Diabetic Kidney Disesase

Authors C. Hasslacher[1], G. Wolf[2], P. Kempe[3], E. Ritz[4]

Affiliations
[1] Diabetesinstitut Heidelberg
[2] Klinik für Innere Medizin III, Universitätsklinikum Jena, Jena
[3] Diabetes-Schwerpunktpraxis, Ludwigshafen
[4] Nierenzentrum, Heidelberg

Definition

The course of diabetic nephropathy in patients with type 1 or type 2 diabetes is as follows:

- Changes in urinary albumin excretion
- Decline in glomerular filtration rate (GFR)
- Development or intensification of hypertension, dyslipoproteinaemia or other complications typical in diabetes patients.

The nephropathy stages and associated secondary diseases are given in **Table 1**.

Screening and Diagnosis

Screening once a year by determining the albumin concentration in the patient's urine (**Fig. 1**). Annual determination of estimated GFR (eGFR) is recommended because the kidney function of diabetic patients can be limited even without albuminuria (e. g. with ischemic nephropathy).

Exception: patients with greatly restricted life expectancy and presence of factors which can lead to transient elevation of urinary albumin excretion, e. g. as with physical exertion, illnesses with acute fever, infection of the urinary tract, improperly controlled diabetes, poorly controlled hypertension, heart failure.

The diagnosis "diabetic nephropathy" can be assumed to be highly probably if there is a persistent albuminuria, i. e. the albumin / creatinine ratio in the patient's urine exceeds 20 mg/g for men or 30 mg/g for women when measured in two samples separated by a period of 2 to 4 weeks (**Fig. 2**).

Differential Diagnosis

Indications of a kidney disease that is not diabetic are:

a) With presence of elevated urinary albumin excretion:

- Pathologic urine sediment (particularly dysmorphic erythrocytes, erythrocyte cylinders or leukocytes),
- Rapid increase of proteinuria,
- Extremely high proteinuria (> 6 g / 24 h)
- Rapid rise in creatinine
- Atypical sonographic changes of the kidneys, i. e. especially contracted kidneys or asymmetric kidney size.
- Type 1 diabetes diagnosed less than 5 years ago.

Nephrology referral for further work-up is strongly recommended!

b) With absence of elevated urinary albumin excretion:

Renal insufficiency without micro or macro albuminuria is usually ischemic (hypertensive nephropathy). The therapy is largely that for treating diabetic nephropathy. Further imaging studies (duplexsonograph, MRI) are recommended in cases of suspicion of renal arterial stenosis, e. g. with asymmetric kidney sizes, abdominal vascular murmurs, hypertension that is difficult to control (more than four antihypertensives), rise of serum creatinine to more than 50 % of the initial value caused by ACE inhibitor or AT_1 receptor receptor block therapy, or small kidney on just one side (sonograph).

Further Diagnostic Work-Up

- Ocular fundus
- ECG, with exercise as appropriate
- 24-h blood pressure monitoring

Last update
3/2014

Bibliography
DOI http://dx.doi.org/10.1055/s-0034-1366327
Exp Clin Endocrinol Diabetes 2014; 122: 391–394 © J. A. Barth Verlag in Georg Thieme Verlag KG Stuttgart · New York · ISSN 0947-7349

Correspondence
Prof. Dr. med. Christoph Hasslacher
Diabetesinstitut Heidelberg
Landhausstr. 25
69115 Heidelberg
Tel.: 0 62 21/6 53 19 70
Fax: 0 62 21/6 53 19 79
c.hasslacher@diabetesinstitut-hd.de

- Lipids (total, HDL and LDL cholesterol, triglycerides)
- Foot status (pulses, Doppler peripheral pulses, tuning fork test).

