CI:** Cl_{Crea}<30ml/' dose red GFR 30-50ml/', OH, >80j, hypoxemic acidosis ⇒ **48h preop & v ICM stop**
- **Gliflozins SGLT2-Inh., Pat. Info Ind:** (obese) Dm2 w SU a/o meformin, comb w GLP-1-Agon. w CHF a/o albuminiuria f PoHI; wt & BP 2-5%↓, fasting & pp PG↓, **SE:** genital myocosis, ketoazidosis w acute co-morbidity, statin levels↑ (Invokana ® & Crestor ®), osteoporosis?, limb-ischemias? Fournier gangrene ?? **CI:** GFR<30ml/') Dapagliflozin e(**Forxiga®** Tbl. 10mg qd; Xigduo XR® (+ metformin 1000mg) qd; **Qtern** (+saxagliptine 5mg) qd), empagliflozine (**Jardiance**® Tbl. 10/25mg qd JardianceMet® (5/12.5mg+metformin 500/850/1000mg) BP; Gyxambi ® (10mg +linagliptine 5mg) qd)), canagliflozin (**Invokana®** Tbl. 100, 300mg qd, for CKD (Cl_{Crea} >30ml/', Vokanamet® Tbl. 50/850 – 150/1000mg qd), saxagliflozine (**Onglyza®** Tbl. 2.5, 5mg qd, ertugliflozine (**Steglatro®** Tbl. 5mg qd; Segluromet® (Tbl. 2.5mg + metformin 1000mg) qd; Steglujan (+sitagliptine 100mg)
- **GLP-1 Analogues** (wt 2-5%↓, pp PG↓, **Ind:** lowering of (basal) insulin needs: semaglutidee (**Rybelsus**® p.o. Tbl. 3, 7 u 14mg qd **Ozempic**® Pen 0.25 - 2mg sc 1x/wk PoHI.); liraglutide (**Victoza**® 0.6→1.2→1.8 mg qd), Degludec (**Xultophy**® & insulin degludec 0.36mg & 10E→increase to 1.8mg & 50E qd, PoHI f comb w SGLT-2 a/o insulin, BMI>28m/kg2), lixisenatide (**Lixumia**® 10µg →20µg qd) & insulin glargine (**Suliqua**® «100/33»: 3µg & 9E→ up to 20µg & 60E qd od «100/50»: 5µg & 10E→up to 20µg & 40E qd), dulaglutide (**Trulicity**® Pen 0.75→4.5mg sc 1x/Wo, PoHI), exenatide (**Bydureon**® 2mg sc 1x/Wo; **Byetta**® 5ug sc BP x1-2 Mon ⇒10ug sc BP), **comb GIP/GLP-1 Analogs:** tirzepatide (**Mounjaro ®** 2.5, 5, 7.5, 10m, 12.5,15mg s.c. 1x/Wo; **SE:** nausea, gradual dosing (increase 1-2wkly), «Ozempic-Face»; orforglipron p.o. (HbA1c -2%, Phase 3), Retatrutide (p 15)
- **„Gliptine“ Ind:** combined or mono-Th, hypglycemia, weight neutral: Linagliptin (**Trajenta**®) Tbl. 5mg qd (no Ds adaptation in CKD), Sitagliptin (**Januvia**®, Xelevia®) Tbl. 100mg qd (crea-Cl<50ml/': 50mg; <30ml/' / dialysis: 25mg), Vildagliptin (**Galvus**®) 50mg qd (**CI**: GFR <60ml/'), Saxagliptin (**Onglyza**®) Tbl. 5mg qd **CKD (Cl <50ml/'→halbe Ds**; CKD (!) together with metformin without CKD. **Jentadueto**® 2.5/ 500, 2.5 850, 2.5/1000mg BP , **Janumet XR**® 100/1000 qd od 50/1000 BP, less GI-SE), **Velmetia®, Galvumet®, Combiglyze ®**)
- **Sulfonureas (SU): SE: Hypoglycemia, wt↑**, secondary failure
  Gliclazid e(**Diamicron®** 1-4Tbl MR 30 1-0-0, no need to check PG before car driving) , glimepiride (Amaryl®) Tbl 1-4mg 1-0-0, glibornuride (Glutril ®) Tbl 25mg 2-1-0, glyburide = glibenclamide (Daonil® **SE:** prolonged hypoglycemias (metabolites!), metformin/glibenclamid (Glucovance®), **CKD Glinide** to meals: repaglinide (**NovoNorm®** Tbl. 0.5, 1, 2mg tid
- **Glitazone** delayed effect on PG after 4-8Wo; pioglitazone (Actos®) Tbl 15⇒45mg qd, Competact® Tbl. 15mg pioglitazone & 850mg Metformin) BP;
  SE: wt↑, CHF., osteoporosis?, cvR↑? bladder cancer ?; **CI:** HF NYHA >I, pregnancy, LFT↑, **tx duration max 2yrs**
- **Orlistat** (Xenical®) Tbl 120mg pre-meals; **Ind:** BMI≥28m2 & Dm 2 (+1 OAD); proof of success (6mo wt 5kg↓ a/o HbA1c 0.5%; max tx duration 2yrs, Acarbose (Glucobay® Tbl 50⇒100mg tid), **SE:** flatulence

Insulin? never too early often too late **Ind: poor metabolic control** (HbA1c>8% w OAD, PG fasting>10mM, Sy, ketonuria); e.g., Glucophage & **Insulin w self-adaptation** Levemir / Lantus / Tresiba (8-16E evening (0.2E/kgKG PG fasting>6mM x 3d ⇒2-4E↑; PG<4mM ⇒2-4E↓, ⇒ 0.5-1E/kgKG) od NovoMix 30 2/3-0-1/3; Humalog 50 Mix 3xtgl to meals, poss.& glp-1 agon., **nutritional counselling** (CH-, fat- & kcal amounts) **(transient) switch to (basal-bolus) insulin** (p7): **Pregnancy & breastfeeding** (p12), anabolism (cystische fibrosis), painful polyneurophathy; **severe co-morbidity (CKD** (pause OAD!)**, HF, LF, sepsis / AMI / ICU / perioperatively** (p11)

Steroid-tx: insulin resistance & hepat gluconeogensis↑, β-cell-Fct↓ (->OAD inefficient) ⇒ **pp PG >11.1mM** (prednisone morning (↓), (after-)noon↑↑, evening↑) **TH:** dose- & T1/2-dependent! **HumalogMix 50** 0.1E /kg bw / 10mg prednisone, max. starter dose 50E) 2/3 morning & 1/3 noon, full dose in the morning only if meals are secured; inpatients-> Steroid favorite KISIM-KSA. PG 12-15mM: Metformin (CKD?) & GLP1-Agon?

7) BP ≥140/90mmHg ⇒ ACEH / AT II-Blocker (stroke, microalbuminuria >120mmHg?, if 24h-BP↑; BP_{syst} Nacht/Tag>0.9 -> evening dosing; **Target:** alb/crea50%↓ u/o<1g/d, crea 30%↑, K<6; **⇒ & diuretics** (GFR>30/': thiazide (“Co-“); <30/': torasemide (-200mg morning)) ⇒ **a/o βblocker** ⇒ **a/o Ca-antag.**, a/o **mineralocorticoid-antagonist** (MRA →S.2, finerenone (Kerendia ®) f CKD with Dm2, PoHI); **cave:** orthostasis / syncopes mainly in elderly pat, indivualised Tx

8) Dyslipidemia (p15) in 2° prophylaxis, poss. Statins & ezetimibe or PCSK-9-Inh., **OSAS** (p2)

9) Fatty liver (Metabolic, non-alcoholic Fatty Liver Diseases (MAFLD) / Steatohepatitis (MASH), **FIB-4-Index** ⇒ (Fibroscan / US / liver biopsy) → **LFTs (1-5) yearly**,↑ ⇒ F/U 3mo, >1.5x↑⇒ Hbs-Ag, HCV-Ab, transferrin-saturation >45%, **Tx:** wt! C2! hepatotox. drugs! (statins?), Resmetirome (leberspezif, T4-βAgonist),, Efinopegdutide

10) Gout: production↑ (90%, Tu, Psoriasis, hemolysis), renal clearance↓ (10%, CKD, thiazides, ASS, ua), **RF:** uric acid↑ (>400uM 0.5% pa, >600 30% pa), pH↓, temp↓ **DG:** typ. inflamm. sy, joint puncture (cristals), nephrolithiasis (Uric acid i.U > 600mg/d) **Tx-acute: Indozid** 200-400mg/d, **colchicine** (D: Colchicum-Dispert® Tbl, Colchysat® Sol 1mg hrly max 1mg(CKD)-8mg (GI-SE, CYP3A4↓) initally, then 1mg/d), **prednisone** po (0.5mg/bw x 2-3d/ lokal; **chron:**: mediterrean diet, weight↓, beer↓, coffee↑, VitC↑, allopurinol (Zyloric® Tbl 50(CKD)-300mg qd (-BP) 4Wo after podagra-attack; b Cl-Crea>50ml/' urikos-urics: probenecide (Santuril® Tbl. 500mg 1-2Tbl. BP – qid, CI: urate stones), if hypertensive losartan, if dyslipidemic statin

11) Vaccination: Ind Co-Morb. (www.meineimpfung.ch); **influenza** (1x/J) **pneumococci** (1x Prevenar CHF 90.-, no oblig. reimbursement)

12) Gastroparesis: frequent small meals, low fat, avoid bloating dietary fibers, mashed, chew well, if pp hypoglycemias fruit juices / lemonade to meal, avoid C2; **Tx:** domperidone trial (Motilium ® ling. Tbl. 10mg before meals) or metoclopramide (Paspertin ® Tbl/Gttes 5mg to meals) **Insulintx** adapt Inj.-Meal-Intevall, Actrapid ® as pp bolus; **DD:** celiac disease in pat w Dm type 1

Proposal for GP if **HbA1c>8%**, unsatisfactory control / compliance, final visit a treatment center

“Bei Dm werden empfehlen wir Kontrollen wie folgt: bei jede Visite PG, BP & wt, 3 mtl HbA1c & Inspektion d diab. Füsse & Schuhe, 6-12 mtl Lipidprofil & Microalbuminurie, jährl. Ophthalmologie“; auch Empfehlungen d ERB & DFB weiterleiten. Die beiliegenden Richtlinien vom MedNET Bern sind zielführend. Der Patient kann auch zur vorübergehenden Optimierung d Blutzucker i d diab. Sprechstunde überwiesen werden. Bei therapieresistentem u/o rezidivierendem Uebergewicht und Adipositas sollte der Patient an ein Metabolisches Zentrum überwiesen werden.»

10. Hyper- & Hypoglycemic Derailings

"Sweet dreams may have bitter endings"

Keller U. In: Schifferli J. Intern. Notfälle 09; Diab Care 03; 26: S109-17 & 27: 1873-8, Obstet Gynacol 05; JCEM 2009, 94: 709-28

DD: Insulin deficiency ("forgotten", expired, ampoule leakin, needl clogged), infection, other stress, steroids, initial present

SY: Polyuria/-dypsia, nocturia, weight loss 10%↓/2Wo, visual problems, Tachypnea, **infection?** (History, focus?)

DG-NF: Blood gas analysis (BGA), Chemogram, lactate, S_{Osm}. ECG (initial S-K↑, after Insulin K ↓↓"no pot, no T, but U")

- **Ketone bodies** (acetoacetate> β-OH-butyrate>acetone (n <0.5mM) i urine or (better) in Blut with **PG-device Freestyle β-Ketone-strips!**
- Patients on insulin pumps: if PG remains elevated despite correction by pump ⇒ change to pen & basal-bolus injection

DD metabol. acidosis: anion gap (AG) =Na - ($HCO3^-$ + Cl^-) = 8-12mM, expected P_{CO2} (mmHg) = [HCO3-] + 15

- Not diabetic w normal AG: uremia (SO4, PO4, urea), rhabdomyolysis

- Not diabetic with AG>12: ketone bodies a) alcohol (PG<10mm, β-OH-butyrate >2mM (n <0.5mM) > >acetoacetate, cave: urine-keto-Stix ® or nitroprussid poss neg, because only purple due to acetoacetate & acetone → **Freestyle ® β-ketone-strips** measure also β-OH-buturate), **b) fasting ketosis** (AG typ 5-10, ketonuria +++, HCO3- >18 mM β-), **salicylates, metanol, (m)ethylenglycol** (Tx: alcohol!), **lactate** (>4-5mM; lack of O2l [shock, CHF, anemia, met-Hb, intox. with CO, CN, NO], hepatic, biguanids, typ Kussmaul-breathing patter & low pH-value despite only moderately elevated ketones)

Diabetic with hyperglycemic derailing

A) Diabetic Ketoacidosis („DKA"): mostly Dm 1 (initial dg or "forgotten" Insulin → leaflet for patients) SGLT-2-Inh. !

Dg: PG>14mM, pH<7.3, HCO3<15mM, AG>12mM, U-ketone ≥+++ (va Acetoacetat, Freestyle ® β-ketone-strips)

poss. pH>7.3 if DKA & vomiting (poss. acute abdomen = "Pseudoperitonitis/Gastritis diabetica") ⇒ HCO3 & aniongap? (sa)

B) hyperosmolar derailing usually Dm 2 (often infections, sa)

Dg: PG>33mM, pH>7.3, HCO3>15mM, AG<12mM; U-ketones +, $S\text{-}Osm_{eff}$ >320mOsm

$S\text{-}Osm_{eff} = S\text{-}Osm_{measured} – urea = 2xNa + PG$ (mM) + OH; Dm-derailing explains coma if $S\text{-}Osm_{eff}$ >320 mOsm/l

TH: generally for both DKA und hyperosmolar, mortality DKA ≤5%, hyperosmolar ≤15%

→ instable/polymorb./DKA Pat need **intensive surveillance** (IPC/IMC/SIC) for insulin-perfusor, **K-F/U**

1) Fluids! Requirements: past wt – current wt (correct within 24h, but max 10% of bw within first 12h), hyperosmolar (8-10L) > DKA (6-8L), if GCS 14-15 free drinking, **cave:** brain edema (even with aequate tx, **RF** children & ΔS_{osm}>3mmol/h↓)

- 1. hr: 1L (20ml/kg/h) 0.9%NaCl iv, thereafter dep. on CVP & $S\text{-}Na_{korr} = Na_{gem} + 0.3x(PG-5)$,
- 2-7 hr: 3L/6h 0.9% NaCl, 0.45% NaCl if Na_{korr}>135mM (if Na>155 ⇒ only 0.5mM/h↓)
- Hypotension / CHF⇒ 1L/h (CVP <3cm), 0.75L/h (3-8), 0.5L/h (8-12), 0.25L/h (>12)

2) Insulin 0.1-0.15E/kg Humalog ® / NovoRapid ® / Apidra ® iv Bolus; sc if pH>7.25, PG<20mM; GCS>12

⇒ Perfusor (50E insulin / 50ml NaCl 0.9%, initially 0.1E/kg/h od NovoRapid ® / Humalog ® sc 0.2E/kg/2h → to be adapted during course !

⇒ **Goal-PG:** 6-10mM; **1-2h PG-F/U**; PG↓ <2.5 od>4mM/h ⇒ insulin x2 od /2,

PG<15mM ⇒1L Glc 5% i 5h iv, don't stop insulin (0.5E/h bis pH>7.3); pause insulin if K<3.3mM

3) KCl 30-40mmol/h (K<3mM pause insulin); 20 (K=3-4); 15 (K=4-5); 10 (K=5-5.5); pH>7.1 K-requirement↓ ⇒ next lower step

mild cases: 20-30mmol K/ L NaCl (**cave:** hyperosm. & acidosis ⇒ K falsely ↑ (K 0.5mM↑ pro pH 0.1↓ od 10mOsm↑)

4) Phosphat (PO_4^{3-})↓: esp. in DKA, substitute if <0,3 mM or symptomatic (weakness, paresthesia, persist. coma) ⇒ p14

5) Other thromboprophylaxis, poss gastric tube if atony or vomitus

- **NaHCO3** (1.4%=167mM,) if pH<6.9, **Ds:** BE(mval) x bw(kg) x 0.1) = mmol over 2h, **Ca & Mg** if arrhythmic

6) F/U 1hrly (1-6h) ⇒ 2hrly (6-24h): PG, K, Na 4stdl: VBGA, S_{Osm}, Urea, Crea, Cl

30% Amylase↑ (Pseudopancreatitis diabetica), CK↑, Hematemesis; pulmonary edema, Crea by Jaffe methods falsely ↑ if ketones↑

if switching to insulin sc, overlap insulinperfusor for 2h, basal-bolus insulin correction, diab. consult

Cave: «**TIND**» (treatment-induced neuropathy of diabetes): Non-length-dependent neuropathic pain and dysautonomia if (too) rapid lowering PG → **HbA1c-lowering <3% / 3 mo if intial HbA1c >9%**

Hypoglycemia (b Dm p8, insulinoma p22)

DEF adult: Whipple Trias PG<2.8mM & Sy (<2.2mM ohne Sy) **& responsive to carbs ⇒ DD:**

Lab (ideally with Hypo!): PG, insulin, C-peptide, lactate, ketone bodies, free fatty acids, cortisole, HGH, IGF-1, crea

1) „Factitia":

- **Insulin** (PG (mM) / Insulin (mU/L) <0.11; C-peptide <35pM)
- **Drugs (asserve urine): OAD** (protracted! →24h-surveillance), insulin & C-peptide↑), Venlafaxin ® ao SSRI, MAOI, Tramadol ®, Tavanic ®, sulfonamides, INH, NSAIDs, P oentamidine, chinine, ACEI, ARB; non-selective β-blockers, antihistamins

2) typically „fasting" (i.e. = >6h pp)

- **Insulinoma** (p22, outpatient (16h (fasting after lunch), VP 08h: PG >3.8mM NAD) or inpatient fasting test), **sulfonylureas** (asserve blood), **NNR-Insuff.** (p6, P-Insulin↓), HGH-deficiency,
- C_2, Liver- (lactate?), kidney- (crea?), heart (BNP)-failure., tu (insulin, IGF-1/2, SST), malaria, glykogenosis, MCADD-Mangel (p 25, hypoglycemia & CK & FFS↑),

3) typically "postprandial" (pp „dumping"): → **"mixed meal test"**

- **Post-bariatric** (p 15,): ca 0.2%, OR 2-7, F>M, pp upright > pp supine) **Tx:** lay down pp; carb-restriction, GLP-1-analogues / SGLT-2 inh ? PoHI (Art 71, template LUKS), "gverstich" (endoscopic tightening of anasthomosis / transoral gastric outlet restriction, MECCO-Study (LUKS)?, ultima ratio: reversion of surgery?
- Autonomous dysregulation, nesidioblastosis, Insulin-Ab (IAA↑, C-peptide<Insulin, **RF:** lymphoman/ myeloma, other autoimmune / rheumatic disorders)
- **early phase of Dm2**, **Tx:** nutritional counselling (low carb meals, lower glycemic index, Maizena ®), Acarbose ®, Hered. Fructoseintol. ("fruit intolerance")

4) Insulin independent (fasting a/o pp): "NICTH" non-islet-cell tumor-induced hypoglycemia (e.g., IGF-1, IGF-2, somatostatin, (GLP-1?)), tu/liver metast.

TH: 10-20g CH (→ p8!), PG F/U 15', 1h, 2h, 4h), poss. glucagon (Baqsimi ® nasal PoHI), poss. somatostatin 0.1mg sc 8h **& search for causes!**

- if Hyperinsulinemic (SU/insulinoma): octreotide (Sandostatin® 0.05 – 0.5mg sc 8h) / pasireotide (Signifor® 0.3-0.9mg sc BP); diazoxide (Proglicem® Cps 25mg tid, 3-8mg/kg/d), glucocorticoids (e.g., Solucortef® 100mg iv/d, DD Addison-Sy!) ,poss. combined with GH, Ca-blocker (Nifedipin ®, Diltiazem ®), GLP-1 analogues / SGLT-2 inh.? (p 9)

Prg: poor if prolonged hypoglycemia, pathological imaging (MRI), polymorbid or handicapped before event.

Cave: repetitive hypoglycemias → frontal brain syndrome

11. Dm in Medicine, Surgergy & Dialysis

"A seriously ill patient is grateful to see a diabetologist rather sooner than later"

KHK: DIGAMI BMJ 97;314:1512-5 & Circulation 99; 99:2626-32, ICU: NEJM 01; 345: 1359-67 & 06;354:449-61 vs 09; 360; 1283-97

Medicine: TARGET-PG: fasting (5) 7 – 10 mM, NO HYPOs, (measurement 2-3x/d w OAD, 4-6x/d w insulin, 2-4h w perfusor)

In hospitalized Pat: switch from OAD to insulin advisable (esp. metformin contraindicate in CKD & ischemias, better control of PG in acute phase w functional insulintx) ⇒ **PG-curve KISIM-KSA** w **RF = CIR** & **CH counts, pat. info, indivualized diabetes diet KISM**

Blutzucker (BZ)

Messungen:
- ☐ bei Frühstück
- ☐ bei Mittagessen
- ☐ bei Abendessen
- ☐ vor Bettruhe (22Uhr)
- ☐ Nachts (02Uhr)

Novorapid® oder Humalog ® subcutan (sc) in Bauch

1. Korrektur
Zielbereich 5.5-7 mmol/l
"TP" = Tagesprofil (bei Frühstück, Mittag- u Abendessen)

Kontrollen

2. Essen je nach Kohlehydrat Menge (g KH) evtl. nach Mahlzeit spritzen

Isst nichts (<10g) 0 E
Isst wenig (20g) 1 E
Isst Hälfte (30g) 2 E
Isst alles (60g) 4 E

3. Resistenzfaktor (durch Arzt festzulegen)

Startkriterien (x2 bei >1Kriterium)
- ☐ CRP >100mg/L
- ☐ Prednison >10 mg/d
- ☐ Sepsis, PCT>0.5ug/L
- ☐ >60 E Insulin/Tag
- ☐ BMI > 30 kg/m2

Im Verlauf
x↑: BZ-Abfall <3 mM oder Anstieg auf >7mM
x↓: BZ<4mM oder Abfall ≥50%

DEPOT
☐ **Levemir®** ☐ **Lantus®** **sc i Oberschenkel um 22Uhr**
25% d Gesamtinsulindosis bei Eintritt um 22Uhr als Depot
Im Verlauf 50% der Gesamt-insulindosis des Vortages

Datum	Zeit	BZ	<4.0	"TP" 4.1-7.0	"TP" 7.1-9.0	4-stdl 9,1-13.0	4-stdl 13.1-16.0	2 -stdl 16.1-19.0	2 -stdl 19.1-21.0	> 21	Zwischensumme	Total Nach 23Uhr nur 50% der Dosis E	E	Zeit	Visum Pflege
Beispiele															
Start	*18:20*	*13.6*	*isst wenig*			*3 E*					*1 E*	*4 E*	*x2 (PCT 1ug/L, zu Hause 64E Insulin)*	*8 E*		*18:25*	*V. Wyss*
Verlauf	*21:30*	*12.5*	*Patient isst alles*			*2 E*					*4 E*	*6 E*	*x3*	*18 E*	*16 E*	*21:40*	*V. Wyss*
Start				**0 E**	**1 E**	**2 E**	**3 E**	**4 E**	**5 E**	**6 E**	**0 E** **1 E** **2 E** **4 E**		**x1** **x2**				
Verlauf	.....:.....		**s**	**0 E**	**1 E**	**2 E**	**3 E**	**4 E**	**5 E**	**6 E**	**0 E** **1 E** **2 E** **4 E**		**x1** **x2** **x3** **x4** **x5**				
	.....:.....			**0 E**	**1 E**	**2 E**	**3 E**	**4 E**	**5 E**	**6 E**	**0 E** **1 E** **2 E** **4 E**		**x1** **x2** **x3** **x4** **x5**				

Surgery: TARGET-PG: 7 - 9 mM (peripartum / sectio 4.5-7mM), HbA1c: 7-8% (to be adapted individually!)

Basically for hospitalized pat. MDI w **basis-bolus-regimen** subcutanously (sc) **quick-guide** Insuline sc (p.13); **Basals Insulin = Depotinsulin:** Levemir (poss. Lantus), **Bolusinsulin:** Humalog/NovoRapid/Apidra (Actrapid s.c. for prolonged action for 4-6h)
Inulin dose calculated automatically in KISIM. Daily insulin prescription by arrangement: **Dm 2** surgical intern after diab. consult; **Dm1 & derailed Dm2** diab consult
Poss. delay surgery if despite MDI PG>12mM in view of increased periop morbidity & mortality
„Staging"-late complication (p7)**, nutritional and diabetes consult** on admission! (≈25-35 kcal/kg/d, nutrintional parameters & check lab values (p14))

Perioperative Therapy (SOP KSA, periop use of insulin pump, Insulintx same day surger (SDS), training lecture, FAQ).

- **daily profile** = PG morning (7h), noon (11h), evening (17h), before bedtime (22h), if risk for nocturnal hypoglycemia 02h, if PG <7 od >12mM 2 hrly
- **Insulin-injection scheme** adapted to carbohydrate count with NovoRapid ® / Humalog ® / Apidra ® sc if PG > 7mM even in undiagnosed DM

Variable insulin requirement dep. of resistance to insulin. RF=CIR 1-5x in exceptional cases up to 1000U/d dep. on type of Dm / patient / stress level / morbidity.
Start with low insulin doses, thereafter increase 1-2U gradually to PG-goal ⇒ dose to be adapted individually, uncertainties / fluctuating PG → diab consult

cave: Increased risk of hypoglycemia at night ⇒ 22 - 07 Uhr inject only ½ insulin dose!
Tresiba ®, Ryzodec ®, Xultophy ® with up to 72h duration of action

PRE-OP DAY pause OAD from the evening before. At 22h apply 25% of previous daily insulin dose (Σ basal and boli a/o mixed insulin) as Levemir ® sc. If mixed insulin has already been injected for dinner, inject Levemir ® only if PG >10mM

DAY OF SURGERY (OP-DAY, SX-DAY)

a) Non-derailed Dm (PG<12) & whs food intake at noon & small interventions i regional anesthesia/LA standby
- Pause (oral) antidiabetics (OAD) on Sx (pre)day. Clear fluids without sugar until 2h preop; no G10% humalog infusion
- With basal bolus setting, usually inject basal unchanged + post-injection regimen sc (psb)
- For mixed insulin, give 25% of the previous daily dose as "basic" insulin sc (Levemir) + post-injection regimen sc (psb)

b) General anesthesia or longer procedures under regional anesthesia
- **Dm without insulin:** pause OAD for 24h (caution: ketoacidosis m SGLT-2). OP-day fasting, daily profile, no insulin-glucose infusion
- **Dm with insulin treatment:** "Normal" insulin distribution basal / boli 50%/50%. **In the morning of the surgery:** Pat. need glucose & insulin periop. (reduces ketosis, catabolism) Þ from 7h 10E NovoRapid Inf in 1L G10%: 100ml/h (b cardiac and renal insufficiency w volume problem 50ml/h), additionally apply 25% of the previous daily insulin dose (Σ basal + boli) as Levemir sc in the morning & post-injection regimen (e.g., NovoRapid ® sc).
For pump patients, run basal rate + post-injection regimen (psb). If persistent PG>12mM consider insulin perfusor iv (psb).

