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Screening for diagnosis of early stages of diabetic kidney disease

Badania przesiewowe w rozpoznaniu wczesnej fazy cukrzycowej choroby nerek

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S u m m a r y

Early diagnosis of diabetic nephropathy seems to be an important part of the evaluation of patients with diabetes. It allows early nephroprotective treatment and makes possible resulting decrease of chronic kidney disease (CKD) progression and attenuation of CKD-related cardiovascular risk. The following paper describes possibilities of screening: assessment of urinary albumin excretion and assessment of so called early kidney function loss. Different definitions of microalbuminuria and macroalbuminuria (proteinuria) used in clinical practice are specified, along with practical advices regarding urine sample collection and storage. A definition of early renal function loss is also given. The reader will find also a practical algorithm that may be used for screening of diabetic nephropathy. At last, factors leading to falsely positive diagnosis, that need to be taken into account in practice are listed.

Key words: diabetes, diabetic nephropathy, screening, albuminuria, microalbuminuria, early kidney function loss

S t r e s z c z e n i e

Wczesne rozpoznanie nefropatii cukrzycowej wydaje się być ważnym elementem diagnostyki chorych na cukrzycę. Pozwala ono na wczesne wdrożenie leczenia nefroprotekcyjnego, a co za tym idzie, zmniejszenie progresji choroby nerek (PChN) i zmniejszenie ryzyka sercowo-naczyniowego związanego z PChN. Poniższa praca omawia możliwości badań przesiewowych – ocenę wydalania albumin z moczem i ocenę tzw. wczesnej utraty czynności nerek. W pracy podano różne definicje mikroalbuminurii i makroalbuminurii (białkomoczu) używane w praktyce klinicznej, a także praktyczne wskazówki dotyczące pobierania próbek moczu i ich przechowywania. Podano także definicję wczesnej utraty funkcji nerek. Czytelnik znajdzie tu także praktyczny algorytm, mogący znaleźć zastosowanie w badaniach przesiewowych w kierunku nefropatii cukrzycowej. W końcu, podano także czynniki mogące prowadzić do fałszywie dodatniego rozpoznania, które muszą być wzięte pod uwagę w praktyce.

Słowa kluczowe: cukrzyca, nefropatia cukrzycowa, badania przesiewowe, albuminuria, mikroalbuminuria, wczesna utrata czynności nerek

Early stage of diabetic kidney disease (DKD) may often be asymptomatic. It may be classified as 1st or 2nd stage of diabetic nephropathy according to old Mogensen classification, manifesting itsef only as hyperfiltration with or without histopathological changes (like thickening of glomerular basement membrane and mesangial expansion). In this stages, however, microalbuminuria is not present and as kidney function is often normal (or GFR may even be increased because of hyperfiltration) the clinical diagnosis may be not easy, although increased urinary albumin excretion below the microalbuminuria range may happen and may suggest the diagnosis.

Additionally, as shown in many recent publications, in patients with diabetes an early loss of the glomerular filtration may occur. It could be defined as accelerated decrease of kidney function, which happens in 9-32% of patients even before the development of microalbuminuria, and in 31-42% in patients with microalbuminuria but no overt proteinuria (1, 2). The decrease of renal function (GFR) is often defined as being higher then 3.3% per year. Such GFR decrease is rather easy to find, as in a vast majority of patients serum creatinine is regularly assessed and eGFR calculated.

As it seems therefore, an early diagnostic of and screening for DKD must involve an assessment of

Table 1. Classification of albuminuria.

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Urinary albumin excretion (UAE) (mg/24 h)	< 30	30-300	> 300
UAE (μg/min)	< 20	20-200	> 200
Urinary albumin/creatinine rate (UACR) (mg/g) Men Women	 < 20 < 30	 20-200 30-300	 > 200 > 300
UACR (mg/mmol) Men Women	 < 2.5 < 3.5	 1.5-25 3.5-35	 > 25 > 35

urinary albumin excretion rate as well as of GFR decrease. Both examination must be performed in a prospective manner in given time intervals.

MICROALBUMINURIA

Microalbuminuria is defined as urinary albumin excretion (UAE) higher or equal then 30 mg/d but not higher then 300 mg/d (3, 4) in 24 hour-sterile urine sample, collected in a standardized manner. If UAE is lower then 30 mg/24 h, it is regarded as normal (although it is suggested that cardiovascular risk may increase with albuminuria increasing even in the normal range). Other definitions of micro- and macroalbuminuria are shown in the table 1.

