Complications of diabetes – diabetic nephropathy

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Diabetes mellitus

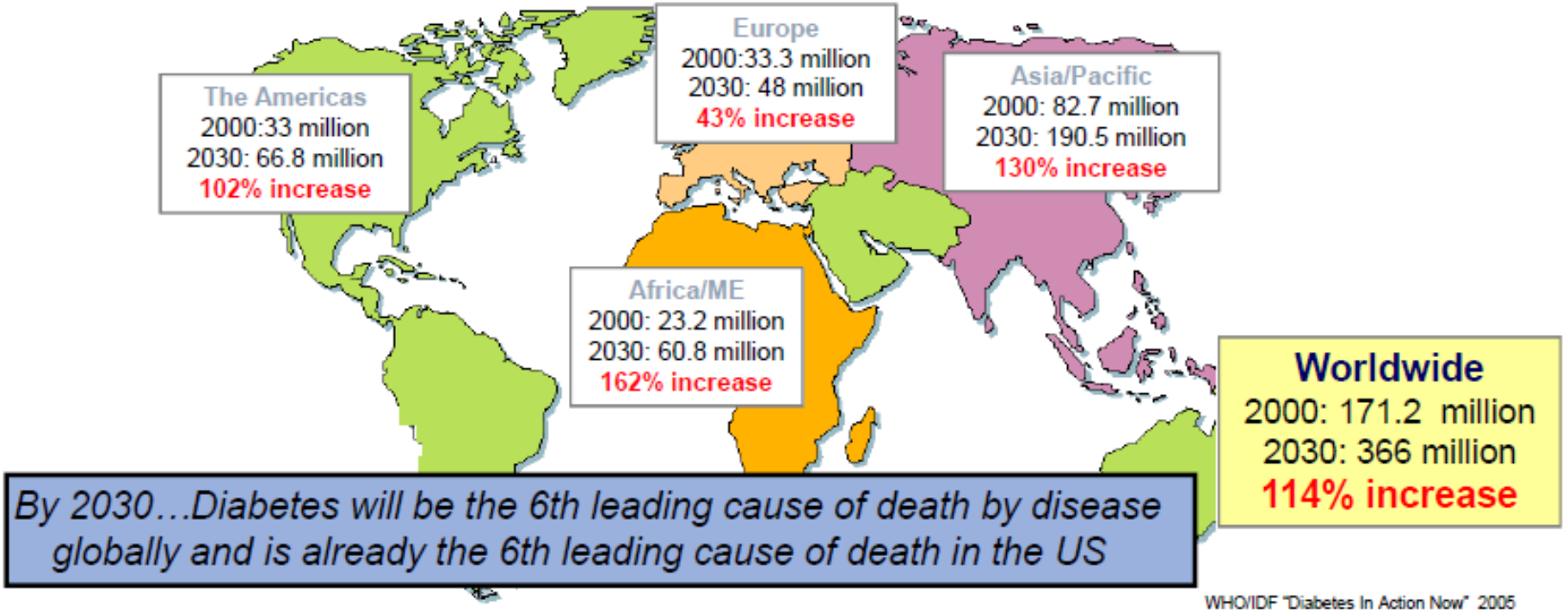
- chronic disease causing high mortality, invalidity and morbidity all over the world
- whole world: cca 170 mil. (2000) $\Rightarrow$ 366 mil. (2030)
- prevalence in Czech rep.: cca 8 %

  → : DM type 1 7,2%

  DM type 2 91,4 %

The Global Diabetes Epidemic

- Obesity and Type 2 diabetes are both experiencing epidemic growth, resulting in a tremendous human suffering and economic burden to society.
- Growth is disproportionate in Asia, Middle-East, Russia, and developing countries.



By 2030…Diabetes will be the 6th leading cause of death by disease globally and is already the 6th leading cause of death in the US

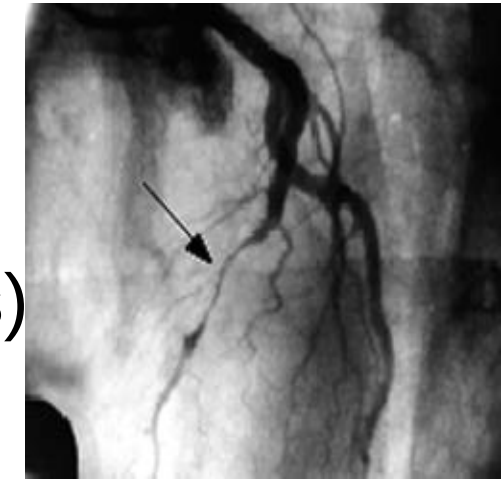
WHO/IDF "Diabetes In Action Now" 2005

Diabetes mellitus

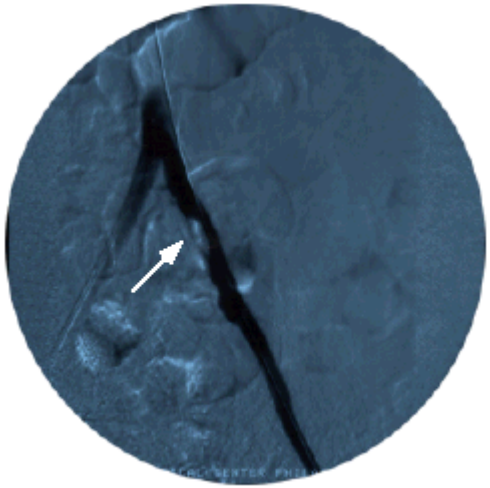
- **<u>complications:</u>**

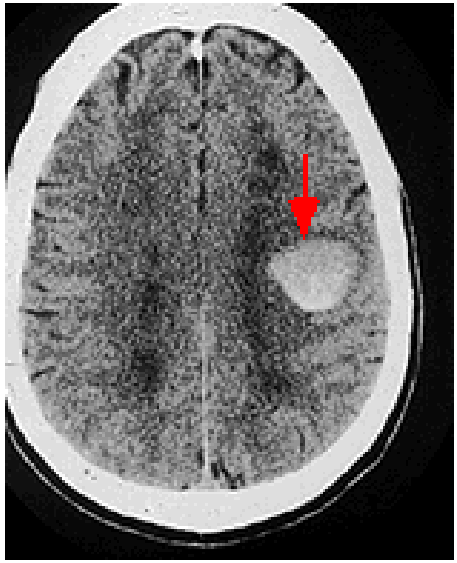
A/ macroangiopathic (atherosclerosis)

– Ischemic heat disease



- Chronic lower limb ischemia





- Cerebrovascular disease

Diabetes mellitus

- **<u>complications:</u>**

B/ microangiopathic

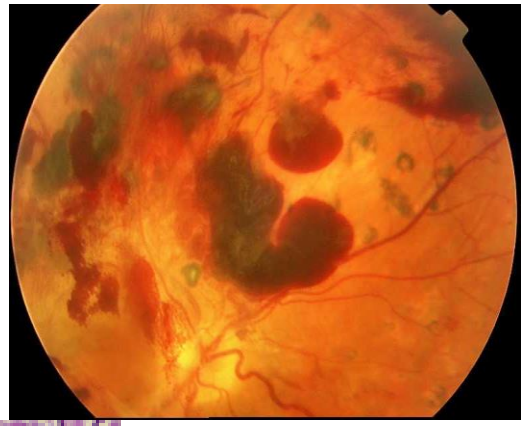
- retinopathy

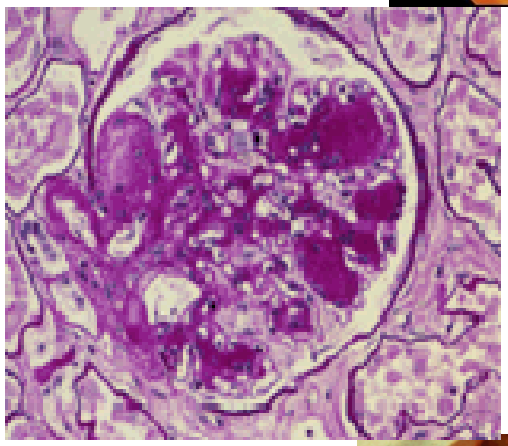
(60%)

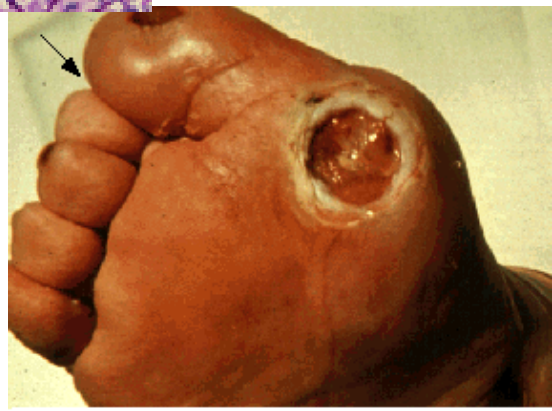
- nephropathy

(25-45%)

- neuropathy (50%)







Diabetic kidney disease - DKD

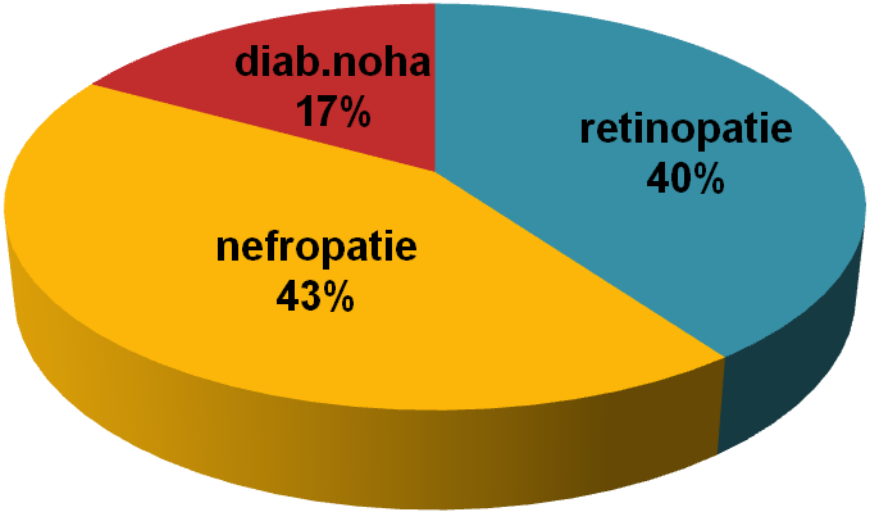
- clinical syndrom caused by specific morphologic and functional changes of kidneys in patients with diabetes mellitus typu 1 or 2

- major clinical sings: **persistent proteinuria**
  hypertension
  decreasing renal function

Epidemiology of DKD in CZ

- **2015:**
  858 000. ptx with DM
  (91.7% type 2)