If renal insufficiency occurs, exclusion of

- Secondary renal hyperparathyreoidism (measurement of serum calcium and phosphate, parathyroid hormone, Vitamin D)
- Anaemia (Hb < 13 g/dl for men, Hb < 12 g/dl for women: renal aetiology can be assumed if other causes such as disturbance of iron balance, chronic inflammations, gastrointestinal bleeding, etc., have been excluded. Anaemia occurs earlier in connection with diabetic nephropathy than with other kidney diseases.

Therapy Objectives and Therapy

The development and progression of diabetic nephropathy can be accelerated by:

- Insufficient blood sugar control
- Hypertension
- Smoking
- Anaemia (perhaps)
- Increased protein intake.

By influencing these factors, one can prevent or at least slow down the development and/or progression of diabetic nephropathy.

Since patients with diabetic nephropathy have an excessive cardiovascular risk, consistent treatment of the other cardiovascular risk factors, in particular increases in LDL cholesterol and increased platelet aggregation, are likewise required.

This also applies to diabetic patients with nephropathy that is primarily due to ischemic conditions (i. e. without albuminuria).

Diabetes Control

- In primary prevention of nephropathy, one should aim for an HbA1c level between 6.5 % (48 mmol/mol) and 7.5 % (58 mmol/mol). The upper half of this range (7.0 – 7.5 % [53 – 58 mmol/mol]) applies to patients with macroangiopathic complications or impaired hypoglycaemia awareness.
- In secondary prevention, one should aim for an HbA1c level under 7.0 % (< 53 mmol/mol) if clinically relevant macroangiopathy or hypoglycaemia awareness impairment can be excluded.
- As a rule, the HbA1c level underestimates the quality of metabolism control in cases of kidney insufficiency (GFR at 60 ml/min or lower), in particular with parallel erythropoietin or iron therapy.

Important

The following points are of special importance when renal function is declining:

- Metformin: contraindicated if eGFR < 60 ml/min
- Glucosidase inhibitors: no recommendation can be issued, due to a lack of studies
- Sulfonylureas: as a rule, reduce the dose (exception: gliquidone); contraindication if eGFR < 30 ml/min.
- Meglitinides: Dosis reduction when creatinine clearance ≤ 30 ml/min.
- Pioglitazone: possible
- DPP4 Inhibitors: dose reduction if eGFR < 60 ml/min.

Incretin mimetics:

- Exenatide: dose reduction when creatinine clearance between 50 and 30 ml/min; contraindication when creatinine clearance < 30 ml/min.
- Liraglutide, Lixisenatide: contraindication when creatinine clearance < 60 ml/min.
- Insulin: dose reduction in most cases as disease progresses.

Blood Pressure Control

Normotensive type 1 and type 2 diabetics with persistently elevated urinary albumin excretion should be treated with an ACE inhibitor if this can be tolerated, otherwise with an AT_1 blocker.

The systolic blood pressure of hypertensive patients with nephropathy should be reduced strictly < 140/90 mmHg. Target blood pressures should be selected individually depending on:

- Urinary albumin excretion (target blood pressure should be decreased when proteinuria increases).
- Cardiovascular comorbodity

Pharmacologic therapy should rely primarily on the following medications:

Type 1 Diabetes

ACE inhibitors[1] – unless they cannot be tolerated, in which case AT1 blockers – alone or in combination with diuretics and/or other substances.

Type 2 Diabetes

AT_1 blockers or ACE inhibitors[1] alone or in combination with diuretics and/or other substances.

Further Therapeutic Measures

1. Platelet aggregation inhibition, e. g. with aspirin 100 mg/die (also for primary prophylaxis of cardiovascular events in nephropathy patients).
2. Reduce LDL cholesterol < 100 mg/dl.
3. Patient should quit smoking.
4. Normalisation of elevated protein intake to 0.8-1.0 g/kg body weight per day.
5. Treatment of anaemia in accordance with its underlying cause
6. Balance of impaired phosphate calcium metabolism by phosphate binders, vitamin D or vitamin D analogues.

