Diabetic nephropathy (DN) is a frequent complication of diabetes types 1 and 2 and it is the most common cause of chronic renal failure. In addition, DN contributes to the development, progression and grade of development of other complications of diabetes, especially cardiovascular and, therefore, it significantly modifies the further course of the life and prognosis of patients.
Definition of DN

- Diabetic nephropathy is a chronic progressive disease with proteinuria, hypertension and gradual reduction of renal functions.
- It is caused by microvascular impairment of the kidneys and together with diabetic retinopathy and neuropathy, it is one of the symptoms of generalized microangiopathy.
Pathogenetic mechanisms of DN(1)

► Metabolic factors
- products of glycosylation
- polyol pathway
- hexosamine pathway
- alteration of the structure and function of glycosamines

► Hemodynamic factors — disproportional afferent vasodilatation, increase of GF and glomerular pressure

► Genetic factors
Pathogenetic mechanisms of DN(2)

- Diabetic renal hypertrophy
  - increased activity of growth factors and cytokines
  - cellular cycle disorders
- Impairments of cellular signalization
- Renin-angiotensin system
- Oxidative stress
- Endothelial dysfunction
Clinical stages of DN

- Stage 1 (hyperfiltration-hypertrophic)
- Stage 2 (latent DN)
- Stage 3 (incipient DN)
- Stage 4 (manifest DN)
- Stage 5 (chronic renal failure)
Stage 1
(hypertrophic-hyperfiltration)

- Increase of glomerular filtration by 20-40%
- Increase of renal plasma flow
- Tight metabolic control causes normalization of these abnormalities
- Glomerular hypertrophy, dilatation of capillary loops, hypertrophic-hyperplastic tubular changes
- Increase of renal volume detectable e.g. by sonography
Stage 2 (latent DN)

- Increase of glomerular filtration may persist
- Elimination of albumin is within the normal range and no other clinically relevant abnormalities are present
- Blood pressure is normal
- Renal biopsy reveals thickening of basal membranes, initial expansion of the mesangium and increase of the extracellular matrix
- Histological changes develop 2-4 years after duration of diabetes
Stage 3 (incipient DN)

- It develops in diabetic patients after 6-15 years of duration of diabetes
- This stage is characterized by abnormal elimination of albumin - microalbuminuria (MAU 30-300 mg/24 hr)
- MAU has a higher predictive value for cardiovascular mortality than for the development of manifest DN in patients with type 2 diabetes
- Increase of GF and nephromegalia persists
- If MAU persists, GF falls to normal values and it is gradually reduced to subnormal values
- Blood pressure is increased
Elimination of albumin in urine

- Normolabuminuria
  < 20 µg/min.
  < 30 mg/24 hr.

- Microalbuminuria
  Transient
  20-70 µg/min.
  30-100 mg/24 hr.
  Persisting
  70-200 µg/min.
  100-300 mg/24 hr.

- Manifest proteinuria
  >200 µg/min.
  >300 mg/24 hr.
Microalbuminuria

- MAU occurs in 20% of diabetic patients with type 1 diabetes and in 38% of type 2 diabetes patients.
- Patients with type 1 diabetes with MAU have a higher prevalence of other microvascular complications, e.g. proliferative retinopathy and blindness or peripheral neuropathy.
- MAU has a higher predictive value for cardiovascular morbidity and mortality than for the development of manifest DN in patients with type 2 diabetes.
- Risk of development of manifest DN is higher in patients with type 1 diabetes with MAU than in type 2 diabetes patients with microalbuminuria (50% vs. approximately 20-40%).
Stage 4 (manifest DN)

- Proteinuria is higher than 500 mg/24 hr.
- Proteinuria is increased by 15-40% per year in this phase and it is often manifested by nephrotic syndrome.
- Most patients have arterial hypertension.
- Target values of BP are < 125/75 torr.
- Reduction of GF occurs at a speed of approximately 0.17 mL/s/year.
Therapy of manifest DN

► Best possible metabolic compensation
► Antihypertensive therapy - BP < 125/75 mm Hg

(ACEi, ARB)
Ca blockers, diuretics, selective beta blockers
Dose titration follows a change of BP and influence of proteinuria
Proteinuria is the indicator of suitability of nephroprotective therapy

► Hypolipidemic therapy
► Antiplatelet therapy
► Protein intake limitation
► Salt intake limitation
Recommended interventions

► BP control (<130/80 mmHg)
► RAAS blockade to
  ▪ help achieve BP goal
  ▪ reduce proteinuria
  ▪ minimize kidney damage
► Glycemic control to preserve kidney function
► Dietary protein/phosphate restriction to lessen proteinuria?
Dual Significance of Proteinuria

- Proteinuria results from injury to glomerular circulation
  - Increased proteinuria is associated with progressive kidney disease
- In diabetes and hypertension, proteinuria is also an indicator of injury in systemic circulation
  - Proteinuria is associated with increased CV risk.
Stage 5
(chronic renal failure)

► It develops on average 7 years after the occurrence of proteinuria
► It requires iniciation of the dialysis - transplantation program
► Patients have high cardiovascular risk and other organ complications of DM
Histology of DN
Particulars of the clinical picture of renal failure in diabetic patients (1)