INTRAOP SCHEME

SIMPLIFIED: Insulin sc as Multiple Daily Injections (MDI)
IND: all DM patients, incl. sectio (target PG 4.5-7mM), except indication for schme INTENSIVE
- G10% insulin-Infusion ongoing (50-)100ml/h
- **PG-control** (strip device)**& insulin dosing sc: 2** (4-6) **stdl**
- **Insulin:** NovoRapid ® /Humalog ® / Apidra ® (**NOT** Actrapid ®)
- **Dosierung dependent von PG**

PG < 4 mM ⇒ 100ml G20% iv immediately (stat!)
PG 4-6.9 ⇒ check PG 2hrly
PG 7-8.9 ⇒ 1-2U Insulin s/c (Belly, upper arm, thigh)
PG 9-11.9 ⇒ 2-4U Insulin s/c (Belly, upper arm, thigh)
PG 12-15 ⇒ 4-6U Insulin s/c (Belly, upper arm, thigh)
PG >15 ⇒ 6-8U Insulin s/c (sa, cave: cumulation)

Check **after 2h**: if PG > **12mM** despite injections
⇒ consider scheme **INTENSIVE** w Humalog ® Perfusor iv

INTENSIVE: Insulin Perfusor iv
IND: DM-Pat postoperatively on ICU, poss. pat with PG>12mM despite MD sc
- G20% 20ml/h **without** supplements
- **PG controls** (strip device / lab value): **1-hrly**
- **Insulin:** NovoRapid ® / Humalog ® / Apidra ® / Actrapid ®
- **Perfusor solution:** 50 E NovoRapid ® / 50ml NaCl 0.9%
- **Dosing dependen on PG**

PG < 4 mM ⇒ 100ml G20% iv, stop perfusor
PG 4-6.9 ⇒ 1ml/h (=1E/h)
PG 7-8.9 ⇒ 2ml/h
PG 9-11.9 ⇒ 3ml/h
PG 12-15 ⇒ 4ml/h
PG >15 ⇒ dependent on clinical signs & symptoms

- **Potassium/Kalium:** <4mM: max 20mval/h KCl short infusion

POSTOP: ICU: → ICU/IMC-scheme, **recovery room / ward:** PG-daily profile → Bolus-insulin-MDI sc (2hrly control only if PG <7 or >12mM), Prehosp. therapy (OAD, Iinsulin) re-start after lunch if uncomplicated course & well controlled PG, else follow guidelines / SOPs:
- **nü:** 10 E NovoRapid in 1L G10% 100ml/h m Nachspritzschema & allfälliges Basisinsulin, **parenteral** ≈ 2/3 d Tagedosis i TPN (p14) & NSS
- Ward Insulin continued as basal (≈ ½ of daily total insulin dose) & bolus-insulin-MDI to correct PG & cover carbohydrates (insulin 1-4U/10g CH!),
- if recurring PG > 12 mmol/l→ **diab consult**

Dialysis: Dose adjustments a) with progression of kidney failure & b) at start of dialysis

Hämodialysis (HD) **Glucose-Goal:** PG <11mM at the start of the HD session; check capillary glucose before leaving the dialysis unit (>5mM if driving)
Insulin: At the start of dialysis an increase of total insulin dosage of up to 30% may be required; thereafter **a) Basal:** Reduction of up to 25% on HD days **b) Preprandial bolus:** reduction by 10-15% before a HD-session
In patients with altered cognition and a shortened life expectancy, consider administration of long-acting degludec 2x/wk at the end of the HD-sessions

Peritoneal-Dialysis (PD): **Day:** 2L Glc-Lsg 30' before meals tid, **Nacht:** non-resorbable Isodextran-Solution (=Glc polymere) at 10pm
Nutrition: protein enriched (1.2 g Kg bw), CH-adapted, include Glc in bag (3x1.36%&1x3.86%≈150gGlc ⇒ Resorption 60-70% b. CAPD, 30-50%)
A) Basal insulin: 50% of previous daily dose (alternativ Cycler m nächtlicher Glc Lsg peritoneal ⇒ PG↑ morgens, poss. Levemir v BR)
B) Insulin f CH in meals & PD-bag:+2/4/6E Humalog sc f ≈1.5/2.5/4% Glc-Beutel (≈12.5/25/35g Glc/L),
e.g., daily dose 40E; Day 20E (= 50% v. 40) ⇒ distributed to 3 bag: 7 – 7 – 6E (b 3.86% Glc-bag: 13 – 13 – 12E); night 13E (30%x40), bzw. 19E b. 3.86% bag
C) Correction Insulin: Adapt to PG nü / pp (mM): - / <2.5⇒ -12E; <2.5 / 4.4mM ⇒ -8E; <4 / 6.4⇒ -4E; **<8 / 11⇒ ±0E**; <13 / 22⇒ +4E; <22 / >22⇒ +8E; - / >22 ⇒ +12E

12. Pregnancy

"Love is a boogie-woogie of hormones"

Diab Care 07;105-260; NEJM 04:351: 241-9 & 05;352:2477-86; JCEM 07:8:S1-47, **Notification of maternity** (no franchise & deductible in pregnancy)

Dm: Target-PG: fasting 4.5-7mM; pp <8mM. **optim. PG before start pregnancy** (Decgludec ®, Levemir ®, Insulatard ®)
Dm1 discuss CGM a/o pump (-10% more TIR, % large f gest. age & neonatal hypoglycemia ↓), **Guideline Dm1 & pregnancy (G) F**
Insulin requirement: 1. trimester (↓), 2.& (3.) trimester ↑↑ (up to 300%, if suddenly ↓⇒ placentar insuff.); postpartum ↓↓ (psb)
Ophthalmol F/U before pregnancy & each trimester (Retinopathy risk ↑ if HbA1c ↓↓?), Fructosamin (no<285uM, ≈ PG letzte 3Wo ≈ HbA1c 6.5%), consider **psychosocial Aspects**
PCOS v SS: metformin (Glucophage ® until Dg pregnancy; if hyperglycemic ⇒ switch to insulin

Gestational diabetes (GDM) Pat. Info, guidelines F&K KSA, USB DD: preceeding Dm2

Risk factors (RF) for GDM: **St n makrosomia** (>4kg) **/ abortion, pos history f GDM / PCO,** > 25yrs, BMI >25 kg/m^2, Ethnicity (Africa, Asia, Balkan, Hispanics). RF explain 50% of → general screeining recommended (inkl. SGED). Risk = continuum dep. on PG!
DG: PG >4.8mM fasting (6h fast, nocturnal hunger attacks?) **without RF** 24-28GW **with RF** on Dg Pregnancy (<10-16 GW)
PG self measurement, poss. CGM (Time in Range "TIR" 3.5-7.7mM >70%), poss. **75g oGTT 8h fast ≥5.1; 1h≥10; 2h≥8.5 mM** (1 value pos ⇒ GDM; if fast >5.1mM no oGTT needed!) **TH: benefits: less peripartal compl.** (infant deaths, dystocias, Fx, paralyses, neonatal IPU or ikterus), prescription template
Nutritional (25-30kcal/kg/d) **& diabetes counselling** (PG measurement, morning ketonuria ≥++ ⇒ late CH-snack), **BP-Tx** (psb),
PG fast a/o before bedtime ≤5.3mM ⇒ Levemir ® od. Insulatard ® od. Huminsulin ® Basal (0.15U/bw),
PGpp: 1h <8; 2h ≤7.0mM ⇒ NovoRapid ® / Humalog ® initial 2-8E z MZ Insulin dosage table (low risk for hypoglycemia due to insulin resistance)
F/U: wkly until PG ok, then if on diet falls → F/U in Gyn, if on insulin EDM 1-4wkly, CGM?, Dm 1 pump?
- higher prevalence for Gestosis **EPH/HELLP**-Sy (headache, epigastr.pain, Edema, BP↑, Proteinuria)? ⇒ poss Ketodiabur, BB, Chemogr
→ **Aspirin** 100mg/d if gestosis risk after 12GW and Dm Typ 1 & 2.

Dm-Risk 30%/5J (Pat. Info!) postpartal weight reduction (counselling, lifestyle, Sport) & >3mt. breastfeeding
→ F/U at 3 mo: PG fast >7mM / HbA1c >6.0% ⇒Dm 2; ≥5.6mM / ≥5.7% ⇒ Lifestyle & counselling; <5.6mM / <5% ⇒ idem & 1-3j PG at GP
Lung maturation: Betamethasone (Celestone®, T1/2 36-54h), 12mg x 2d ⇒ GDM risk & insulin requirement ↑↑: **a) on diet:** Insulatard ® 10-0-0-10E x 3-5d; **b) insulin-dependent:** basal +10U – 0 – 0- +10U, bolus x1.5-2 f 3-5d; risk f ketoazidosis on steroid & β-agonists ↑↑

Peripartal Insulintherapy Guidelines F&K KSA D & F, USB

- "preventive" hosp. (initiation of labor >12h) Th unchanged, ideal 38GW. Colostrum collection (≈5ml/d) after 36GW?
- Evening prior to birth / sectio: basal insulin as usual, complete form G F for Dm1 & 2, GDM w insulin
- During labour / birth Target-PG 4.5-7mM (assess 1-2hrly)
- On admission: morning of the section or birth „in sight": (pat fasting): no Insulin sc; stop pump
- **Insulin-perfusor Ind:** Dm2/GDM m fasting PG >7mM resp.. **Dm1**
Infusomat® 50E Actrapid / 500ml 0.9%NaCl /24h (≙0.1E/ml) initially: 1/48 der previous daily dose per h;
if in previous 12-24h depot insulin injected ⇒ ds 50%↓; if addtl. Glc Inf (poss.) add insulin to prefusor dose
(1-) 2h PG-F/U: <4-4.5mM⇒Insulin 50%↓; >6.5-7mM⇒Insulin 50%↑ (Steroidth b >10E/h)
- **Peripartal Glc-inf. Ind:** GDM w basal insulin without oral CH feed, PG <4mM, ongoing labour / stress
Glc 10% 1L/10h (≙ 10g Glc/h); **PG F/U 1-2h** ⇒PG<4-4.5⇒ insulin stop or Glc 50%↑ (Glc is venotoxic!)

- After removal of placenta: Target-PG **5-8**mM preprandial
- **Dm1: cave hypoglycemia** → Insulin ↓↓ to 1/4 previous daily dose, sc Insulin if CH po; adj. PG target, CIR & wt.
- **Dm2 & GDM:** stop insulin stop, PG-TP → diab. consult if preprandial PG >8mM
- 1-3d postpartal w Dm1 insulin dose 50(25)% of dose before pregancy, meals: 0.25E/10gKH, 10-20g CH after breast meals
x

ΔHormones in Pregnancy

Thy: **HCG↑↑** (hyperemis gravid., twins) → fT4↑ (2-10%). TSH-suppr (10-50% 1. Trim), TBG 2x↑, TT4, TT3↑, T4 & Jod-need ↑ (250ug/d, **Natalben Plus ®** (200ug) oder **Burgerstein Schwangerschaft** ® 150ug) instead of Elevit ® (contains no iodine); **Th-target: TSH: 0.3 - 3mU/l**, fT4 upper Norm, poss. fT4-Index **F/U: 4, 8, 12, 16, 20GW & postpartal TSH-Screening?** all vs. risk (i.e., >30Yrs, infertility/ abortions, typ. clin. Sy (Score!), pos history, goiter a/o iodine deficiency areas, TSH↑ a/o pos TPO-Ab (risk for abortions 2-5x↑, preeclampsias 2x↑, IQ↓ offspring of SCH, postpart. thyroiditis↑, progressive hypothyreoidism), Dm1, St. n. ICM, RAI or STx. **Guidelines:** 1) pregnancy 2) postpartal / pediatric **Placental passage:** TRAb (fetal surveillance (sonographic goiter?), iodine, β-blocker, CBZ>PTU, T4 20-50%, T3 not al all
- Hypothyreoidism: ab SS T4 Ds ≈30-50%↑, Beginn T4-Subst: TSH>(Trimester)Norm u/o pos TPO-Ak va b Risiko-SS diskutieren
- Graves D.: Dg. in pregnancy: TSH, fT4, TRAb (neg & 12 Mon Th -> stop th ?), ⇒ 18 GW, TSH, fT4 (goal: upper Norm), TRAb (falls ↑) → US Gyn (fetal HR, goiter, SGA, amniotic fluid↓) ⇒ 4-6wkly **Tx:** PTU (1. choice, RR-teratogenicity 16%↑), CBZ (RR-teratogenicity 32%↑), poss β-Blocker if symptomatic (vomitus)
- Postpartum = silent thyroiditis (5%, Dm1 25%); hyper (2mon)→ hypo (TPO-Ab↑, 4-12 mthly) → 80% euthyr.; F/U 4-8 wkly
- Breast feeding: PTU up to 300mg or CBZ up to 30mg, probalbly without relevant side effect on baby
Adrenal: CBG ≈3x↑, HC- & Florinef ® needs ≈50%↑?, **stressprophylaxis** (incl. supp. !), birth 50mg HC q8h, **DD:** Cushing-Sy: red striae, hirsutism
- aPR & Aldo -10x↑,pProgesterone -1000x↑ (antialdost.), if K↓↓ od BP↑↑ → Conn-Sy?: Renin↓, ARR↑, (poss prog/aldo<20); Tx: 2. Trim. Eplerenon? amiloride?
Pituitary: size 100%↑ (-1.2cm), PRL ≈10x↑; IGF1↑, "GH"↑ (from placenta (non-TRH responsive), hypophyseal GH↓), S-Osmol↓ & P-Vol 40%↑ (Oxytocin 10% ADH-effect)
- Prolaktinoma: symptomatic tumour growth in 3% (micro-) up to 30% (maroadenoma)
- no injection of milk +/- failure of other axes ⇒ DD lymph. hypophysitis; Metopiron ® i Cushing's disease; hemorrhagic birth ⇒ **Sheehan-Sy?**
- adapt dosing of thyroid medication (+30-50% gem. fT4), poss. also HC-Ds; Subtly prepare women for possible inability to breastfeed
- Vasopressinase activity of placenta, mainly in late pregnancy ⇒ mimics „Diab. insipidus"; Tx: adapt fluid addition ↑, poss nocturnal Minirin ®
- Spontaneous births also possible with (pan)hypopituitarism & multiple axis failures, oxyocin i.v. or nasal postpartal for breastfeeding currently not yet possible
Bones: Ca po 1.5g/d, 4% BMD↓ w breastfeeding ⇒ Risk f Osteoporosis; placental **PTHrp**: transient Ca ↑ (if addtl. Vit D -> 1.25 hydroxylase ↑)
BP-Tx (>160/110mmHg) **Methyldopa** (Aldomet®) Tbl 250-1000mg tid, **SE:** hepatitis; **Metoprolol** (Beloc®) 50-200mg qd, **nifedipine** (Adalat ret®) 20-90mg BP, **amlodipine** (Norvasc) 5-10mg qd, **labetalole** (Trandate®) 200-400mg po tid, 20-80 mg iv/30' (max 300mg), 1-2mg/', **SE:** growth retard., poss. nitroprusside (Nipruss®) 0.5-10mg/kg/' =20-600ug/', Hydralazin (Apresolin® aus D), poss. eplerenone in 2./3. Trim. if prim. Hyperaldo (Dg: suppr. Renin) **NEVER:** ACEIH, ARBs, renin antagonisten (Malformations of the kidney and urinary tract)
Postbariatric: Guideline KSA G F Increased risk of premature birth, SGA, lower risk fro GDM & maternal morbidity.

13. Diabetes Counselling & Insulintherapy

The 3 important things in diabetes: education, education, education. The diabetic who knows the most, lives the longest. P. Joslin

Allg. Diabetesfachberatung vermittelt Grundinformationen, Folgeerkrankungen, Therapiemöglichkeiten, Hypoglykämien
- Betreuungskonzept neu entdeckter Dm Typ 1, Konzept stationäre Betreuung schlecht eingestellter Diabetiker KSA
- **Kontrollen** (Merkblatt für Pat.): Prinzipiell **jährlich** Kontaktaufnahme m DFB b Langzeitpat.,va m HbA1C über Zielwert, PG-Wahrnehmungsstörungen,Spätkomplikationen (Fusspflegeberatung! PoHI Podologie), **Pflasterprobleme** bei Sensoren & Pumpen

Insuline (5x3mlPenfill Amp.oder Fertipen5x3ml)**, cave:** trübe NPH-(e.g., Insulatard) & „Mix"-Insuline 20 x kippen vor aufziehen
- **Applikation: Injektionsmenge** poss. >40E auf 2 Injektionsstellen aufteilen, **Injektionsort:** Bolus & Mischinsulin: Bauch; Depot: Oberschenkel, auf wechselnde Injektionsorte achten (Lipodystrophie, Hämatome), «**Insulin-Accelerators»:** temperature (Sauna!), exercise, massage
- «**if you don't know what to do?**»: ask the patient, adapt (reduce) insulin dose, eat less, check injection site
- **Humalog®, Humalog Mix® 25 / Mix® 50, Abasaglar**: Humapen Savvio 1-60E, LuxuraHD ½-30E, Kwikpen1-60E
- **NovoRapid®, Levemir, Insulatard, Tresiba®** (100 & 200E/ml), **Ryzodeg®** (30% NovoRapid, 70% Tresiba), Novopen5 1-60E, NovopenEcho Plus ½-30E, InPen, Flexpen1-60E, FlexTouch 1-80E (nur NovoRapid, Tresiba & Ryzodeg), FlexTouch 2-160E (Tresiba 200E/ml), **Xultophy®** (1 Ds=1E Tresiba + 0.036mg Victoza; max 50 Ds/Tag, nur T2D)
- **Apidra®, Lantus®** (100E/ml, HWZ ≈ 22h)**, Toujeo®** (300E/ml, HWZ ≈ 28h): Click-Star 1-80E, Solostar1-80E
- **Spritz-Ess-Abstand:** NovoRapid / Humalog / Apidra unmittelbar vor (od nach) Essen spritzen; PG <5mM nach dem Essen

Pumpen Checkliste Start: KSA **Bestellformulare:** Medtronic **670G**, **780G,** Roche **Accu-Chek Insight, Solo, Insulet Omnipod**, **Hybrid Closed Loop Systeme** (u.a. Medtronic 780G & Guardian 4; Minimed 740G, Dexcom G6,Tandem t:slim X2, Ypsompump CAM APS)
Insuline: Humalog/NovoRapid/Apidra Stechamp à 10ml od 3ml Penamp, Insumane Infusat U 100 5x 3.15 ml Amp
Merkblätter Berechnung v Basalrate & Bolus Insulin (gem. RF = CIR), Blutzuckertagebuch, Hypoglykämie & Ketoazidose
Wichtig: bei Pumpenstopp sofort mit Basisinsulin beginnen, Boli wie bei Pumpentherapie

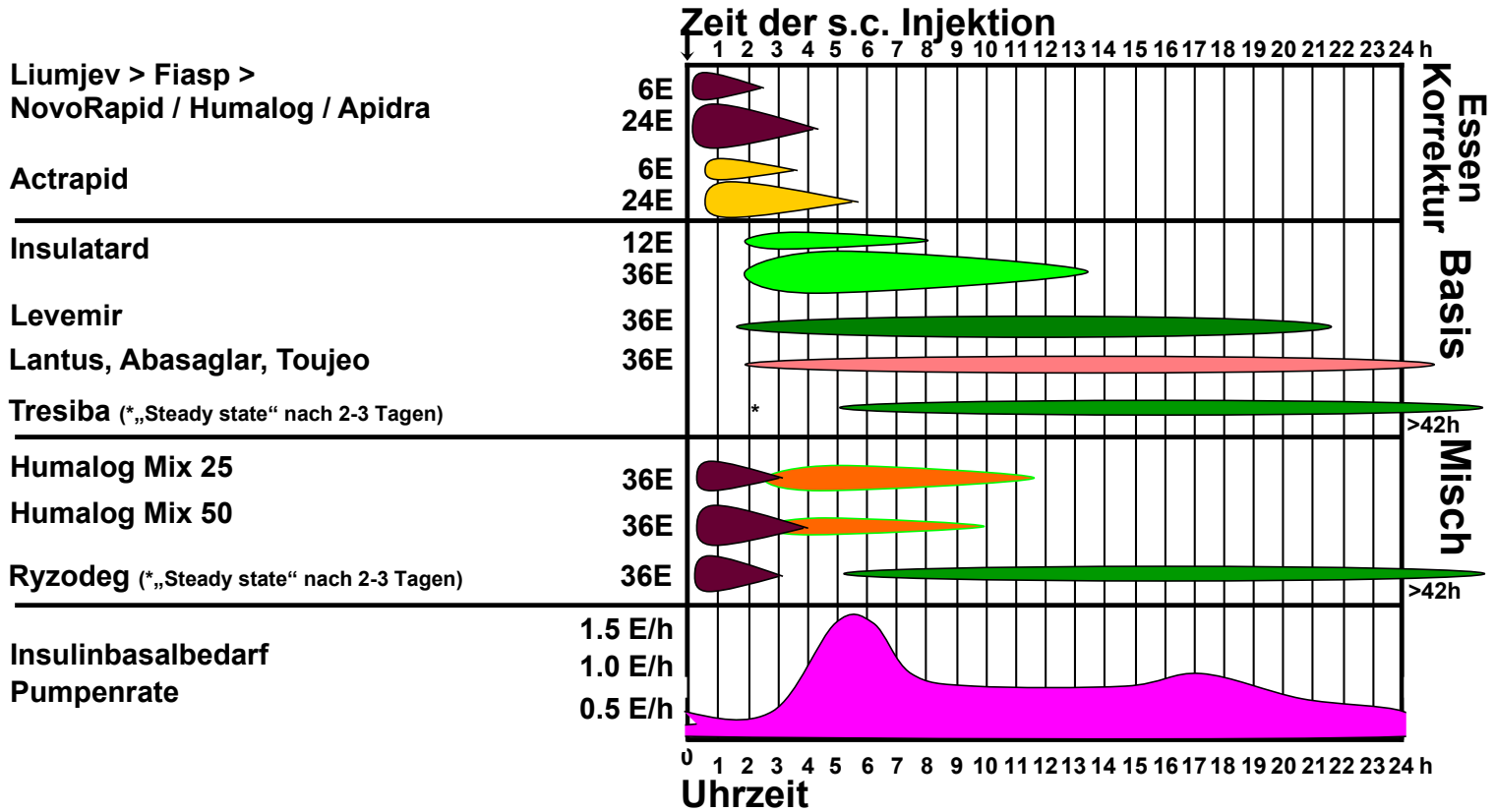
"CGMS" (continuous glucose measurement senor, 72-144h. **Analysis:** short, extensive, nutrition. **cave:** PG falsch↑ mit Paracetamol, Vit C), **Rp Verschreibung FachMD EDM** **Ind:** Dm m (nächtliche) **Hypo** II u/o NF-Kons./Hosp wg Hypo u/o schwerer „brittle Dm", , **HbA1c>8%,** Dm1 plus **(geplante) SS** m HbA1c >7% bzw. zum Erreichen d Zielwerte (nü <5.3, pp <7mM). **Unerklärte PG-Schwankungen** b guter Compliance, **Verkehrsbeurteilung**, DawnPhänomen, **Diskrepanz PG zu HbA1c**,
- Freestyle **Libre** **Ind:** «Dm m. FIT», Dg PG über 2Wo (KSA-ID Libreview 05321468 kein Pumpenconnect, **Libre 2** (mit Hypo-Warnung), **Libre 3**, **Guardian 4 & InPen**
- Roche **Eversense** (PoHI; **Ind:** Langzeit 3-6Mon.) **Dexcom G6** **Ind:** PG-Kontrolle über 1 Woche (noch keine Pumpenverbindung)
- Medtronic (PoHI nur nötig falls komb. m. Pumpe)

Messgeräte (how-to einlesen, Diabass SecureSend); alle CAPD-tauglich *plasmareferenziert, Roche:* Accu-chek (Aviva,Nano,Mobile), *Ascensia:* Contour (next one / AC Guide / Instant), *Abbott:* **Freestyle (Lite**, Freedom Lite, **Precision Freestyle Ketone-Streifen** *(messen β-Hydroxybuturat!)*, Insulinx (HbA1c)), *Ypsomed:* mylife Pura / Unio, *nicht CAPD tauglich:Life scan*: One touch (VerioFlex / IQ)

Lanzetten f Stechhilfe: *Ascensia:* Microlet Lancets(25G),Klinion soft fine color(28G), *Lifescan:* One touch Comfort (22G) / Delica, *Roche:* Accuchek Fastclix(30G) *Abbott:* ThinLancetten(28G)

Pen-Nadeln: *für alle Pens:* Mylife Click fine(**4**/5/6/8mm), BP Micro-Fine ultra(4/5/8mm), BP Autoshield Duo(5/8mm). Flexpen, Flextouch, Novopen 5: NovoFine (6/8mm), NovoTwist (5/8mm)., Bei extremer Spritzenphobie poss. «iPorts» (keine KK-Lst)
Nadeln 4mm, auch bei Adipositas. Injektionsmenge aufteilen: Depot >40E, rasche Insuline>20E
Ev Alkohol Tupfer**, Baqsimi ®** i.n. **Ind:** anamnest. schweren Hypo Grad III, poss. GlucaGenHypokit → Haltbarkeit → Gratisumtausch nach Ablauf in Apotheke
Ketonkörper Messung ? poss. im Kapillarblut **Freestyle β-Ketone-Streifen** bei DmTyp1, Pumpentherapie, SGLT-2. Früher Ketodiabur® Urinketonteststreifen

Wirkdauer v Insulinen sc schematisch → Insulindosierungsschema KSA ambulant (, alt" PG in mM od mg/dl)**, stationär,** Patienten-Info über stationäre Insulintherapie am KSA, *Spezielles Wirkprofil von Degludec (Tresiba®)



14. Clinical Nutrition & Counselling

„Man ist, wie man isst“… gilt für ALLE Menschen !

SMF 05; 47: 1163-70, NEJM 11; 336:1495-8, Eur J Clin Nutr 2010; 64:887-93; www.espen.org, www.geskes.ch, www.nutritioncare.org; weitere

Energy requirements **total 20-25kcal/d*kg current weight** (for target-weight add or substract % kcal) **= basic metabolic rate** 20-25kcal/kg/d (10% lower for elderly & obese pat) **& stress/morbidity** 10-50%↑ (1°ΔT↑⇒10%↑, T4↑ / ICU -30%↑) **& activity** 10-50%↑ (in bed +10%, mobile+20-40%, heavy labour +100%; **e.g.** (≈kcal/h f 70kg, outpatient): supine 80; seated 100; standing 150; walking (5km/h) & bicycle (15km/h) 250; swimming (0.4km/h) & golf 300; eerobic 490; tennis 420; jogging (10km/h) 500; squash 600. ⇒ ≈24h hiking to ”burn” 1kg fat↓

Proetin: 0.8-1.2g/kg/d: urine-urea (mM/24h) / 6 = g prot. turnover/d (n ≈1g/kg / d; more precise: U-Urea x 0.028 ≈ 70gN/d x 6.25 = gProt/d + 3g Prot-losses/d)

Fluid: **20-35**ml/kg/d (dep. on underlying diseae / balance / age) **Electrolytes** (mmol//kg/d): Na 1-2; K 1-3; Ca&Mg 0.3-0.4 each; Cl 5-6, PO_4^{3-} 0.3-0.8

Malnutrition 20% d Pat! (Pat-Info “Mangelernährung trotz Überfluss“, Ernährungsempf. b Appetitmangel)

DG: Screening m. **Nutritional Risk Score** (NRS), **BN KSA** →**Ernährungstherapie gem. EFFORT (D E F I)** (psb), Wunden / Dekubiti

Labor (DD Akutphasereaktion)**: 1. Basis: BBPiff, E’lyte, Crea, Urea, Quick,Protein, Lipide, PG, Leberenzyme, Amylase 2. Viscerale Proteine: Albumin**<28g/dl (nur ohne akute Erkrankung!), **Präalbumin (Transthyretin)** <120mg/L (kürzere T1/2, Verlaufskontrolle), 3**. Immunität↓: Lymph**<1200/mm^3, **4. Muskelmasse↓: Crea iU** (p 2) <80% (mild) <40% (schwer); **5. Lipide: β-Caroten** (<1.5uM), Retinolbindendes Protein <20mg/L, **Cholesterin** <3mM, **6. Spurenelemente & Vitamine**: **Eisen:Transferrin**<1,5g/L (hepat. Proteinsynthesemarker), **Ferritin**<20ug/L, **Vit. B12** < 176 pM (≈230 pg/ml), **Erythrozcyten-Folsäure** <300nM, **Zink** <10uM; **Selen** <0.8uMM; **25OH-Vit D**<25-50nM

Anorexia nervosa **Anorexiekonzept, Uebersicht Essstörungen; «Reizdarm»:** Sprue, IBS, FODMAP, >50J.-> Colo; Mastozytose, Endometriose, Porphyrie

Refeeding-Syndrom **RF:** Zu rascher Nahrungsaufbau nach wt.verlust (>5%/Mon, >7.5%/3Mon, >10%/6Mon) e.g., nach Malnutrition, C2 Abusus, Anorexie **Sy:** innert 1-3 Wo Na-Retention m Ödemen, P-PO4↓ (<0.32mM idR m ZNS-Sy, Coma, RhaBPomyolyse, Hyperparathyr., Insulinresistenz), K↓, Mg↓, Ca↓, Zn↓, Vit B1↓ **TH:** oral > enteral > parenteral; **inital nur 50% d Kalorienbedarf** (10 → 20 → 30 kcal/kg/d bzw. Flüssigkeit in ml/kg /d über 1-2 Wo, poss Zusatz m Trinknahrung / Sondenkost/parenteral); **Elektrolyte gem Labor** (Bedarf sa): **PO4** Phosphat Sirup KSA 500ml 10mmol=15ml tid, Phoscap Bichsel® 5 Cps à 100mg=3mmol qid, K-PO4 Amp 1mmol/ml 100ml ad inf (nicht m Ca^{2+}), **K** KCl Hausmann 2 Drg tid (745.5mg=10mmol K/Drg), K-Effervetten Hausmann 1 Braustbl =30mmol K tid;iv: KCl 15% Amp à 10ml (20mmol K) **Mg** Mg-Card Granulat (5mmol) od Effervetten (7.5mmol) oder Lutschtbl (2.5mmol) tid, iv: MgCl Amp 50% à 2ml (4mmol=1g Mg) **Ca/Vit D** Calcimagon BP (p16), **Vit B1** Benerva 300mg po / iv qd, **Multivit.** Supradyn, doppelte Ds x 7d, iv Soluvit & Vitalipid je 1 Amp tgl, **Zink** Zn-Glukonat Burgerstein Tbl. à 30mg qd, iv ZnCl Amp à 10ml (5mmol Zn), **Selen** (CH: Selenase 500ug/Trinkamp=CHF 8.-; D: Cefasel 300ug/Tbl = 80Rp), **Fe-** (Ferrinject 100-250mg iv) subst ab d7, **KO:** Vitalsy, Bilanz (nicht m H20 „überschwemmen!, max +1L /d), Oedeme, wt / BMI, E‘lyte d1-7 tgl, je n Schweregrad u Verlauf

Stufen d Ernährungstherapie **Frühzeitiger Ernährungsberatung** (KSA, **PoHI**;, Algorithmus Medizin & Chirurgie)

- **Ind:** Präsente od absehbare Malnutrition (>3d <500kcal /d bzw. NRS-Screeing), Pat. Info , **EFFORT: NNT Mortalität 36, Komplikationen 25!**
- **MD-Consult:** Malnutr. m Refeedingrisiko, parent. Ernährung, Kurzdarm-Sy (p27), **Ziel: ENTERAL! sa bald & sa viel wie nötig!**

1) Wahlkost "**if the gut works, use it or loose it**"; je n Energiebedarf / AZ; **Pat. Info**

Nährwert (1kcal = 4.2J, Ernährungspyramide) **Prot:** 4kcal=17kJ/g **Fett:** 9kcal=37kJ/g **KH*:** 4kcal =17kJ/g **OH** 7kcal=28kJ/g

„Standard“ 2000kcal i g/d (%Energiegehalt) ≈95g (≈20% d kcal/d) ≈80g (≈30%, 2.5% ess FS) **≈180g (≈50%)** F<20g/d; M<40g/d

***Diabeteskost im KSA⇒ fixierte KH** (Haupt-MZ / Spätimbiss-Dessert) **2400kcal: je ≈60 / 20g; 2000: je ≈50 / 20g; 1600: je ≈40 / 10g; 1200: je ≈30 / 10g**

2) Kostformen Keine unnötige Einschränkungen b Krankheit Spezialfälle (poss Consult EDM): Medizin Ind f. ERB, **Dm** (p7), **Adipositas** (p15), **Dyslipidämie** (p15), **Hämodialyse** (1-1.2g Prot/kg, ≤1g PO4, ≤4-6g NaCl, ≤3g K, H20: Urin+500ml), **Steroidth.** (1.2g Prot, Fett↓, 1200-2000kcal, KH↓, no Grapefruit), **NaCl↓** (5-6g), **Energie- & Eiweissreich**, **Gicht** (wenig Fleisch, C2), **IPS, Chirurgie:** Ind f. ERB, Bypass, Prä-Sx Karenz, Postop. Kostaufbau, n. Magen-Bypass, indiv Diabeteskost, Chylothorax **Pädiatrie:** Legen Magensonde Früh- u Neugeborene

3) Trinknahrungen (**Sortiment KSA**, **USB**, Vit K ⇒ OAK anpassen) Kalorien & Proteinanteil normal **(a)** od erhöht **(b)** bzw. fettfreie Präparate **(c)**

Präparate (Indikation, idR kalt geben, Ergänzungsnahrung, div. Aromen), pro 100ml,	Energie,	Prot,	Fett,	KH,	Spurene./Vit
a) Fresubine Protein Energy (1-2x/d, laktosearm, Portion 200ml)	150kcal	10g,	7g,	**13g**,	1/8
a) Resource Protein (USB, faser- u laktosearm, Portion 200ml)	125kcal	10g,	4g,	**14g**,	1/8
b) Resource Compact (faser- u laktosearm, Portion 125ml)	250kcal	10g	10g,	**30g**,	¼
b) Ensure Plus (KSA, faser- u laktosearm, Portion 200mml)	150kcal	7g,	5g,	**20g**,	1/6
c) Enlive Plus Drink (KSA, **2h präop** “Carboloading“, fettfrei, fruchsäurearm; Portion 200ml)	150kcal	6g,	0g,	**36g**,	1/3

4) Sondenkost (**Sortiment KSA**, **USB,** Protokoll, Einbezug ERB KSA, Material, Einlage (Freka, Compat) nasogastral od -intestinal, **Bedarf>4 (-8)Wo** ⇒ **PEG** (Einlage, Entfernung) **Sondenkostaufbauschema:** (initial kontinuierlich m Pumpe (b Jenunalsonde, 6h Nachtpause zur Verminderung v Aspirationen ist umstritten), 20-40ml/h-weise steigern, Portionengabe asap; **SE**: Diarrhoe, Elektrolytstörungen, Hyperglykämie, **Tx:** Paspertin 10mg tid, Oberkörperhochlagerung, Trend RV ⇒ **Insulinpflichtiger Dm**: MZ a) innert 1-2h ⇒ Humalog; b) 4-6h ⇒ Actrapid c) über 24h ⇒ Actrapid-Perf, Levemir (b Nachtpause), Lantus, Austrittsplanung PEG, Freka-Button, Richtlinie HomeCare KSA & SZ, PoHI Heimernährung, Medi via Sonde, Zermörserbarkeit Tabl.