Important

- Avoid x-ray contrast agents!
- Avoid non-steroidal anti-inflammatory drugs!
- Treat urinary tract infections with antibiotics!
- Watch out for accumulation of medications in cases of kidney insufficiency!
- Adapt medications to reduced kidney function!

[1] In addition to their renal protective effects, ACE inhibitors have been shown to exert favourable effects on inhibition of the progression of retinopathy and cardiovascular mortality.

Monitoring and Long-Term Control

The following parameters should be checked two to four times per year, depending on the nephropathy stage:

- HbA_{1C}, lipids,
- Blood pressure (including self-check and 24-h measurements as needed),
- Serum creatinine, urea and potassium,
- Urinary albumin excretion,
- Calculation of eGFR or measurement of creatinine clearance (**Fig. 3**).

Beginning with stage 3, i.e. when creatinine clearance < 60 ml/min, check the following in addition:

- Haemoglobin, haematocrit,
- Serum phosphate, serum calcium,
- Parathyroid hormone, Vitamin D, as applicable.

Refer to nephrologist for special management issues or if eGFR falls < 30 ml/min.

Annex

Table 1 Nephropathy stages (new classification) and associated diseases.

Stage/description	Glomerular filtration rate (ml/min)	Albumin/creatinine ratio in urine (mg/g)	Remarks
kidney damage with normal kidney function			blood pressure normal but rising, or hypertension; dyslipidaemia; developing coronary and/or peripheral artery; retinopathy and neuropathy
1a microalbuminuria	≥ 90	w 20 – 200*m 30 – 300*	
1b macroalbuminuria	≥ 90	w > 20 – 200* m > 30 – 300*	
kidney damage with kidney insufficiency (KI)			hypertension; dyslipidemia; prone to hypoglycaemia; existent coronary and/or peripheral artery disease; retinopathy; neuropathy; development of anaemia; bone metabolism disorder
2 low KI	60 – 89	all ranges possible†	
3 moderate KI	30 – 59	usually decreasing	
4 high KI	15 – 29	usually decreasing	
5 terminal KI	< 15		

* If concentration measurement without reference to urinary creatinine: 20 – 200 mg/l
† If concentration measurement without reference to urinary creatinine: > 200 mg/l