- number of complications
  248 000



Ročenka ÚZIS 2015

Epidemiology of DKD

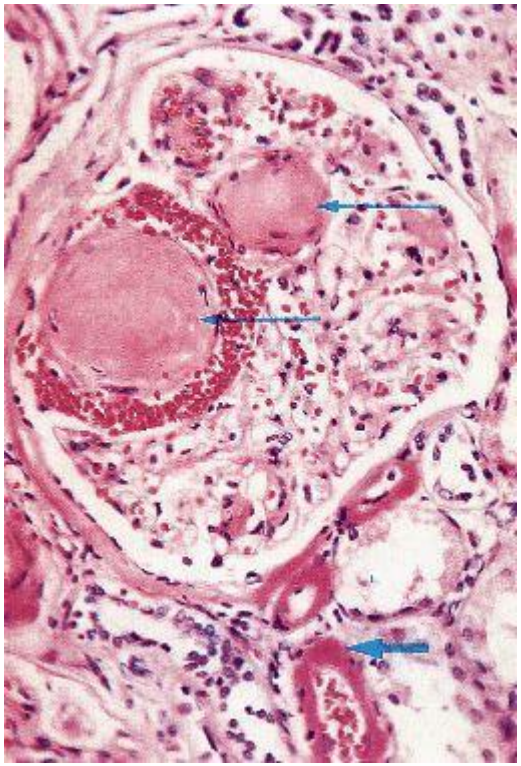
- ***DM type 1***
  during 10 years onset of DKD in 4% ptx
  25 years……. 25% ptx

- ***DM type 2***
  during 5 years onset of DKD in 10% ptx
  20 years……30% ptx

Morphologic characteristics of DKD

- thickening of glomerular basal membrane
- accumulation od mesangial matrix → expansion of mesangial space in glomerulus
- oppression of glumerular capillaries → loss of filtration surface - **diabetic nodular intercapillary glomerulosclerosis**

  (syndrom Kimmelstiel-Wilson)

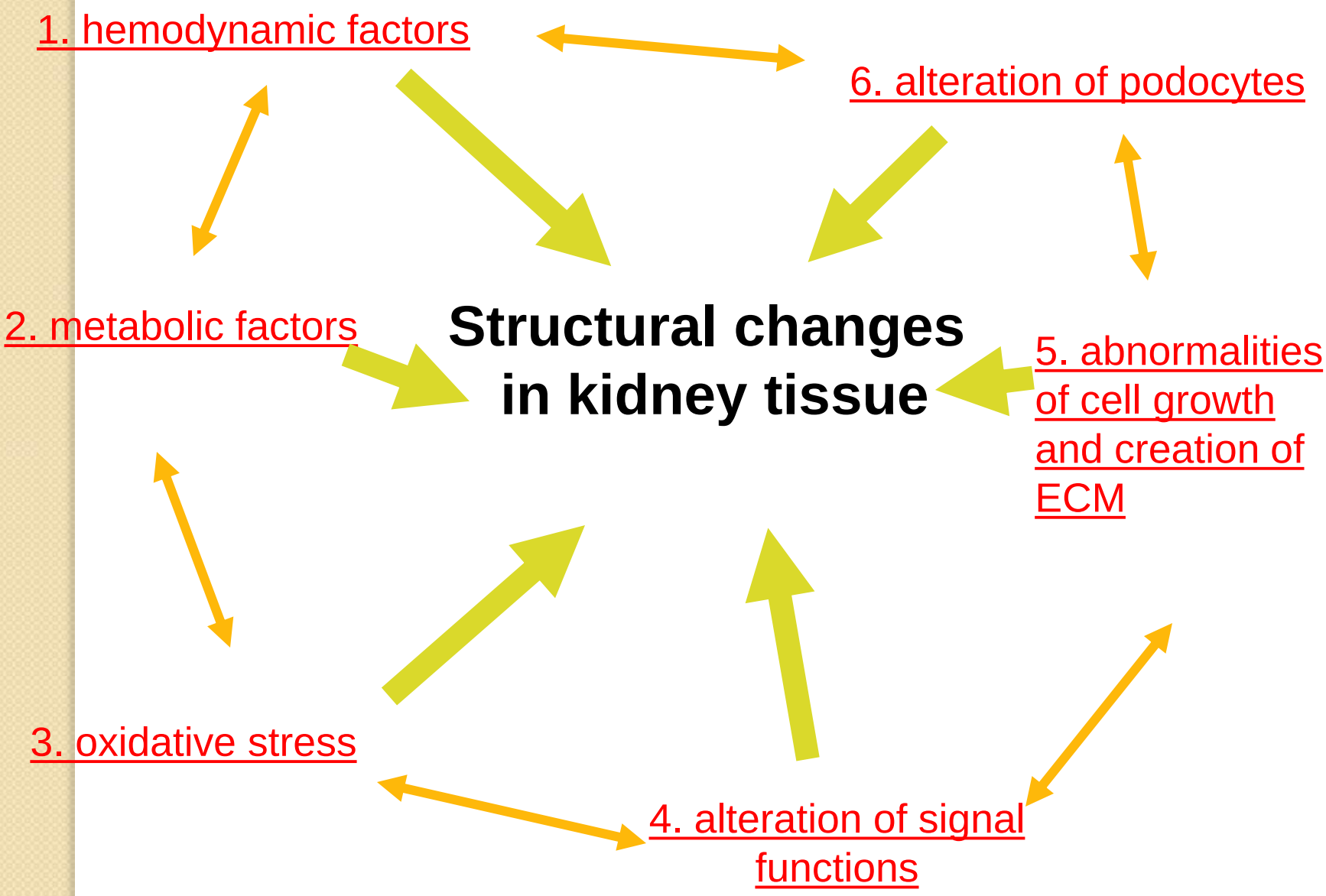


Pathophysiology of DKD

- As a result of interaction of both metabolic and hemodynamic factors we can see structural changes of kidney tissue

- **metabolic factors**:
  persistent hyperglycaemia, oxidative stress, glykosylation of proteins, polyol pathway of glukosa metabolism…
- **hemodynamic factors**:
  systemic and intraglomerular hypertension → lokal produktion of cytokines and growth factors (PKC, TGF_{β}…)

Pathophysiology of DKD



Diagnosis of chronic kidney disease/diabetic kidney disease (CKD/DKD)

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.

*Relative to young adult level.

**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

GFR categories (KDIGO 2012)

GFR category	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Evaluation of GFR

- We recommend using serum creatinine and a GFR estimating equation for initial assessment.(1A)

- We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B)

- Report eGFRcreat in adults using the **2009 CKD-EPI creatinine equation.**

- Excretory, endocrine and metabolic functions decline together in most chronic kidney diseases.
- GFR is generally accepted as the best overall index of kidney function.
- We refer to a GFR <60 mL/min/1.73 m2 as decreased GFR and to a GFR <15 mL/min/1.73 m2 as kidney failure

Definition of chronic kidney disease - criteria (KDIGO 2012)

Criteria (either present for ≥3 months)	Abnormalities of kidney structure or function
Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g [≥3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 mL/min/1.73 m^2 (GFR categories CKD 3a–CKD 5)

CGA staging of CKD: examples of nomenclature

Cause	GFR category	Albuminuria category	Criterion for CKD
Diabetic kidney disease	G5	A3	Decreased GFR, Albuminuria
Idiopathic focal sclerosis	G2	A3	Albuminuria
Kidney transplant recipient	G2	A1	History of kidney transplantation
Polycystic kidney disease	G2	A1	Imaging abnormality
Vesicoureteral reflex	G1	A1	Imaging abnormality
Distal renal tubular acidosis	G1	A1	Electrolyte abnormalities

KDIGO CKD Classification by Relative Risk

				Albuminuria stages (mg/g)				
				A1		A2	A3	
				Optimal and high normal		High	Very high and nephrotic	
				<10	10-29	30-299	300-1999	≥2000
GFR stages (mL/min per 1.73 m² body surface area)	G1	High and optimal	>105	Very low	Very low	Low	Moderate	Very high
			90-104					
	G2	Mild	75-89	Very low	Very low	Low	Moderate	Very high
			60-74					
	G3a	Mild to moderate	45-59	Low	Low	Moderate	High	Very high
	G3b	Moderate to severe	30-44	Moderate	Moderate	High	High	Very high
	G4	Severe	15-29	High	High	High	High	Very high
	G5	Kidney failure	<15	Very high	Very high	Very high	Very high	Very high

Levey AS, et al. *Kidney Int.* 2011;80:17-28.

Metabolic and clinical complications of CKD/DKD

- appearing early, even from CKD3 (GFR < 60ml/min)
- **impairment of Ca-P-vitD metabolism** – *secondary hyperparathyreoidism* , renal bone disease = **CKD- MBD**
- **secondary anemia** (and its consequences)
- **metabolic acidosis** (and its consequences)
- **uremic symptoms:** nauzea, vomiting, diarhoea, pruritus

Therapeutic approaches at CKD/DKD

- **treatment of anemie** – iron, erytropoetin
- **treatment of renal osteopathy** (CKD-MBD) – vit.D, Ca supplement., P-binders
- **treatment of hypertension**
- **diet restrictions**

Diet restriction in CKD

- creatinin 150-250umol/l:

- 0.8g protein/kg/day
- energy intake 140-150kJ/kg/day
- phosphate intake 1-1,2g/day
- low sodium intake if hypertensis or oedema are present
- fluid intake according to diuresis

Diet restrictions in CKD

- creatinin 250-600umol/l:

- 0.6g of protein/kg body weight/day
- energy intake150-160kJ/kg/day
- phosphate intake 0,6-0,8g/day
- calcium intake 1,5g/day
- sodium intake 80-100mmol
- fluid intake according to duresis
- ketoanalogs of essential aminoacids to improve anabolism (Ketosteril)

Non-diabetic nephropaties of diabetic patients

a/ glomerular – primary and secondary GN

b) non-glomerular

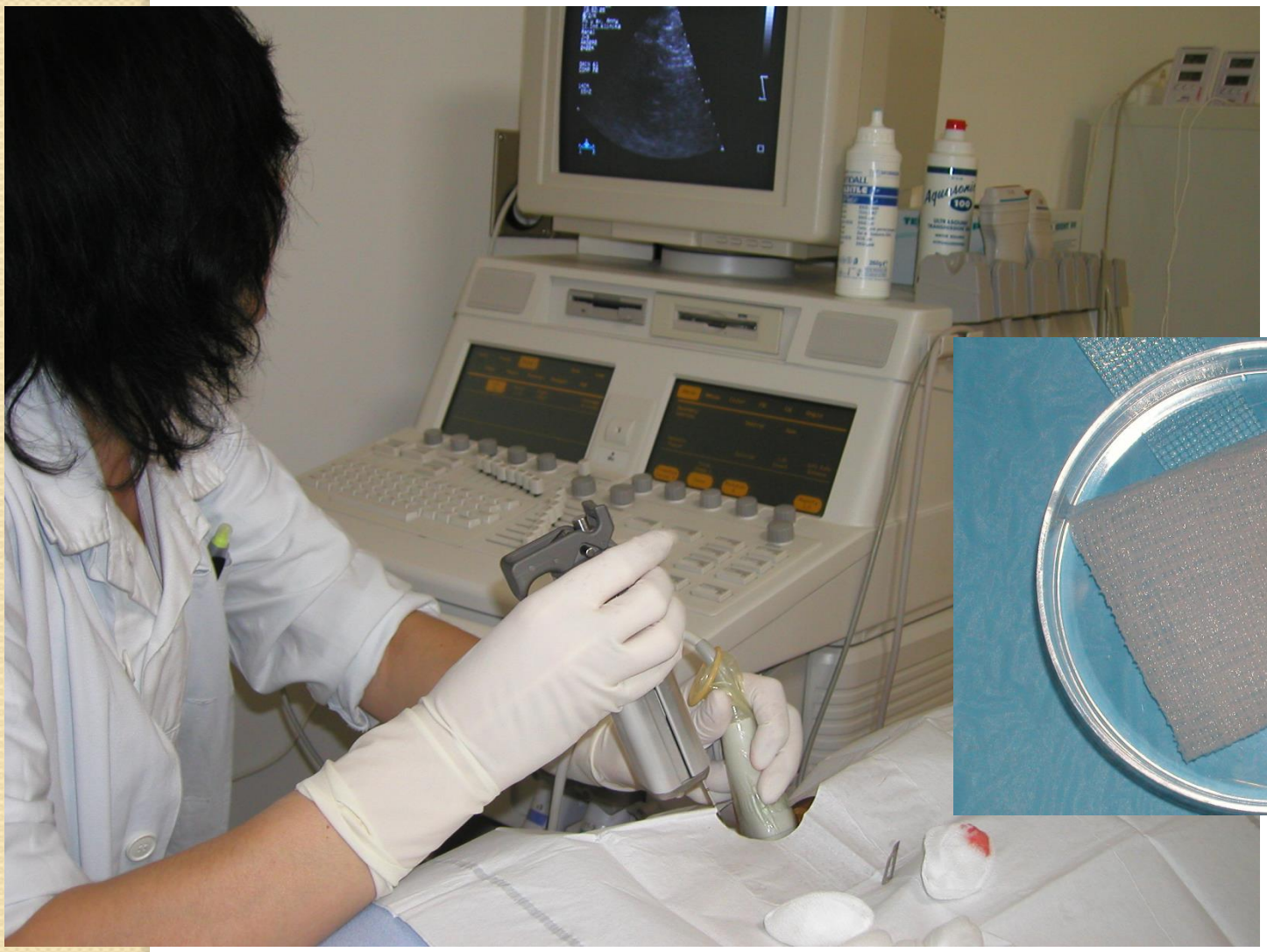
- **renovascular disease (RVD) stenosis of a.renalis, hypertensive nefrosclerosis**
- **tubulointersticial nephritis**
- **others**