Präparate (Indikation alle Produkte purin-, laktose-, glutenfrei & natriumarm), pro 500ml	Energie,	Prot,	Fett,	KH,	Spurene./Vit
Peptamen HN (**Verdauungsstörungen**: Malabsorption, **Kurzdarm / n.GIT-Sx,** IBP (Crohn/Colits)	665kcal	33g,	25g,	**78g**,	1/3
Peptamen AF (IPS)	750kcal	45g,	32g,	**67g**,	1/3
Nepro HP (**Niereninsuff** m Cl_{Crea}<30 ohne Dialyse, 1.8kcal/ml))	900kcal	41g,	49g,	**74g**,	1/2
Isosource Protein Fibre (**Proteinbedarf↑** IPS, postop., Radioth, Dekubitus, Dialyse m n K & $Po4^{3-}$)	665kcal	33g,	22g,	**80g**,	1/2,5
Isosource Energy Fibre (**Normalbedarf mit Fasern,** hochkalorisch, Langzeit)	800kcal	30g,	31g,	**96g**,	1/2,5
Isosource „Standard“ (Normalbedarf, f**aserfrei**)	525kcal	20g,	18g,	**71g**,	1/3
Novasource GI control (USB, **Normalbedarf mit Fasern**)	550kcal	20g,	17g,	**72g**,	1/3
Novasource GI forte (KSA, **Normalbedarf mit Fasern**, **hochkalorisch**, **Langzeit**)	750kcal	30g,	30g,	**92g**,	1/3
Fresubin 2kcal HP (fibre) (Standard, hochkalorisch, mit Fasern)	1000kcal	50g	50g	**84g**	1/2
Impact Glutamin (KSA, n-3, Arg, RNA: **elektive Viszeralchirurgie, Trauma**)	550kcal	32g,	15g,	**73g**,	1/3

5) Parenterale Ernährung **Ind:** >3-8d erwarteter >50% enteraler Karenz (je n Ernährungzustand) **Zusätze** (Zugabe i durchmischte Lsg; danach Lsg 24h haltbar) **1. Soluvit N** (wasserl. Vit) & **Vitalipid** (fettlösl. Vit) je 1Amp, **2. Addaven N** Spurenel. 1-1.5 Amp **oder Peditrace** (bei Fe-Ueberladung) **3. poss. Actrapid** b DM1E/10gKH i Beutel, Perfusor; **4.** poss. **Dipeptiven** L-Ala u L-Glu b Hyperkatabolie & KMT f opt. N-Bilanz; 0.3g/kg/d (=1.5ml/kg/d) i PE-Beutel, **Cl** Crea-Cl. < 25ml/min, schwere LF, pH < 7,2 **F/U: Tgl.** wt & Bilanz (Ziel: Na i.U. >20mM, Na/K i.U >1, n U-Vol (>15ml/kg bw/d), **d1 - d3 tgl** Na, K, PG, P04, Tg (>4.6mM bzw. >10mM → Lipidlsg red. bzw. stop); **wchtl.** Ca, PO4, Cl, Mg, Zn; TG, INR, PTT, Bili, alk. Phosph., GOT, Lipase, Alb, Crea, Urea (falls isoliert ↑ -> Aminosre-Lsg reduzieren), CRP, BB, Eisenstatus

Präparate	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	PO_4^{3-}	mOsm/L	ml,	Energie,	Prot, Fett,	KH,	Spurene./Vit.
SMOFkabiven (1, 1.5, 2L)	80	60	5	10	70	25 mmol	1500	1970ml,	2200kcal	100g, 75g,	**250g**,	zugeben (sa)
SMOF peripher (1.2L, i.Res.)	30	23	2	4	27	10 mmol	850	1206ml,	800kcal	38g, 34g,	**85g**,	zugeben (sa)
SMOF EF (1.5L, Elektrolytfrei, KSA)						4 mmol	1300	1477ml,	1600kcal	75g, 90g,	**187g**,	zugeben (sa)

15. Dyslipidemia & Obesity

A successful diet is the triumph of mind over platter

SÄZ 11; 92: 55-6, Pharmakritik 05; 3: 9-12; JAMA 04; 292: 2585-90; Lancet 05; 366:1849-61 BMC Nephrol 2004, 5:17; JCEM 2010; 95: 4823-43

Dyslipidämien primäre/familiäre Formen oft durch sekundäre Ursachen verstärkt

A) PRIMÄR (genetisch; „DD-Regel“: **TC↑⇒DD:** polygen, FH, FDB; **TC↑&TG↑⇒ DD:** FCH, Remnant, sek.; Rarinome), **TH: immer**

Dyslipoproteinämie	Präv., Genetik	Klinik	"KHK"	Lipide
I. HYPERCHOLESTERINÄMIE (FH) A) "gewöhnliche" **polygene** (IIa)	PoHI f genet Test nötig! ≈1/10,10% fam.,rez?	Risiko für FH Unspezifisch	+	TC&LDL-C ↑, TG n
B) Aut.-dom. Hypercholest (IIa, b) - FH: LDL-Rez Defekt - FDB: Fam Defkt Apo-B100	1/500, Aut-dom - >700 Mut - 1 Mut ⇒genet.Dg	**Xanthelasmen**, Tendinöse Xanthome, Arcus cornealis	++++ va b Lp(a)↑	LDL-C & TC ↑↑ ⇒ **DG FH** altersabh<20 20-29 30-39 >40 1°pos FA 5.7 6.2 7.0 7.5
II. KOMB HYPERLIPIDÄMIE A) FCH (Fam. comb. H., IIb, IV) B) Remnant Disease (=FDL=fam. Dys-βLipoprotein, III)	1/200, Aut-dom ApoB-Ueberprod 1/10'000, Aut-rez ApoE2/E2 (KK-pfl) Genotyp v 1% d pop.	**A) Xanthelasmen**, Arcus cornealis **B) Xant. striata palmarum** nur 5% d Genträger haben Sy	++ +++	**TG & Apo-B >1.2g/L & LDL-C** **VLDL-Remnants (IDL)↑** TG/TC>1 & fluktuierend
III. HYPERTRIGLYCERIDÄMIE A) Fam. (IV, V: VLDL↑, V: Apo-CII↓) B) Chylomikronensyndrom (I, V: LPL↓ od Apo-CII-Defekt)	 1/500; GPIHBP1-Defekt? 2-4/Mio,?	 **Allg:** Eruptive Xanthome, **Pankreatitis** (va TG>10 → viele Chylomikronen) sek. Urs & Th psb	 -	 TC n-↑; a)**TG↑** (**KH⇒** va VLDL↑↑) b)**TG↑↑**(**Fett⇒** va Chylo↑↑) Aufrahmen b 4°C
IV. HYPO-αLIPOPROTEINÄMIE	(aut-rez)	DD: Tangier, Fish eye, LCAT	+++ / -	HDL-C↓ b n TG

B) SEKUNDÄR (erworben); **VP zur DD:** PG, TSH, Leberwerte & Crea, Urinstatus

- Metabolisches Sy (p9), **PG:** IR⇒LPL↓⇒Lipolyse↑⇒ zirkul. FFS↑⇒ hepat VLDL-Prod↑/Katabol.↓⇒TG & ApoB↑ & HDL↓, LDL_{Tot}→ ; HL↑⇒ small dense LDL↑, LDL↓

- C2/OH: TG↑ b prim. Hyperlipoprot, HDL (↑) b Gesunden, **Dg & Tx:** Auslassversuch (mind 2Wo), **Medi:** TG↑: Steroide, HAART (p27), unsel. β-Blocker, Diuretika, Tamoxifen, IFNα, TG & TC↑: Immunsuppr. (CyA), Olanzapin, Roacuttan, HDL ↓: anabole Steroide, B-Blocker

- Östrogene (hohe Dosen, SS); TG & HDL-C↑; **Hypothyreose** (LDL-C↑, TC bis ~10 mM), **Cholestase** (TC 7-15 (-40) mM, LpX↑ **Tx:** Quantalan, Colestipol;

Nephropathie (TC 6-12 mM, TG n-5mM, LDL-C↑, b schwerem nephr. Sy TG↑), **Dialyse**: TG↑, **SIRS** (Chol.↓ (HDL↓), TG↑), **HIV, Anorexie** LDL-C↑, **parenterale Ernährung** TG↑, **Myelom:** TC&TG ↑, **myeloprolif. Sy**:TC↓, TG↑, **Bexaroten** (Targretin®, revers., dsabh. RXR-Fct ↓ i Hepatocyten) **HGH-Mangel:** TG ↑,Glycogenose 1 TG↑

DD Xanthome bei n TC: β-Sitosterolämie **DG:** Pflanzensterole ↑, **TH:** Quantalan, Colestipol

Tx: Mediterrane Kost Olivenöl, Nüsse, Wein, Fisch, moderat (rotes) Fleisch & Salz, <30% Kal/d als Fett, <5% tot Kalorien/d, gesättigte / Trans-Fettsäuren; „non-fried“, Fasern↑), **u&o «Functional Food»**; Kaffee & Schoggi, **≥2cvR ⇒Lipid Screening:** ⇒ **Th-Ind & Ziel** (mM) risikoadaptiert **10J cv Risiko** (**QRISK**, AGLA)

LDL-C↑: Statin: 5mg Crestor (FH) ≈ 10mg Sortis (Dm) ≈20mg Zocor (Dm; **rel. CI:** Amiodaron, Verapamil, Dilitazem, Amlodipin) ≈ 40mg Selipran (CKD) ≈ 80mg Lescol, **10% cvRisiko↓/mM LDL-C↓**, **LDL(ApoB)-Ziel: <3 / 2.6 / 1.8** (<0.8g/l) **/ 1.4mM** (<0.65g/l) (low / moderate / high /very high risk & sek. Prophylaxe) **SE:** dosisabh, 10% **Myalgien**, 1% CK <10x↑, <1%o Hepatopathie u/o RhaBPomyolyse m Crea↑ (20% fatal; RF CYP3A4-Hemmer (e.g., Amiodarone, Amlodipin, Fluoxetine, Fluconazol, Ritonavir, Grapefruit), Gemfibrozil, Cyclosporin A, Alter >70, CKD, LF); **KO:** 0→3→6mtl,Muskel-Sz >3d⇒CK <10x↑; Leberwerte <3x↑; **poss & Ezetimibe** (Ezetrol® & Atorvastatin (Atozet®), Ezetrol® & Simvastin (Inegy®), **Statin-SE od Nichterreichen d Zielwerte:** Retry n Th.-pause (1-3 Mon); Th d übrigen cvR!, **Bempedoic Säure** (Nilemdo®Tbl 180mg qd od Nustendi® 180/10mg qd), **PCSK9-Inh** CH ≈5'000.-pa, **Evolocumab** (Repatha®, 140mg sc 2-wchtl. **KK-Ind.**) **Alirocumab** (Praluent®, 75-150mg sc 2-wchtl. **KK-Ind.**), siRNA **Inclisiran** (Leqvio® 284mg 6mtl sc **ind:** zusätzl./anstelle v Statin b LDL-C >1.8 sek. Präv; >2.6 fam. Hypercholest (prim & sek. Präv), Colestryramin (Quantalan 1-2Sachet in 2dl. BP)

TG >1.7mM - >10mM (Chylomikronen Sy) PG: Dm Entgleisung, C2, prim. Hyper-TG, Sacharose (Softdrinks, auch Fructose i light Getränken); SS (E2), Medi sa, **SY:** akute Pankreatitis (Amylase ev. falsch ↓), Mikrozirkulationsstörung (Parästhesien, neuropsychiatrische Symptome), eruptive Xanthome; (Pseudo)-Hyponatriämie

Tx: Acute: Fasting! (NPO, nourishment/energy-, fat & C2-abstinence), LPL↑: Inf 40E Actrapid ad 1L Glc 20%/d & Fragmin 5000 sc qd, olezarsen?, plasmapheresis

Chronic: Weight & C2, fat↓ (<30% fat↓ (≤25% of calories, 50% of which MCT)e.g., Ceres®, essent. FS, 1 Tbsp sunfloweroil), low-fat protein-suppliers), **fast-acting CHO↓** (if PG↑ initially insulin-therapy), Sport **nutrition counselling!**, **Icosapent-ethyl** (Vazkepa® Cps 2g BP **Ind:** PoHI Art. 71b required, TG>1.7mM under statins for patients after MI or very high cvR;), **Fenofibrate** Lipanthyl® Tbl 200M bzw. 267M qd, **Orlistat** (psb), **TG>10mM:** Nutritional fat<15%

Adipositas ”Myths & Facts”, DEF: Uebergewicht BMI ≥ 25; Adipositas Grad I ≥30; II ≥35; III≥40 kg/m²

Anamnese Status: wt. Verlauf (Kind, 20j, SS, max., min., Kuren, Ziel-wt), **cvR** (p7, Bauchumfang (F>88cm, M>102cm)), **Medi** (Antidepressiva, neuroleptics, antikonvulsivs), **personality** (Binge-Eating, EDNOS (eating disorders not otherwise specified), affective disorder, **social stigmatization & discrimination**), **Mahlzeiten-Struktur** (Esstagebuch, oder einfachere (Verlaufs-) Checklisten Was, wie oft?, Ess- u Bewegungsverhalten)

Wahrnehmungsstörung: Δ kcal Aufnahme – Bedarf (p14), fettarme Eiweisslieferanten

Komplikationen: Dm &CVI 3x↑, KHK2x↑ (<65j), psycho-soziale Probleme (inkl. Sexualität), **periop. Risiko↑, Arthrosen, div. Carcinome**

Tx: NUR Kombination v Verhaltensänderung, Kalorien↓ & Bewegung↑ langfristig konservativ erfolgreich ! (Merkblatt)

ERNÄHRUNGSBERATUNG! (Therapiekonzept, KEEA KSA & SZ, Einzel- vs. Gruppenth. e.g., **„BASEL“**, Weight Watchers), realistische **Ziele setzen** Δ300kcal/d ⇒ Δ1kg/Mon; ab 3-5% wt↓ → Sekundärkompl↓) **& keine Modediäten** „**high protein low carb**“ whs langfristig leicht effektiver als „low fat“ **1200-1600kcal** Nahrungsfasern↑, fettadaptiert, komplexe>einfache KH, non-caloric „sweet“ drinks (KH kcal > Bedarf ⇒ Fettverbrennung = 0 für 3-4h & Umwandlung v KH→Fett (0.5L Cola ≈ 10g Fett), **<1200kcal Diät nur ausnahmsweise** (e.g., präop); nicht über längere Zeit (Mangel ua v Vit. u Ca^{2+})

Psychiatr./psychosom. Th. d Essstörung & Selbstwertgefühl (KEEA KSA & SZ, poss. Fluoxetine (Fluctine®) Tbl. 20-60mg qd, Lurasidon (Latuda® Tbl. 40, 80, 120mg, qd)

Semaglutide (Adip: Wegovy ® 0.25-2.4mg PoHI dokumentiert Motivation Pat (500kcal/Diat, begeitende ERB, Aktivität) & % wt.verlust n 4 Mon (7% b BMI 35 bzw. 5% b BMI >30 / >27 m Dm kg/m2 & 10 Mon (zusätzl. 5%), Dm 2: Ozempic® 0.25-1mg s.c. wchtl. (0.4mg/d = 2.8mg/Wo s.c., po Rybelsus 3mg p.o; -15% kg, ; poss f PoHI OGTT PG>11.2mM? **Liraglutide** (Saxenda® 0.5-3mg s.c.-> change to Wegowy ® use 50% of current Saxenda ® dosage), **Retatrudie** (Triple Glucagon-GIP-GLP-1 Agonist): up to 25% reduction of body weight **Orlistat** (Xenical® Tbl. 120mg bid-tid nach PoHI;, BMI≥35 od >28kg/m2 b Dm2 & OAD, n 6Mt bw>10% , 5kg↓ b Dm, HbA1c >0.5%↓; max. 2J. **SE:**Steatorrhoe,

Operation (Gastric Sleeve bei BMI >50-55 →) prox. Laparaskop. Roux-Y-Bypass), interdiszpl. Zentrum gem. Richtlinien www.smob.ch; **sorgfältige Pat.-Selektion!** (Co-Morbiditäten, rel CI TVT/LE, OSAS), Flyer für Pat «Adipositaszentrum KSA&SZ» **Leitfaden Bariatrie KEEA KSA**

- **Ind: KK-pflichtig BMI>35 (50)kg/m² bzw. 30-35 m Dm2 n 2 (1)J erfolglose kons.Th & Wille f mind 5J. Follow-up** (**Compliance-Vertrag** visieren!)
- **Präop. Abklärungs-Checkliste: Pat-Info & Informed consent,SMOB-Consent**
- **Peri-/Postop.: Verordnungen Chirurgie KSA, Kostaufbau** p14; **10% Akutkompl.** (Nachblutung, Obstruktion, Anastomosen-Insuff, Arrhythmie, LE)

F/U: Nachsorge Bariatrie / Kurzdarm-Sy, Ernährung, HAz Empfehlung, ABP-Sz -> Susp of Leckage (früh postop) / Stenose (ab 2-3Wo postop) / innere Hernie (Monate postop (pp) ABP-Sz,) / → **chirurg. Consult** m Frage n Oesph-GIT-Passage m ICM bzw. CT-ABP u/o Gastroskopie n 12-24Mon **Bewegung↑** (Katabolie --> Muskelabbau);, Anpassung / **reduzieren v Insulin/OAD, Diuretika, Antihypertensiva**; **Vit. & Spurenelem.** Medi-Uebersicht Supradyne® Energy QD (Ueberdos. B6 → Migros Actilief All-in-one®; Unterdos. Fe, Zn, Vit B12 → WLS forte® aus D, Tardyferon® QD (poss Ferinject® 200mg iv 6-12 mtl), Kalzium 1.5g/d, K-Zitrat Tbl b Hyperoxalurie; **Bei Mangel:** Vit.B12 Amino®1000ug 3-1mtl.sc / Vitarubin oral od Vit B12 Ankermann po qd, Vit.D® 0.3ME 6-3mtl.po, Folvite® 1mg QD, Zink Burgerstein® 30mg QD-qid, Kupfer; Vit.A (β-caroten Carotaben® Tbl. 25mg qd – BP in SS, da nicht teratogen; poss. Burgerstein (CH) oder Jenapharm (D) 20 do 100 Cps à 30'000E; Vit. A Amp i.m (D), Kontrazeption!)

Probleme: Zufriedenheit→ Chirurg. Re-Evaluation wenn **EWL<50%,** poss. GLP-1 Analoga (Saxenda 3mg/d, CHF ≈ 500.-/kg pa, PoHI (Art 71, Vorlage GLP-1 LUKS); **Ind:** wt. Zunahme & hohes chirurg. Risiko, **Spätdumping→ Tx:** SGLT-2 Inh (p9), sonst Hypp-Th (p10), MECCO-Study (LUKS)? **Diarrhoen:** Loperamid, Tinctura opii 2% Trpf, selten Octreotid s.c. (>3L Fl/d verlust), Amitryptillin; **Fettstühle** Creon® Cps tid, **Gallensteinrisiko** Ursodesoxycholsre (Ursofalk®, Ursochol® 1-2 Tbl. 500mg qd), **Nephrolithiasis** (Hyperoxalurie va b dist. Bypass u biliodigest. Anastomose; Th. Nahrungs-Oxalat↓ u Ca↑, Urocit® 1-2 Tbl. z. Mz), **Bacterial Overgrowth** m Blähungen & (stinkende) Flatulenz → Perenterol, Metronidazol (Flagyl® Tbl. 500mg tid x 10d), Rifaximin (Xifaxan Tbl. 550mg x 2/52, PoHI) **postop. Osteoporose**: Ca, Vit D, Proteinbedarf! , **Reflux** (20% n sleeve): PPI; **«Bauch-Sz» DD** demasierte Porphyrie: PPI; **OAK:** Marcoumar gem. Q > NOAK (Apixaban Eliquis® Tbl.5mg BP?) ; **Dermatochalasis & Lipödem m Sz** → plast. Chir.!, Dumping-Sy (→ERB), **Vit.B6-Intox** (Norm: 35-110nM; Sy: Parästhesien, neurol. Sy), **Suchtverlagerung, orale Kontrazeption unzuverlässig** (va b biliopankr. Diversion) → **Schwangerschaft** 1-2J «no go» wg Katabolie

16. Bone & Calcium Metabolism

Aging is inevitable...maturity is optional.

JCEM 03; 88: 581-7; Swiss Med Wkly 2020; 150:w20362, NEJM 04: 350: 2033-49 & 12; 366: 225-33, Calciumrechner, www.svgo.ch

Ca-Bedarf/d: 0.8-1.2g; **Ca/L**; Milch ≈ 1g, Mineralwasser: Valser/Eptinger ≈ 500mg, „H_2O“ ≈ 50-100mg, **Ca-Fragebogen MD & Pat**

Osteoporose **Lebensrisiko f osteop.-Fraktur (Fx): F** 40%>M 15% ⇒ 2% Healthcosts, doubling of overall mortality risk after osteoporotic fracture

DG: pathol. Fx (inadäq. Trauma, Grö>3cm↓, Rückensz)⇒**Rx** BWS/LWS ap/lat (Rx ohne Trauma bei F>65J & T-score<-1; F (&M) >70J m T-score <-2.5;Follow-up nur lat.), Szinti (Vd a Tu), Ganzkörper CT/ MRI (Myelom?)

- **Risikofaktoren (RF) F**>80% prim **(5-10j postmenop); M**>50% sek; **Fx-Risiko>2): I) Anamnese: Steroide/T4** (BMD -1SD=10%/J↓), **Hypogonad.**(<40j, >6Mon, 1-2%/J↓), **Age** (1%/J↓, F>50J, M>70J), **FA** (Peak bone mass (20-40j) = 70% genetisch), **Immob**, **Malnutrition** (Bariatrie), **CKD**, **BMI<18**, **OH**, **Vit. D↓**, Hcy,FamHx, pHpt, smoking, antiepileptics, glitazones, acidosis, rheum. arthritis, Hepatopathy, Inflammat. Bowel disease (IBD), mastozytosis, cystic fibrosis
- **II) Densitometrie** (DXA Femur, LWK 1-4; **Ind:** Dg, v Th-stopp, Fx, <-2SD → **sek. Ursache suchen**; **Verlaufsko.** n 2 (high risk) – 15J. (low-risk)
  - **Z-score** (altersaptiert) f prämenop. F u M<50J, sonst **T-score** -1SD↓ ⇒ Fx-risk 2x↑ (Hip) - 1.5x↑ (WS); -3.7SD ≈ 37% Knochen↓, trab. bone score b Steroid
  - **T-score ≤-2.5:** ”Osteoporose”-> Th b Fx-risk↑ (psb), BMD-F/U 2j; **≤-1:** "Osteopenie" BMD-F/U. 2-5j, Ca&VitD; Fx-risk↑↑⇒Th; **>-1:** ”NAD”
  - **KK-pflichtig** Steroide >3Mon, chron Malnutrition, Hypogonad.(F nur <40j), pHpt f Sx-Ind, Fx b inadäqatem („Sturz aus Stehen“) Trauma, Th-Verlauf n 2J, T-score <-2.5; **nicht KK-pflichtig:** Postmenop, pos FA, Organ-Tx, klin u/o radiol Vd a Osteoporose (sa)
- **III) "Turnover"**(va trabek. Knochen, für Therapiemonitoring, nü, 2.Morgenurin, proteinarme Diät) **Anbau:** (knochenspezif.) **Alk.Phos** (>50%↑⇒Osteocalcin) **P1NP** (N-terminal Typ I procollagen **Abbau: C-Terminale Crosslinks (CTx) i P od U** (nü, 2h Morgenurin), kein Fleisch am Vorabend; IV) Knochenbiopsie b. Susp of renale u/o metabol. Knochenerkrankung
- **VP** BBPiff, BSR (b CRP<5mg/l), Chemogr (Crea, SGOT, Prot, Ca, PO4, Alk.Phosph), TSH, Testo/E2, 25-OH-Vit D, poss Mg, iPTH, U-Ca/Crea, U-PO4/Crea, 24h-FUC, S & U-Protein-Immunelektrophorese, Tryptase v Vd a Mastocytose

TH: Sturzprophyl.! (Sedativa, BP-Th, Orthostase, Visus, Stolperfallen (Teppiche, Kabel, Nachtlicht), Hip-Protector, **Training, Fracture Liaison Service (FLS)**

- **Ernährung** (1g Ca^{2+}/d) ⇒ **Calcium falls in Nahrung <800mg/d** (Ca-Fragebogen), **Ds:** 500mg BP, **K-Citrat** Eff. 30mval BP, **Vit D** (**Ind:** 25OH-Vit D<75-125nM, **Ds: 800**-1500E/d (ViDe3 8-15Trpf/d, Vit D3 Streuli 0.3ME ½ Amp 3-6mtl po/im); GFR <30ml/' ⇒ Rocalctrol Cps 0.25-0.5ug 1-2x/d, b art. Hypertonie: Thiazide)
- **Frakturrisiko „Frax-Score“** a) **T-score** (-1SD⇒Fx-risk x2↑), b) **RF** (Geschlecht, Alter, Steroide>1-3Mon (www.riskcalculator.fore.org, DXA >40j & RF, frühere Fx, tiefer BMI, Turnover↑ (Fx-risk x2↑) → **Medikation abhängig vom Frakturrisiko (SVGO 2021)**

a) Antiresorptive Therapie (ab moderatem Frakturrisiko 10% (F> 50J., M >70J) – 50% (100J.)

- **Bisphosphonate** BMD <2.5%/J↑ ≈ CHF 400.- pa, **Therapiepause n 3-7J.?** (BMD T-score >-2.5, Rx LWS - keine Fx?) **CI**: Reflux (PPI od iv Gabe), GFR<30ml/', ZahnMD (1/10'000Kiefer-Osteonekrose RF: iv Gabe, Dm, Steroids), Augenentz, VHFli?: **Alendronat** (Fosamax®) Tbl 70mg/Wo, **Risedronat** (Actonel®) Tbl 35mg/Wo **Ibandronat** (Bonviva®) Tbl 150mg/Mon, **3mg iv, Zoledronat** (Aclasta®) 5mg Kurzinf. Alle 18 (12-24) Mon. b GFR >50ml/';
- **Denosumab** (Prolia® 60mg sc 6mtl. x 5-10J., ≈ CHF 600.- pa) **Ind:** postmenop. T≤-2.5; Mamma-Ca m Aromataseinh. bzw. Prostata-Ca m Hormonablation & Frax↑, **SE:** Hypocalcämie; Infekte (HWI, LRTI), Gliedersz, atyp. Femur-Fx, Langzeit?? **Nach Stop: Bisphosphonate f 1-2J** wg. Osteoclasten Rebound!
- **HRT/Testo** ⇒Dexa 1-2%/J↑; **SERM Ind:** Menop. >2-5j u/o Mamma-Ca Risiko↑ **Raloxifen** (Prophyl-Ind., (RF+T-score <-1.5); nur WK-Fx↓ → poss komb. m Fosamax): Evista® Tbl 60mg qd; **Bazdoxifen** (Conbriza® Tbl. 20mg qd) **Tibolon** (Livial® Tbl 2.5mg qd, ab 1J pmp, p17), **SE:** Klimakt. Sy., TVT, CVI?

b) Knochenanabole Therapie (bei sehr hohem / imminenten Frakturrisiko (e.g., erste 2J n osteoporot. Fx) mit PoHI auch als First-line Th

- **Teriparatid** (Teriparatid Mepha®, Terrosa®, Movymia®, (Forsteo® 50% teurer) Amp 750ug/3ml; 20ug/400U sc/d x24Mon, sequentielle antiresorpt. Th; Ca-F/U,Dexa 7%/J↑ **Ind:** Fx unter Bisphosphonaten, Zusatzvers. (KK-Gesuch)
- **Romosozumab** (Evenity®, Sclerostin-Inh.) 2x105mg sc mtl. x 12Mte → Denosumab 12Mon. → Bisphosphonat x 2-5J **Ind:** ”Major Osteoporitic Fracture” (MOF; Wk, Hüfte, Becken, Humerus) + T-score ≤3.5 (LWS od Hüfte) od 2xMOF od SVGO 2000 ”very high risk. **SE:** Hypo-Ca; **CI:** KHK, CVI, cvR?