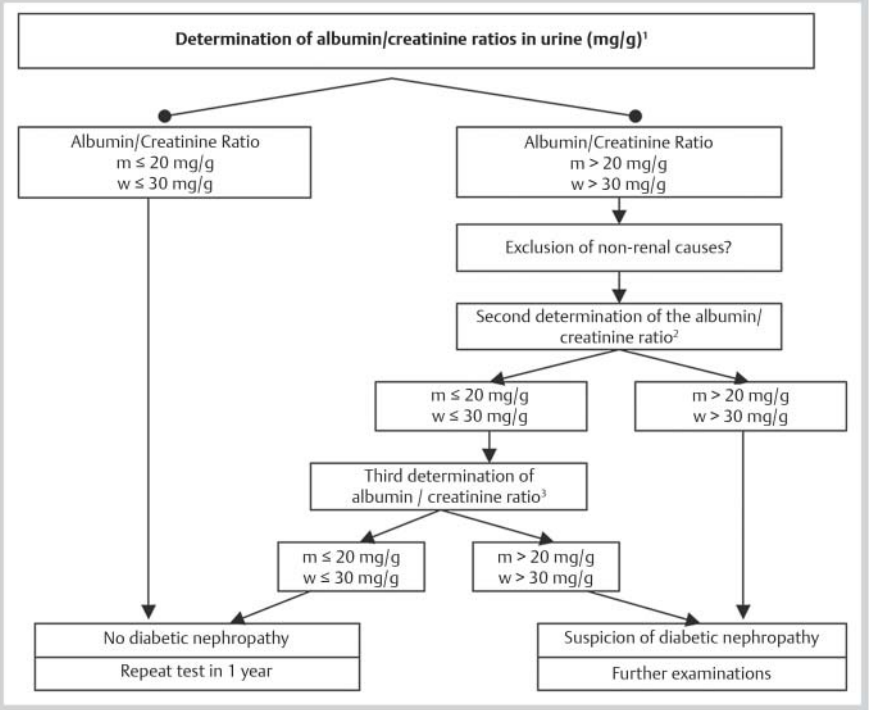

Fig. 1 Examination for diabetic nephropathy.
[1] When using test strips, one must take the detection sensitivity of the albumin concentration into account. The following are suitable for albumin concentrations < 200 mg/l: Micraltest II, Microalbu-Stix.
[2] Albumin concentration can be temporarily elevated, e. g. with physical exertion, acute illness with fever, infection of the urinary tract, poorly controlled diabetes, poorly controlled hypertension, heart failure.
[3] A laboratory chemical method should be used for the second check. This allows graduation of albuminuria for higher concentrations:
Microalbuminuria:
m: 20 – 200 mg/g urinary creatinine
w: 30 – 300 mg/g urinary creatinine
Macroalbuminuria:
m: > 200 mg/g urinary creatinine
w: > 300 mg/g urinary creatinine

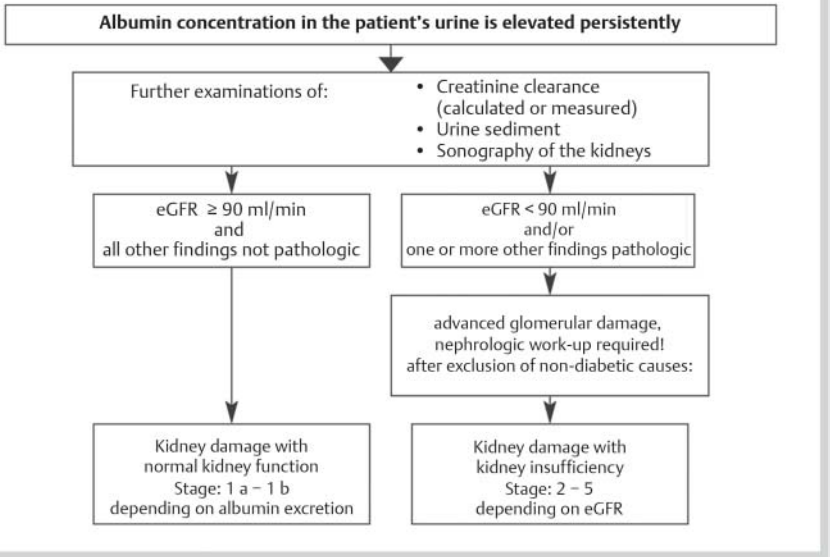

Fig. 2 Diagnosis of diabetic nephropathy – algorithm.

Serum creatinine concentration gives only an approximate and not an exact reflection of kidney function because it is influenced not only by renal creatinine clearance but also by endogenous creatinine production. With elderly patients and patients with little muscular mass and activity, the serum creatinine level often leads to a significant underestimate of the loss of renal function. This is why measuring creatinine clearance directly or estimating glomerular function with the help of the Cockroft Gault formula or the MDRD formula are more reliable.

a) Cockroft-Gault Formula:

$$\text{Creatinine\_Clearance[mL/min]} = \frac{(140 - \text{Age}) \times \text{Weight[kg]}}{(72 \times \text{Serum\_Creatinine [mg/100mL]})}$$

For female patients the value has to be multiplied by 0.85.

b) Simplified MDRD Formula:

$$\text{Glomerular\_Filtration\_Rate[mL/min per 1.73m}^2\text{]} = 186 \times \text{Serum\_Creatinine[mg/dl]}^{-1.154} \times \text{Age[years]}^{-0.203}$$

For female patients the value has to be multiplied by 0.742.
For patients with black skin colour the value has to be multiplied by 1.21.

This formula should not be used for patients with acute kidney failure, unstable kidney function, extreme obesity, cachexia, or pronounced oedema.

Fig. 3 Calculation of creatinine clearance.