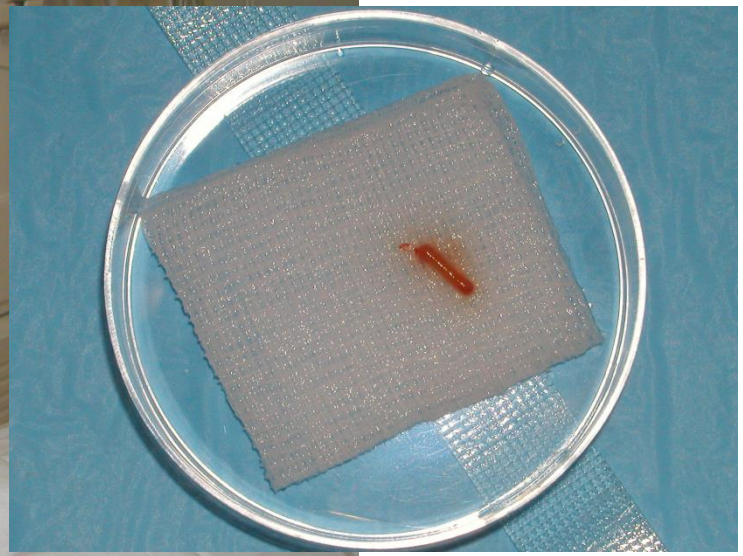
c) iatrogenic damage to kidney - nephrotoxic agents

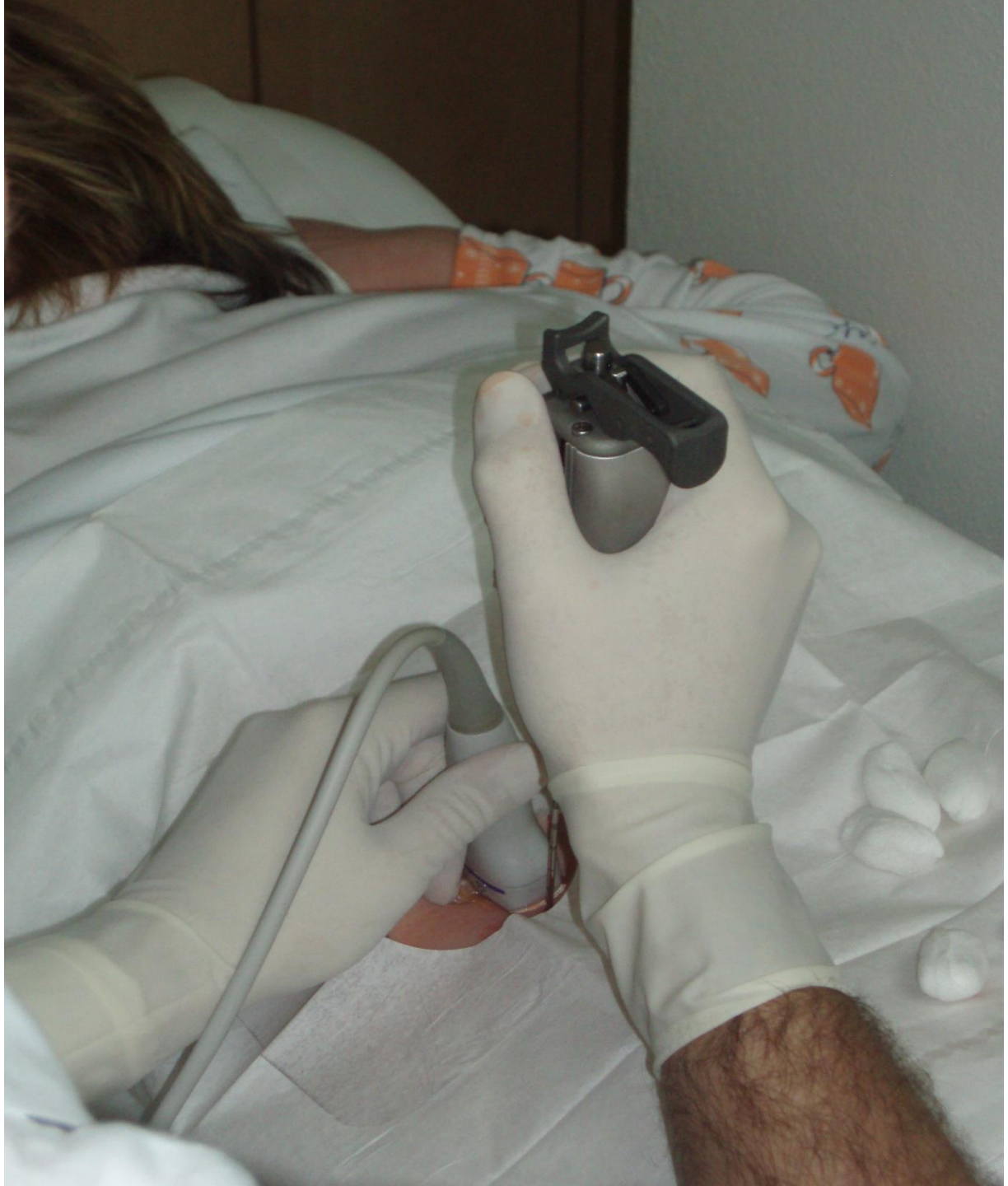
→ **radiocontrast media**

→ **drugs (non-steroidal antiinflamatory drugs, antibiotics –aminoglykosids)**

Renal biopsy







Diabetic ptx – Czech registry of renal biopsies 1999-2001

- Number of RB: 1946
- **Number of diabetics** **196 (10,1%)**
- Dg according to RB:
  - KSW 80 (40,8 %)
  - **other GN** **95 (48,5 %)**

    (IgAN 17.5 %, membranous GN 11%, nephrosclerosis 11%, vasculitic 9%)
  - non-diagnostic RB21 (10,7 %)

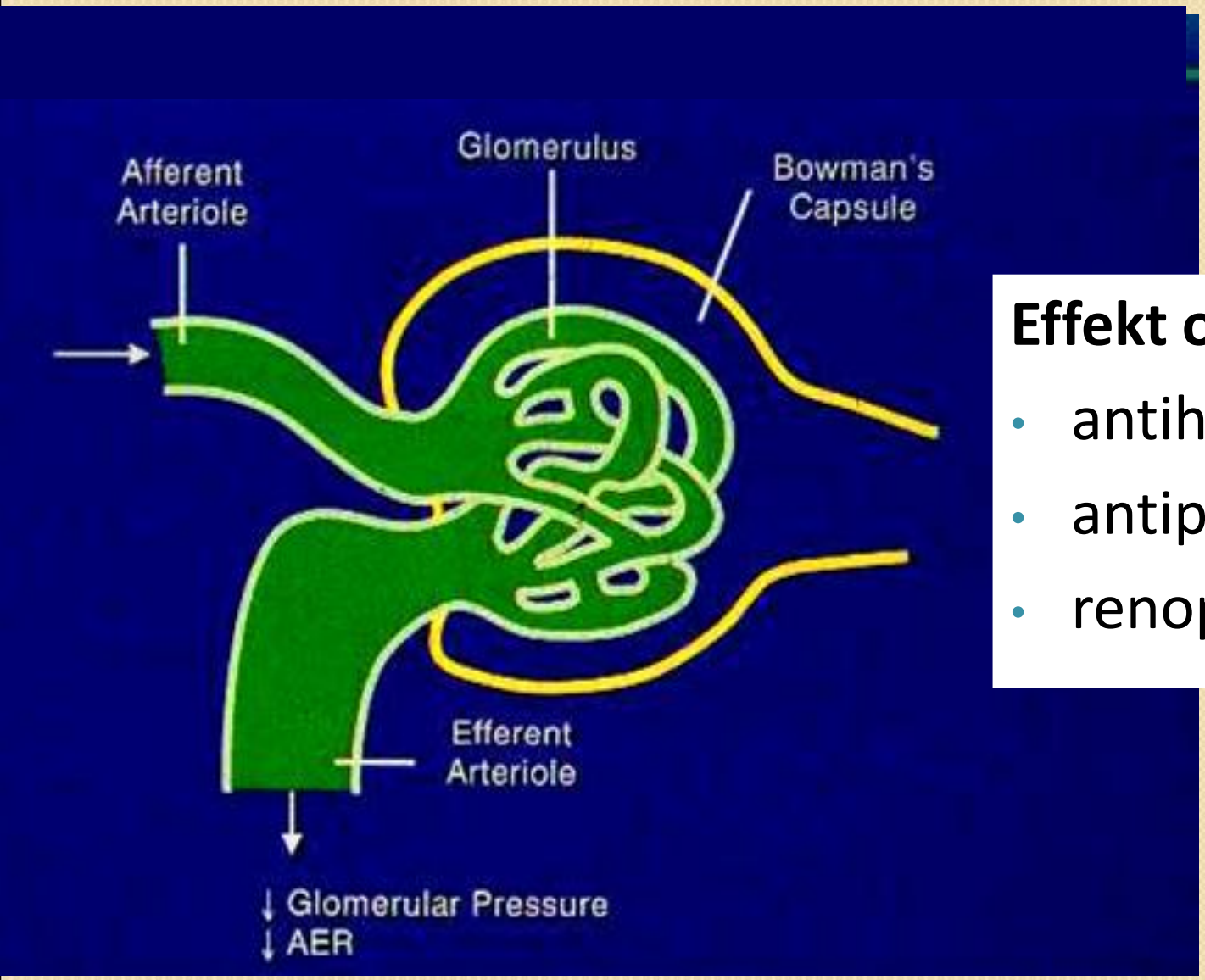
Rychlík et al, NDT,2004

Therapeutic options to influence the progression of diabetic kidney disease

Basic therapeutic approaches in treatment of diabetic patient with nephropathy in 2018