Hypercalcämie (2% d pop, meist symptomlos, poss Depr., ment. Sy, Polyurie, Nephrolith, CKD); **"Krise"** Ca>3.5 (ΔPsyche→Koma)

DD: pHpt (amb) > **Tu** (hosp, Mamma&Lunge (PTHrP), Plasmocyt.) > **CKD&Thiazide, ”Renni” >1,25Vit D** &A, Li (p28) > immob, rhabdomyolysis., sarcoidosis (granulomatöse Entz., auch extrapulmonal!) > **FHH** (Familiäre Hypocalciurische Hypercalcämie: pos FA (Loss of function Mut. Calcium-Sensing-Receptor (CASR)-Gen), jung, U-Ca↓↓ [**FE Ca <1% = <0.01**: Spot- U-Ca × P-Crea / P-Ca × U-Crea, UCrea >10mM, sonst FE-Ca falsch tief; DD: CKD], keine Th) > T4↑, M. Addison

TH: NaCl 0.9% 500ml/h iv (& Furosemid Lasix® 40mg iv 6h zur Volumenkontrolle b HF od CKD), **Bisphosphonat** (Zometa 4mg iv über 30Min bei Cl-Crea >30ml/', sonst Xgeva® 120mg sc), **CT** (Miacalcic® 10E/kg bw sc od iv x48h (Tachphylaxie!), **Ketokonazol**® (250mg tid - qd), **Prednison**® (0.5mg/kg), Dialyse

prim. Hyperparathyreoidismus **1 Adenom 75%** > 2-5 Adenome 15% > Hyperplasie 10% (va CKD u. MEN, p22) > Li **DD: FHH** (sa)

DG: >2x **P-Ca↑**(poss. obere Norm); **P-PO4↓**, Mg (↓), U-Ca/Crea↓ (va b CKD!) ⇒↑, U-PO_4/Crea↑; **PTH n-↑** (>25pg/ml); Crea, 25-VitD

- **Dexa** (Radius&WS&Hip); Ca (↑) ⇒ **Ca-Belastungs-Test** 1g Ca po (Brausetbl) ⇒PTH basal & 2h (norm: >50%↓)
- **Lokal.: US** (80/90%, rund/oval, **hypoechogen**, hinter / am Pol d Thy, scharfer Rand m Gefässen) → Sestamibi **Szinti** (70% (Cinacalcet)/90%) → ^{18F}**Cholin PET/CT** → **NSD-Punktion**

TH: Kons Bisphosphonat, (Thiazid?), Cinacalcet (Cinacalcet Devatis® / Mimpara® Tbl. 30→60mg po BP→qid) **SE:** Nausea, Ca^{2+}↓ ⇒ Ca & Vit D Subst.,) **Phosphat** Sirup KSA 500ml 10mmol=15ml tid od Phoscap Bichsel® 5 Cps à 100mg=3mmol qid, KEINE Thiazide! **F/U:** P-Ca2 & PO4, Crea, DXA, **vs Sx typ. Adenom, <50j, P- Ca>2.9mM; T-score <-2.5** (any site), **GFR<60ml/' od 30%↓,** Lokal m intraop. PTH? Poss. “**Cinacalcet Trial”** um Besserung d Sy zu testen, **Cave:** präop Ca↑↑ & Alk. Phosp↑ ⇒ **postop „hungry bone“**: postop schwere Tetanie mit P-Ca↓↓, Mg & PO4↓) **Tx:** psb

Hypocalcämie

DD: PTH↓ (postop PTH<10pg/mL, Thy/pHpt, AUI), **Vit D↓,** Mg↓, alkalosis >hypercalciuric Hypocalcämie (n U-Ca/U-Cr!) > genet. (AUI, Pseudo-Hypo-PTH, Barakt Sy (PTH↓, deafnes, CKD)

SY: akut: Parästhesien (perioral, Akren) ⇒Tetanie (Chvostek, Trousseau) ⇒Laryngospasmus, cv Kompl., Epilepsie; chron: ektod. Dystroph. (Haut, Katarakt, Haare, Nägel)

TH: Calcium 20ml (=1880mg) Calciumgluconat oder Ca-Glubionat (4.4mmol = 180mg Ca2+) x 10' iv Bolus nachfolgend 0.5-1.5mg Ca2+/kg/h i Glc 5% iv oder 1-2g po tid **z MZ** (Ca-Carbonat; PPI→Ca-Citrat), **Mg-Oxid** Sachets, <0.5mM⇒2ml 50% (=1g) iv, Ca u/o Mg **NIE** i PO4-Lsg*, **Calcitriol** (1,25-OH_2-Vit D = Rocaltrol® 0.25-1,5ug BP x 2/12), Paricalcitol (Zemplar® Tbl. 1-2ug s.c.) ⇒ **Vit D** ViDe3 (50000 x 1 Wo → 1000E qd po) od **Dihydrotachysterol=Alphacalcidol** (1-Hydroxy-Vit-D Analogon, hepat. 25-hydroxilierung nötig, A.T.-10® 10Trpf ≈ 0.25ug – 3ug/d Rocaltrol, längere $T_{1/2}$),**Forsteo**® (BP!) od **Natpar**® (PoHI m KV71 HMG), **Ernährungsberatung,** Thiazidversuch unter Kaliummonitoring

Osteomalazie / sek Hpt: oft asympt., Knochen-Sz, Osteoporose, Sy d Malabsorption., PO4↓ (b CKD↑), Alk. Phosph↑

DD: VitD↓ (25-VitD ab <75nM, outdoor <1x/d), **GIT↓, LF, CKD, Medi** (PO4↓: Antiepilept; Antacida, Ferinject) > **FGF-23↑** (P-PO4↓, FE-PO4↑; **DD:** genet. (FA?), mesenchym. Tu **Dg:** PET (FDG -> Octreotid) **Tx:** Phosphat p.o., Rocaltrol, poss. Burosomab (FGF23-Ak)) > NaCl reiche Diät (U-Na↑⇒Ca-Cotrsp⇒U-Ca↑⇒ Ca-Verlust) > Vit D dependent Rickets (VDDR I, II, x-linked) > Fanconi Sy

TH: Ca, PO4 & Vit D (poss. Rocaltrol), **Dialyse:** CaCO3 Tbl à 0.5g 1-4 z. MZ & Rocaltrol 0.125-0.5mg qd, (Paracalcitol, Cinacalcet) S-PTH>500-1000⇒Sx

Heterot. Ossif: NSAID, Radioth, poss. Zoledronat (Aclasta®) 5mg Kurzinf., **F/U:** Ca, PO4, Crea BP -2d; poss Ca iv

M Paget: 50%Knochen-Sz/Deform (Becken>Femur>TibiaSchädel>LWS), Alk. Phos↑⇒Szinti⇒Rx; **Sz-Tx:** Bisphosphonate x 2-6/12 (CT 100E nas BP)

”CRPS” M Sudeck/Charcot **Dg:** Klinik! Rx/MRI **Tx: Ergo/Physio, Zoledronat** (Aclasta®) 5mg Kurzinf. **Vit C prophyl.** 500mg BP x3/12, Pred 0.5mg/kg x 6/52 ausschleichen

17. Female Gonads

„Ich weiss es nicht!“ Sigmund Freud auf die Frage „Wie versteht mann die Frau?“

Update AKB NEJM 03:349: 776-88 & 04; 353: 2578-88 & 14; 37:119-29, JCEM 18; 103; 1258-64, JAMA 11;305 267-274, SMF 17; 17: 284-90

DEF: Metrorrhagien: Blutung ausserhalb Menses ⇒Gyn., **Hypermenorrhoe**: starke Mens.blutung (Hb!); **Polymenorrhoe:** Zyklus <21d; **Oligomenorrhoe**: seltene, unregelm. Menses, Zyklus >35d; Zyklusstörungen finden sich in 2-3% d F i Reproduktionsalter Normaler Zyklus:

Amenorrhoe

1°: keine Menarche -16LJ. (Norm ≈12.5LJ, FA?, Abklärung ab 13LJ, Telarche/Pubarche <14LJ, (Norm≈10.5LJ)) **DD:** Gonadendysgenesie/Turner (Checkliste D: I; F); --> Karyotyp; **2°:** keine Menses >3 (bei regelm. Menses) - 6Mon (bei unregelm. Menses)

DD: Ausschluss SS/Laktation, **Hyperandrogenämie** (PCO; CAH; NCCAH (psb); TU (NNR: DHEAS↑, Ovar: Testo↑>5nM, AFP↑, US), Cushing-Sy; Hyperthekose; **genitale Ursachen** (n. Curettage (Asherman-S.), Tbc, Müller-Duct-Abnormalities), **Hypogonadismus DD**

1° „ovariell“: E2↓, **FSH↑ DD „POF“** (primary ovarian failure) = Menop <40j, **DDD:** AUI (p22), Turner/fragiles X-Chromosom, St. n. Radiatio/Chemoth.;

2° „hypophysär“: E2↓, **FSH↓ DD** „post-pill“, PRL↑; TSH ↑/↓, Hypopituitarismus (→ p23); genet. Sy (Mutation GnRH (m. Anosmie →Kallmann-Sy), Pit1, Prop1 → Genetik)

3° „Hypothalamic (RED-S)“ E2↓, **LH↓**, FSH↓, **LH/FSH<1 DD** Female Athletes Triad (Sport / Stress / Anorexie) / Co-morbidity (Leber / CKD / entgleister Dm)

DG: Anamnese (FA, BMI↓↑, Sport, ”Stress”, Co-Morb., Medi), Galaktorrhoe, Tannerstadium, Androgenisierung (psb) → **β-HCG i.U.**

⇒ **VP d3** (-d5, Follikelphase!) b. Zyklus bzw. n Gestagen): E2, FSH, (LH), SHBG, Testosteron, PRL, TSH, fT4, Chemogramm; **Densitometrie**

poss. **Gestagentest:** Duphaston Tbl 10mg BP x10d ⇒ Blutung n 2-10d = **pos.:** → funktionsfähiges Endometrium, genug E2, intakte anatom. Verhältnisse (bei F <40J. oft falsch pos) **DD:** FSH↑: POF (Ovarialreserve?--> AMH); XO/XX (Turner-Mosaik), 46 XY (Swyer-Sy); FSH→↓: PCO, Hypophyse↓, **neg.:** postmenopausal (>45j, FSH↑,>1J. A.), Ovarialdysplasie; **Estrogen-Gestagentest: pos:** --> funktionsfähiges Endometrium → **DD:** Hypophyse, fct. Regulationsstörung; **neg:** Endometrium↓ (sa) Androgen-Insensitivity-Sy

TH: kausal (Lifestyle!, **Rücksprache m Gyn,** Grundsätze) **a) prämenopaus.< 45-50J** → Ziel: regelm. Abbruchblutung+ Östrogensubst.; **Kontrazeptiv** e.g., Minulet® (30ug Ethinyl (E)-E2, 75ug Gestogen), Mercilon® (20ug E-E2, 0.15 Deogestrel), Yasmin® (E-E2 30ug, Drospirenon 3mg), Diane 35/Ellacnelle/Cypresta 35/Cyprelle 35/Holygerne® (E-E2 35ug, CPA 2mg); **Kontrazeptiv Zyklisch / HRT** Cyclacur®, Trisequens N®, CyloPremella® …Tbl, Estragest® Pfl x21d, Progynova® Tbl 0.625 (-1.25)mg/d & Duphaston 10mg x 10d/(-3)Mon, b. PCOS Metformin; **b. Kinderwunsch & sek. Hypogon:** GnRH-Pumpe bzw. Gonadotropine, **b. Kinderwunsch & anov. Zyklen**: Clomifen, Metformin (off Label): RED-S: reversible, poss. Kisspeptin? **b) Menopausale Hormonth «MHT». <60J. od <10J seit Menopausebeginn Pat. Info! Benefit:** Flush↓, Osteoporose↓, Colon-CA↓ **vs Risk:** Mamma-CA (5J-Risiko <1.67%: ok; >5%: n) , TVT, cv-10J.-Risiko (<5% ok; >10% n); Migräne **”früh”** Zykl./HRT (sa); **spät: “Continuous-combined”** Femoston conti ® (Dydrogesteron + Estradiol); Estradot Pfl® &Duphaston® (Dydrogesteron) /Utrogestan® (mikron. Progesteron), Estalis Pfl (Norethisteron + Estrogen)® **E2-Ersatz** Tibolon (Livial® Tbl 2.5mg, ab 1J pmp m Klimakt. Sy, Vorteil: vag. Blutungen↓, Libido↑, Gerinnung NAD; CI: Endometrium-Ca, HDL-C↓); Raloxifen (Evista® Tbl 60mg, (Evista® Tbl 60mg qd, >55j bzw. Menop. >2-5j wg Flushes, Osteoporose,p16); **„Flushes“ E2** (sa)**, SSRI** e.g., Citalopram® Tbl. 10-20mg qd od Efexor® ret Tbl. 75 – 150mg qd x4/52, ≈50% Sy.red; **SE:** Nausea, Obstip), **Megestrol** (Megetstat® Tbl 40mg qd, **SE:** Endometrium-Ca, TVT, Spotting, **Clonidine** 0.1mg/d, steigern (SE: Mundrockenheit, Obstip); **Gabapentin** 300mg tid, 30% Sy.red., SE: Fatigue **St n Hysterektomie** nur E2 nötig: Estradot® Pfl. 50-100ug 2-3x/Wo; Progynova® (Tbl 2mg E2-valerat qd ⇒TG&HDL↑)

Hyperandrogenismus

Androgene= Testo+ Androstendion + DHEA(S); 98% gebunden an SHBG+Albumin

DEF: Hyperandrogenämie: Androgene↑; **Hyperandrogenismus:** Androgene↑ + Symptome (Akne, Hirsutismus, Alopezie); **Hirsutismus:** 5% d. ♀, androgenabh. Areale; **Hypertrichose:** Haarwuchs↑ ohne männl. Verteilungsmuster **Virilisierung:** deutliche Vermännlichung (Hirsutismus, Alopezie, Stimme tief, Klitoris↑)

Hirsutismus: Hirsutometrie > 7 Pkt (Leidensdruck subjektiv!); DD: PCO (+/- Adipositas); **Idiopathisch** (idR Hirsutometrie < 15 Pkt, Menses NAD, n Androgene); **Medi** (Partner m transderm. Testo, Anabolika, Steroide),

Hypertrichose: DD: hereditär, **Medi** (Cyclosporin, Phenytoin, Minoxidil), reaktiv/lokal nach Lasterth/Elektrolyse

Hyperandrogenismus: DD Ovar (PCO (bis 75%), TU (Testo > 5 nM, <0.2%), HAIRAN; SS; postmenop. Algorithmus); **NNR** ((NC)CAH (<5%), TU (DHEA-S↑, Cortisol↑)

DG: (d3): Testo, SHBG, 17-OHP, Androstendion & DHEA-S (falls (↑): LDDST, n Androgene 50%↓), **250ug ACTH-Test** (17-OHP & Cortisol)

TH: OC mit antiandr. Gestagen (30-35ug Ethinylestradiol (E2) + Cyproteronacetat od. Drospirenon); ab 40LJ max. 20ug E2), e.g., Diane 35/Elleacnelle, Cypestra35, Cyprelle35, Yasmin; **poss. zusätzl. Antiandrogen alle CI IN SS; immer Konzeptionsschutz! TH-Erfolg erst nach 6-12 Mt** (≈ 30%↓ Behaarung). Cyproteron=Androcur® 10-50mg (d1-15) SE: Libido↓; wt↑, Thrombembolien; **OFF-Label:** Spironolacton (Aldactone 50-200mg/d) SE Thrombembolien!, Finasterid (Proscar® 2.5--> 5mg, KK Gutsprache nötig!) **Kosmetisch:** Epilation, Laser/Elektrolyse (Verödung der Haarfollikel; SE: Verbrennung, Depigmentation), Eflornithin Creme11.5% bid (Vaniqa®, nicht kassenpflichtig, CHF 150/2Mt).

Polycystische Ovarien (PCO) = «*Metabolic Reproductive Syndrome*» Checkliste D; F AusschlussDg →DD

DG (2 v. 3): 1) Hyperandrogenismus (Hirsutismus, Akne, Alopezie, Androgene↑) **2) chron. Anovulation** (Oligo-/Amenorrhoe) **3) US: Polyzystische Ovarien** (Hyperstimulation: mind. 1 Ovar mit ≥12 Follikeln 2-9 mm Durchmesser, mind. 1 Ovar ≥ 10 ml). **PG:** Steroidsynth.störung Ovar& NNR, Insulinresist.

BT: LH> FSH, SHBG↓, Testo(↑); PRL, TSH, β-HCG; IGF-1 **DD:** NCCAH (17OHP basal > 6nM, stim. >30nM), NN-/Ovarial-TU (US; Testo>6nM, DHEA-S> 16µM); **Begleiterkr. :** Metab.Sy/Insulinresistenz (HbA1c 3-5jährl., BP, Lipid…GP):10% Typ 2 D.m.; 30% NAFLD (GOT/GPT/γGT); RF f. Endometrium-Ca

TH: wt↓; Metformin (off label; 500mg qd-> 850mg bid bis DG SS); **Hyperandrogenismus:** s.o.; **Oligo-/Amenorrhoe:** Ziel: regelm. Abbruchblutung; poss. Kons. Gyn. **Kinderwunsch->** Ovulationsindukt. Letrozol 2.5mg qd od Clomifen 50mg (Serophene®); Folvite 1mg qd **Kontrazeption:** IUP (Mirena), Diane35 (<35.LJ, cave Raucher, RF), FertIL-Studie

Congenitale Adrenale Hyperplasie (CAH) = Adrenogenitales Sy (AGS) (Pat. Info)

PG: 90% heterologus recombination CYP21A2→A1Pseudo ⇒21-Hydroxylase↓ ⇒ cortisol (u aldosterone)↓⇒ACTH↑⇒adrenal-hyperplasia a androgens↑

Prevalence 1/100, aut-rez carrier 1/25, **„NCCAH” = non-classical CAH** (“late onset AGS”) **M:** „Pubertas präcox“, **F:**“juveniles PCO“ u Wachstum↑ od asympt.

DG: 17OH-Prog basal d3 (**FP** & “Pille”>LP), **08h** (ACTH) > 20h), **n<6nm, AGS >30nM; 6-30nM ⇒ 60’ n 250ug ACTH-Test** heterozygot: > 30-50; homozygot non-classical: < 300 / 500; class.: >300 / 500nM, Cortisol „subnormaler Anstieg“ → **Gentest** (n. PoHI, DNA asserv. b VP) **Genotyp entspricht nicht Phänotyp; Compound Heterozygote:** Phänotyp passt besser zur milderen Mutation; **Heterozygote:** erhöhte 17 OHP Spiegel nach Stimulation, können aber asympt. sein, (**Pädiatrie:** 21-Hydroxyl.↓↓: 1/14'000→ 2/3 **klassisch** (F-Baby: Virilis.+Salt-waste+Addison n 1-2Wo) od 1/3 **„simple virilizing“**(weniger starker Enzymdefekt), **Dg:** 17-OH-Progest 2-3d n Geburt>300nM (n<3, Frühgeb.↑) **Tx:** Dex 0.5mg/d i SS; 11-βHydroxyl.: 1/100'000 ; Virilisierung+“mineralocorticoid excess“ (DOC↑), Dg: DOC (&Comp.S) ↑ >435 nM 30' n. 250ug ACTH iv; PRA ↓ im Stehen)

TH: interdisz. m. Pädiatrie / Gyn! CAH: Stressprophylaxe! Florinef® 0.05-0.2mg (Ziel aPR, Elyte, RR n) **Kinder:** Cortisol 5-10mg tid, Florinef 0.1mg ½-2/d), **Erwachsene:** Prednison/Prednisolon 0.5-2mg z. Nacht, poss. HC tags; OC mit antiandr. Gestagen **NCCAH: Erwachsene:** OC mit antiandr. Gestagenen, poss. Dexamethason 0.25mg jeden 2.d (cave Knochen), Efmody (Chronocort ®, EU, with inscurance's cost approv., **Ds:** 1/3 – 0 – 2/3

Pränatal/SS: Genetik! ab pos SS-Test Dex 20ug/kg v BR (bei ♀Foetus!) Ziel: 17OHP & Testo n plazentagängig; falls beide Eltern aut rez Träger → nur 1/8 d. Föten at risk (♀), 7/8 no risk; **Monitoring: cave: Androgenexzess vs. Cushing-SE d. Steroither!** BMI, RR / Puls, Hypercortisolismus) ♂: TART (Palpation/US)? ♀ Hyperandrogenismus? (17OHP) Androstendion no → Overtreatment; DHEAS↑→ Undertreatment; Androstention: Testo (AD/T-Ratio): AD/T > 4 bei ♀oder AD/T >1 bei ♂ + LH, FSH ↓↓ → adrenale Hyperandrogenämie; Progesteron bei ♀ mit Kinderwunsch < 2 mmol/l; normales Spermiogramm--> gute Therapiekontrolle (bleibt aber noch Jahre nach schlechter Therapie beeinträchtigt)

18. Male Gonads

With testosterone, every human being understands, acts, and looks like a man

Endocrinologist 02; 12: 321-32, BMJ 03: 327: 301-2, 172: 624-7; JCEM 05; 90: 1280-6; UpToDate 10, NEJM 07; 357:1229

Production/d (% testicular/adrenal): 4 (old) - 8 (young) mg testosteron (95/5%) > 10ug estradiol (15/85%) > 2ug estron (5/95%)

Hypogonadism **Total testosteron ↓** (TT, **age-dependent <6-12nM**) **u/o spermiogenesis↓** (psb)

DG: Libido u/o erection↓ (morning, LSI, **IIEF15**), energy↓, sports / power / endurance↓, work↓, size↓, depression, sleepiness

- Sec. sexual hair↓, shaving<1x/d, testicular vol.↓, muscle↓, gynoid fat↑, infertility, gynecomastia, osteoporosis

- **prepubertal**: eunuchoid., tall stature, high voice, no beard growth, female pubescence, infantile genitalia & small prostate

- **BT 08h:** tot. testosterone (poss. 2x, shift worker), SHBG, LH, FSH, E2, PRL, red BC (Hk↓), iron status, PG, Alk. Phos., Pyr/Crea iU, Dexa
  TT 8-12nM & SHBG↑ → **calc FT?** www.issam.ch/freetesto.htm **age, antiepileptics** /steroids, dysthyroidism; cirrhosis (SHBG↓: obesity, androgen., acromegaly)

A) primary **LH bzw FSH >10mU/l↑, LH or FSH peak n. GnRH >30mU/L**

Testes↓ orchidometer, < 12-15ml (4.5x2.5cm) **DD: Klinefelter Sy** (80% XXY, poss mosaic, XX-males (translocation Y on X) eunuchoid [i.e., testes size 10ml, long legs, „arm span" 5cm > size, gynoid]. Pubertas tarda, infertil, gynecomastia, low social class, tendency for thrombosis, psych. disorder, epiliepsy, metabol sy, www.klinefelter.org); cryptorchidism, orchitis, chemotherapy, trauma, radiotherapy, idiop.

DG: karyotypising, US-testes (if conspicuous palpation) & poss biopsy (ad urology), spermiogramm (psb)
poss HCG-Test (5000E Choriomon® x d1-3 im⇒TT d1&4, E2 d1&2 in the morning;, TT 1.5-2.5x↑, E2: 2.3-2.9x↑) **Ind**: „testikular reserve", e.g. bonderline low testosteron and DD prim / sec

B) secondary/tertiary **FSH & LH→↓** (typ. <5 (<10) mU/l), **$LH_{peak\ a\ GnRH}$ <15mU/L** (or $FSH_{peak\ n\ GnRH}$ <10mU/L)

DD: PRL↑, hypopituitarism (p23), obesity (BMI>40m/kg2 (>35: tot testo & SHBG↓, (calc) fTesto n), co-morbidites, stress, morphine, male athlete triad» (excessive training, malnutrition, eating disorder); idiop., CAH (p17), isolated GnRH deficiency (Kallmann-Sy 60% (Anosmie⇒ HNO f.Olfactometrie) normoosmic variant 40%), genet. Testing., substiutionsth, 1x therapy breakt as reversible in 10-15%)), Prader-Willy-Sy, Bardet-Biedel-Sy, Laurence Moon Biedel Sy

DG: MRI sella (with and without contrast i coronary a sagittal fine layering; resolution b 3mm)
GnRH-test (100ug GnRH iv 09Uhr: LH & FSH 0', 30', 60') **DD:** PADAM (see below): peak LH ≥15mU/L (100%/70%)

C) combined

DD: Co-morbidity (metabol. sy, critical illness/HIV, CKD, LF, Dm, hemochromastosis), noxae (C2, opiates), medication (steroids, aldactone, anabolic steroids → psychosom. care kenneth.duersteler@upk.ch), **„PADAM"** ("partial androgen deficiency of the aging male" = climakterium virile="LOH" late onset hypogonadism) **PG:** inaktive GnRH(?), SHBG↑⇒fT↓, **≥ 3 sy & tot. testo <** age-adapted reference value (p30) & symptoms

Tx: PoHI, poss. 3-6 mo trial if symptomatic & T 8-11nM, met. Sy & >65y restrained indication, T-undecanoat **Nebido®** 4ml à 1000mg, ½-1 amp slowly i.m. 0, 6, 12 Wo⇒ 10-14wkly), T-enantat (**Testoviron depot®**125-250mg 2-4wkly im), unesterified T (**Tostran®**, **Testavan®**, 25-100mg 4-8 strokes **KK-Ind OAK m Xarelto** n HMG-71**; KK-Probleme:** T-propionat (**magistralrep**) 2(-5)g ad 100g Nivea cream or Excipial mfu (= misce fiat unguentum), 25-50 mg qd = 1.25 - 2.5 g ointment w measuring spoon, **cave** exposure to partner & child!; **SE & CI:** OSAS/HF, Hk>52, desire to have children (→Kryodepot), libido & aggression↑, BPH no absol. contraindication (DRU, micturition, incontinence) & Ca? (PSA>4ng/mL), HDL-C↓ (cvR & ergometry?), Hyperestrogenemia? -> VTE/LE-risk↑ -> aromatase inhibitor (Aromasin®)

F/U (0 ⇒ 3 ⇒ 6-12 mthly): prostate (sa), gynecomastia, **BT:** BC, liver/lipd value, PSA (<4ng/ml >60j od <2.6; bzw.< 0.4/J↑)

Erect. dysfct: Viagra, Levitra, Spedra (about 50% effective), „active" vacuum pump, intrapen. inj. (caverject ®), **urolog. a. angiol. Abkl. w cvR** "Post-Finasterid-Syndrom"?

DD: org (T↓, Dm, co-morb), medi (BP, noxae, beer before LSI!), urogenital sy/trauma, psychosocial (marriage (miss vs mistress), stress)

Gynecomastia **DEF: „Tanner" ≥2**, i.e., gland.>2cm or > than areola, often asymmetric, mild forms frequent!

(„Tanner" 1: gland<areola; 2: gland≥areola; 3: gland>>areola; 4: areola on gland; 5: flat areola)

DG: - palpation, **US** breast (consult OBGYN) & testes (consult urology), poss mammography

- **BT** (per DD): **tot. testosteron**, SHBG, **estradiol,** estron, **LH**, FSH, **βHCG**, AFP, TSH, PRL, chemogramm

DD: adipomastia (pseudogynecoomastia): fat↑, small gland, **e2/testo-ratio↑**(often bilat.) **puberty** & **senium** (prävlence 30-50%), **obesity↑** (aromatase↑⇒e2↑) > **HIV,** cachexia / refeeding; **testo↓:** hypogonadismus (sa, higher ca-risk in Klinefelter), renal insuff.; cirrhosis **e2↑:** Tu (testicular HCG or E2 (Leydig (E2↑⇒FSH/↓⇒T↓), Sertoli cells (AFP & βHCG↑), hyperthyreoidism (Aromatoase & SHBG↑) **Drugs: aldactone** (10-25%; 100% >100mg/d), **antiandrogen** (Casodex 50% >Zoladex 25%>orchiectomy10%)**, HAART,** anabolics (DHEA), lithium (clearance of androgen precursors ↓⇒Aromatase⇒ E2↑), ketokonazol, tricyclics, benzo, neuroleptics (except leponex), digoxin, phenytoin, INH, amiodaron, ACEI, Ca-antag (Nifedipin>Diltiazem), cytostatics, D-penicillamin, H2/HCL-blocker, hair water with e2, aso, **noxae** (OH, opiates, Cannabis); **idiopathic** (25%, increased conversion testo to E2 in fat?, affinity to SHBG Testo>E2)

TH: reassure pat. (40-80% spontaneous regression., bilat no precancer, unilat⇒mammogr.& FNA w. XXY), poss stop drugs/noxae (sa)

- **<1-2Y** („acute", reversible), w pain/stress: **Tamoxifen®**(10mg BP x3-6/12 transient effect), anastrozol (Arimidex® Tbl 1mg qd)

- **>1-2Y** („chronic", fibrosing) or Tanner stage ≥3, usually irreversible, **watchful waiting** vs surgery (liposuction vs exzision)

Prophylaxis: prostate-Ca Th up to 50% (sa) → low dose bilat. radiatio (12-15 Gy one fraction vs over 3d)

Infertility (i.e. no pregnancy despite 12mo of unprotected & regular LSI; 10-20% of couples; **DD:** M 20%, F 38%, idiop.