- Usually a polymorbid patient with advanced micro- and macrovascular complications of diabetes
- Accelerated course of cardiovascular complications in type 2 diabetes patients
- Peripheral diabetic neuropathy is accelerated by uremic neuronal impairment
  (paresthesias, cramps, loss of sensitivity especially in peripheral parts of the lower limbs)
Particulars of the clinical picture of renal failure in diabetic patients (2)

► Worsening of the symptoms of advanced autonomous neuropathy (severe hypertension combined with orthostatic hypotension, gastroparesis, impairment of intestinal motility, silent myocardial ischemia, paresis of urinary bladder, erectile dysfunction)

► Worsening of the syndrome of diabetic foot (neuropathy, ischemic and mixed etiology)

► Tendency to more severe anemia compared to non-diabetic patients with comparable GF
Acute worsening of stabilized CHRI in DN

- Administration of nephrotoxic medication (ATB, NSA ...)
- Contrast nephropathy (coronarography, arterial angiography in the lower limbs)
- Coronary angioplastics
- Aortocoronary bypass
- Heart failure
Basic principles of prophylaxis and therapy of DN

- Try to achieve good metabolic compensation of diabetes
- Regularly monitor microalbuminuria in case of negative finding of protein in urine
- Monitor BP and continually maintain BP within normal ranges
- Thoroughly treat associated urinary infections
- Avoid increase of protein intake above 1 g/kg of body weight, with CHRI 0.6 g/kg body weight
- Ensure substitution of renal function in patients with CHRI via dispensarization in the predialysis consultant department
- Renal transplantation is an optimal method of therapy of CRF for most diabetic patients
Prophylaxis of DN

**Primary prophylaxis**

- Prophylaxis of development of microalbuminuria
  - Most important is good metabolic control of diabetes

**Secondary prophylaxis**

- Prophylaxis of progression of microalbuminuria to manifest proteinuria
  - Most important is good control of BP and early initiation of therapy with ACE inhibitors
Substitution of renal function in DN

- Extracorporeal hemodialysis
- Peritoneal dialysis (CAPD, APD)

Transplantation therapy
- preemptive transplantation from a living donor
- preemptive transplantation from a cadaverous donor
- transplantation of a cadaverous kidney
- combined transplantation of kidney and pancreas
Particulars of therapy of CRF in DN (1)

- Hyperkalemia is often present because of hyporenin hypoaldosteronism and metabolic acidosis
- Need to reduce doses of insulin with gradual disappearance of functional renal parenchyma
- Observe contraindications for oral antidiabetics because of their extended elimination and high risk of serious and prolonged hypoglycemic conditions
Particulars of therapy of CRF in DN (2)

- Early provision of preparatory measures for dialysis therapy (creatinin <400 µmol/L)
- Type of dialysis therapy is selected by the patient after consultation with his/her nephrologist
- Creation of AV fistula is often difficult (atherosclerosis, mediocalcinosis)
- Time needed for sufficient development of AV fistula is usually longer in diabetic patients than in other individuals (6-8 weeks)
- Vaccination against hepatitis B
Particulars of therapy of CRF in DN (3)

► Acceleration of progression of atherosclerosis, neuropathy and retinopathy occurs within the scope of reduced renal function

► Early initiation of substitution of renal function

► Quality of life of dialyzed diabetic patients is markedly lower than in non-diabetic patients
Survival of patients in PDL

- Survival of patients with diabetic nephropathy during dialysis therapy is approximately by 50% lower than in patients with other causes of CRF.

- 62% of dialyzed non-diabetic patients but only 30.2% of dialyzed diabetic patients survive 5 years.
Practical recommendations (NKF-K/DOQI)

► Creation of A-V fistula
GF 25 mL/min/1.73 m² = 0.42 ml/s/1.73 m²
(Calculation of GF according to Cockroft and Gault formula)

► Initiation of RDT

Clinical signs
Nausea, vomiting, uremic pericarditis, pleuritis, enteritis, hyperhydration, hypertension that is resistant to antihypertensives, malnutrition

Laboratory indicators
GF 10 mL/min/1.73m² = 0.17mL/s/1.73m²
Nephropathy of non-diabetic etiology in diabetic patients (especially type 2)

- Ischemic renal disease
- Athero-embolic renal disease
- Renal artery stenosis
- Nephroangiosclerosis
- Renal papillary necrosis
- Urinary tract infection (chronic TIN)
- Membranous nephropathy
Clinical picture typical for DN

- Long-term history of diabetes
- Presence of diabetic retinopathy
- Long-term occurrence of MAU that slowly proceeds into increasing proteinuria
- Nephrotic proteinuria precedes a development of renal insufficiency
- Microscopic hematuria is not present
- Renal biopsy is not indicated
Indications for renal biopsy in a diabetic patient

- Fast development of proteinuria
- Reduction of GF which does not correspond to a course of diabetes
- CRI without proteinuria or diabetic retinopathy
- Glomerular hematuria
- Discrepancy between the size of the kidneys and the clinical-laboratory finding
- Short history of diabetes
- Diabetic retinopathy is not present