- **blockade of renin-angiotensin system (RAS)**
- **proper compensation of arterial hypertension**
  (blood pressure below 130/80)
- **metabolic compensation**
  - normoglycemia
  - normolipidemia
- **other regime measures** (protein restriction…)

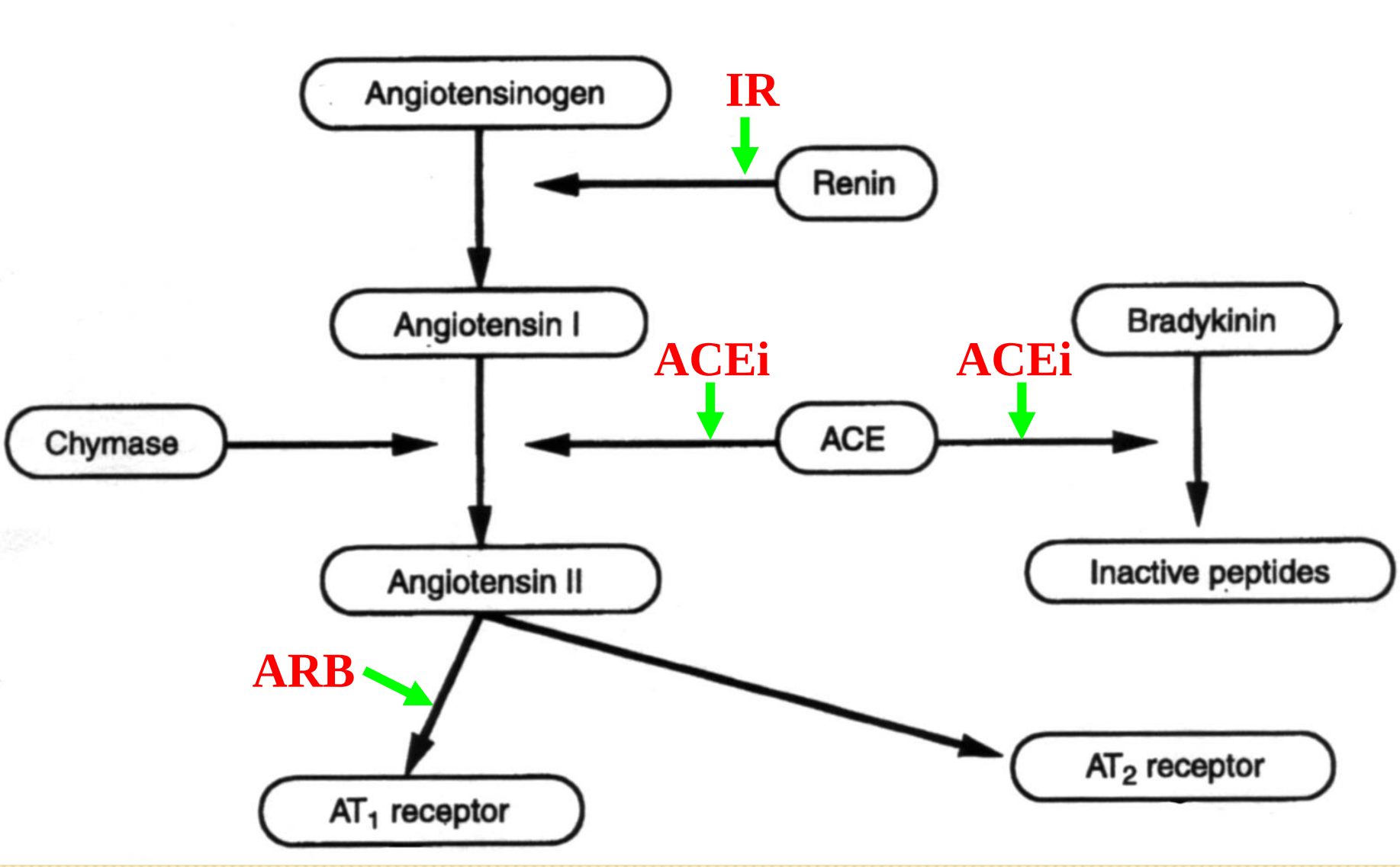
Mechanism of ACEI on intraglomerular hemodynamics



Effekt of RASblockade

- antihypertensive
- antiproteinuric
- renoprotective

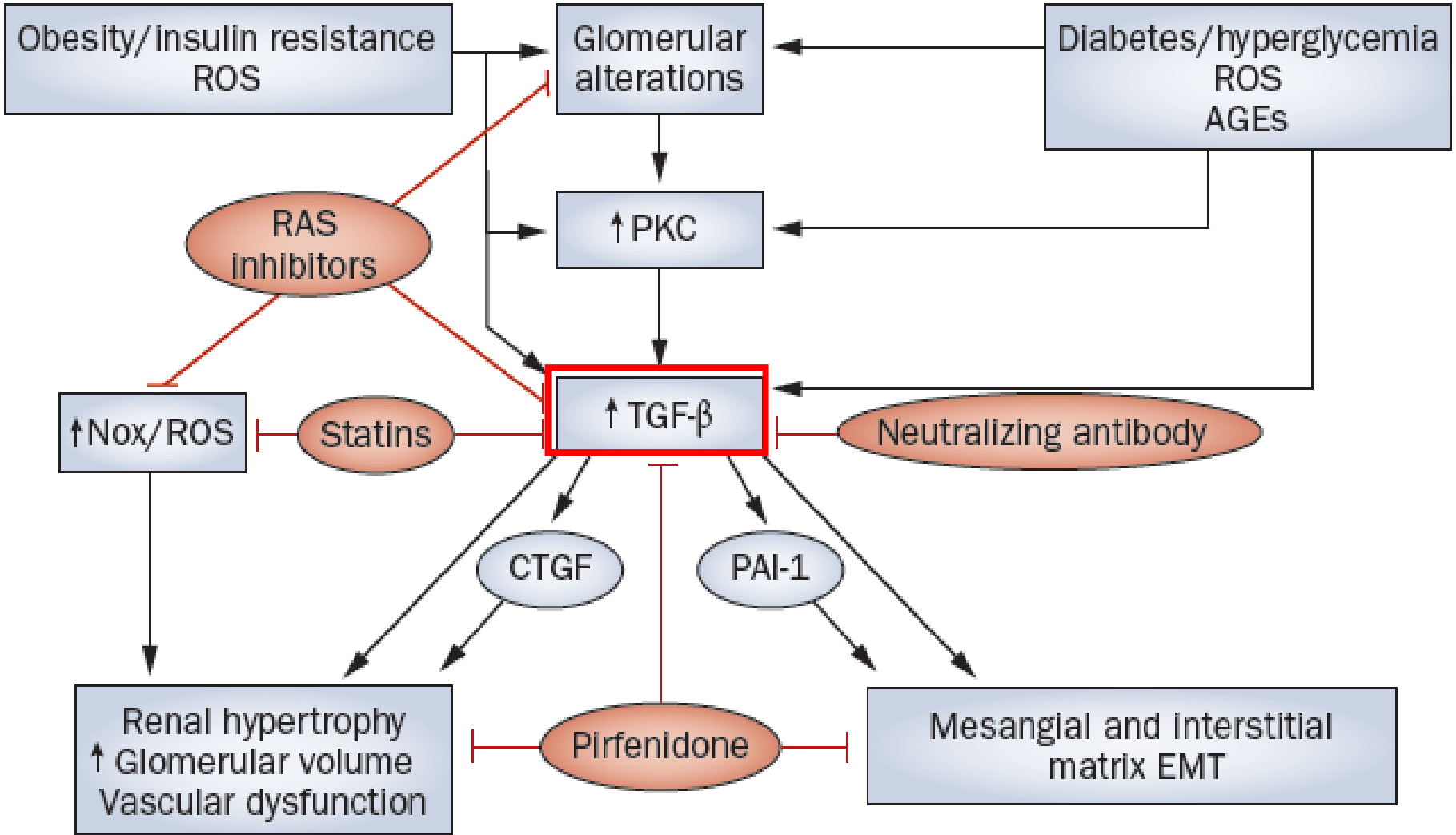
Blokátory RAS – klinické použití



New pharmacological treatments for improving renal outcomes in diabetes

Anne-Emilie Declèves and Kumar Sharma

Nat Rev. Nephrol. advance online publication 4 May 2010;

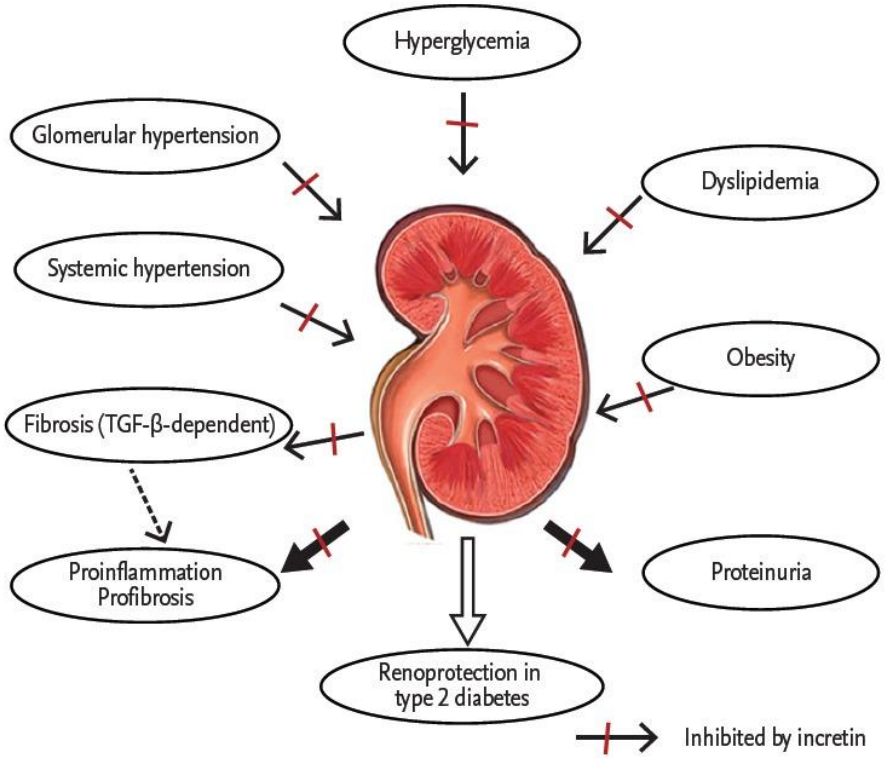


New antidiabetic drugs and impact on DKD

- **GLP-1 agonists**
  - sitagliptin,
  - vildagliptin
  - saxagliptin

- **DPP4 inhibitors**
  - exenatid
  - liraglutid

Effekt: ↓ albuminuria
↓ production of TGFβ
(↓ inflamation and fibrosis)