DG: testo, SHBG, LH, FSH, HIV, chlamydia, hepatitis C & B, VDRL&TPHA, consult urology (varikozele?), **Spermiogramm** (USB) **Proc:** abstinence >48h & < 7d⇒vial to Endo⇒Masturb. (@home) ⇒within 1h UFK, min. 2x zw. 7Wo-3 Mon. **No:** vol 1.5-5ml, >15Mio/ml >39Mio spermia per ejaculate (<5Mio/ejaculate → genet. testng, >15% morphology, >58% vital; >50% motil, ; **% IVF-fertility w %Motilität** 83% at >14%; 63% at 4-14%; 8% b <4%
Femal Infertility → consult OBGYN reproductive division

TH: Gondotropin: a) human: hCG (Choriomon® 1500U 3x/wk sc; Pregnyl ® 1500U 3x/wk sc: Merional® 150U 3x/wk sc) x4-8wk, followed by combination w b) rFSH (Puregon®, Gonal-f ®, Ovaleap ®, LH (Luveris 75, cheaper); after pretx w hCG, in combination w hCG, mostly 3x150U/wk sc, rarely GnRH-w insulinpump (Zyklomat® Pulse Set sc 2stdl 20ug w 3° hypogonadism ⇒ a 3-12mo Re-spermiogram ⇒ „via naturalis"; poss ICSI, **before all Tx need to get PoHI!**

19. Hypothyroidism & Radioiodine

In subclinical hypothyroidism, absence of evidence does not mean evidence of absence…rather absence of funding
NEJM 95;333 964-9; JCEM 97;82:771-6 & 03;88;5710-6; 05;90:5489-96; EJCI 04;34:365-70; Arch Int Med10;170:1996-2003, Clin Endo 11;74:384-7

Jodid (J^-)-Bedarf:100 (Kinder), 150 (Adult), -250 (SS&Stillzeit) ug/d; „**Plummern“:** >500ug/d hemmen Thy akut; **Gehalt: Nahrung:** Kochsalz (rot od. grün) 20ug/g, 1 Ei 25ug; Meerfische 100ug/100g, KJ-Tbl 65mg; ug*7,7=nmol; **Medi:** 200mg Amiodaron≈75mgJ (T1/2≈50d); Rx-Kontrast 100mg-10g J, e.g., Iopromid (Ultravist®) 150 -370 mg/ml (e.g., IVP / CT 1–2 ml/kg bw, Phlebographie 50–80 ml, Herzkatheter 40–60 ml); Natriumioponat (Colegraf®) 330 mg/Cps à 500 mg (Therapie Thyreotox. Krise, Blockierung Dejodase), Povidonjod (Betadine®), Pat Info «Schilddrüsen-Ratgeber»

Thy-Teste “Irrungen & Wirrungen” TSH -50%Tagesvariation, Winter > Sommer, M ≥ F, pulsatil

TSH (fT4)-Screening nicht sinnvoll bei kranken hosp. Pat!: F>40J (b suggest. Sy), Goiter/Thy-Leiden, ΔMenses, VHFli, LDL-C↑, Dm1, M Addison, Th m Amiodarone od Li (3-6mtl), SS b pos TPO-Ak, Turner-Sy,
Generelles Screening in Risikosituationen (e.g., in der Schwangerschaft & bei kranken hosp. Pat) umstritten. 3 Hauptprobleme:

1. **SS:** TBG↑⇒T4, T3↑, TSH↓ (4-10), fT4↑ (1.Trim., Effekt von B-HCG) **Richtlinien:** 1) Schwangerschaft 2) postpartal/Pädi (S.12)
2. **Medikamente: TSH↑:** u.a. **Amiodaron**, Dopamin-Antag, M.Addison; “Makro-TSH» (→ PEG Fällung), **TSH↓: Steroide** (>100mg/d), Statine, Salizylate, Dopa (>1ug/kg/') Bexaroten, Metformin; **fT4↑: Fragmin, Amiodarone**, β-Blocker, Lasix, Valproinat, FFA↑, TBG↑., **fT4↓: Antiepil.**, Salicylate, Alb↑, **T3↓:** Dejodase↓ (Amiodarone, Iopansre, PTU, β-Blocker, Glucokort., Euthyr.sick), **Alle (Hormon) ELISA↑: Biotin** (Supplemente?, Haarausfall?) bzw. Streptavidin-Biotin-Ak
3. **Euthyroid sick Sy:** Phys. “Hibernation” durch Fasten/Krankheit T3↓, fT4↓n↑, TSH↓n↑(≥0.1-≤10), fT4/T3>20, rT3↑ (DD: 2° Hypothyr)

Hypothyreose **Prävalenz:** Subklinisch (**SCH**) 7%; Manifest 2% d pop, **F:M=9:1; >40-60J** (>70J. Norm >6mU/l?)

DD: 1°: AUI* (Has > silent/postpart./GD, pos Ak ⇒ poss **APS** suchen (p 22)) > **St n Stx/RAJ/Rx** > **Medi** (J^- (Amiod, Rx), Li^+, Alemtuzumab b MS, Checkpoint-Inh., Interferon α, Ethionamid; akute CKD)>**de Quervain** (5-26%) >/Resist. Iodmangel (weltweit in Endemiegebieten (Süd-D) häufigste Ursache!)
2°: Hypopituitarismus (p23, TSH ↓n↑ (max<15mU/l); **Bexaroten** (Targretin®, reversible, dosisabh. RXR-abh. Hemmung TSH Expression in thyreotropen Zellen)
SY: zT oligosy. (“Altersdepression”, Fibromyalgie) → Objektivierung m **Zulewski-Score** (<2: n; >5: Hypothyr):
Heiserkeit; Gehör↓; Parästhäsien; Haut: a) kalt, b) dick bzw. trocken, c) Schwitzen↓ (je 1Pkt),
Periorb. Oedem, Obstipation, wt↑, Verlangsamung, ASR-Relaxationszeit↑, Alter <55j
BT: TSH, fT4, T3, **TPO-Ak**; CK↑, LDH↑, LDL-C↑, Hb & Na↓ (renaler Na-Trsp↓ & SIADH, cf p24); Crea & Harnsäure↑
TH: L-Thyroxin (Tirosint® WeichCps inkl. 12.5ug & bei PPI, Euthyrox® alle Dosen gl Preis u Bruchrille, Eltroxin® 50&100ug) **Ds** (n tot Stx) **≈1.6ug/kg ≈ kg−Alter+125** 50⇒75⇒**100** ⇒125⇒150⇒200ug, poss. 12.5ug hinzugeben, typ. nü 30’ v Frühstück, Resorption 10-30%↑ bei Einnahme v BR; persist. Hypothyreose Sy (DD: Polymorphismus Dejodase Typ 2, Zulewski-Score im Verlauf) **poss. trial T4&T3** (T3 Novothyral® bid, T4 & Cynomel (F, tid, short T1/2 of T3))
T4-Resorption↓: Gastritis / H-Blocker / PPI, Calcium, Eisen (Multivit.), Cholestyramin, Al3- (Sucrafat), Soja, Kaffee, Nahrungsfasern (Einnahme <60‘ postprandial). Bei Präparatwechsel Kontrolle n- 4-6wk. Biol. T1/2 T4 ≈ 8d ≈ 190h; T3 ≈ 19h (mehr SE!) **Resorptionstest** b Vd a Malcompliance (**DD:** “therapy-refractory»); poss. wkly dosing (under supervision?), abendlich Einnahmen “mit Zähneputzten»
Th Indikation bei subklinischer Hypothyreose (SCH, isolierte TSH↑ m n fT4 & T3): **SS-Wunsch, Endokrine Orbitopathie, Goiter, Sy** (Th-Versuch 6 Mon?), **TSH>10mU/l & TPO-Ak↑** (→ Progredienz zu manif. Hypothyr. whs.), **Alter <70J., Nikotinabusus,** LDL-C↑ (ca 10% Senkung)
F/U: falls Sy nicht besser od atyp. ⇒ ACTH-Test, **Dosis-findung gem TSH** (n i 1-4Wo) 1⇒3⇒6⇒12mtl, **ad Haz**
- **Erhöhter T4-Bedarf: SS → ab Dg T4-Ds ≈50%↑** (p12); Herzinsuff (Resorption↓), Nephrot. Sy (TBG u T4 Verlust im Urin)

Myxödem-„Krise“

SY: ausgeprägte Hypothyreose typ.: T↓, P↓, AF↓, Serosatransudate, poss GCS↓, **RF:** Co-Morbidität (Infekt) od Medi (Immunth, Amiodarone)
BT: TSH, fT4, T3 (Abnahme *v* Th-beginn!); typ. Anämie, respirat. Acidosis; Lc&Na&PG↓, CK↑
Cortisol („basal“ <550nM ⇒ Susp of NNR-Insuffizienz ⇒ Cortisolgabe, elektiv 250ug ACTH-Test)
TH: L-Thyroxin L-Thyroxin Henning® (D, 300ug iv, dann 100µg/24h iv qd), perorale Th n Stabilisierung & normal. fT4.
Hydrocortison: 50-100mg 8h iv wenn P-Cortisol <550nM Supportive Massnahmen: Beatmung; Fluid/Vasopressoren, PASSIVE warming, iv. Glucose, ggfl. empirische Antibiotika

Radiojod (RAJ)- Szintigraphie & Therapie **(1Ci = 37GBq; 1mCi = 37MBq)**

DG: $Na^{99m}TcO4$ (^{123}I bei Dosismetrie für Therapie) 5% falsch neg b pap. Thy-Ca
7MBq=0.2mCi; Fct-studium nur b geplanter RAJ-Therapie: **RAJ-uptake** n 2h -10% , 4h 5-15%, n. 24h &48h 20-40%
↑ **GD** (typ. uptake: diffus & uptake >60-80% n. 24h, **Tox. Adenom** (1Knoten, suppr. Rest, uptake 40-60% (50% b 5cm), **multifokale Autonomie** (multiple Knoten, uptake 40-60%)
↓ **Thyreoiditis** (DQV, Has, postpart./silent, Interferon), **Factitia&T4-Th** (Tg↓), **Iodexposition** (Cordarone, Desinf.- & Kontrastmittel, Meeresfrüchte,. (n CT/Koro 3-6Mon, n ERCP/Lymphographie 1-10J warten⇒I-24hU<100mg/d)), Goiter ovarii

TH: ^{131}I $T_{1/2}$ 8d; **ambulant:** USA 100mCi; CH 5mCi…
a) Hyperthyreose: Exacerbation (fT4 & Tg↑) unter RAJ! Thyreostatische Vorbehandlung vermindert “thyroid storm” periinterventionell & post-RAJ Hypothyreosen, führt aber zu einer höheren Rezidivrate. **Proc: high-risk Pat (cvR)** Thyreostatika 3d vorher -4d nachher pausieren, dann Carbimazole rezeptieren (NeoMercazole Tbl. 5mg 1-2 tid für 4-12Mon (TSH F/U) & Abschirmung mit Propranolol (40mg BP – tid); **jungen fitte Pat** CBZ stop >7d vorher bis 4d nachher pausieren
- **GD 370-555MBq = 10-30mCi,** 50-95% Späthypothyreose od Re-RAJ nötig b **Rezidiv**, Progredienz d **EOP** 25%--> **Steroidschutz** (p 20)
- **Tox Adenom: 10-30mCi,** 80% Euthyreose, poss Goiter (nodös, low TSH) 50mCi (fraktioniert 3x)
F/U n RAJ b Hyperthyreose: 2-4wchtl (poss nur VP, post-RAJ thyroid storm), sobald fT4, T3 no ⇒ 3⇒6⇒12mtl.⇒ GP
b) Ca: F/U gem Endo/NUK-Schema 30 (low risk) – 100 mCi (high risk), präth. Uptakemessung ?; b Rezidiv kumul. 1500mCi?
TSH>30mU/l: T4 6Wo od T3 2Wo Stopp od rhTSH (Thyrogen®) 0.9mg im d1&d2⇒d3 150mBq ^{131}I⇒d5 scan, Tg d1&5, Prämed $Li\text{-}CO_3$ 300mg tidx7d
SE: dosisabh, “Sicca-Sy”, va Sialoadenitis ⇒ prophyl. Zitrone/Kaugummi nach (!) RAJ, 2° Tu (Leukämie?)
Schwangerschaft: 12-18 Mon n RAJ-Th. möglich (USA 6Mon), Kontrazeption obligat, pro 5 mCi ⇒ 1Wo kein enger Kontakt
Uebersicht NUK-«Theragnostics»

20. Hyperthyroidism & TSH-Suppression

"Hormone" (greek): impelling, exciting, setting in motion…

Lancet 03; 362: 459-68, JCEM 03: 88: 3474-81 & 05; 90: 5234-40, NEJM 16; 375:1552-65; SMF 05; 5: 933-5, www.basedow.ch

Hyperthyroidism **Prevalence** 2.5%, **F**>M, **Pat Info «Schilddrüsen-Ratgeber»**

DD: Graves' disease (GD; young F, EOP (60%), TRAb) > **Autonomy** (TMNG) >45j, palp. nodules, iodine deficiency) > **Thyroiditis**

RAI uptake↓ **: DQV** (Pain, BSR↑ , **Th.** no CBZ/PTU! NSAID → Prednison (15mg/dx1/52 -> tapering), Colchicine), **Silent** (**RF**: Interferon-Th, postpartal, no pain, transient T4↑, TPO-Ab↑ → risk of hypothyrodism↑), **Amiodarone** (psb), > **HCG** **(hyperemesis grav) / Pregnancy** (max 12 GW) > **Factitia** (Tg↓), secondary (TSH α-subunit↑, fT3/fT4>0.3, SHBG↑) or pituitary T4-resistance, Goiter ovarii;

SY: may be atypical („senile dementia", hypopkaliemic thyrotox. period. paralysis "HTPP"), quantification & F/U→ **Zulewski II Score**

typical: Nervosität; sweating↑ (DD); palpitations; stool frequency↑ ; wt↓ (despite appetite↑); sleep disturbances

Hyperkinetic movements; warm and moist skin; pulse>90, hand tremor; goiter ≥ I ("palpable thyroid"), EOP (sb),

DG: TSH↓ , fT4 only↑ (iod.expos., amiodarone, NTI, steroids, B-blockers), **T3** only↑ (early phase); if pill/PG→ measure fT3

-TRAb (Sens in GD 90%); TPO-Ab; SHBG↑, Transglutaminase-Ab (celiac dis. i 5%); consider Ca^{2+}&PO4↑, PTH&Hb↓, Glc↑, Thymus hyperplasia.

-Thyroid-US, scinti DD: Infl or suspect adenoma (Na^{99m} TcO4; cave: Rx contrast), consider densitometry (esp postmenop), ECG

a) GD: Carbimazole NeoMercazole® 2-3Tbl 5mg tid x 4wk⇒F/U fT4 & 15mg (qd) (-30)mg x 8wk⇒3(-6)mthly Ds↑↓ n TSH x tot. 18 (6-24) Mon, **poss. low dose continuous therapy.** 2.5-5mg qd ?; **SE:** 10% allergies (pruritus, exanthema), hepatitis, leukopenia→ if infection (T>38.5°C, "sore throat")⇒ ad Az; **PTU** 20/100 tbl. propycil® 2-4 tbl 50mg tid if PG/breastfeeding, **SE:** hepatotox. Immunetherapies (e.g. Rituximab) in studies

- Propranolol Inderal® Tbl 40mg qid⇒ qd; Retard "LA" 80 or 160mg/d⇒ Target: pulse 60-80/', **Vit D+Ca** Calcimagon® BP until 3mon euthyroid, if RF or postmenop.; **Pretibial myxedema** Betnovate tid, **conception protection until** euthyroid, in paralysis K-Subst & low carb diet as long as hyperthyroid.

- Recurrence (30-50%, **RF: GREAT-Score**) ⇒ repeat 18mo CBZ (<40y) vs RAI (>40y, **CI:** PG; CAVE: EOP) vs Stx (goiter II-III).

Endocrine Orbitopathy (EOP) mild: -40%, severe: 10% (PG,nicotine)⇒ **Ophthalmolog. Cons.**& VF in susp. EOP

Sy: "Nomen est omen": Graefe (eyelid stays back in downward gaze), Dalrymple (upper eyelid retraction), Stellwag (rare blinking), Moebius (convergence weakness), periorb. Oedema, conjunctivitis->exophthalmos (Hertel>20mm; no<18)⇒ double vision /motility (upward gaze↓) ->visus↓

Tx: euthyroidism, nicotine stop; Lacrovisc tid (cool), eye bandage, head end of the bed↑, Torem 10mg/d, **selenium** (100ug BP x 6/12; CH: Selenase 100ug/amp=CHF 1.10; D: Cefasel 100ug/Tbl = 70Rp). **severe & active EOP: Prednisone** 6 wks 1x wk 500mg → 6 wks 1x wk 250mg Solumedrol iv (4.5g cumulative Ds!) ; **RAI-Th:** from T_0 0.5mg Pred/kg po x1/12, tapering x 2/12; poss. 50ug/d T4-Th from 6. Week aft RAI, aft depending on TSH), **RAI** (**Ind:** double vision, motility↓), **Stx** (**Ind:** visual acuity↓ , chronic EOP), **Teprotumumab** 10/kg bw i.v. -> 20mg/kg bw i.v. 3-weekly 7x, Rituximab 500 mg iv once), Mycophenolate 500 mg bid 24/52, add-on iVCG; **Prg:** 60% improved, 30% idem, 10% worse despite Tx

b) TXA/MFA RAI (Dose dependent on uptake, GD: 300Gy) **Ind:** Sx-Morb↑, 3d Hosp NUK (patient must be continent & self-sufficient), 10% radiation thyroiditis (fT4⇒↑↑), --> **F/U:** Endo aft 6 mos, NUK aft 3 & 12 mos, then ad GP f annual TSH checks.

Poss. enucleation/**Stx** (preop. euthyrosis w/ CBZ/PTU, poss. "plummering" (CBZ+Iopanic acid 500mg 2x/d (psb)), **RFA** (LUKS, esp if node vol. <12ml)

F/U: TSH 3mo-2 yrs (GP, b/c late hypothyroidism, esp aft RAI-Tx in GD), mb Dexa aft 6mo, aFib→CHA_2DS_2-VASc score, poss. NOAK

TSH Suppression Syndrome (TSS)

DD: see above ("subclin. hyperthyroidism"); "euthyroid sick" in hospitalised pat (f/u aft 1 wk) depression (metoclopramide test for DD?), bexarotene.

Course: 25-50% spontaneous normalisation, 5% progression to overt hyperthyroidism, aFib, osteoporosis, mortality? Every 6-12mos. f/u

Contrast media (ICM): Overt ICM-induced hyperthyroidism rare (0.1%, masked hyperthyroidism w/ TSH in lower norm poss. in iodine deficiency (D).

ICM/iodine exposure prophylaxis: emergency TSH if at risk, i.e., iodine deficiency (D), pos. thyroid history, old age a/o cv risk. **CH** (no iodine deficiency) **if TSH<0.3mU/L** and iodine contrast examination urgent (CT/PCI) ⇒**Leaflet KSA D F, LUKS** or **USB D F**

Tx: if subclin. Hyperthyroidism: **TSH <0.1mU/L:** antithyroid Dr/RAI; **TSH 0.1-0.3mU/L:** dep. on RF (aFib, osteoporosis, age, Sy)

F/U: Thyroid values day 1 (if TSH <0.01mU/L on day 3, 7, 14, 28; "formally" until urinary iodine excret. normal, Elective definitive Tx depending on etiology.

Amiodarone-induced thyrotoxicosis (AIT) **F/U TSH q3mo**, if borderline on Amiodarone q1mo.

Type I: Iodine-induced if "latent" hyperthyroidism (**US**: TXA (vol >30ml; nodules >1cm), GD (hyperemia, TRAK, EOP), scinti (>5% uptake/24h).

Type II (more common): Toxic thyroiditis (**prev. euthyroid, US** NAD (vol <20ml, nodules <1cm) IL-6↑≈ 500fM (150-1100), CRP↑ (?), scinti (<5%-uptake aft 24h), Doppler vasc.)

Often mixed type I & II !

DG: TSH, fT4(-index), T3, T4, TRAB, TPO-Ab, **Thyroid-US** w/ Doppler (increased Vasc indicative for type I).

TH: stop amiodarone? (consult cardiologist, no influence on course of hyperthyroidism, T1/2 100d).

Consider Stx early (!) esp in type II & mixed forms, fT4>60pM, EF<40%, goiter >20ml, >1mo persist. Hyperthyroidism (w/ prednisone poor prgn).

Prednisone (0.5mg/kg qd) & **βB** (Inderal 40mg qid); & **CBZ** (15mg tid; no CBZ in absence of nodules (US) or only mild hyperthyr.)

if aft 2 weeks **a) fT4>30%↓** (⇒ type II): CBZ stop, Pred. til T4 no, poss. Iopansre (Colegraf® 500mg BP); b) fT4 (→↑⇒ type I): Prednisone stop; CBZ (20mg tid-qid); Perchlorate Irenate® psb, longer duration of Tx, cautious tapering; β-blocker

Thyreotoxic crisis **Mortality 10-20%, clinical Dg!**, periph. thyroid values sometimes only moderately elevated

Dg: T>38.5°C, P>110/', CNS-Sy (agitation, nausea, delirium, psychosis, lethargy, convulsion, coma), HF, GIT/Hep-Sy.

RF: only in 30% pre-existing thyroid dysfct, I-exposition in latent autonomy (TSS); co-morbidity (e.g. infections), post-Sx

Tx: ICU, Inderal (1mg iv/5' to pulse<100/'⇒ 40-120mg po q8h to pulse 80/', mb **Esmolol** 0.25-0.5mg/kg iv⇒ 0.05-0.1mg/kg/'); **carbimazole** (20(30)mg poq 8h, mb thiamazole **(Favistan® , D)** 40mg **iv** 8h (p 28); **PTU** 600-1000mg po/rectal⇒ 200mg q4h); "**Plummer" before Stx with iodine: Lugol Sol** (13drp. 5%-sol tid = 3 x 81.25mg iodine or **"AKW-Army" K-iodide Tbl.** (Tbl. 65mg 1-1-1 x 10d) **1st Ds. Iodine only 1h AFTER carbimazole**, **in case of iodine allergy: perchlorate** irenate® (from D→ emergency dose in hospital pharmacy, Na-ClO_4 initially 1g = 45drps (ideally 4h before ICM exposure)⇒ 15drps

tid (after eating b/c GI-SE) x7d; **SE:** ICM tox;) or Li-carbonate; **dexamethasone** (1mg BP)→ Stx aft 2wk, **DVT prophylaxis (Liquemin?), Panadol** 1g QID (no NSAID & heparin: displaces T4 of TBG), **active cooling if therapy resistant -> Stx "à chaud"**, poss. plasmapheresis.

21. Goiter & Thyroid "Cancer"

"The diagnosis and treatment of thyroid cancer is not an exact science"

Thyroid 09; 11:1167 & 10; 20: 1235-45; Am J Clin Pathol 09; 132: 658-65; Lancet 13; 381: 1046-57, SMF 13; 13: 1058-9, JAMA 15; 313:926

Goiter (Pravalence 5-10%, F>M), Pat info «Schilddrüsen-Ratgeber»

Normal Thyroid <20-25ml or size lobe ≈ thumb end phalanx

DD: Bland (80%) > dysthyreosis > Ca > Iodine-deficiency (dietary <25ug/g Crea, main cause for endemic goiter (prevalence - 30%), drugs (Lithium, thyreostatics), toxins (thiocyanate SCN^-, cabbage, manioc-cassava, smoking)

Grad I: palpable; **II**: visible; **III**: visible from a distance, retrosternal; **a**: adenoma; **d**: diffuse, «normal» aging

DG: a) Palpation from dorsal (w H_2O-gulp): **Node** (60-80% in 60yrs; sonography >>Palpation); **Lymphnodes, neck circumference** (cm)

- palpabel, growing, >1-2cm (US conspicuous (TIRADS)? PET-pos?) ⇒ **FNA**; similar Ca-risk uni- vs. multinodular goiter
- multinodular: FNA dominant nodule (dep. on TIRADS >1-2cm); >4cm: esp. if growing ⇒ hemi-Stx w histology

b) US-Thyroid & Ln Ellipsoid-Vol (ml) = length x with x depth (cm) * 0.53; **objectivizing growth** template KISIM, Pat. Info FNA

NO Dg of malignancy be US alone! Risk categories: **TI-RADS** (→ calculator)

Ln: missing fatty hilus, rounded (short axis >0.5cm), hypoechogenic, cystical, microcalcifications, peripheral blood flow (Doppler)

⇒ **FNA**; **CT-Tx:** if Susp of intrathoracis goiter, poss b Ca, cave: ICM b Autonomie

c) TSH, fT4, T3, TPO-Ak (↑⇒Thy-Ca 2x↑, Thy-Lymphom 75x↑), **Calcitonin (CT) & Procalcitonin** (p 22, poss. Calzium-Stimulationsstest)

- TSH **>4mU/l⇒T4-Th**; **<0.3mU/l ⇒ scintigraphy,** wenn kalter Knoten → poss FNA

TH: active surveillance F/U je n FNA / US & RF f Ca / Phobie 0.5-2jährl. m. US, poss. "nur" klin F/U b GP, Stop Nikotin

- **vs strumectomy** (Stx, subtotal 7-10ml remnant (→euthyr) or „near total" 1- 3ml remnant (→hypothyr.))

Ind: large goiter, >4cm, node (US (TIRADS), cytologie (Bethesda) +/- mutation analysis, radiation in childhood),

preop BT: BB, Na, K, Ca, crea, INR TSH, **postop. hypocalcemia RF & Tx:** psb

- vs suppressive T4-Tx: if basal TSH >4mU/l, target TSH (0.1) 0.3-0.5mU/l, cave: hyperthyroidism SE

- vs RAJ: 30% Vol↓ (> T4-Th), radiation SE, **Thermoablation?** (ca 50% vol.red.--> ad LUKS), **EtOH-Injektion**: rez. non-solidd (ie liquid) benign (FNA!) cysts

Differentiated Thyroid Cancer (Thy-Ca) „SOP" USB, i.e., papillar & follicular (medullary (MTC) → p22)

Prevalence F>M, autopsy 5-10%, mortality <1%, **⇒ the true art is to identify those, that are truly malign!; cave Screening!**

DG: FNA (3x w purple/(blue) needle a 10ml syringe, US-guided; puncture dominant nodule in multinodular goiter, NSD-Punktion)

Bethesda-Classification (% prevalence, % „malign" acc. pathology (**cave:** pathology overestimates biologic malignancy!)

- I **Nondiagnostic** (20%, ≤5%; insuff. N of follicels) ⇒ Re-FNA in 6-12mth? (thicker 20-22G needle, US-guided FNA (3x)), poss US/Szinti
- II **Benign** (50%, ≤3%; macrofoll., low cell count, colloid rich) ⇒ reasure pat ⇒ clin. F/U (GP) in 1 (-2) yr (as 5% FNA false neg)
- III **AUS** (atypia of undeterminded origin,1%, 10%; microfoll, ⇒ galectin-3↑TPO↓?) ⇒ re-FNA 6mo, earlier if growth, Afirma Gene Expr. Classifier (PoHI)
- IV **Follicular neoplasia** (10%; 25%; onkocytic?)⇒scinti⇒"cold"⇒Hemi-Stx⇒Histo (fast cut?: invasion into capsule & vessels.?)
- V & VI **«Malign»** ((5%, >60%); 5%, >95%; differentiated (papillar/follicular, psb) >anapl > others (lymphoma, sarkoma) ⇒ Hemi (<4cm) or total Stx

TH: SOP follow up KSA, depending on risik factors for malignancy, size & expansion

Staging: TNM? AJCC? MACIS? USB/KSA? → **Tumorboard** (KSA; USB, LUKS)

Very low risk T1 ≤1cm, unifocal? multifocal??, N0 (≤5 Mikrometastasen ≤0.1cm),M0

→ **active surveillance** (>40J., 80% pap. adenoma, growth 10%, Ln-metastasis 1-2% in 15yrs) vs RFA vs hemi-Stx, no RAJ, TSH-goal 0.5-2mU/L

low risk T1b, T2 (> 1 cm, < 4 cm) od T1a multifokal (m), N0-N1 (>5 x >0.2-3cm), M0, histol. gut differenziert, papill. Ca m. vasc. invasion

→ individ. Therapieentscheidung bez totaler / Hemithyroidektomie & RAJ gem. Abwägung Risiko/Benefit & Patientensituation

high risk T3 (≥ 4 cm, extrakaps. Invas.), T4, N1 >3cm, alle M, histol. ungünstige Differenzierung

→ totale Thyreodektomie, zentrale modif. neck dissektion & RAJ & T4-Th m TSH-Suppression 0.05 - 0.1mU/l.

Histo ≈ 80%papillär typ zytologische Zeichen: Grooves, helle Kerne m Nukleolen ("Annies eyes"), cytopl Inklusionen, Psammomkö, Papillen)

≈10% follikulär [benigne Sonderform: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (**NIFTP**). Bekapselte neoplastische Follikel. Nachsorge nur mit US 1x/Jahr; † >75%onkozytär, insulär], **≈5% medullär** (p22, 20% MEN, Sx, T4-Substitition, keine RAJ, Follow-up: CT (doubling time<2J → schlechtere Prg), PCT, poss. Lokale Radioth (40Gy plus Boost v 10Gy) **<1% anaplast**. (meist kein J-Uptake ("Redifferenzierung" m Roaccutan 1.5mg/kg po x 5/25 v RAJ?), T4-Substitution, palliat. ext. Radioth n R1-Resektion, Chemoth gem Onkologie (radiosens. m Doxorubicin, Sequentiell m Paclitaxel od Mitoxantron 7mg/m2 1h iv d 1, 7, 14, 21)

Sx: Hemi- (very low risk) bzw. totale **Strumektomie** m modif. (Erhalt d M. Sternocleidomastoideus) Neck-Ln-Dissection

- Tumorinvasion in Halsweichteile ⇒ tot. Neck-dissection (Morbidität↑, radio-iodine assisted Surgery?),
- „Zufalls-Ca" b Goiter-Sx ⇒ Komplettierungs-Stx innert 1 Wo;
- **cave: falls RAJ-Tx: postop initial KEINE T4/T3-Th** (RAH ab low-risk, Ziel TSH>30mU/l)
- **Postop. Hypocalcämie**: 5% transient, 0.5% persist. **RF:** Postop D1 PTH <10pg/ml, PO4 postop >1.4mmM, **Prophyl. Vit D** 0.3M E po präop

Tx: Ca po 1g tid – qid m MZ, poss. iv (p16), **Mg** (p16), **Rocaltrol** initial 0.5ug BP → Ca-Kontr., **Pat.instruktion!**, poss. Forsteo 20ug s.c BP (PoHI KK?!)

Ziel: P-Ca^{2+} korr. 2.1-2.2 mM, 24-U-Calcium <7.5mM/d wg Nephrocalcinose, Normophoshatämie (Ca^{2+} - PO4 Produkt < 55mg^2/m^2 , falls PO4-Anstieg →CaCO2 v MZ, Alfacalcidol),

Langzeitkompl: Stammganglienverkalkungen & Katarakt

RAJ: 4Wo postop u TSH>30mU/L **^{131}I-Th** (50mCi) zur Ablation von Rest-Thy (unvollständige Sx /Restgewebe?), wenn kein Fokus ausserhalb des Thy-Loge ⇒ **T4-Th** (1.6ug/kg) po ⇒ n 3 Mte Tg Bestimmung unter TSH Suppression, falls Tg >0.9ng/ml **2. ^{131}I-Th** (100mCi) n rhTSH i.m. (Thyrogen® 0.9mg im d1, d2, n 24h (d3) RAJ-Th & Tg, Schwangerschaft ausschliessen vor RAJ!,

Jodrefractory Thy-Ca: a) "**Re-Differentiation**" abh. v Mutationsstatus) → RAJ Aufnahme ↑: trametinib (MEK) dabrafenib (BRAF) selpercatinib (RET pos MTC), Selumetimib (NRAS), Apatinib od Lenvatinib (Anti-VEGF Lenvima®, Survival 4 → 18Mte, SE (40%) Hypertonie, Nausea, Diarrhoe, PoHI!), b) unabh. v. RAJ: **Sorafenib** (Nexavar® 2 Tbl.200mg BP; Median-Survival 6->12 Mon, SE: Haut (HFS), Alopezie, Diarrhoe (je 70%, poss. Dosisred.); PoHI! (CH 100k pa!)