In the physiology, albumin is filtrated in the kidney by glomeruli and reabsorbed in the tubuli, although a small amount of albumin may be excreted (in healthy adult it is about 7-10 mg per day (5), or 6-7 μg/min (6)). The excretion of albumnin is not stable. Results may change in time and, additionally, may be influenced by many factors, listed in table 2.

Table 2. Factors and diseases influencing albuminuria and potentially causing microalbuminuria (based on 5, 7, 8).

Acute and chronic infections (urinary tract infections)
Intensive physical exercise
Diabetes decompensation
Blood pressure increase (non-dippers)
Severe heart failure
Menstruation
Insufficient hydration
Tobacco smoking
Urological disease (neurogenic bladder, prostate diseases)
Diseases of blood vessels (diffuse atherosclerotic lesions, renal artery stenosis)
Chronic kidney diseases (glomerulonephritis, interstitial disease)

The above statements implicates that single assessment of albuminuria is diagnostically unreliable. This fact is also recognized by different guidelines, that make a diagnosis of microalbuminuria possible only when 2 of three different urine samples collected within 3-6 months period, confirm the diagnosis (9). An algorithm that may be useful in diagnosing microalbuminuria, is shown on figure 1. It should be stressed that the diagnosis of diabetic microalbuminuria (i.e. DKD) is possible only after exclusion of other reasons of increased urinary albumin excretion.

Increased UAE may be estimated uusing different methods: immunoenzymatic (ELISA, enzyme-linked immunosorbent assay), radioimmune (RIA, radio-immuno assay), chromatographic (HPLC, high performance liquid chromatography), immunoturbidometric, immunodiffusion or by immunoblothing.

Golden standard in the diagnostics of albuminuria is based on its estimation in 24-hour urine (5), however, as correlation of the results with the results achieved in the morning urine sample is high (10), the latter method, as more comfortable, is often used for screening. Screening is than often performed using morning urine, and using semiquantitative strip tests. If the result is in the normal range the test should be repeated after one year. If the screening is positive, at first a presence of all factors or diseases that may have influenced it (listed in table 2) should be excluded. Next, albuminuria should be assessed using one of the mentioned above quantitative methods. The positive results must be confirmed, according to guidelines, by at least one additional positive results out of two, performed after 3-6 months.

Assessment of albuminuria should be assessed directly after urine collection, however it is acceptable to performed it within 3 days (if stored in 4°C) or 2 weeks (if stored in – 20°C) (11), avoiding estimation in urine of ph of 5,5 or lower (12).

A persistent significant albuminuria indicates increased vessels' permaeability and may be regarded as an early sign of a dysfunction of glomerular arterioles and, therefore, as an early sign of DKD (13). It should be remembered, however, that significant microalbuminuria may be present in 2.2-9.4% of healthy subjects aged 50+ (14, 15), although even in these healthy subjects a cardiovascular risk is greater, if albuminuria is higher than 7.5 μg/min (15).

In patients with type 1 diabetes microalbuminuria appears in parallel to other signs of endothelial damage: hypertension and retinopathy. In patients with type 2 diabetes, microalbuminuria may also reflect a generalized endothelial dysfunction. However, as hypertension appears in those subjects often many years before nephropathy, and often even before diabetes is diagnosed, diabetic retinopathy is much more reliable marker confirming that nephropathy is of diabetic origin. If no retinopathy is