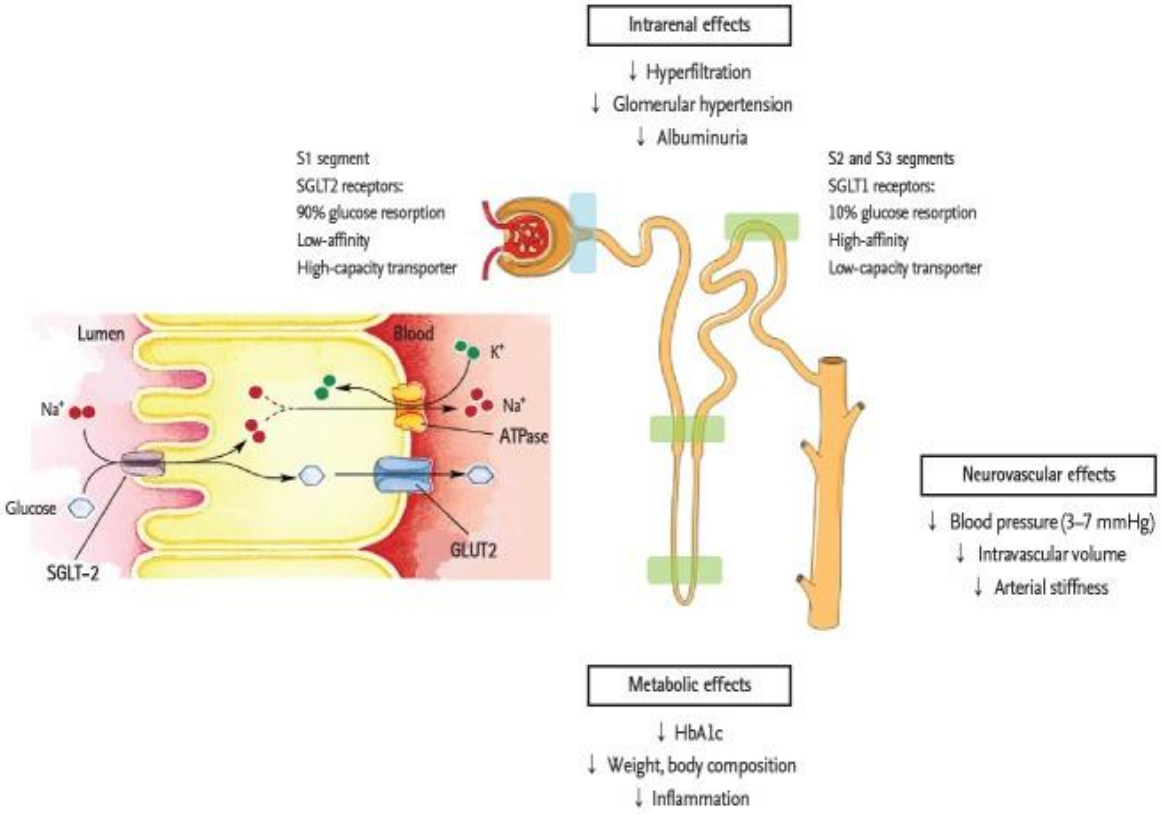


Kim Y. et al, KJIM 2017;32, 11-25

New antidiabetic drugs and impact on DKD

- **SGLT2 inhbitors (gliflozins)**
  - dapagliflozin
  - empagliflozin
  - canagliflozin

Effekt:
↓ albuminuria
↓ hyperfiltration
↓ glomerular hypertension



Kim Y. et al, KJIM 2017;32, 11-25

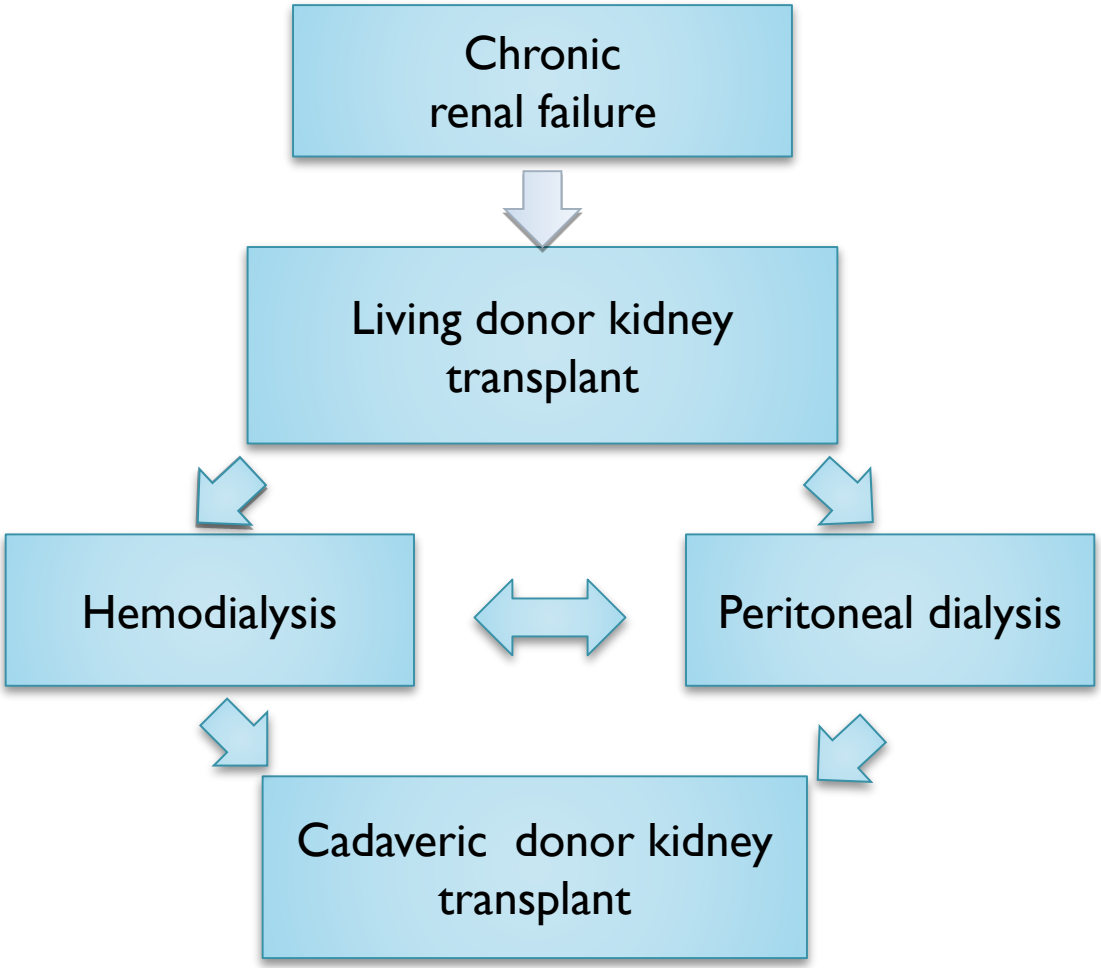
Renal replacement therapies (RRT)

- ***hemoelimination techniques***: hemodialysis
  hemodiafiltration
- ***peritoneal dialysis:*** continuous ambulatory PD
  automatic PD (cycler-assisted)
- ***kidney transplant***: cadaveric (deceased) donor
  living donor

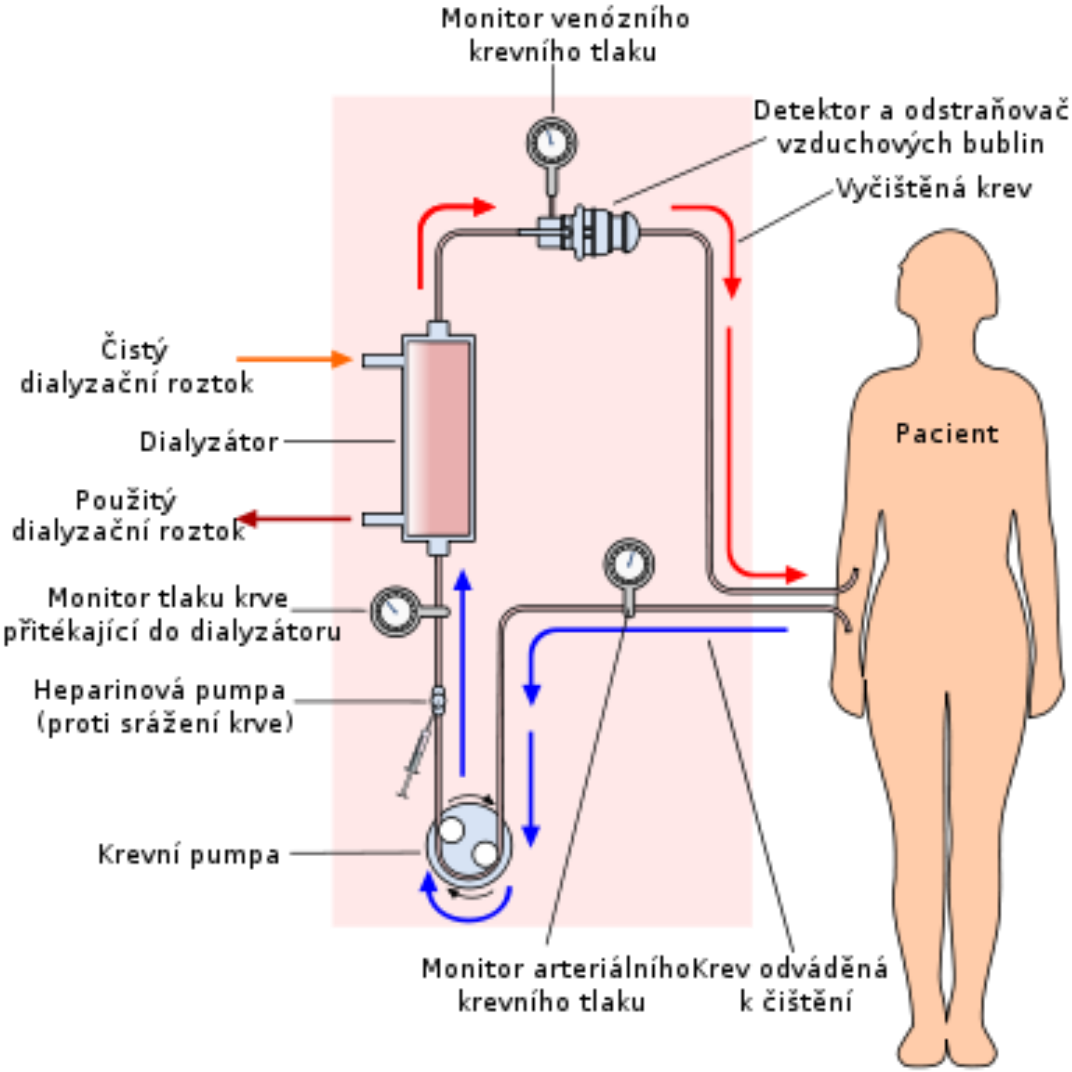
RRT - comparison

	excretor. Function	metabol./ endocr.	availability
1. HEMOELIMINATION 1.1. hemodialysis 1.2. hemofiltration 1.3. hemodiafiltration	+	–	immediate
2. PERITONEAL DIALYSIS 2.1. CAPD 2.2. APD – cycler assisted	+	–	weeks
3. KIDNEY TRANSPLANT	+	+	months-years