Suppressive T4-Th 100 - 200 (250) ug/d gem. Risiko → **Ziel-TSH** (mU/L) very low 0.3 - 2, low <0.1 - 0.3, high <0.01- 0.1; "max." <0.01

F/U: alternierend NUK / Endo, Rezidiv meist innert 5(-10)J., Klinik, TSH, fT4, **Tg** &Tg-Ak (Tg-Sens↑ wenn TSH>30mU/L)

- **Tg** >2 ng/ml → US, >10 u/o steigend ⇒ RAJ-Szinti b Jod <150µg 24h-Urin ⇒ (poss. probatorisch) RAJ 50-100mCi, neg Szinti poss FDG-PET-CT
- nach 5-10 J.Follow-up ohne Rezidiv → **Anpassung d Risiko-Beurteilung u TSH Ziel** (high-risk ⇒ low-risk ⇒ Subst. T4 m TSH 0.5-2mU/L)
- postmenopause **Osteoporoseprophylaxe** & poss. Th b Osteopenie (p16).

22. Polyglandular Endocrinology

"You only find what you look for, and you only look for what you know"

Best Pract&Res Clin Endo Metab 09; 23:667.75; 252:504; JCEM 00; 85: 3222-6; SMF 06; 6: 299-303 & 12; 12: 972-5, Gentests: www.eddnal.com; www.sgmd.ch

Autoimmunes Polyglanduläres Sy (APS) DEF: ≥2 typ. Organen befallen, F 75%

APS I: Pg: Mut AIRE-Gen **A**utoimmune **P**oly**E**ndocrinopathy **C**andidiasis **E**ctodermal **D**ystrophy - **klass. Sy** (CMC, HypoPTH, M. Addison); **nicht klass. Sy:** endokrin (DM1, Dysthyr., POF/Hypogon, GH-Mangel, Hypopit.) & nicht endokrin (Urtikaria, Pneumonitis, Perniziosa, Hepatitis, interstit. Nephritis) & ektodermale Sy (Vitiligo, Alopezie, Amelogenesis imperfecta). Screen. b 1 klass & > 1 nicht klass Sy.

APS II: 20-30J (f>m, pos. Familienanmnese, aut-dom, HLA-DR3) HAS (GD) >M Add > Dm1 > POF / Hypogonadismus > Perniziosa, Sprue / "Laktoseintoleranz" / mikrospop. lymphozytäre Kolitis, Vitiligo/Alopezie; Myasthemia gravis, Sjögren Syndrom, TTP, Antiphospholipid Syndrom, Ak gegen Cyt P450

APS III = APS II ohne M Addison, **IPEX**-Sy (**I**mmunodysregulation, **P**olyendorinopathy & **E**nteropathy, **X**-linked Mutation FOXP3 Gene)

POEMS: Plasmocytom⇒ **P**olyneurop (senso-motorisch), **O**rganomegaly (Leber/Milz), **E**ndocrinopathy (Hypogonadismus, M. Addison, pHpt, Hashimoto, Dm), **M**-Gradient (Ak pathogenetisch?), **S**kin changes (inkl. Oedeme); **SE Immun-Checkpoint Inhibitoren** (PD-1; CTLA-4, -> Thyroiditis (p 19/20), Hypophysitis (p23), Dm "1" (p8), Addison (p6))

DG: APS II-Screening: Thy & pos FA od ≥2 Manifestationen od Erst-Dg M. Add / Dm1 (Prävalenz APS b Dm1 -15%)

- **TPO-Ak & TSH; 21OH-Ak & 250ug ACTH-Test** (poss aPR$_{llegend}$); GAD-Ak (poss IA2- & Inselzell-Ak), PG nü, Vitiligo
- **Intrinsic Factor-Ak** ⇒ pos ⇒ Gastroskopie 5jährl, va b VitB12 u/o Holo-Tc↓ (poss.MMA, makrozyt. Anämie = Spätzeichen), **FSH/LH, P-Ca++**
- **Transglutaminase-IgA-Ak** (mit Gluten-Kost!, oft atyp./ohne GIT-Sy, Fe/Vit-DMangel ⇒Duodenalzottenbiopsie; hoher Vd u neg Ak → tot IgA u HLA-typ.)

TH: poss. T4, HC (Stressprophylaxe!), Vit B12 (Amino®1mg 1x/d f 1 Wo, 1x/Wo f 1Mon ⇒ 3mtl, Vitarubin oral od Vit B12 Ankermann po qd), 5-jährl APS-Screen (va bei vermehrten Hosp., Verschreibung/Erhöhung Antidepressiva, Antiemetika, Antibiotika) , Alopezie: Baricitinib Tbl. 4mg qd x 36 Wo?

Multiple Endokrine Neoplasie (MEN) DEF: ≥2 typ. Organe befallen, Stammbaumvorlage

Genotyp-Screening b. Pheo (p4) **od MTC** (psb & p 21), **Tu-manif <30 (-50)J.; ≥2 MEN-typ/multifok Tu, pos FA**

Guidelines SGED, PoHI, informed consent & 4.5ml EDTA Blut ⇒ Clinical Exome (TruSight One Expanded, ca 6'900 Gene, CHF 4000.-, KSA Fr. Dr. Cecilia Bracco CoVisum f PoHI m. AL-Nr. ⇒ falls pos ⇒ Fam.Screen/Psychol. Beratung; **Kinderscreen?** va b MEN II da prophyl. Stx b 634/804-Mut ab Geburt jährl. vs 1x<5j b MEN I., Mutation-negative Pat. («Phenocopies») mit besserem Verlauf u Prg; EDM-Gen-Experten in CH

MEN 1 (**Wermer-Sy**, aut.dom, Chrom 11q13, >1000Mut, **Menin**) **pHPT** (95% d.F, i Jugend, Hyperplasie); **Entero-Pankreat. NET** (40%, oft duodenal: Gastrinome > Insulinome (<40J.) > andere NET, oft maligne, psb); **Pituitary Tu** (30%; PRL> inaktiv >GH od ACTH)

NB: Faziale Angiofibrome (88%), Hautkollagenome (72%), Karzinoide (10%), Thymus, Kinderscreen umstritten

DG: Sy (Ca↑, Ulkus, Hypoglyk, PRL↑) ⇒ Genotyp & BT: Ca, (PTH), PRL; <40J. PG, >40J. Gastrin, IGF1, FUC → 6-12mtl. Tx: Leflunomide ?? →**Lumen-1 Studie?**

MEN 2 (**Sipple-Sy**, aut.dom, Chrom 10$_{cen}$-10q11.2, **RET**-Proto-Oncogen/Tyrosinkinase):peak Inzidenz ca 30LJ (Typ IIB im Kleinkindesalter med. Thy-Ca)

gute Genotyp-Phänotyp Korrelation (dh Familien haben Tu n. gleichem Muster); Kinderscreen sinnvoll

A (>90%): **medulläres Thy-Ca** 99%, initial Hyperplasie **DG:** US-Hals & FNA, Calcitonin (CT) >100ng/L(>20ng/L→Calcium-Stimulationstest), Procalcitonin (PCT) >0.1ng/L (ohne Infekt!), PCT / CT-ratio >2 bzw. va >5 prg ungünstig, **Staging:** DOPA- PET-CT **TH:** Chirurgie, vandetanib (Caprelsa® Tbl. 300mg qd Ind: n PoHI b „sympt., rapid-progressive" MTC, SE: Diarrhoe, Rush, Hypertonie, QT↑), selpercatinib (RET-Mut) u/o DOTA-TOC-Th **KO:** US, DOPA-PET/CT je n Tu manif in Absprache m Onko > **Pheo** (50%, oft bilateral/multipel) > **pHPT** (20%) > cutaner „Lichen amyloides" (juckend)

Familial Medullary Thyroid Cancer (FMTC): nur C-Cell Tumor, aber aggressiv → Familienscreening! Ggt. mit Megacolon (M. Hirschsprung) od. Lichenamyloidose

DG: CT (auf Eis!) n<2.8pM; **ProCT** n<0.15ug/L

MEN 3 (=Gorlin; <5%): kein pHPT, **aggr. med. Thy-Ca**, mukosale Neurinome (e.g., Zunge (100%), volle Lippen), Marfanoider Habitus (65%),

MEN 4 (aut.dom, Chrom 12p13, **CDKN1B,**-p27,KIP1): pHPT, Pituitary (anterior), Adrenal, Renal, Gonadal Tu

Others **Mc Cune Albright:** Gonadale Tu (⇒Pubertas präcox), Akromegalie, Fibröse Dysplasie, Cafe au lait; **Neurofibromatose (NF) Typ 1:** Café au lait, Neurofibrome, 2% Phao, duod Somatostatinome, Lisch-Knötchen d Iris, Opticusgliome, ossäre u vask.Dysplasien; **Von Hippel Lindau (VHL):** Inselzell-Tu, (bilat.) Pheo, Zysten I Pankreas/Nierenzell-Ca, ZNS/Retina-Angiome⇒CVI, endolymph Tu. **Succinyldehydrogenase SDH-B/C/D** (Familiäre Paragangliome (Glomustu, 20% Pheo), & GIST → **Carney-Dyade**, **p5**), & GIST & Pulm. Chordome (**Carney-Trias**; p5); **Carney-Komplex** <30j, "Endokrinome" (Steroid-Tu in NNR (Cu-Sy, mikronod bilat. NNR-Hyperplasie) + Hypophyse (20% HGH-Tu), Thy, Gonaden (Sertoli-Zell Tu) & (Vorhof-)Myxome, pigmentierte "Spots" an Haut (Lentigines, Schwannome) & (Genital, Auge, Lippen), Pg:Inakt-Mut.regul. subunit type 1A of protein kinase A (PRKAR1A)

Neuroendokrine Tumoren (NET) (früher "Karzinoid", "APUDOME") Patienteninfo D, F, I

Sy b Lebermeta**: "**dry **Flush" (DD!), Diarrhoe** od „Colon irritabile"**,** "Asthma", venöse Teleangiektasien, paraneoplastische endokrine Sy, «Hedinger Sy»: re Herzinsuffizienz wg Tricuspidal-Fibrose (→ TTE, 6-mtl., poss. Klappenersatz), intest. Obstruktion, Pellagra, Muskelschwund, **70% Hormoninaktiv**

DG: Biomarker: 5-Hydroxy-Indolessigsäure im Plasma (5-HIAA; Sens 95% [Ileum!] / Spez 80% falsch↑: Tryptophan in Ananas, Avocado, Bananen, Nüsse, Schokolade, etc, Reserpin, SSRI, Zöliakie) **Chromogranin A** (va prognost. i Verlauf, 65% / 90% [CKD, HF, Gastrin↑, PPI, Hyperthyreose, Prostata-Ca, Diarrhoe…) **Biopsie →**

Grading: histol. Diff. / CI-67/ Mitose Index: **G1**: hoch / ≤2% / <2; **G2**: hoch / 3 - 20% / 2-20%; **G3:** wenig / ≥20% / ≥20%, poss. Synaptophysin (neuro). **Lokal**: US/CT/MRI ABP. (Sens. ≈70%, Spez ≈85%), Octreotid-Szinti . (Sens. 80%, Spez 90%), Ga68-PET-CT (pos. 80-90% → bessere Prg), FDG-PET-CT (pos. 50% → schlechtere Prg)

TH: NET-Tu-board Aarau-BS, Sx, Lanreotid (Somatuline Autogel® 60/90/120mg 4wchtl tief sc, auch zur Selbstinj.) oder Octreotid (Sandostatin-LAR 30mg q7-30d, poss. sc 0.1-0.5mg tid), DOTATOC (NUK-USB), Sunitinib, Everolimus bzw. Xeloda&Temozolamid n Rücksprache m Onkologen, bei Flush ERB, INFα; , undiff NET: Cisplatin &Etoposide **PRG:** 5JÜR: G1: >90%, Meta & G3: <30%, Hedinger Sy:

Lung NET (Carcinoid): ESMO Guidelines (MEN1, DIPNECH), CaSy (serotonin) > CuSy (ACTH) > Acromegaly (IGF-1, GHRH), PTH (Ca), **Dx:** Chromogranin A, 5-HIAA, ev. NT-proBNP > cortisol/ACTH > IGF-1 > Ca, CT/MRI, Ga68-dotatate PET/CT, ev. FDG-PET/CT, ev.TTE, Histological Grading, **Tx: Control of functional syndrome** (f.e. SSA, steroidogenesis inhibitors), comorbidities and therapeutic interventions (e.g., spriconolactone, potassium, etc.), local: tumor resection, advanced: tumor resection, systemic therapies (SSA, everolimus, etc.)

Insulinom (15%) (benigne in 90%, kl. Tumor): **Sy:** nü Hypoglykämien (selten nur postprandial), wt↑, **DD: p10**

- **Fastentest ambulant** 16h (ab Mittagessen nü), BT 08h: PG >3.8mM NAD, ansonsten **Hospitalisation** 72h*: nü, 2-3l KH-frei Fl.(Tee, Mineral,Bouillon), PG & VP (PG, je 5.5ml Serum & EDTA-P) 6h, 2h <3.3, 1h<2.8 ⇒ **Abbruchkriterien: PG <2.2mM** (n PG M3.4mM, F2.9mM) **& Neuroglykop-Sy** (p8, "serial-7"100-7= -7=…)⇒ VP⇒ 20g KH po **Dg:** Insulin(pM)/PG (mM) (>30,"ansteigend"), Insulin >11pM bzw >3uE/l, C-peptid n>200pM; Urinketon neg; β-OH-Butyrat <2.7mM (n. 24, 48 &72h bzw. b Abbruch m. Medisens Precision messen), ΔPG↑ >1.4mM 10'- 30' n Glucagon 1mg iv. **Lokalisation tricky! US** (endoduodenal/ intraop), **MRI, CT** (früharterielle Phase?), **Angiographie** d A. pancreatica m Ca^{2+}-Insulin-Stimulation (2-4x↑) in V. hepatica (Prof. Th. Pfamatter, USZ), **Ga68-Exendin4-PET/CT** (NUK USB), **intraop. Palpation** m (rout.!) Chirurgen, falls maligne: Octreotid-Szinti f SST2-Rez. Bildgebung

TH: Sx; präop: Maizena v BR, Diazoxid (Proglicem® Tbl. 25mg, 100-600mg qid; SE BP↓, Nausea, HF, Oedeme (poss. Torem), Hirsutismus) + Hydrochlorothiazid (Esidrex 25-50mg BP), Dex 0.5mg v BR nächtl. MZ; Phenytoin, Everolimus

Gastrinom (10%): (va MEN I, maligne 80%), **SY:** zT multiple Ulzera, sekret. Diarrhoe (gr Vol, persist. b Fasten, 2x [Na+K]=Osm$_{Stuhl}$), Karzinoid↑ **DG:** Gastrin nü >500pg/ml (n<100, Antazida & Vagotomie (Dm, Billroth II),<400, atroph Gastritis (pH>2) & Kurzdarmsy <700), poss. Sekretin-Stimulationstest: 2U/kg Sekretin iv (-10', 0', 10', 15', 30',: Δ nadir-peak >200pg/ml ⇒ Tu **TH:** Sx u/o PPI

Sonstige (<5%): Glucagonom (gr. Tu, 50% metastasiert b Dg) Erythema necrolyt. migrans, 75% Dm2, wt↓; P-Aminosäuren↓, Anämie, BSG↑ **DG:** Glukagon nü n<20 (>50pM), **Somatostatinom** (gr. Tu, 80% metastasiert b Dg), Steatorrhoe, Ga-steine, Dm2, wt↓; **DG:** Somatostatin basal↑ **VIPom** ("WDHA" (wässrige Diarrhea (persistierend 3l -10L trotz Fasten!), K & HCL↓, „pancreatic cholera") **TH:** Sx, präop Sandostatin 50 - 200(-400)ug BP s.c.-> LAR 30-60mg monatl., NaCl 0.9%/d iv m K (bis 300mval/d); Imodium 2-12Cps/d;

23. The Pituitary

Die Hypophyse ist der Dirigent des endokrinen Orchesters…und die wahre Perle unseres Körpers

Richtlinien SGED-AWMF; Lancet Diab Endo 22; 10: 804-23; N Engl J Med 03; 349: 2023-33; Lancet 07: 369: 1461-70, **SwissPit Registry**

Adenom; Mikro<1cm<Makro; 50% PRL > 20% „Inaktiv" > 15% HGH > 10%ACTH (kl.Tu!) >> TSH, LH, FSH, Pat.Info

SY: psb, Menses, Kopfsz (Apoplex?) **Gesichtsfeld (VF)** b Dg, 1-2Wo n Th (Sx, Medi), n 3mtl (1.J Makro) bzw 6mtl. (1. J Mikro, 2. J Makro), dann jährl.

DG: Mikro: PRL, poss. IGF1, 1mg DST ()1ug ACTH-Test, fT4, T/E2; **Makro:** PRL, T/E2, IgF1, fT4, 1ug ACTH-Test b. "random Cortisol" <500nM, P-Na

MRI Sella (dynamisch mit & ohne ICM, coronarer & saggitaler Feinschichtung; Auflösg 3mm) **DD: «Incidentaloma»** ≈10% d pop**, Adenom, Kraniopharyngeom** (CT Verkalkungen, Zysten), Rathke Zyste, Dysgerminom (Keimzell-Tu), Meta (Lunge, Mamma), „Granulome", Hypophysitis

F/U hormonell inaktiv: Sx (>1.4cm3, MRI T1-hypo & T2 hyperintensen Zysten, Hypopit., ophthalmol. Ausfälle)
vs kons. (MRI&VF-F/U n (3) 6-12mtl, Mikro n 6J, poss. 6J ⇒ stop (10% growth, 90% stable), **FIPA** (AIP-Screening <18J., GH/Makro <30J)

Prg: 💣: Shape ≥3 & ki67>3%, Mitosen >2/10H, p53+**, Progred. Tu/Ca:** Re-Sx u/o Radioth., Carbegolin, → **Temozolomide** (Temodal®, Kons. Onkol

Prolaktinom

SY: Hypogonad., F 20% Urs v sek. Amenorrhoe/Infertitlität/Osteoporose; **Galaktorrhoe** F 50% (bis 25% Galaktorrhoe trotz n PRL), M 30%,

DG: S-Prolaktin DD: funktionell (PIF, Stress, idR <1U/L / <50ug/L), **SS/Stillen** (<10U/L; regred m norm. 4-6Mon postpart.)**, Medi** (<4U/L, E2↑, Prog, Paspertin, Neuroleptika (ausser Leponex, Abilify), Tricycl, Opiate…), **Big-PRL** (<40% PRL-Wiederfindg), **Thy↓, CKD&LF, eiwessreiche Mahlzeit**, **Tu** idR >4 fache Norm (<1cm⇒<4U/L ; >2cm ⇒>20U/L cave: Hook-Effekt); **MRI-Hypophyse** b PRL >2000 od >400 mU/L m Sy & ohne Erklärung, im Verlauf nur falls PRL↑, **visual field (octopus)**

TH: Symptoms ? Cabergoline (Cabaser® Tbl. 1, 2mg; Dostinex® Tbl. 0.5mg; 0.5- 4mg ½-2x/Wo); **bromocriptin** Parlodel® po 2.5mg↑ abends – 25mg BP **SE**: impulse control disorder (M: hypersex.; F: shopping spree), Valvulopathie **non Ergot-Derivate: quinagolide** Norprolac® Tbl. 25ugx3d ⇒50ugx3d⇒75ug poss. **Pramipexol** (Sifrol® Tbl. 0.125mg → 1.5mg/d), **Ropinirol** (Requip® Tbl. 0.25mg → 4mg/d), **Rotigotin** (Neupro® Pflaster), **F/U:** 3mtl, Einblutung? **Liquorrhoe?** (→β-Trace), **Ziel:** Menses, PRL i d (unt.) Norm, 10% Resistenz auf Dopaminagon. → Sx? Radioth?

Absetzversuch n 2J (Mikro, 50% Rezidiv) - 5J (Makro, 70% Rez.), postmenop falls PRL n, kein Tu i MRI od Vol >50%↓ & >5mm zu Chiasma⇒ 6-12mtl F/U

SS: Wachstum 3% d Pat (Mikro bzw. Makro); Parlodel (poss. Dostinex) n pos SS-Test stop (Mikro) bzw. länger (Makro);F/U 3 bzw. 1mtl (keine VP! Kopfsz? bzw. Sy/Perimetrie ⇒ /MRI) → sympt. Wachstum: Dopaminagon. Th od Chirurgie (2.Trim) oder postpartal; Stillen ok

asympt. Pat: PRL-F/U 6-12mtl ohne Th; **Sx:** Nutzen (SE d Medi, Zysten, VF↓) vs Risiko? **Neuroleptika:** poss Aripipazol (Abilify®)

Acromegaly Leaflet for patients D, F, I

SY: photo history (ID, permis) shoes, rings, dentition, tongue, Hidrosis 1; carpal tunnel sy (CTS), arthralgias, metab. Sy, art. Hypertension & hypertensive heart disease, OSAS, colon Ca-risk 2x↑

DG: IGF-1 (↓: age, SIRS, LF, C2, obesitas, anorexia, HRT po; ↑: renal insufficiency (IGFBp ↑↑, fIGF1 ↓), pregnancy, sports, adolescence, fT4↑) → **HGH suppression w 75g Glc** -> HGH after 60', 120' n<2.6mU/l (cave Dm: false neg with chronic hypergycemia); random GH no<1mU/L (2h pp increases specificity); if MRI negative -> GHRH 1 -> **NET?** (pancreas, GIT) -> CT-chest-aBPomen-pelvis -> ^{68}Ga-DOTATATE PET-CT scan or ^{111}In-OctreoScan -> Petrosal sinus sampling

TH: Transsph. adenomectomy (60% cure, especially for HGH 0/30/60' before discharge <4.6mU/L (90%/70%)), preop Tu-reduction 1-6/12 preop Th with
- **Octreotide** (Sandostatin LAR® 10->20->30->40mg/mth im)**, Pasireotide** (Signifor LAR®) 20->40->60mg/mth im (second line), F/U Glc) or **Lanreotide** (Somatuline Autogel® 60mg/90mg/120mg 4-8wk deep sc, also for self-inj.); 90% biochem. Response (especially if **hypodens T2-MRI**, anticipation of effect and side-effect tests. Sandostatin 100mg sc with control of IGF-1 and HGH? after 6h), **Side-effect:** Pain after Inj, diarrhea, nausea, flatulence&ABP-Pain (Tx: Creon®), gallstones, evtl & cabergoline Dostinex® -2-8mg/wk); poss & clomiphene Serophene® Tbl. 50mg qd (men only!); **poss & Pegvisomant** (Somavert®) 10-20mg qd sc, paltusotine? VF& MRI 1x/y (because of possible tumor growth), control liver values, discontinuation trial after 3-5y, if necessary additional eucaloric **«low-carb» diet** (<50g CH/d, e.g., 35g CH, 155g fat; 115g prot)
- **Radioth** b Rest-tu n Sx (konventionell:48-50G vs 20G in 8 Frakt/11d; Linac/Gamma-knife (kleiner, umschriebener Tumor: LAR stop→n 6Wo 100ug sc tid x 2/12→stop→Rx n 2Wo→LAR); Lutetium-DOTA-TOC), maligne Formen: Temozolomide n onkol. Kons

F/U: 3/6/12mtl, standardized: **IGF1 n**, HGH post Glc <1mU/L (<2.6mU/L; random (0'/30'/60'/120/240' <6.5mU/l), hypopit., VF, MRI, Met-PET?, US-ABP, Colonoscopy (5y)

Hypopituitarismus IGF1↓& LH↓ ⇒ TSH/FSH↓ ⇒ ACTH↓⇒ ADH↓ (⇒Pinealom/Hypothal. Läsion?), oft Begleit-PRL↑

DD: Tu > St n Sx/Rx > Empty sella / St n **lymphocyt. Hypophysitis** (typ adip. F m Kopfsz, "Sehstör", 1/3 d F Hormonausfälle, v.a. ACTH, TSH, DI) > Apoplex (Kopfsz, poss VF↓) / Post-Schädel-Hirn-Trauma / Sheehan-Sy (postpartal, keine Milch)>Hämochrom>"Granulom">genet. Störung

SY: je n Hormon HGH&PRL (p23) ⇒ LH/FSH (p17, 18) ⇒ TSH (p19) ⇒ ACTH (p6) ⇒ ADH (p24)**; poss Kopfsz**
Sehstör „bitemp. Hemianopsie"**, Behaarung↓** (Axilla, Pubes, fehlende lat Augenbrauen), **Pigm.↓** (Areolen), **Rhinoliquorrhoe** (postop, β-Trace)

BT: IGF1 & HGH, PRL, Testo/E2 (postmenop FSH/LH), fT4, 1ug ACTH-Test (Latenz 2Wo, poss IHT), P-Na, poss. Genet. Abkl.

Grö/ Staging: MRI, Octopus, Neurochir. Consult; "Apoplex"? (zT Sy: Kopfsz, Visus↓, Hypopit, Fieber etc)

TH: Cortisone (p6), T4 (p19), E2/Progest. (p17); Testo (p18); HGH (psb), ADH (p24); SS (p12) oft Rezidiv b Kraniopharyngeom

HGH-Mangel

SY: oft asympt (Adynamie, Asthenie, Muskel↓ Fett↑, Dyslipid., cvRisiko↑?) ⇒ f Dg 2 (b Hypopit 1) pathol. **Stimulationstests** nötig

DG: GRF&L-Arg (1ug/kg GRF iv@0'⇒0.5g/kg Arg iv x 30'); GH @ (-15), 0, 30', 60', 90'; n>11; <7ug/L⇒Th; SE:Flush), **IHT** (p6, peak GH n>13ug/L; <8⇒Th), glucagon (1mg iv ⇒ peak GH n>8ug/L) > **IgF1** (<11 (40%/95% cave: Opitate) bzw. 17(85%/68%) nM)

TH: IGF-1↓ & pathol. Stimulation ⇒ HGH (Norditropin® 5/10/15mg, Genotropin® 5/12mg,, Saizen® 8mg, Omintrope® 5/10mg, Humatrope®6/12/24mg) sc v BR 0.3→0.6→1→1.5mg(1→3→4.5E q6Wo, **Somapacitan** (long-acting HGH 0.04-0.16mg/kg/Wo) **Ziel:** IGF-1 n, CHF 7-15k/Jahr; b peak GH 8-13mU/l **Th** je n Sy Depr/Adynamie/Osteop./cvR, alte, dicke M brauchen weniger GH, **SE:** Arthralgien, Oedeme, IGT, Akromegalie

Hypophysen-Sx auf Neurochirurgie tgl Endo-Consult ! (S-Na↑↓ p24 -> „HHL-Block")

- **präop. BT:** obligat **PRL, fT4, Synacthen-Test,** poss. HGH&IGF1, Testo bzw E2 (postmenop FSH/LH), VF, HHL-Block
  Pat. anweisen (inkl. Bericht): Marcoumar & Plavix 7 Tage, ASS 100mg 5 Tage, Xarelto 3 Tage **präop. pausieren**
- **periop** b jedem Pat **Fortecortin** T-Sx 4mg iv VOR Einleitung (ausser M. Cushing, p5) **T4 Subst** falls fT4<8pM
- **postop:** T+1: 2mg iv ; T+2&3 (08h): 1mg iv; **T+3: S-Cortisol 07h** ⇒ >450nM: stop; 250-450: HC bei Stress!; 100-250: HC 10-20mg morgen; <100: 15-30mg HC/d, **Notfallausweis, Stressprophylaxe** v Dimissio, **Selbsthilfegruppen** f Pat & Angehörige
- D.i.(1-3d) ⇒SIADH (2-7d, <2L Zufuhr H2O/d) ⇒ D.i. (p24): 12h HHL-Block, Fl.-bilanz/Gewicht (-1.5L/12h od -1.5kg/24h ⇒ Minirin 1ug sc, p24)
- **amb.:** n 1, 3, 6 Mon postop (basalen Hormone,1ug ACTH-Test); VF/MRI n 3-6Mt (Neurochir.), wt.↑ (va n. Kranioph.-Sx)

24. Water & Salt

Ce qui est important en medicine, c'est de comprendre avant d'apprendre.