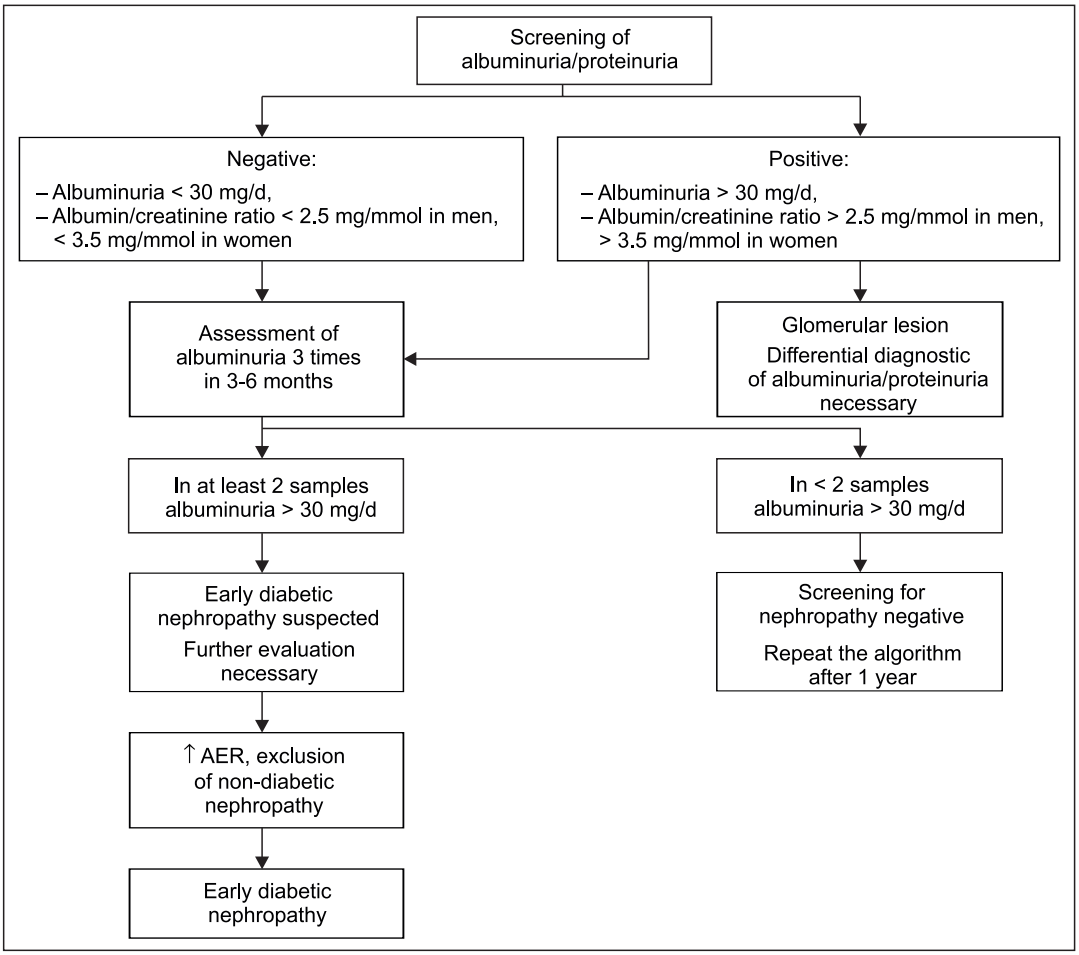

Fig. 1. Diagnosis of early stages of diabetic nephropathy based on albuminuria. AER – albumin excretion rate.

present, other than diabetic causes of albuminuria should be excluded.

The possibility of presence of non-diabetic micro- or macroalbuminuria should be however regarded not only in such case. Other suggestive signs are:

- Fast progression of albuminuria/proteinuria in the absence of hypertension or in subjects with well-controlled blood pressure and well-controlled glycemia.
- No improvement of albuminuria/proteinuria in spite of normalization of blood pressure and improvement of glycemic control.
- Fast progression of GFR decrease.

In such cases a fast referral to a nephrologist is necessary. In some cases kidney biopsy cannot be avoided.

According to the guidelines of Polish Society of Diabetology, screening of UAE should be performed in all patients with type 1 diabetes in whom the time of the disease duration exceeds 5 years (9), it should be however mentioned that if the time of the disease is longer than 3 years, already 6.4% of in those patients have microalbuminuria (16). In 18% of patients with type 2 diabetes microalbuminuria is present already at the diagnosis (18). Therefore screening should start immediately after it.

EARLY KIDNEY FUNCTION LOSS

The possibility of this other than microalbuminuria manifestation of early stage of DKD, defined as progession of a GFR decrease faster than 3.3% per year, was recognized only in the recent years. In the first publication regarding this issue (1) the authors focused on fast kidney function loss in some microalbuminuric patients. It was additionally concluded that GFR loss is not necessarily connected with albumin loss. That would mean that a hypothesis stating that a decrease of renal function is rather secondary to microalbuminuria (as in the Mogensen classification) may be not always true.

The implication of this would be that screening for microalbuminuria may be not sufficient for diagnosis of early stages of DKD and serum creatinine estimation is also necessary for this purpose. Indeed, the guidelines recommend once-a-year creatinine estimation regardless from UAE (9). It is questionable, however, which formula should be used to eGFR calculation. It seems that the MDRD formula is easier to get from the laboratory as the Cockroft-Gault formula (although better in obese patients (18) usually must be calculated by the doctor. The future may belong to the CKD-EPI formula, which may

be useful in estimating the precise GFR if the value is over 60 ml/min. It should be remembered that both MDRD and CKD-EPI formulas may lower the GFR about 20% (19).

In the next years more and more attention will probably be paid to uric acid estimations. It seems that higher uric acid concentration may predict an early kidney function loss in diabetes, identifying very early patients at risk (20).

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