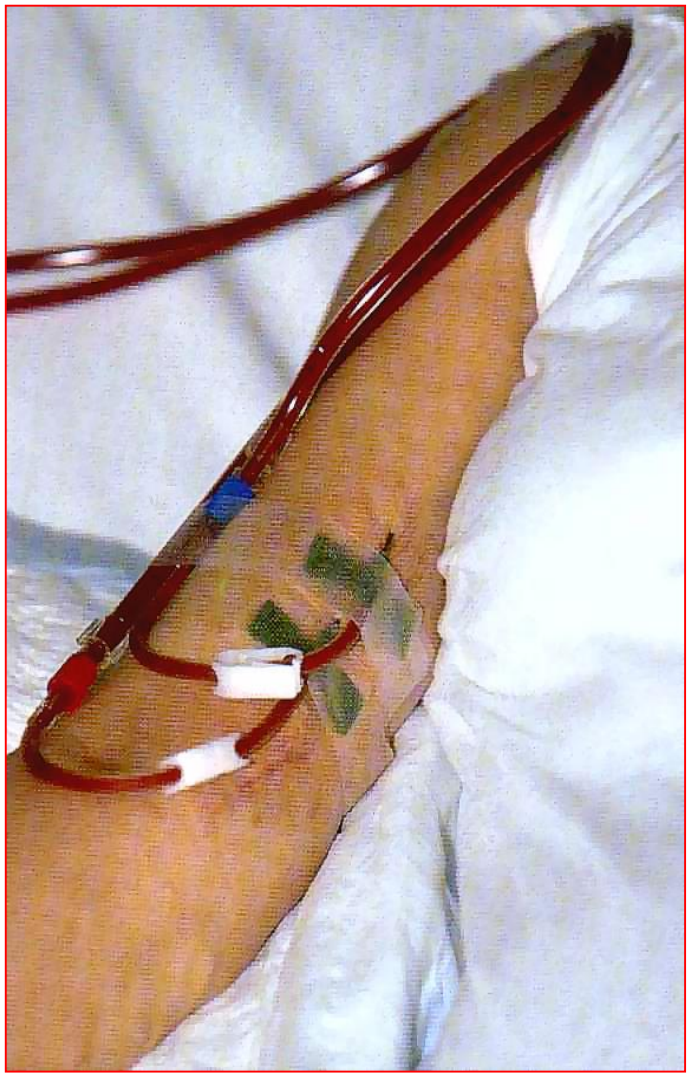
RRT – algorithm

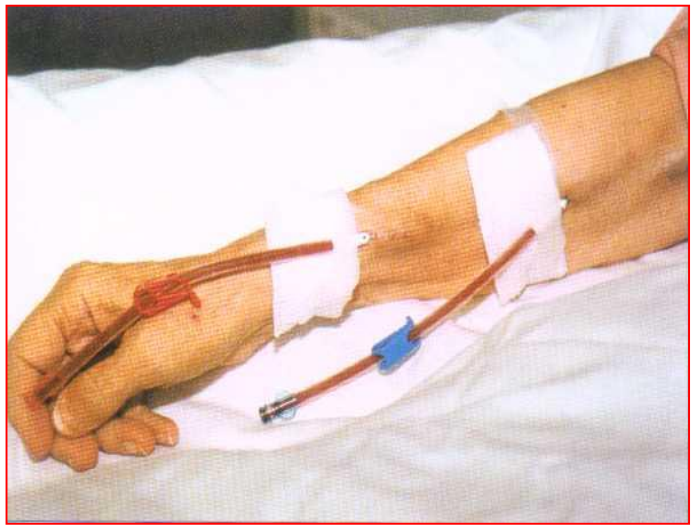


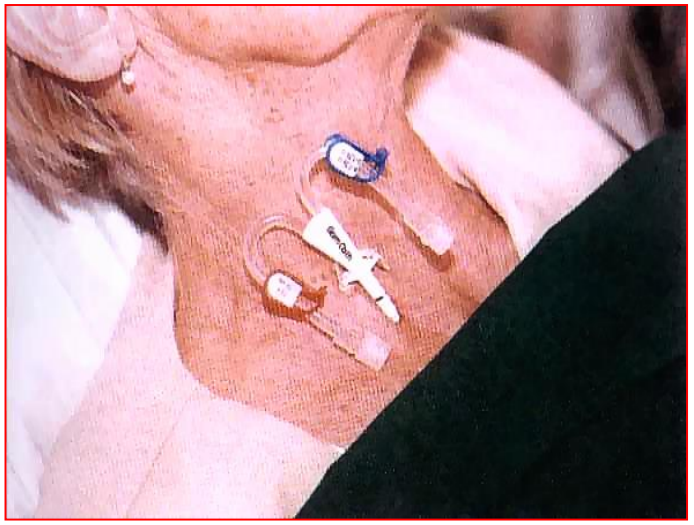
Principle of hemodialysis

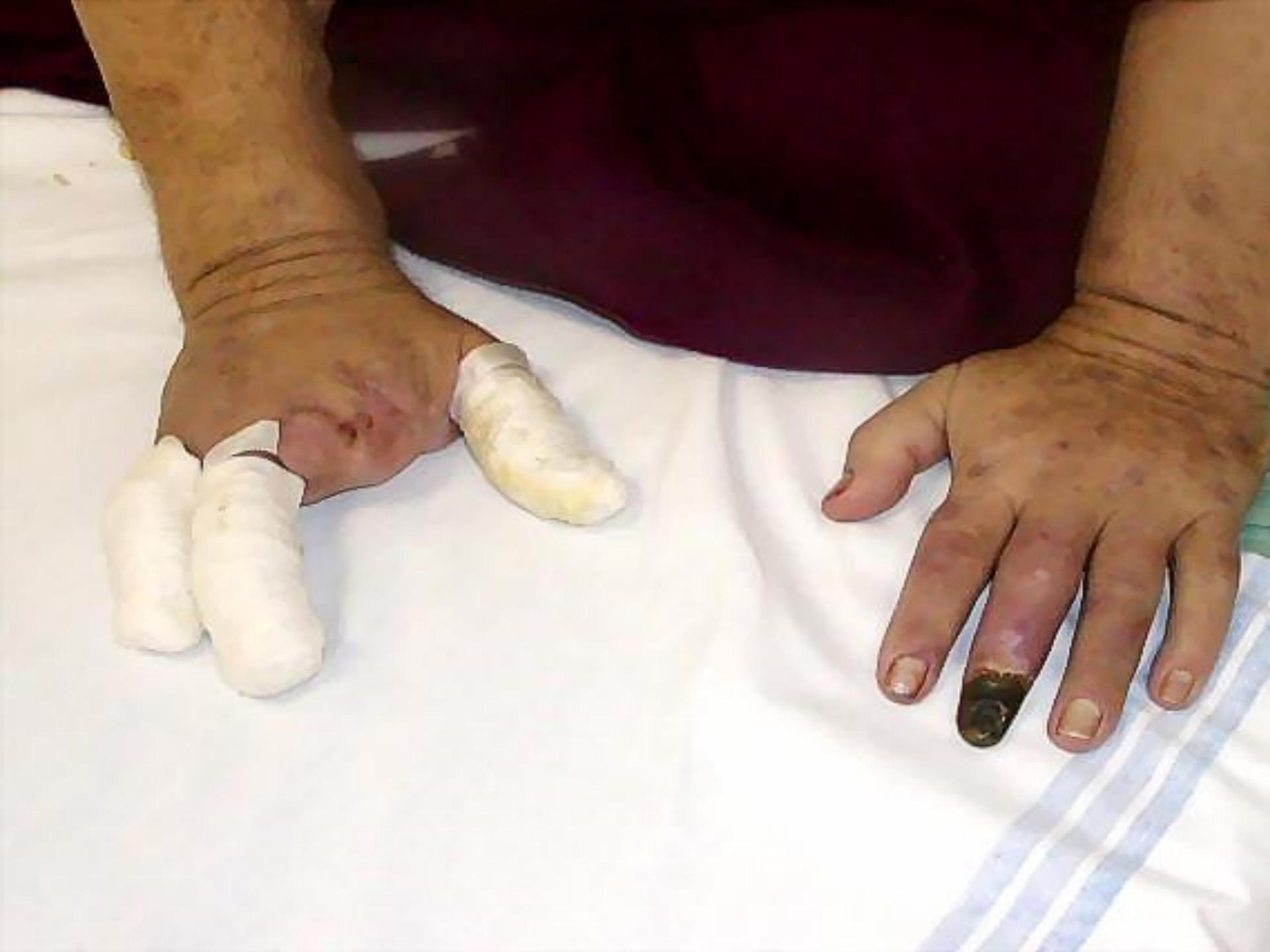


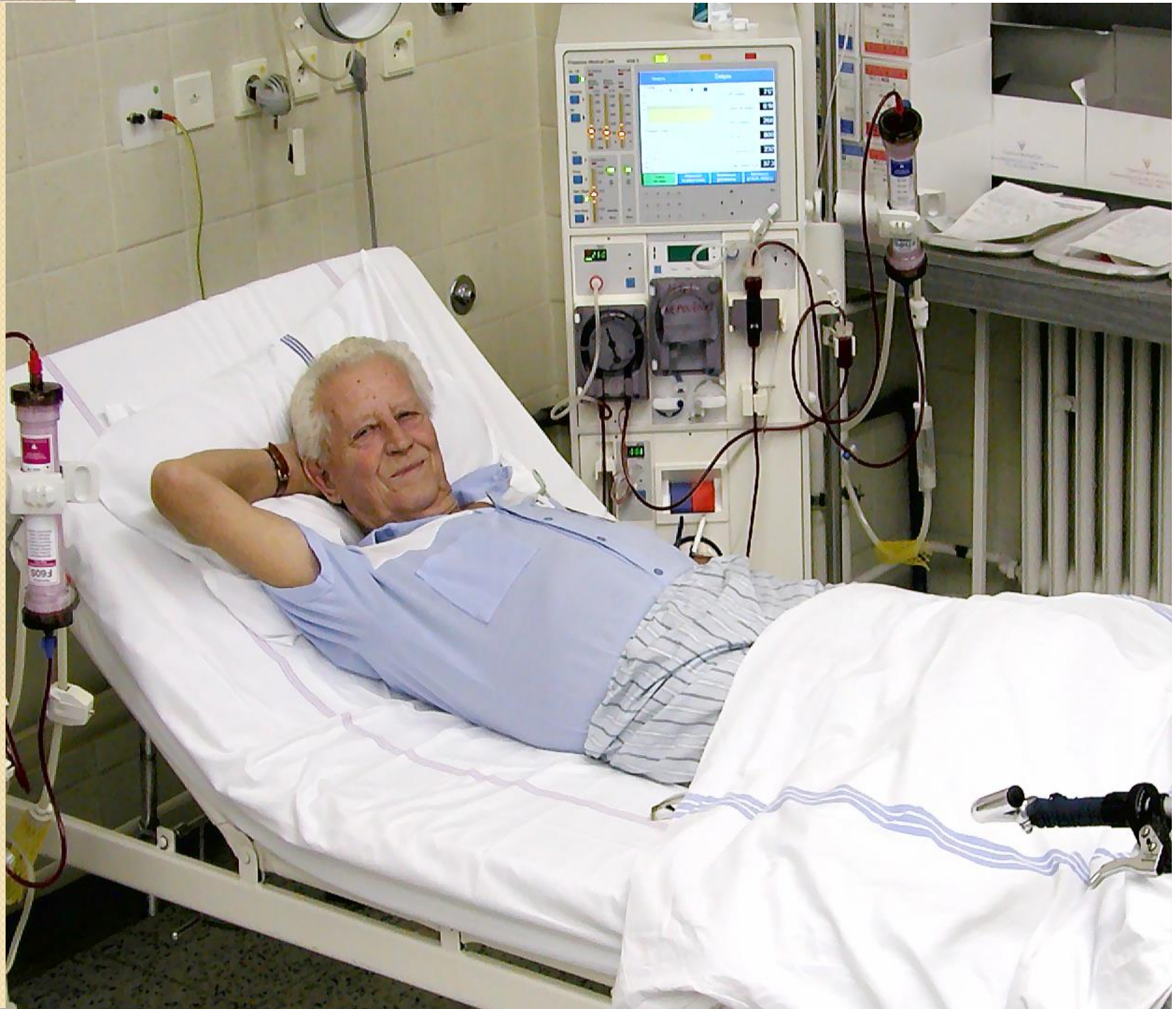
Vascular accesses for HD





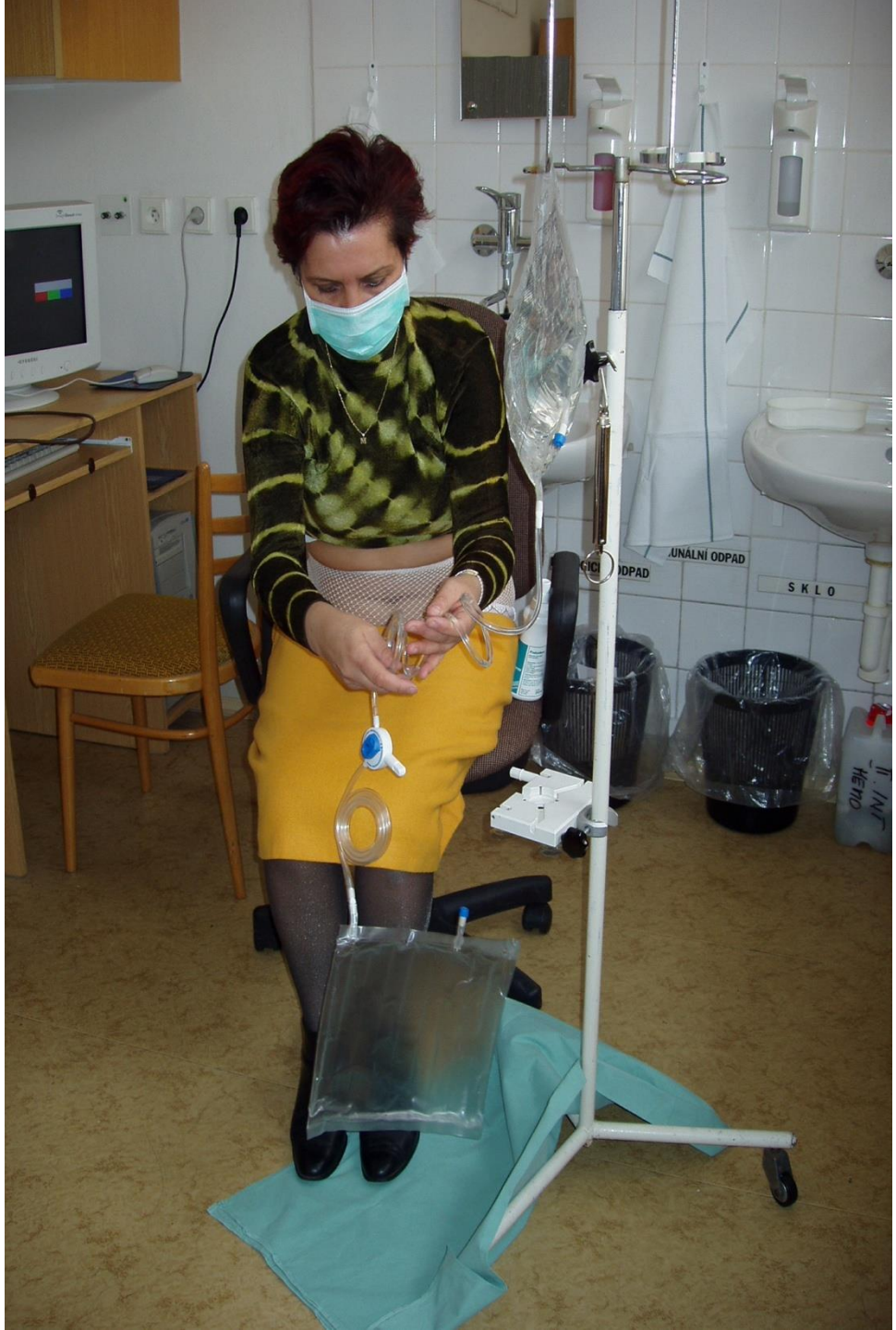






Peritoneal dialysis