Becker 2001; Lancet 98; 352: 220-8; Arch Int Med 99; 159: 333-6; BMJ 06; 332: 702-5, www.mdcalc.com ,

1) Osmolality P & U? (mmol/kg H2O⇒Freezing point↓): **P_{Osm} or S_{Osm}: 280-300** mmol/kg = 2x(Na+K)+PG +Urea (+OH +NH3)

- **Renal extraction fraction: Pre-renal Indices (Bock)** e.g. Na: (U_{Na} x P_{Crea})/(P_{Na} x U_{Crea}) x100 n 1-2%, prerenal <1%
- **Range U_{Osm} young:** 50 - 1200mOsm/d ≈ 18 – 0.75L/d **vs. old**: 100 – 700mOsm/d ≈ 6 – 0.85L/d **& Thiazide/NSAID** 300-700 mOsm/d ≈ 0.85 – 2L/d
  Maximum renal water clearance in middle age: 10L/d healthy; 5L/d renal injury; 1-2L/d NSAID, Thiazides (therefore Hypo-Na with normal drinking volume!)
- **„Posterior pituitary evaluation“**: Sodium, potassium, creatinine, urea and osmolarity in plasma AND spot urine. In addition, copeptin in plasma

2) Hydratation? Edema, **weight trend**, volume balance, Orthostasis, neck veins (0°/45°, HJR), HR, Mucosa, **Urea**, uric acid, Hk, Alb

- **H_2O-loss** 1,7-20 L/d (1-10L skin&lung (sweat ≈100mM), Faeces 0.1-5L/d ; Urine 0.8-20L/d

3) Dynamics? Acute Δ-Na ⇒ acute Sy ⇒ acute Th vs chron. (>48h) ⇒ oligosy ⇒ slow Th, **volume balance?**

- **Acute Hypo-Na & Sy: NaCl 3% Bolus** (100ml iv over 10min -> P-Na 2mM↑), Na-F/U 1h
- **Chron.: aim:** P_{Na}↑ <10mM/d (Pont. Myelinolysis!, **RF:** C2, K↓); if apl. Urea 100ml = 30g Inf 30' 4-8h, 30-60g tid with orangejuice, Lasix 20mg iv 8h (H2O reabsorption↓)
- **Infusions** ***%→mM Na*: 0.45%** → *77*; **0.9%** → *154*; **3%** (=0.925L 0.9%+75mL 29%) → *513*; **5.9%** → *1009*; **29%** → *4959*; Aequifusine →*40* (K 20); Ringer→*131* (K 5.4); Mixed (Glc/NaCl 2/1)→*51*; Glc 5%→*0; **Δ P_{Na} n 1L Inf:** Inf_{Na} – S_{Na} / (0.5xkg +1)*

Hypo-Na DD: **“*Pseudo*”** (P-Osm↑)**: PG↑** (S-Na 1.5mM↓ pro 5.5mM PG↑), Hyper-Tg; ContrastAgents, Mannitol; Hyperprot./Myelom → (a)BGA; **Pit-Adren-Insuff/ Hypothyr**

I) U_{Osm} <100mM/kg & P_{Osm}<280mM: ”habitual Polydypsia” ((Beer-) Potomania, Tea&Toast-Diet) **Pg:** <1000mOsm/d Na⇒renal Cl_{H20}↓

TH: H20↓ & NaCl ↑ (“Water”: Na <0.5mM, Bouillon: Na 120mM, NaCl 0.9%: 150mM, Seawater: Na 170mM)

II) & U_{osm} >100mM/kg (U_{Na}>30mM; cave false high under diuretics!**) → Pre-renal Indices (Bock)** (P & U: Na, Creatinine, Urea, Uric acid)

a) FE_{Urea} <35% & $FE_{Uric\text{-}acid}$ <20% (or FE_{Urea} >35% & $FE_{Uric\text{-}acid}$ <12%)

→ **Vol↓ Diuretics** (→stop!)**, *Aldost↓, CSW*** (***Polyuria & U_{Na}>50*** *DD: SAB (S-BNP↑) CisPlatin)* **TH:** NaCl 0.9% (-3%) *& Florinef Tbl 0.1mg qd*

U_{Na}<20mM/kg: **Diarrhea, Vomitus** (P-Cl↓)**, Loss to “third space”** (Pancreatitis; Burning, Trauma), Marathon; **TH:** 2-3L NaCl 0.9% iv/d

→ **Vol↑** (Na-Ret., U_{Na}<20mM/kg): **Heart failure, cirrhosis TH:** H20↓<0.5L/d, Loop**diuretics**, Aldactone
Nephrot. Sy, NSAID, pregnancy (Reset Osmostat & Oxytocin)**, TH:** NSAID stop, Furosemid, if appl. Dialyse

b) FE_{Urea} >35% & $FE_{Uric\text{-}acid}$ >12% → Renal failure (Crea↑); S(I)AAD (**S**yndrom (**I**n)**A**däquater **A**nti-**D**iurese)**, TH:** H20↓<0.5L/d

SIAD (P-ADH↑ or renal ADH Sensitivity↑ ; Stress/Disease↑ (“SAAD” Syndrome of stress-adapted antidiuresis)

DG: U_{osm} >100 (> S_{Osm})**, P_{Na}<135mM P_{osm} >280mOsm & U_{Na} >30 mM,** P-ADH/Copeptin not helpful for Dg**)**

H_2O-Excess (L): (1-P_{Na} /130)x0.5xkg)**, Rule of thumb:** each 4mM difference from 140mmM Na ↑↓ ≈ 1L H2O ↑↓

DD: Medi (ACEI, SSRI & tricycl. AD, Mo, NSAID (Prostagland.↓)**,** Carbamazepin, Cyclophosphamid, Antra, Ecstasy, Ciprofloxacin, Cisplatin)**, Tu** (SCLC ua)**, Stress/Pain/Nausea, Lungs** (Pneumonia, Tbc)**, CNS-Tu / Apoplexy / Withdrawal / Sx** (5-7d postop, Glc 5% Inf!)**, HPA-Insuff, TSH↑,** Porphyrie, HIV, **SIAD-like but no SIAD:** Thiazide associated hyponatremia (hypo- or euvolemic), Cerebral Salt Wasting (hypovolemic)

TH: Treat underlying disease + correct concomitant Hypo-K (K 0.5mM ↓ pro 10mOsm od pH 0.1↑; Correct Hypo-Mg+

1) Fluid restriction (Uosm <500mOsm, UNa+UK/PNa <1) (<0.5-1L/d broth, fluid intake)

2) Free water clearance↑ (Uosm >500mOsm, UNa+UK/PNa ≥1, “th-refractory”) 1) → **a) «Osmoles» substitution: Urea** 30 (15-60)g (0.25-0.5 g/kg/day) in O-juice (30g = 500 mOsm), monitor BUN (Stop/Pause if >53mmol/L, *cave*: increasing dynamics especially if GFR <60mml/L), CI: crea >176umol/L, baseline BUN >28,6 mmol/L, bilirubin >34umol/L, hepatic encephalopathy, digestive hemorrhage, gastric ulcer), **protein enriched diet**, **NaCl Tablets (2-3g/Tag), SGLT2i (off-label) / ↑dietary Protein, NaCl 3%** if severe Sy (Vomiting, reduced vigilance) iv: 150ml 3% iv over 20’ boli -> 1-3x -> check Na (Goal: Na↑ 4-6 mM in the first 2h, then 0.5mM/h; po: Tbl. 1g tid) **cave:** „isotonic“ NaCl 0.9% (300mOsm/L) leads to P-Na decrease because of AVP-fixed high Hyper-U-Osm (>300mOsm/L), despite an initial possible increase.

b) U_{osm}↓ if >500mOsm Tolvaptan n PoHl (Samsca® CHF100/d, Jinarc® CHF70/d, Tbl. 7.5 - 30mg, prefer for chron Hypo-Na e.g. every 2-3 Tag (costs), LFT! Interaction CYP3A4-inhibitor: Klacid ®, Grapefruitsaft), **Loop diuretics**

Hyper-Na: ***“Pseudo”*** Hypoproteinaemia/Alb. →corr. sodium from (a)BGA

I) Na>H_2O-Intake: iatrogenic, disrupt. thirst sensetion (U_{Na}<5mM; neurosurgery (A comm.ant), Tu, >65j);

II) Na<H_2O-Loss: UNa<20mM D.i., Kidney (CI)**, U_{Na}>20mM GIT** (Lactulose)**, Skin** (Sweat≈100mM; Fever:ΔT1°C↑⇒Δ1L↑)

Diabetes insipidus (D.i.)

DG: Polydipsia&Polyuria (Urin>50ml/kg/d (>2d &bw↓) **S_{Osm}>295, P_{Na} >145mM ⇒ U_{Osm}<300** (part 300-600 (800)) **→ DD:**

I) AVP-Resistance (nephrog. D.i.) **DG: Copeptin (a) >21.4pM → DD:** CKD, Urin-Solute↑ (PG, Urea↑, Ca↑), K↓, SS, Li^+, Cetafovir, Aminoglycoside, Cisplatin

II) AVP-deficiency (central D.i.): neurosurg. (1-5d postop, Copeptin 1d postop <2.5pM) > Idiop. > Tu/Granuloma/ischäm > Infect> AUI, Preg.> hereditary

III) Primary Polydipsia (“PP“, habitual Polydypsia)**:** initial Na↓-n, less drinking at night & less Nycturia

DD II) vs III) (if appl. re-estab. of tub. osmo-gradient w. Bouillon/Isostar / fluid restriction (Fluid intake < Urine volume, poss. Minirin1ug sc x 7d night)

a) Overnight-Water deprivation from 8 p.m. fluid restriction⇒ **2.** Morning-Urine ⇒ Exclusion D.i.: U_{Osm} >600-800mosm or U_{Osm}/S_{Osm} >2,5 ⇒ sonst b)

(In the past: Controlled water-deprivation test in outpatient setting : Urine 06a.m., Breakfast without flid, no Nicotine, during test only solid food
⇒8h of fluid deprivation v 8-16h; **Aim/Termination.: Na ≥147mM**; U_{Osm}>600 (800) od U_{Vol} <90ml/3h, Weight↓>3-5%, BP↓, HF>100/, fever if after 6h fluid deprivation P_{Na}<145mM (od S_{Osm} <300 mosm) → b))

b) 3% NaCl-Inf-Test 3% NaCl i.v. 250ml Bolus → 0.15ml/kg/min until Na>147-149mM (vBGA)

⇒ Primary Polydipsia: Copeptin >4.9 pM ; AVP-Deficiency (central D.i.)**: Copeptin (a) <2.6 pM = complete, (b) ≤4.9 pM = partial**

c) Arginine-Stimulation test : if b) not possible L-Arg-HCl 21% Braun 0·5 g/kg bw (max 40g) in 500 ml NaCl 0·9% infused over 30’ →Copeptin 60’ n >3.8pM; <=3.8pM → AVP-Deficiency

TH(DI):Fl↑po/Glc 5% iv/NaCl 0.9%;**Aim:** S-Na 0.5-1mM/h,10mmol/d↓, **H_2O-Need (L)**: Rule of thumb:1L Glc 5% → Na+ 4mM↓ od (*S-Na/140 – 1)* x 0.5xkgKG,thrombosis prophylaxis

- >4l Diuresis / Nycturia: **Desmopressin** (e.g., **Minirin®**) 0.5-4µg iv/sc ≈ 10-80µg nasal (1-8 Sprays=0.1-0.8ml; Nocutil® **Start:** 10µg) ≈ Melting-Tbl. “Melt” 60-120ug 1-2 (-3) x daily (**Start:** 60µg)
- **Thirst sensation intact?** Yes: drink to thirst (routinely omit / delay Desmo. -> ↓hyponatremia); No: Management difficult! (Dysnatraemia) ⇒ daily Weight (fix. Fluid intake)
- **AVP-Resistance** (nephrog. DI): Comilorid Mepha® Tbl 5/50mg 1-2 Tbl qd-bid, NSAID (Indocid 50-150mg po or Brufen ret 800mg qd), Minirin -40ug/d sc, NaCl po↓ (Stop Lithium?)

Desmopressin-induced Hyponatremia => Educate on the **‘Desmopressin Escape’ Method** = Delaying or omitting a dose (up to several times/week) of Desmo until Aquaresis & Strong Thirst occur => Signal for next Desmo Dose

F/U: Weight, Balance P & U Na, K, Crea, (Urea, Osm) daily ⇒ 1x weekly ⇒3 monthly (cave thirst sensation↓ with Age)

Neurosurgery: 12-24h fluid balance, P&U-“Block I” (Na, K, Crea, Urea & Osm) Stressprophylaxis? PG?

25. Rare Diseases & Inborn Errors of Metabolism

Genomes speak biochemistry, not phenotype

rev. *M. Baumgartner* (***DA Stoffwechselkrankheiten 044 266 7111***), https://inbornerrors.ch

Overview nutrition, **Flyers rare diseases** (DE, FR, IT, EN)

Newborn Screening (NBS, Guthrie-Test) 72-96h after birth.: TSH, 17-OH-progesterone, PKU, galaktosemia, biotinidase, MCADD

ER-Tx: Glc 1-2L 10-20% per Inf qd, avoid proteins ⇒ initially& a 2h **VBGA** for acidosis & hypo-Na
CAVE: highdose Glc **contraindicate in PDH-deficiency a/o lactatacidosis**, administer NaCl 0.9% iv)

PhenylKetonUria (PKU): Incidence 1/10'000, >400Mut.; PAH (=Phenylalaninhydroxylase)↓⇒ Phe↑ → Tyr↓(⇒ Dopa, A, NA↓)
Formen: PKU ⇒ diet required; MPH (mild PKU) ⇒ no diet if Phe<600uM (except in pregnancy!)
Cave: maternal PKU ⇒ fetopathy in mothers with PKU ⇒ family planning!; start diet if desire to have children with target Phe<400uM
SY: Adult: diet mal-compliance (social reasons?) ⇒ attention & performance↓ (Phe >900-1200um/l (>15-20mg/dl)
Neonatal: mental retardation, seizures, spasticity
Tx: low-protein diet acc. Phe-tolerance, supplement essential aminoacids & trace elements (ERB UKBB)
F/U: 1.-10.Yr/pregnancy: Phe 40-250uM (0.7-4mg/dl); after 10/12.Y <600-900uM (<10-15mg/dl), **no** 50-80 uM
Tx if hosp: assure PKU-diet, rel. calory intake to avoid (protein)-catabolism
Prg: normal development & IQ if early and efficient tx

Maple Syrup Urine Disease (MSUD) mitoch. degradation branched-chain AA (Val, Leu, Ile) ↓ ⇒ toxic ketone bodies & Alloisoleucin↑
SY: Adult: metabol. derailment due to catabolism or **malcompliance** (infection, stress, Op, too much protein) ⇒ cerebral edema w vomitus, apathy, ataxia, poss focal neurol sy ⇒ ketoacidot. coma; ⇒ **chron.** ment. retardation, osteoporosis, conc.disorder
- Neonatal: metabol. enzephalopathy: lethargia, drinking weakness, somnolence, cerebral edema, aoma

Tx:- low protein diet (Ile, Val, Leu↓) acc. Leu-tolerance, supplement essential aminoacids & trace elements (ERB UKBB)
- Poss thiamin (cofactor) (5mg/kg/d po), carnitin po if deficiency documented
Target: Plasma-Leu <300-450uM (4-6mg/dl), acc. to plasma-AA; cave Ile↓ (>75uM resp. 1mg/dl, else addition)
Tx if hosp: if imminent metabol derailment acc **Emergency leaflet!** (+ consult UKBB, cave: cerebral edema): prot. fasting max. 24h, force anabolic metabolism (Glc, iv! evtl. Insulin), **detox**: diuresis↑, ev. hemodiafiltration
Prg: b rascher (v 5.Lt.) u konsequenter Th normale Entwicklung und IQ

Methylmalonaciduria (MMA) Vit.B_{12} – dep. mitochondrial degrad. ↓ (Ile, Val, Met, Thr, odd FFA, cholesterol)
⇒ MMA & propionyl-CoA ↑⇒ keto-(lactate)-acidosis/ carnitin↓ / NAGS↓⇒ NH3↑; ev PG↓, Tc-, Lc-penia, ca↓
SY: **Adult** (& neonatal)**: metabol. derailment due to catabolism** or **malcompliance** ⇒ see MSUD
- **Chron. complications**: metabolic stroke (basal ganglia), IQ↓, cardiomyop., pancreatitis, osteoporis, **interst. nephritis⇒CKD**
Tx: ± MSUD (Ile, Val, Met, Thr↓) acc Val-tolerance, L-carnitin 50-100mg/kg/d gem. carnitinstatus / acylcarnitine; hydroxycobalamin 1mg iv od im 2-3x/w b. Vit.B_{12}-sens., argininhdrochlorid (up to 1mmol/kg/d iv or po) b. NH3↑; poss flagyl (10-20mg/kg/d p.o. x 10d/Mon ⇒ endogenous propionacid build-up↓
Target: Urin MMA <960mmol/mmol crea, acc to plasma-AA (Thr>80, Gln<800, Gly<400, Val>100, Met>25, Ile>25 uM)
odd fatty acids (C_{15},C_{17}) <2%
Tx if hosp: see MSUD; maximise excretion of MMA (diuresis↑, carnitin iv, 1mg Vit B12 iv/d)
Prg: depending on the severity of the defect / Th efficiency / frequency of SW derailments (oldest patient to date 45 yrs.)

Medium Chain Acyl-Carnitin Dehydrogenase Deficiency (MCADD): Inc 1/10'000, defect degradation mediumchain fatty acids
Sy: Adult: muscular symptoms, impaired consciousness, vomiting **after trigger** (fasting, sport, alcohol, op, infection)
Neonatal: «Reye-Sy-like»; encephalopathy, ev. early lethal, NBS since 2005
Lab: metabolic acidosis ↑ ammonium, ↑ lactate, ↑**CK**, ev. ↓PG (late), acylcarnitin-profile
Tx: Acute: **Glucose** i.v., long-term therapy: regular meals, know triggers, ev. carnitin
Prg: Normal development with correct therapy

Urea Cycle Defects: Ornithin-Transcarbamylase deficiency (OTC, x-chrom.), Citrullinämie, Arg-Bernsteinsre-KH (ASL), Argininämie, CPS, NAGS; Inc. cumul. 1/8000. insuff. NH_3-detox. from aminoacids decay **DG: NH_3↑** (>80µM), Glutamin↑ (>700µM, Pufferfunktion, «HbA1c des Ammoniaks»)
SY: Adult: **metabol. derailment due to catabolism** or **malcompliance** (triggers: Infection, stress, op, birth, protein load) ⇒ chron neurol sy enzephalopathy, behavrioral abnormalities w confusion, psychosis, lethargy. OTC-females may manifest in adulthood only
Tx:- low protein diet acc. NH_3 / glutamine, suppl. essent. AA & tracelements (ERB UKBB); arginin a/o citrullin dep. on defect
- Na-benzoate a/o Na-phenylbutyrate po (detox NH_3)
Target: NH_3<80µM, plasma-glutamine <800µM, acc. to plasma-AA; Ile>25µM (if below endogenous protein catabolism)
Tx if hosp: Emergency leaflet!; in addtion to Na-benzoate ev Na-phenylacetat e& arginine-HCL iv,; if NH_3>400µM > 4h ⇒ hemodiafiltration
Prg: with rapid (< 5days) & consistent tx normal development 6 IQ possible (OTC-boys often lethal, ASL often IQ↓)

Fructose Intolerance Fructose & Sacharose ⇒ ATP-need ↑↑⇒ uric acid i S ↑, PO4↓⇒ hepat. phosphorylase↓
SY: typically apparent when switch form breast milk to formula ⇒ vomiting, hypoglycemia, fibrinogen deficiency, NH3, fructosuria
Tx i hosp: Glucose iv, avoid syrup meds, saccharose-containing Tbl-coating usually ok
Prg: normal, if fructose, sacharose, sorbitol avoided: no sweet foods, no fruits: "sweets = disgusting"

Glykogenosis Type I: Mut. Glc-6-phosphatase (Typ Ia, G6PC), resp. trsp in ER (type Ib, Leber, Niere, SLC37A4)
SY: recurrent **hypoglycemias** w epileptic fits, acidosis, doll's face, truncal obesity, short stature, failure to thrive, hepato- & nephromegaly, hepat. adenomas, bleeding tendency; **type Ib**: & neutropenia (<1500/µl), leucocyte functiont↓⇒bact. infections, diarrhea⇒ IBD, **type III**: & myopathy
DG: Glc↓ (fasting), lactate↑, uric acid↑, transaminases ↑, TG (u. chol.) ↑; oGTT lactate↓↓; molecular genetics; enzymatics (liver)
Tx: Emergency leaflet! cont Glc-intake: meals 2-4 hrly: slow resorb. carbs (maltodextrin); at night uncooked cornstarch (Maizena ®, Glycosade ®) or pasta at bedtime or tube feeding; limited fructose (vegetables, fruits),; ca-containing soy-based milk products; empagliflozin 10mg/d off label ,poss. allopurinol.
Type Ib: G-CSF (Neupogen®) 2-3µg/kg 2-3x/wk
F/U: >60% carb in meals; target PG 4-6, pp<8 mM; lactat e→↑ (also 24h-urine),TG, uric acids, transaminases; Liver-US 6mthly.; from 14yrs crea & microalbuminuria, gonadal function & BMD, polyneuropathy, ferritin
Prg.: Leberadenoma (⇒HCC!), osteoporosis, CKD, gout. delayed in optimal conditions, cave: hypo's vs overnutrition (Obesity & IR)

Galactosemia: → **Emergency leaflet!**
Mitochondrial Disorders: → http://mitonet.org/links/ (Drs. J.-M. Nuoffer & A. Schaller, Inselspital od Prof. M. Baumgartner USZ)
X-chromosomal Hypophosphatemia: Self-help gorup Phosphatdiabetes

26. Gender Incongruence & -Dysphoria

Happy is the person who knows how to break with circumstances, before they have broken the person
Amicum esse unum animum in duobus corporibus.
Clin Endo 03; 59: 409-18; JCEM 03; 88: 3467-73;SMF 11; 11: 58-64; https://www.wpath.org/publications/soc ; www.transgender-network.ch

Prevalence: 0.5-3% of pop., MF 60/Mio > FM 25/Mio trans-terminologies, legal aspects

DEF. **Persistent** desire to live and be recognized as a member of the opposite sex (= gender incongruence). Is no longer considered an "illness" per se. However, it is usually accompanied by a feeling of discomfort or not belonging to one's own gender and psychological distress (= gender dysphoria).
⇒ **imperative desire for hormonal & surgical Tx, to adapt one's own body to the preferred gender**

DD: **Endokrinological intersex.** (AGS, testikular feminisation); **psych. dist.** (schizophrenia, „self-dg" transsexualism); **Homosexuality** m effeminate behavior, **transvestitism** (does not categorically reject her own sex, less suffering pressure, "after work transsex")

TH:
Interdisciplinary working group due to complexity of the problem & division of responsibility, "Team Basel": psychiatry, psychology, endocrinology, urology, ENT, plastic surgery, gynecology. Surgery, Gyn. formalized and written patient info & consent by MD. Individual and stepwise approach. Different DD & tx for adolescents vs adults
Plast. Surgeon responsible for protocols & scheduling. The following guidelines only apply to adults.

1) First contact **In principle, psychiatrists or psychologists belonging to the working group** upon written referral by external MD (usually psychiatrist) ⇒ **Pat-Info** on procedure & obtaining consent for information exchange within working group & treating MD: female to male (FM) D (F); male to female (MF) D (F)
Von aussen „direkt zur Sx zugewiesene Pat (ie, Stufen 2-5 extern gemacht)⇒„Second look" d Mitglieder d Arbeitsgruppe (Akten, poss Konsult.)

2) Psycholocial stabilisation Tx by external psychiatrist or psychol. (Dg-security & DD, consistency in desire for gender reassignment, stabilization of personality) ⇒ **final report f re-referral to team psychiatrist or psychiatrist**

3) Med. clarification of gonads / co-morbidity: **Proof of normality & exclusion of endocrinopathy & contraindication** for drug therapy & Sx by endocrinologist, signed patient info on hormonal tx → referral to op with report
Status: Internist. Grobstatus, inkl. endokr. St. (Genitale, Hodenvol, Gynäkomastie, Behaarung). FM Zuweisung zu gyn. Zykluskalender
Dx: PRL, FSH, LH, Testo, SHBG, E2, 17-OH-Prog, PSA, TSH, BB, Chemogr, PG
poss 1mg DST HIV, Hepatitis-Serol, Lues, chromos. Analyse, Th-Rx, EKG, MRI b. idiop. Kopfsz od Hypogonad., Gerinnungsabkl.

4) Surgical consultation & Pat. Info:
Exclusion of surg. contraindications & patient information as part of a **consult** ⇒ **report**

5) Opposite-sex Hormonal Tx & „Cross-dressing" **1-2 years regular F/U on endocrinology,** with continuation of external psychological support (psychological stabilization) & everyday life test (testing the external transsexual viability in society; wearing opposite-sex clothing privately & professionally), depending on the canton, gender-neutral first name possible
FM: **T undecanoate im** (Nebido) increasing 500 - 1000 mg 3-mthly poss. **T enanthate** (Testoviron Depot) 125-250 mg bi-wkly im
Ziel&SE: Amenorrhoa, voice break (irrev), clitoris↑, Acne, hirsutism, musculature ↑, Δ psychis, breastatrophy; T middle norm
MF: **Preoperatively** (dual-phase hormonal schedule)
1. **Spironolactone** Tbl. 100-200mg qd; **cyproterone acetate** (Androcur ® tbl. 10mg (cave meningeoma; art. hypertension) qd; finasteride Tbl. 5mg; (Bicalutamid 50mg/d, GnRH-analogues)
   Ziel: Suppression erections, ejakulations
2. **E2:**- **transdermal E2** > 40 J (Estradot) 50 – 100 µg, 2x/Wo
   - **E2** (Estrofem) 1-2mg BP – tid;
   Ziel: Gynäkomastia (50%<B-cup), erection↓, testicular atrophy., female fat distribution., Δ psychis
   SE: Migräne, TVT (Perioperative Management E2 6Wo preop stop? individual decision (associated risk factors (smoking, BMI)? Long immobility expected?) but basically continuing GAHT seems to be safe), worsening of epilepsy, hepatitis (Androcur), PRL(>100ug/L⇒MRI), cholelithiasis

6) Interdisciplinary Decision on Sex Reassignment Sx Personal introduction, questions & **wishes of pat.**, presentation of alternatives (e.g., epithesis), presentation of the **irreversibility** of the Sx (sterility, sexuality), poss phoniatrics. Preop. Communication of decision to external MD & obtaining cost approval from surgeon; postop. legal name & gender change via psychiatric report; before Sx discuss patient info with patient again
FM: Colpohysterectomy, mastectomy, possibly penile reconstruction surgery
MF: Orchiectomy, neovagina, poss. breast augmentation plastic surgery & laryngectomy (ENT), postop. Epilation (PoHI)

7) Lebenslange VerlaufsKo Psychological support, often re-op. necessary, **often difficult patients** (depression, HIV), possibly reop.,<1% regret op, even if outcome poor; lifelong hormone therapy necessary
FM: HRT: cont. testo (T middle norm); **F/U:** BP, Hb, LFT, lipids, testo, osteoporosis, risk for MACE
MF: **Postoperative** E2 low – middle norm (≈ ½ preop. E2-Ds); poss Androcur ® 10mg/d; **transdermal E2** (Estradot ®) 50 – 100 µg, 2x wkly > 40 yrs.; **E2** (Estrofem ®) 1-2 mg BP-tid **F/U:** Mamma, BRCA2- if at risk, BP, lipids & other cvR, edema, prostate (PSA, if available), LFT, bone, prolactin (up to 10-fold increase "physiological")

27. Hormones in Poly-Morbidity

"The good physician treats the disease; the great physician treats the patient who has the disease" W. Osler

Endocrinol Metab Clin North Am. 06; 35:823-38; J Int Care Med 04; 19: 67-82, SMW 05; 135: 451-60; Aktuel Ernaehr Med 06: 31; 235-42

- **Stress hyperglycemia: close PG-monitoring** (day, poss. night) **if >7.8mM → insulin tx goal PG 7-10mM & AVOID HYPOGLYCEMIA & PG variability** ⇒ mortality benefit controversial, causes: **stress**hormones, cytokines, drugs (**steroids**, thiazide, β-blocker, prograf ®, CyA, proteaseinh, atyp. antipsychotics)
- **Pituitary gland:** acute stress: HGH, PRL, HPA ↑, other axes supressed; pronlonged stress: also HGH↓ (⇒growth ↓ in children)
- **Pineal gland:** melatonin-deficit **Causes.** 1° (congenital, anatomical or synthesis deficit, tumors), 2°: shift work/jet-lag, neurodegenerative diseases, blindness, drugs (e.g., β-blocker, calcium channel blockers) **Tx:** Circadin ® 2 mg ret ≈1h before sleep
- **NNR:** Cortisol↑ & blunted daily rhythm initial 5d, tissue-specific titration of glucocorticoid rec. α action→ «**CIRCI**», **Stressprophylaxis!** (p6)
- **Thy:** Euthyroid sick syndrome (p19) with TSH range 0.1 to 20mU, cave: no T4-Substitution, low T3 = prognostic marker
- **Gonaden:** Hypogonadotropic hypogonadism, lipids: Tg↑, HDL-C & LDL-C↓ (prognostic marker)
- **Ca^{2+}**: ion. Ca↓, iPTH↑, esp. bacterial infection, **Procalcitonin (PCT)↑** (ua) ⇒ ***Hormokine*-guided antibiotic therapy in respiratory tract infections"** (evidence grade A, >6000 patients in RCTs!, PSI, CURB-65)

< 0.1 ug/L AB NO !	0.1 - 0.25 ug/L AB no	0.25–0.5 ug/L AB yes	>0.5 ug/L AB YES!

PCT control 6-24 h; AB therapy („overruling")
- **Respiratory or hemodynamic instability, ICU severest comorbidity**
- **PCT <0.1: CAP w PSI V / CURB>3, COPD GOLD IV**
- **PCT 0.1-0.25: CAP w PSI IV & V, CURB>2, empyema, complicated pneumonia, COPD GOLD III, SaO2<90% & 30' intensive therapy**

If on AB therapy:
Reevaluation on 3, 5, 7 d, incl. PCT
- **Stopp AB with same cut offs**
- **Initially very high PCT (i.e. >5ug/L): Stopp when 80-90% decrease of peak PCT**
- **Outpatients: AB Duration (0 to 7d) based on last PCT level**

Endokrin-metabolische Veränderungen bei chronischen Erkrankungen

HIV/AIDS: Wasting-Sy⇒Euthyroid sick, Gynäkomastie wg 1°& 2° Hypogonad, 1° NNR-Insuff, Hypoglykämien (medikamentös. p10)
- **Lipodystrophie: RF:** viscerale Adipositas: **Proteaseinhibitoren** (40% n >1J va b Age↑, HIV Dauer↑, Th-Response↓); Lipatrophie: Nucleosid Analoge (Stavudine, Zidovudine); **PG:** PPARγ↑ u/o SREBP1c↑?, **SY:** Fett↓ (oft irrev.) Gesicht, Extr., poss Fett↑ (Nacken „buffalo hump"); Insulinresistenz m Dyslipidämie (TG↑⇒Pankreatitis, HDL↓), poss PG↑, NASH; selten PCO, Acanth. nigr, Akromeg (IgF1/Insulin); **TH:** ERB (Fett↓, „schnelle" KH↓, OH↓), Sport, Metformin / Pioglizatone (Competact® 85015mg BP), Lipanthyl 200Mqid, Eicosapen 4Cps à 750mg tid-qid; Crestor Tbl 10-20mg (wg Cyp4504A4 Ind m. HIV-Th), Acipimox (?), HGH od GnRH (PoHI), poss HIV-Th anpassen; www.lipodystrophy.info

Cystische Fibrose: Hypogonadismus, **Osteoporose** (Merkblatt); **Maldigestion**, **Dm**: **Dg:** **HbA1c,** CGM?, 2h-75g-oGTT ab 10J.? **Tx:** Insulin (anbol!), CSII? Closed-loop?