- blood is purified by repeated exchanges (influx/outflux) of peritoneal solution by catheter, which is placed into abdomen cavity
- peritoneum acts like semi-permeable membrane
- efficiency is equal to HD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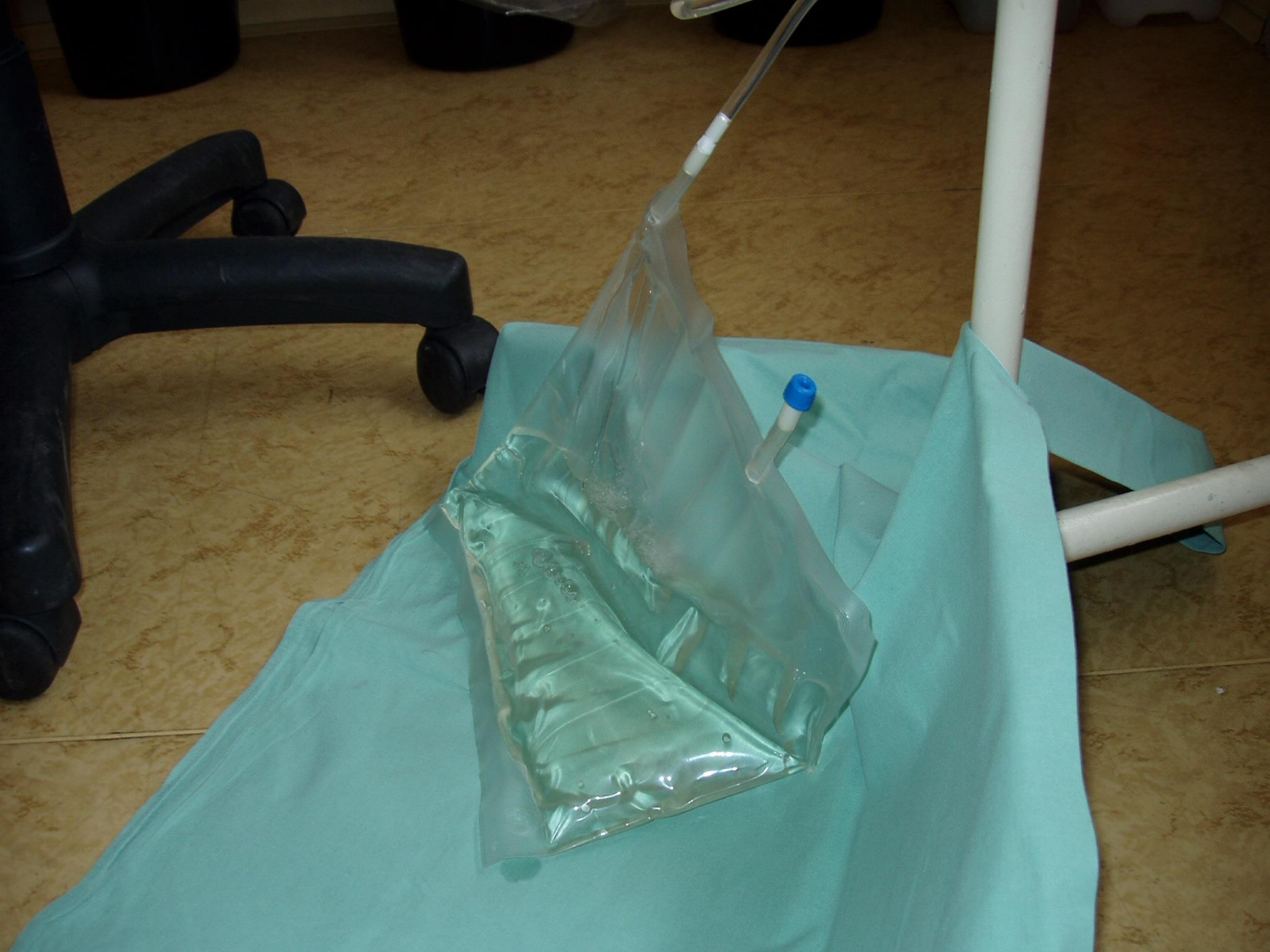
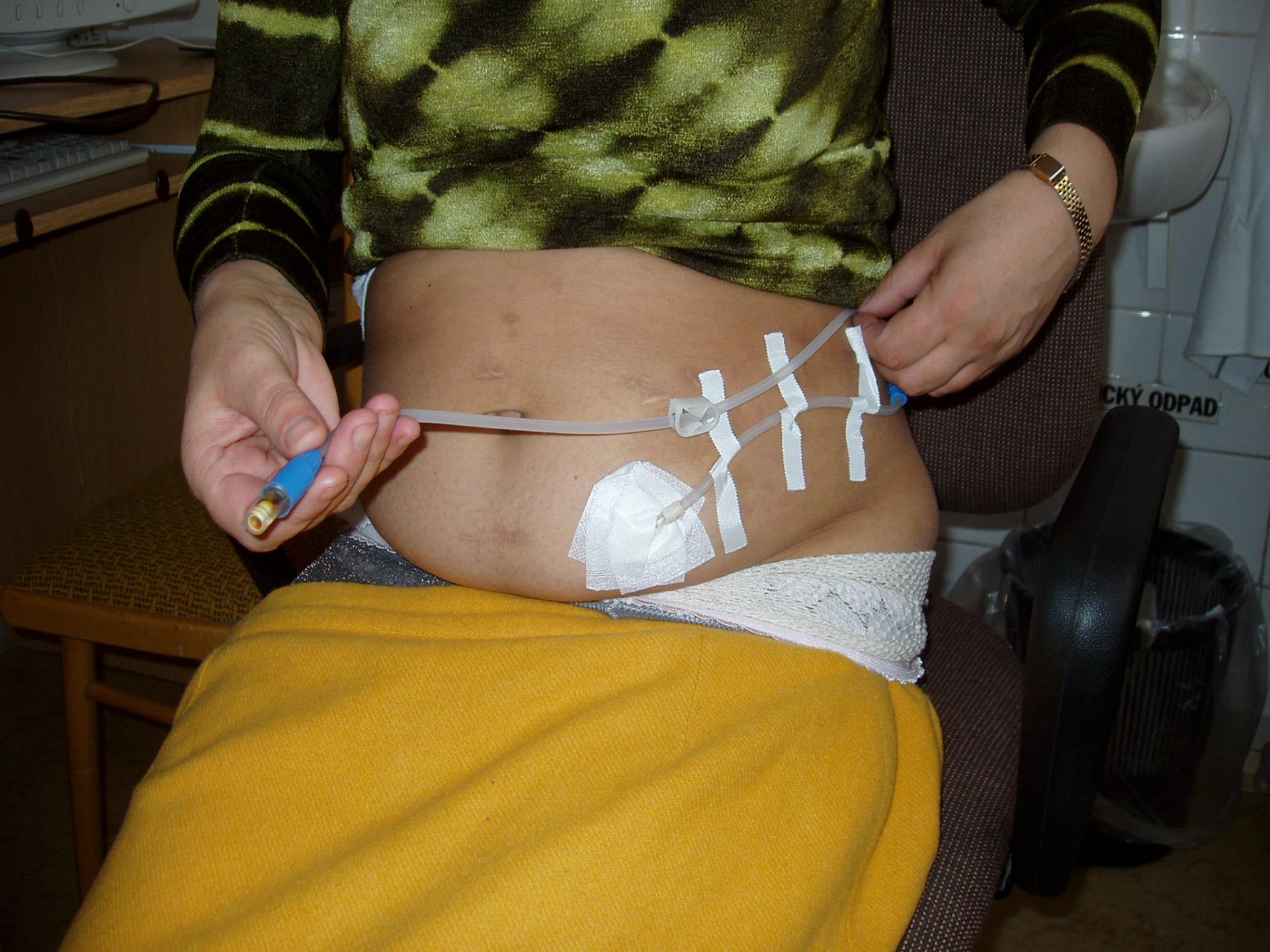



CKÝ ODPAD

Advantages of PD

- continuous way of blood purification
- gradual removal of fluid, no fluctuations of blood pressure and thus longer conservation of residual diuresis
- usually no restriction in fluid intake (according to residual diuresis)
- no blood losses a no need for systemic anticoagulation
- treatment at home

Disadvantages of PD

- gradual fibrosis of peritoneal membrane – loss of dialysis ability
- permanent risk of infection – acute peritonitis
- esthetic point of view – peritonel catheter in abdomen
- bathing restrictions (shower and salty water OK, bath tub NO)
- composition of peritoneal fluid is not metabolic inert (content of glukosa)
- need for permanent life partner

Kidney transplant

- **advantages**: replace of both metabolic and endocrine functions of kidney, return to"normal life", 2x longer survival time versus HD/PD, cost effectiveness

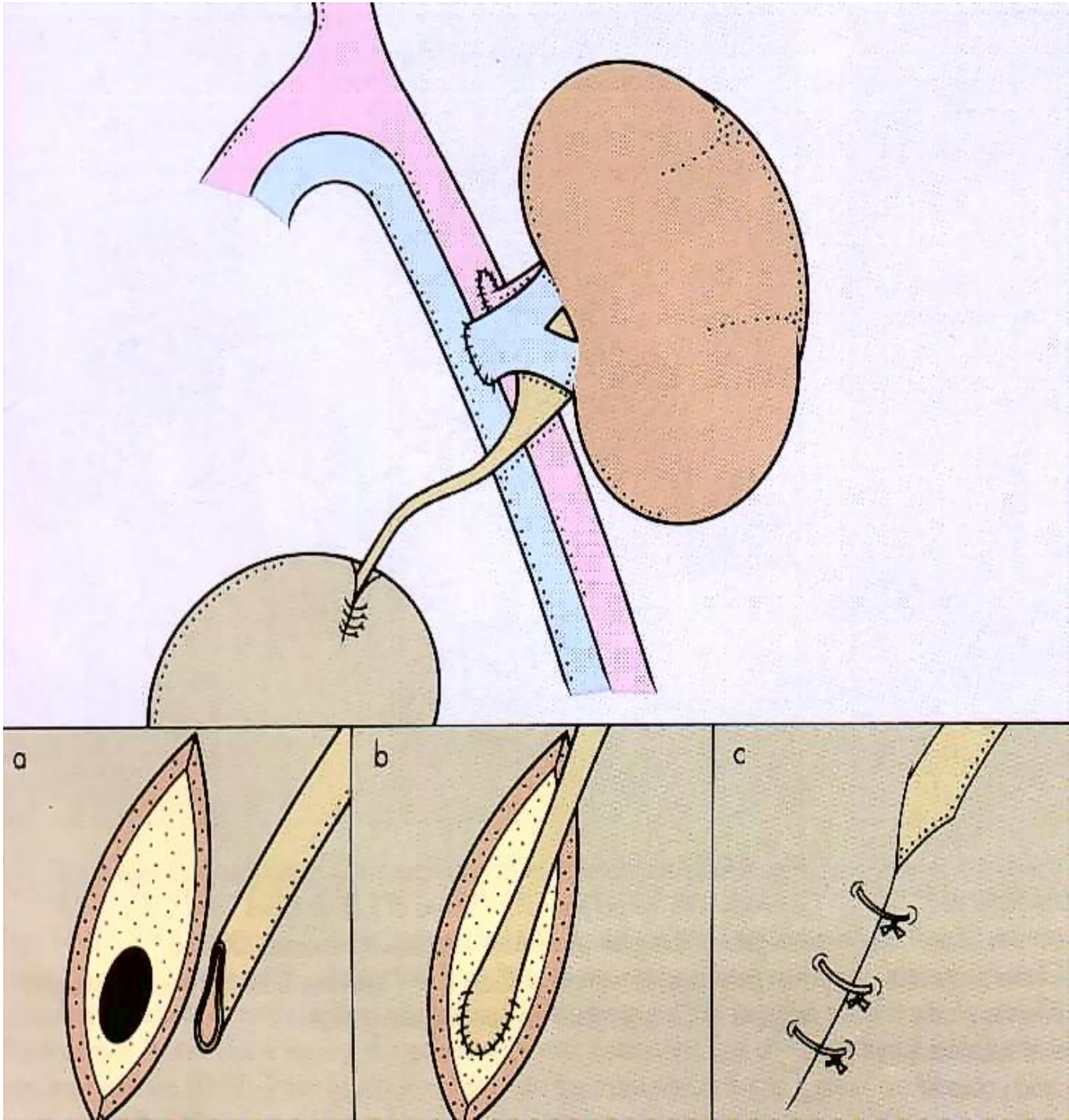
- **disadvantages**: limited availability – necessity to find suitable couple donor x recipient, necessity to use maintenance imunosupressive drug (higher risk of infections and tumours)

Kontraindikace TL

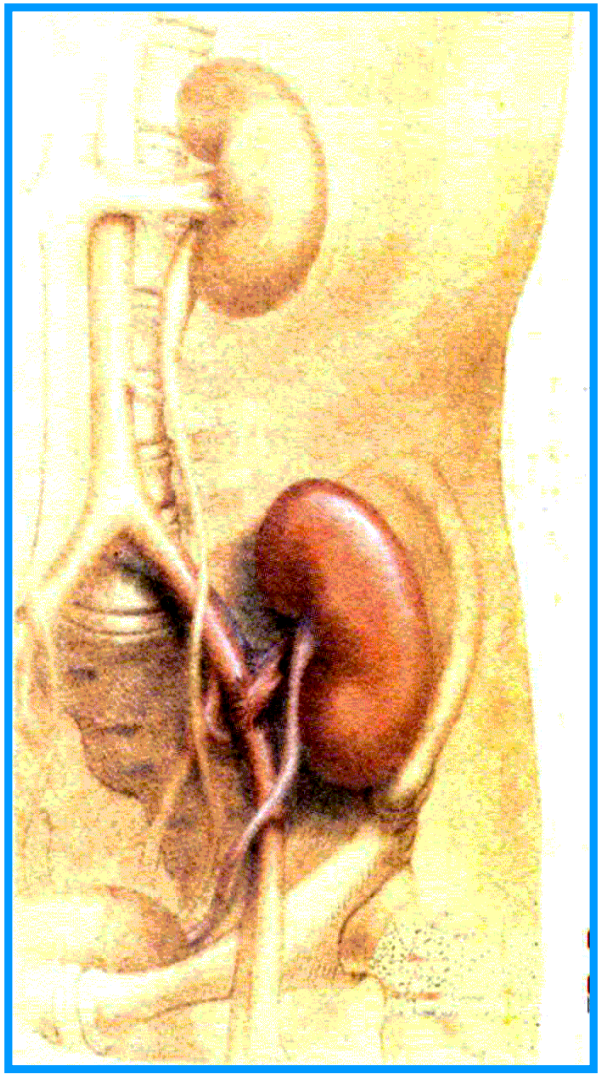
- Nesouhlas s TL
- Maligní a aktivní zánětlivá onemocnění
- Drogová závislost včetně alkoholizmu
- Nespolupracující nemocný
- AIDS/HIV pozitivita ??
- Periferní gangréna
- Pokročilé onemocn.nerenálního původu
- Vícečetné stenózy tepen DK neřešitelné
- BMI > 35

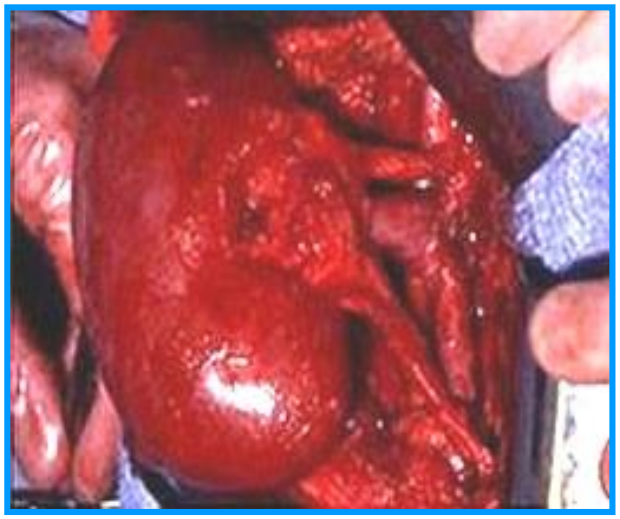
Methods of kidney transplantation

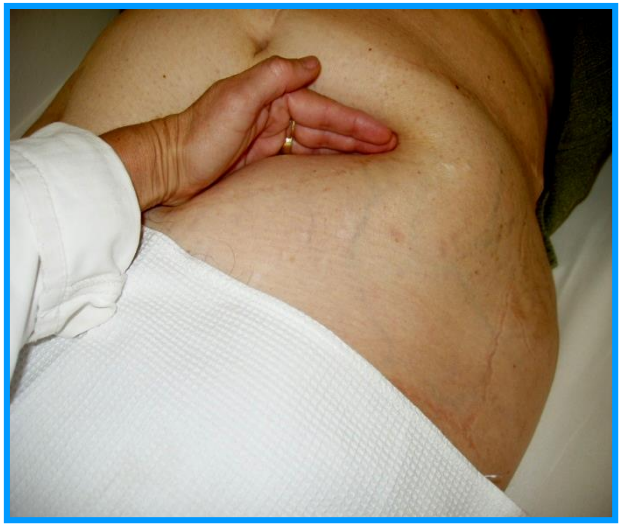
- **living donor Tx** (in CZ 13%, in Western Europe and USA up to 50%)
- **cadaveric donor Tx** (in CZ 87% of Tx)
- **donors:** people with brain death (after craniotrauma, spontaneous brain hemorrhage) or non-hearbeating donors
- in CZ system of „*presumed consent*“


a
b
c

Placement of kidney graft







Results of kidney Tx

- 10-years survival
- recipients: 70-80 %
- grafts: 50-70 %
- both is by 15-20 % better in living donor Tx

- Most common cause of graft failure are death of recipient with functioning graft and chronic rejection
- Most common cause of death of recipient are cardiovascular complicantions (>40%), infections a malignancy

Thanks for attention