Tumoren: Mamma- u Bronchus-Ca: Cushing-Sy (ACTH/CRH↑), prim. NN-Insuffizienz (BPs NNR-Meta), SIADH, **Tumorkachexie** (p14)

Leberinsuff: E2 & SHBG↑, fT↓, Aszites→ Hypo-Na→sek. Hyperaldosteronismus, **Tx:** Spironolacton (Aldactone® 25-200mg/d)

Niereninsuff. / Dialyse (Clearance<50):
- 1-25-VitD↓⇒ Ca↓⇒ sek. Hpt. m PO4↑ (Ziel: <1.6), Rocaltrol (abends, PTH<300: 3x0.25ug/Wk; PTH>300: 0.25-0.5ug/d), Vi De 3 8-10Trpf/d wenn ClCrea>40ml/'),
- Ca-CO3 (3x1-2g z. MZ), "Pseudogicht" (Harnsre↑ u CaxPO4>2.5) Sevelamer, Mimpara
  Ziel PTH ≤ 300pg/ml; b PTH >>400 ⇒ ad Sx (Resektion aller 4 Neben-Thy mit Retransplantation v. 1/8 in Vorderarm);
- Renale Osteopathie (selten Frakturen), Gonaden & HGH (u. Thy)↓, PRL↑,
- Hypoproteinämie, met. Acidosis, S-K↑ ⇒ Diät K-arm, proteinadaptiert (arm b chron CKD (<0.8g/kG/d), norm b Nephrot. Sy)(ERB);
- Anämie:⇒ Erythropoietin (Epo) Substitution b Dialyse;

Alkohol (C2, OH): = "PanTissueToxin" ⇒ Infertiliät/sek. Hypogonad, pankreatopriver Dm, PRL↑, Cortisol ↑ (Pseudo-Cushing, p5); TBG↑⇒TT4↑&Vitamine↓: VitB12, Folsre, VitD⇒Ca&PO4 (u. HypoPTH wg Mg)↓ **Tx:** Vit B1 (Benerva 100mg iv), Ca, Mg, PO4, GLP-1 Agon. als Suchtth.?

Psychol./Psychiatr.-Sy Depr./Asthenie: Hypothyreose, (Alters)-Hyperthyreose, Cushing (inkl. Steroidth), M. Addison, PRL, Hypogonad, pHpt, Akromegalie, **Manisch:** Cushing (inkl. Steroidth), Hyperthyr, **Panikattacken:** Pheo (p4), **Aggress:** Testosteronprod Tu

Hämochromatose: Dm (p7, pankreatopriv & insulinres.), Hypopituitarismus (p23), Hypogonadismus (p17), Osteoporose(p16)

Porphyrie: Wann & Wie abklären ? SIADH (p24), anna.minder@triemli.zuerich.ch

Kurzdarm-Sy: Ursachen: M. Crohn, Mesenterialinfarkt/Trauma/Sx/Bestrahlung, Adipositaschirurgie, **Sy je n Darmabschnitt Duodenum:** Ca (Osteoporose), Mg, PO4, Zink, Fe (Anämie), Folsre; **Jejunum:** Na, K, Glc, AS, wasserlösl Vitamine, Spurenelemente, Ulzera (Gastrin↑) & Gallensteine↑; **Ileum:** Vit B12 (va 50cm vor Ileozökalklappe), Gallensäuren (Diarrhoe, E'lytverluste, va Na, K, Mg) ⇒Colestyramin, Fett (Steatorrhoe), essentielle Fettsäuren u fettlösl. Vitamine; **Kolon:** H2O (Dehydratation), E'lyte (Na, Mg, Ca⇒Steatorrhoe & Kalkseifen, Oxalat↑ b intaktem Colon⇒Nephrolithiasis), mittelkettige TG (MCT)

Tx: Stadium I (Hypersekretion (Wo-Mon); typ Diarrhoe, H2O & E'lyt verlust, Somatostatin 100mg sc tid; Omeprazole 40mg qd)⇒ **TPN** (Bedarf: 25-30kcal/kg/d; Glc 5g/kg/d, Fett 1.5g/kg/d (30% d Energie); AS 1.5g/; 6-8L 0.9% NaCl/d (Na 300mmol, K 150mmol, Ziel Urin >1L/d); **Stadium II** (Adaptation, Stuhlmenge <3L/d, Mon-Jahr); **Kombination / Uebergang** TPN/EE/Trinknahrung/Kost (p14, schritt 6 →1, „slowly but surely", 30-50kcal/kg/d, 50% KH, 20% Prot, 30% Fett (poss. MTC); **Stadium III** Stabilisation, **Langzeitkomplikationen** Anämie, Osteoporose, Kolon↓ Fl.verlust, poss. Loperamid vor MZ & BR, 6-20mg/d, poss. Opiate, Sandostatin, Ca-reiche Ernährung (Nephrolithiasis); **F/U:** 3-6mtl Chemogramm, Fe-Status, Glc, HCO3, Laktat, Blutbild, INR, Fe, Zn, Se, Folsre, Vit B12, B1, A, D, E; Komplikationen: Gas. **Stoma** Gewicht tgl, Flüssigkeits- Na- u Mg-verlust b Ileostoma, **Tx:** Boullion, Omeprazol Tbl. 40 qd - BP; Loperamid Imodium Tbl. 2mg, -8Tbl./d, Sandostatin; Fettstühle-> Quantalan Sach. 1-2 tid, dist. Ileum: Vit B12, Folsre, prox. Ileum: C, B, ADEK, Zn, Cu, Ca, Mg, Fe u poss subst. (sa), Ca-po wg Oxalatsteinen, poss. PoHI f **GLP-2 Analogon** (Revestive®) zur Erhöhung der Resorptionskapazität (teuer!)

Drugs: →Screening & Patientenaufklärung **Lithium**: Hyper- (p20) & Hypothyreose (p21), SIADH od nephrogener D.i. (p24->Amilorid); Hypercalcämie (p16-> Cinacalcet), **Cordarone** (p21), **Neuroleptika** (PRL↑ (p23), Dm (p7f), Adipositas (p13), β-Blocker: Hypoglykämie-Awareness↓ **mTOR/Tyrosinkinase-Inhibitoren:** Glc & LDL-C ↑, **Tyrosinkinaseinhibitoren & Immuncheckpoint-Inhibitoren:** Hypophysitis (Patientenaufklärung); Dysthyreosen (meist destruktive Thyroiditiden! selten M Basedow, p22 & 19); IDDM; M. Add. **Alemtuzumab b. MS:** Dysthyreosen (M. Basedow m (inh.) TRAK) **Abirateronacetat:** NNR-Insuff → Steroidsubstitution, Patientenaufklärung & Notfallausweis, **Ferinject**: Hypophosphatämie (Fe-Carboxymaltose (75%)>Fe-Derisomaltose (8%, Monofer®); meist transient, FGF23 mediiert). **Cytochrome-drug-interactions**

28. This & That

"It takes considerable knowledge just to realize the extent of your own ignorance." → ***basic literature***

Before you examine a patient in the clinic, the corresponding page / section in the pocket guide must be read & understood!

A) Start in the outpatient clinic (EDM KSA):

Concept for continuing medical education CME EDM KSA: continuing education contract incl. catalogue of learning objectives, logbook, www.fmh.ch --> SWIF
Congresses / external continuing education (KSA template for reimbursement of costs; guide for completion; regulations)
Wednesday Swiss Grand Rounds (every intern 1x per year, in English, topics according to Pocket Guide);
EndoDiabNet continuing education for interns & residents every 3 months Thursday afternoon (presence in person desired).
Rotation planning for interns: **Checklist KSA** for the start in the outpatient clinic:
Read out apps for blood glucose (BG) devices to computer, necessary passwords and accesses, etc. -> please check before the first consultation whether everything is available and functioning.
Meeting minutes of (tumor) boards & colloquiae (templates for KSA)

B) Consultation of out-patients ("Sprechstunde"):

Registration of out-patients (Wegleitung "Anmeldungen" KISIM → Dashboard),
Discussion of questions "how to" if possible in the evening report preceeding the consultation, otherwise via supervisor "ad hoc"
Laboratory orders (in principle already in registration, as an exception following consultation, then phone request to outpatient nursing team (KSA Ambipflege) 6819/6813/6815) and order directly in KISIM curve), **genetic tests** (duration of evaluation up to 4 months),
Interpreters ("Dolmetscher" a) in person: organise via administrative staff b) alternatively digital tool: POCKETALK
Missed consultations: 1) SMS E-call; 2) in case of repeated (inexcused) no-shows: case closure after writing final report with copy to referring physician (KSA: KISIM templates stored common favourites EDM)
Patient refuses relevant exam or treamtment: statement of refusal waiver "**Verzichtserklärung**" (D/F), have it signed by patient.
Report to referring physician: After initial consultation, then once a year or when therapy is adapted (KSA KISIM: report templates → common favourites, mail report to secretary for correction & billing, secretary starts workflow for signature/visa)

C) Consultation service of in-patients ("Consultien"):

"On-call" phone KSA 6885 from 8:00-8:00 a.m.; supervisor available at any time for any questions if required, consults on MIC/IPS consult supervisor if in doubt,
Daily **online blood glucose (BG) screen** on neurology & surgery wards with KISIM (KSA): limits BG value >10 and <3.5mmol/l -> document in KISIM curve.
Thyroid-Board ENT ("HNO") Wed afternoon H60.
Background duty during the night (for telephone no. for supervision, see list of secretaries). Consili-report: KKK (short, concise and clear), in particular procedure prescription-like, clearly formulate who checks when and where; tel. feedback to consili-provider whenever possible; when completed: create direct work-flow (in contrast to outpatient reports).

D) Billing:

Billing of consultation hours via **IBI-Care** (KISIM → Ext.Tools)
-> list ALL materials, incl. dressings / sample sensors / ketone bodies; important: credit insulin pump therapy if available; diagnosis codes for statistical purposes;
In each case indicate **complete time needed** (i.e.,reading of consult & referral letter, check lab results, preliminary discussion, way to ward & back, looking for and studying of files, trying to reach ward physician, debriefing (general "rule of thumb" new cons. 60min; follow-up consult 45min.
Also charge for **unscheduled telephone consults and/or e-mails**, dated correctly
If no inpatient case exists: report as "work in absence" (or have case opened) -> discussion with therapist OR (depending on case) have EDM case opened;
List of relevant TARMED codes.
Requests for reimbursement of costs to health insurance companies ("PoHI"): It is important to state that the assumption of costs is made within the framework of KVV Art 71 ("imminent danger") and that previous therapies did not help (most medical officers of health insurers will ask that).
Most medical officers of health insurers ("Vertrauensärzte") do a benefit assessment according to the 9-field model
(for details see here: https://www.vertrauensaerzte.ch/expertcom/71kvv/).
In case of rejection, it is advisable to persevere and talk to the medical officer in person. It may be possible to get a therapy trial (i.e. first three/six months paid by the pharmaceutical company, then the costs are covered).
Procedure for patients with of a suspension of services of health care insurances ("**Leistungssperre**").

E) Emergencies:

Rapid HbA1c (for ambulatory care); ketone bodies capillary (KSA device in large US room 03); Diabetic foot -> see Pocket Guide p.7
"**Hypo-Box**" for ad hoc help in case of evident hypoglycemia (in cupboard between room 25 / room 24); Addison set (ambulatory care).
Emergency transfer from outpatient clinic to INZ: tel. service OT INZ MED 1900, CHIR 1950 (tel. no. transport service: 4780,
REA alarm 999 - ONLY possible via landline!.

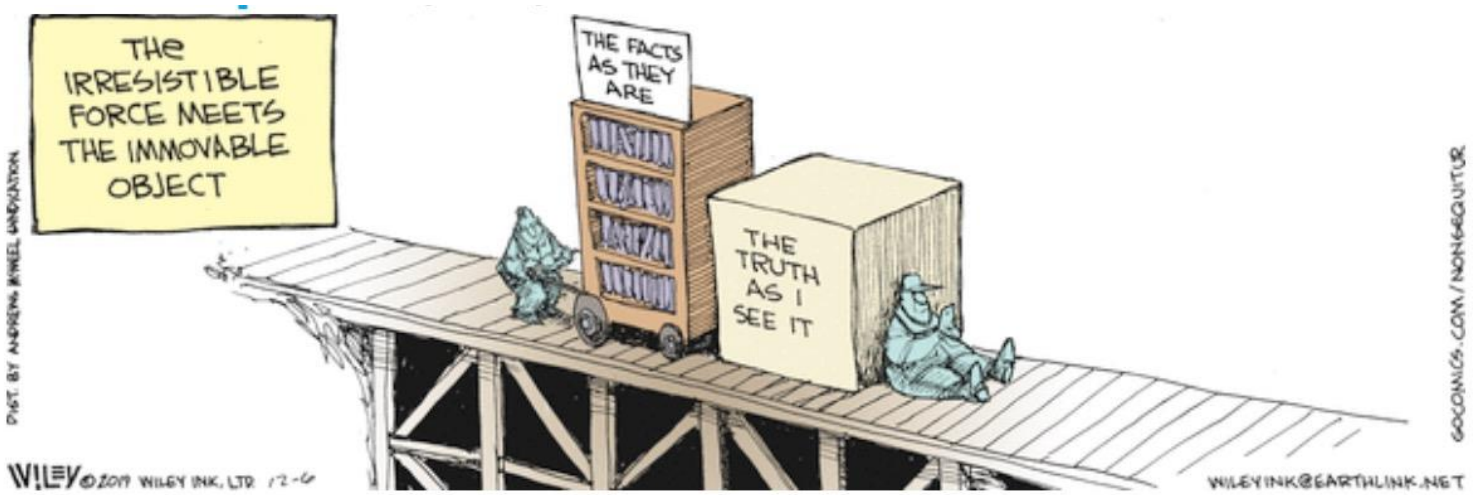
F) Journals

www.freemedicaljournals.com; www.medscape.com, www.amedeo.com, www.unibas.ch; ongoing studies: (according to updated list)

G) EDM-Drugs

dynamic endocrine function tests, compassionate use , administration & crushability of pills.

Suggestions / Wishes / Criticism welcome, also positive ones



29. Phone numbers KSA

Ruf doch mal an…noch besser, geh doch mal vorbei

REA: 999 — **Tel. von extern 062 838 xxxx**

Bereich Medizin		
BL Müller B.	6817	079 480 79 89
Assistentin BM	6818	
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Adler S.	4688 / 4692	079 881 20 22
Batschwaroff M.	6833 / 6880	079 230 97 04
Borm A.K.	9756 / 6818	076 322 06 18
Brinkert M.	4484 / 4481	079 881 17 51
Bucheli Laffer E.	9819 / 6856	079 881 13 99
Buchkremer F.	9535 / 4306	0049 15146411941
Cantoni N.	9844 / 6053	079 881 14 33
Capraro J.	4180 / 6818	079 173 34 15
Conen A.	5902 / 6856	078 653 04 24
Findling O.	9363 / 6675	076 369 15 07
Fiumefreddo R.	9806 / 6880	079 881 21 22
Fuchs G.	6270 / 6053	
Fuchs T.	4440 / 4481	079 881 16 58
Fux Ch.	6820 / 6856	079 760 17 70
Gerull S.	6505 / 6053	079 881 10 87
Grabbe J.	6958 / 6838	078 625 18 78
Haegeli L.	4485 / 4481	076 435 85 34
Hasler P.	4687 / 4692	079 448 13 34
Heizmann M.	6007 / 6053	079 620 66 45
Irani S.	4470 / 4472	079 568 17 48
Janthur W.-D.	5580 / 6053	079 881 13 42
Kahles T.	5945 / 6675	078 973 90 82
Kesten F.	6381 / 6818	079 881 25 09
Kieback A.	5947 / 9601	0049 173 6182394
Kim M.	9788 / 4306	079 109 78 52
Knuchel J.	5701 / 4459	062 823 01 17
Kuntzen T.	4461 / 4459	079 881 16 36
Mamot C.	6064 / 6053	078 880 14 28
Moosmann P.	9515 / 6053	079 777 76 44
Müller B.	6817 / 6818	079 480 79 89
Nedeltchev K.	6676 / 6675	078 749 58 18
Rastan A.	6458 / 9601	079 126 73 16
Riede F.	4483 / 4481	079 881 17 50
Scherer K.	5682 / 6838	079 881 12 49
Schreiber A.	5552 / 6053	078 759 44 99
Schütz Ph.	9524 / 6880	079 365 10 06
Segerer St.	9574 / 4306	079 886 92 88
Streit M.	6950 / 6838	078 626 54 24
Thalhammer Ch.	4701 / 9601	079 254 62 49
Tini M.	4479 / 4472	079 544 82 80
Tröger M.	6721 / 9469	079 544 82 80
Yakupoglu Y.	5957 / 4481	079 881 11 90
Sekretariate	**amb.**	**stationär**
AIN	6812	6399
ANG	4702	
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EDM	6812	
GAS	4464	
OHT	6050	
INF	6812	
KAR	4491	4486
NDT	4306	
NEU	6681	6608
PNS	9393	
PSM	6812	
PAD	6811	
RHE	4691	
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Fa. Härdi (www.haerdi-orthotech.ch)		062 721 1454
Fa. Malgaroli&Werne (www.orthopod.ch)		056 222 3525

OA mbF / OA Medizin		
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	Burgemeister S.	5641
	Engeli L.	6804
	Haubitz S.	9410
	Jakopp B.	4184
	Straubhaar K.	6834
	Arifi T.	4281
	Dziadova V.	6453
	Eckart A.	9517
	Gnehm F.	5554
	Herrmann T.	6836
	Isenring E.	9512
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	Molitor A.	9415
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	Murday S.	9438
	Sonntag A.-K.	6952
	Steiner V.	9449
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	Vollmer K.	6050
	Zihler D.	6050
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	Fiedler H.	6050
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	Merki R.	6050
	Sarinay S.	6051
	Seidl A.-K.	6050
INF	Jakopp B.	4184
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Frauenklinik AA	5746	
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Opthalmo AA	5792	
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Barmelweid		062 857 21 11
Basel (USB)		061 265 25 25
Bern (Insel)		031 632 21 11
Externer Psychiatrischer Dienst		062 834 34 00
Königsfelden PDAG		056 462 21 11
Gesundheitszentrum Fricktal		062 874 50 00
Leuggern		056 269 40 00
Lindenfeld		062 838 01 01
Luzern		041 205 11 11
Menziken		062 765 31 31
Muri		056 675 11 11
Olten		062 311 41 11
Reha Rheinfelden		061 836 51 51
Rheinfelden		061 835 66 66
Schinzn. Aareha		056 463 85 11
Schinzn. Klinik i.P.		056 463 77 77
Tox-Zentrum		**044 251 51 51**
Zofingen		062 746 51 51
Zürich (USZ)		044 255 11 11
Zurzach Care		056 269 51 51

30. Laboratory Reference Values

Hormone sind nur unter Kenntnis v Assay, Pathophysiologie, Alter, Geschlecht, Medi-Interaktionen & Co-Morbidität interpretierbar
Notfallbestimmung möglich, auf Eis abnehmen u zentrifugieren, Thy- & Gonaden-Hormone aus Serum od Heparin Plasma, Wartezeiten

Hypophyse

S-IGF-1 (1nM=7.6ug/l, F luteal > M)

16-39J.	16 - 52nM
40-54J	10 - 40nM
ab 55J	**6 - 30nM**
Susp of GH-Mangel	**<11 (<17)nM**

S-HGH (1ug/l=2.6mU/l=46pM, IF-assay) <11.5mU/L

1 od 2h n 75g Glc	**<2.6mU/L**
Peak n ITT	**>13mU/L**
Peak n GRF&Arg Stimul	>11mU/L

GHRH <60ng/L

S-Prolaktin (PRL) (1ug/L = 21.2 mU/L)

M / F	***86 – 324 / 102 – 496 mU/L***
SS-Trim:	I:≈1000; II:≈2000, III:≈4000mU/L
20' n 0.2mg TRH iv (30' nasal)	<2x↑

Wasser, Elektrolyte, Säure/Base

P-Natrium	***131-142mM***
Bilanz (5-15g/d)	40-150mmol/d
P-Kalium	***3.5 – 4.7mM***
Bilanz (≈3g/d)	60-100mmol/24h
Urin b Hypokaliämie	<30mmol/24h
aBGA pH / -Range	***7.40 / 7.35-7.45***
PO2	*70 – 100 mmHg bzw. 10.7-12kPa*
PCO2	*35 – 45 mmHg bzw. 4.7-6kPa*
Bicarbonat (HCO_3^-)	*22-26mM*
Lactat	*0.5-1.4mM*
Chlorid (Cl-)	*97-110mM*
Base Exzess (BE)	*-2 bis +2mM*
Anionengap (AG)	*8-12mM*
P-ADH / Vasopressin (AVP)	2 - 12pg/mL
S-Osm	***280-300mOsm/kg***
U-Osm	***200-1200mOsm/kg***

Cl_{Crea} (>40J 1ml/J↓) **M 97-140; F 75 -125ml/'**
≈ (140-Alter) x kg x 1.23 / SCrea [uM]; F x 0.85

Schilddrüse (Thy)

TSH **basal** peak 24h, nadir 12h ***0.33 - 4.49mU/L***

n. TRH 20' n 0.2mg iv / 30' n 2mg nasal / 3h n 40mg po:	2 – 25 / 3.5 – 30 / 5 - 35mU/L
fT4	***11.6 - 22.0pM***
fT4-Index	62 – 164 nM
GW – 12 / 13 – 25 / 26 – 40	83 – 166 / 76 – 159 / 66 – 160nM
T4	64 - 163nM
T3	**1.2 – 3.2nM**
fT3	2.6 - 5.6pM
Thyreoperoxydase (TPO)-AK	<100U/mL
Thyreoglobulin-(Tg)-AK	<100U/ml
TSH-Rezeptor-AK (TRAK)	<1.5U/L
Tg (n tot. Stx)	<0.2ng/ml
Jod i Urin (*7.7=nmol/d)	50-200mg/d
Calcitonin pg/mlx0.28=pM,	**< 2.8pM**
2',5',10' n Pentagastrin	<28pM

Kalzium & Knochen

Calcium Ca^{2+} (1mM=4mg/dl)	***2.12 - 2.65mM***
ionisiertes Calcium	*1.15-1.3mM*
Albumin	**35-52g/L**
korr: Alb 10g/L↓↑	⇒Ca^{2+} 0.25mM↓↑
Phosphat $P0_4^{3-}$ (1mM=3.1mg/dl)	*0.8-1.5mM*
PTH intakt (1pM=10ng/L)	**12 - 72pg/ml**
Alkalische Phosphatase	31-108 U/L
Osteocalcin	8-52ug/L
U-Calcium/Crea	0.1 - 0.3mmol/mmol
U-Phosphor/Crea	2.2 - 6mmol/mmol
U-Pyridinolin/Crea	40 - 100nmol/mmol
U-Deoxypy./Creat	8 - 20nmol/mmol
25-OH-Vit. D (1ug/L=2.4nM)	24-132nM
"Vit D-Insuffizienz" (eg, b sek. Hpt)	<50-75nM
1-25-OH-Vit D	43-149pM

Gonaden (F⇒ 3. Zyklustag (Follikelphase; b Amenorrhoe 3d n „Gestagentest")

LH

präpuberal	0.2-5mU/L
F follikulär 3d (0-8d)	**2.4 - 12.6mU/L**
F"midcycle" 9-14d	14 - 96mU/L
F luteal 15-30d	1.0 - 11.4mU/L
F postmenopausal	7.7 - 58.5mU/L
M	**1.7 - 8.6mU/L**
Peak n GnRH (30' od 60')	**>15mU/L**

FSH

präpubertär	<2mU/L
F follikulär 3d (0-8d)	**3.5 - 12.5mU/L**
F "midcycle" (9-14 d)	4.7 - 21.5mU/L
F luteale (15-30d)	1.7 - 7.7 mU/L
F postmenopausal	25.8 - 135.0mU/L
M	**1.5 - 12.4mU/L**
Peak n GnRH (30' od 60')	**>10mU/L**

β-HCG	<4.5mU/ml
Testosteron, total (1nM=28.57ng/dl)	
M 40s / 50s	**8.7 – 31.7 / 7.5 – 30.4nM**
M 60s / 70s	**6.8 – 29.8 / 5.4 – 28.4nM**
M Pregnyltest (max. d4)	1.8-2.8↑
F	0.2 - 2.9nM
FTI = Freier Testosteron Index (%)	
(Testosteron (nM) / SHBG (nM)) x 100	
M / F	20 – 81 / 0.5 – 8%
Testosteron, bioverfügbar (NH4-Sulfat Präzipitation)	
M. / F	2.3 – 14.6 / 0.02 – 0.2pM
Testosteron, frei (Equlibrium Dialyse)	
M / F	38.1 – 142 / 2.1 - 11.1pM

Oestradiol (E2) (3.7pM=1ng/L)

F follikulär 3d (0-8d)	**90 - 716pM**
F "midcycle" 9-14d	243 - 1509pM
F luteal 15-30d	147 -958pM
F postmenopausal	**37 - 145pM**
M	**40 - 161pM**
M Pregnyltest (max. d5)	2.3-2.9x↑

Oestrone (E1) (3.7pM=1ng/L)	
F nadir: Menses; peak: "midcycle"	
M & postmenop. F (E1>E2)	55 - 240pM
SHBG (↑: Age, Thy↑, Zirrhose ↓: Adipositas, DM2)	
M (Testo Th↓)	13 – 71nM
F (PCO↓, SS & E2↑)	18 - 114nM
DHEA-S (1uM=38.7ug/L)	
F 6-29/30-39/40-69J.	2.5-10.3/2.4-6.9/1-5µM
M	2.0 - 11.0µM
DHEA >18 J	5.6-28nM
Progesteron (3.2nM=1ug/L)	
F 0-14d	0.5 - 1.7nM
F Luteal 15-30d (21d)	4.9 - 72.0nM
M	0.3 - 0.9nM
17-OH-Progesteron (3.03nM=1ug/L)	
M & F basal / n ACTH	<6 (3) / 7.5nM
F luteal	<9nM)
heterozygot	< 30 / 50nM

Lipide (TG nü)

Triglyderide (1mM=89mg/dl)	**0.5-2.3mM**
Cholesterol (1mM=38.7mg/dl)	**3.0-5.2mM**
HDL-C	**0.9-2.2mM**
LDL-C	**1.6-3.4mM**

Friedewald (TG<4) LDL=TC - HDL - 0.45xTG

„Inborn errors of metabolism"

altersabhängige Serum-Normwerte für Aminosäuren

Endo-Funktionsteste

siehe Uebersicht

Nebenniere

Cortisol (27.6nM=1ug/dl)	*85 - 638nM*
23.30Uhr i Speichel	**<1 - 2.5nM**
8h n 1 mg Dexamethason	< 50 (90)nM
Urin (FUC, 2.76nmol/d=1ug/d)	< 500nM/24h
FUC/U-Creatinine	**<70nmol/mmol**
30' n 1/250ug Synacthen	**>500/550nM**
11-Deoxycort (CS, 1nM=29ug/dl)	<12nM
8h n Metopiron	>130nM
ACTH Plasma (1pM=4.5ng/L)	7 – 50ng/L
basal, Morgens, ohne Stress	<20ng/L
Aldosterone (2.77pM = 1ng/L)	
aufrecht / 60' liegend	110 - 870 / 80 - 450pM
n NaCl	<240pM
Urin	<33nmol/d

aPR (akt P-Renin: 1ng/L=1.67mU/L=0.0237pM)
(aPR [pg/ml] = PRA[ng Ang I / ml/h] x 8.8 + 6.6)

aufrecht / 60' liegend	2-20 / 2-10mU/L
ARR=S-Aldo/aPR-ratio	**<30 (>35)pM/mU/L**
PRA (PlasmaRenin Aktivität)	0.98-4.18ng/ml/h
S-Aldo/PRA	< 20 pg/ml / ng/ml/h
bzw.	< 555 pM / ng/ml/h

Metanephrin (NM)

Plasma, frei	0.012-0.12ug/L = 0.06-0.61nM
Urin, total	<1500nmol/24h
Urin/Crea	10 - 200nmol/mmol

Normetanephrin (NMN)

Plasma, frei	0.022-0.17ug/L = 0.12-0.92nM
Urin	<4500nmol/24h
Urin/Crea	40 - 250nmol/mmol

Adrenalin (A)

Plasma	4-83pg/ml = 0.02 – 0.45nM
Urin (pmol / 6 ≈ ng/L)	<130nmol/24h
Urin/Crea	1 - 22nmol/mmol

Noradrenalin (NA)

Plasma	80-498pg/ml = 0.5 – 3nM
Urin	<610nmol/24h
Urin/Crea	5 - 45nmol/mmol

P-A u/o **NA**	
3h n Clonidin	**um >40%↓ / <2,75nM**
2' n Glucagon	**<3x↑ / <10nM**
VMS (Vanillinmandelsre)	<33umol/24h
Urin/Crea	<5ummol/mmol

Diabetes mellitus

PG nü *(=8h pp; BG = 0.89 x PG)*	**<5.6 (7)mM**
2h n 75g OGTT	<7.8 (11.1)mM
PG Gravida nü / 2h pp	<5.3 / <7mM
HbA1c Norm DCA / HPLC	**5.7 / 6.1%**
(%-Wert x 10,93) – 23,5 = mmol/mol-Wert	
(mmol/mol-Wert x 0,0915) + 2,15 = %-Wert	
Zielwert b Dm:	**keine Hypos & <7.5%**
Fructosamin	<285uM
C-Peptid	200 – 933pM
C-Peptid/PG (Restsekretion)	**>50**
IR (HOMA) PG mM x Insulin mU/L / 22.5	<1
Insulin-Ak (Insulin-Th n 1000-5000)	<50nU/ml
Alb / Crea i Spoturin	<2.4mg/mmol
	(x10 = Prot.urie/d)

Sonstiges *VBGA ⇒"gratis" ionCa, PG, Na, K*

Creatinine (88.4uM=1mg/dl)	***60-117uM***
Harnstoff (1mM=2.8mg/dl)	*3.4-8.7 mM*
Harnsäure (59.5uM=1mg/dl)	*258-491uM*
Homocystein	5-15uM
β-Carotin	0.76-3.34uM
Procalcitonin	***"normal" <0.06ng/ml***

Antibiotika b LRTI: GP/AECB>0.1; CAP>0.25; Sepsis>0.5; ***Follow-up*** *n 6-24h b Enthaltung v Antibiotika; n 3 - 7d f Stop Antibiotika*

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