Microalbuminuria as a reversible marker of kidney and vascular damage

The excretion of small quantities of albumin in urine was detected in patients with diabetes mellitus about 40 years ago. The term microalbuminuria, defined as urinary albumin excretion (UAE) ranging from 30 to 300 mg/24h was introduced and generally accepted, despite criticism. Persistent microalbuminuria was identified as an early marker of kidney damage and the risk factor for the progression of kidney function impairment in patients with diabetes and in essential hypertension. It was also demonstrated that UAE values even much lower than these necessary for the diagnosis of microalbuminuria are related to the risk for the individual to develop cardiovascular disease. Multifactorial intervention targeted to all modifiable cardiovascular risk factors including albuminuria permitted the regression of microalbuminuria in patients with diabetes and with hypertension which was associated with substantial reduction of the risk of cardiovascular events. Microalbuminuria is actually considered as an ideal target for early prevention of the progression of kidney and vascular damage.

Albuminuria means the presence of albumin in the urine in proper sense of the word. Conventional laboratory methods for the detection of protein in urine are not sensitive enough to identify small amounts of albumin. The first sensitive and specific assay for human urinary albumin in small quantities was a radioimmunoassay developed in 1963 [15]. Later on a number of laboratory procedures for detecting human urinary albumin in small quantities were described [27]. Using these procedures, it was demonstrated that healthy persons either did not excrete albumin or excrete negligible amount of this protein in the urine. Urinary albumin excretion (UAE) measured in 24h samples in 23 normal men and 20 normal women, aged 22-40 years, was 4.7 ± 4.7 µg/min (range, 2.6-12.6) and 4.3 ± 4.8 µg/min (range 1.1-21.9), respectively [17]. Similar values have been reported by other authors and it was admitted that in a healthy non-diabetic population the normal range for the urinary albumin excretion rate (UAER) is between 1.5 and 20 µg/min, with a geometric mean of 6.5 µg/min [13]. The detection of UAER values higher than 20 µg/min (30 mg/24h) but lower than 200 µg/min (300 mg/24h) in a number of patients with diabetes mellitus resulted in the introduction of arbitrary term: microalbuminuria, defined as an UAER of this range, undetectable by conventional laboratory methods [27]. The term: microalbuminuria is criticized because it may suggest presence of some micromolecules of albumin rather than small quantities of normal albumin in the urine. Furthermore it become obvious that the upper
limit for normoalbuminuria should be reduced at least to <10 μg/min when albumin was measured in the overnight urine sample, or to <15 mg/24h when 24-h urine collection was performed [14]. Despite the criticism, both the term microalbuminuria and its definition are maintained in medical books [24], the nephrological recommendations [22], in the current publications [37] and therefore are used in this article.

Microalbuminuria as the marker of kidney damage

Urinary albumin excretion can be affected by a number of factors in healthy subjects and in persons with diabetes [4,14]. The chance to make a diagnosis of microalbuminuria, UAER should be in the microalbuminuric range in at least two out of three collections over a time period of 3 month [13]. Some authors stress this fact by using the term: persistent microalbuminuria [4, 19].

It was demonstrated that the nature of link between microalbuminuria and cardiovascular events, compared with persons with lower levels was associated with an increased risk of cardiovascular events, mainly cardiac death, stroke, and heart failure [3]. These events are associated with increased risk of progression of chronic kidney disease [31]. The complicated pathophysiological mechanisms involved in the development of persistent microalbuminuria were recently reviewed [5,6,10,36] and are out of the scope of this article. Briefly, persistent microalbuminuria reflects either functional and/or structural change in the glomerular filter, which results in the increased albumin leak into the raw urine and surpasses the reabsorptive and metabolic capacity of the proximal tubular cells, or is the sign of defective mechanisms of the reabsorption and metabolism of normal albumin quantities from the raw urine in the proximal tubule [6,10,36]. Both these defects may coexist. Independent of the mechanism causing persistent microalbuminuria, there is general agreement that its presence proves kidney damage [22]. Accordingly, microalbuminuria, even manifested as spot urinary albumin to creatinine ratio (UACR) >30 mg/g for more than 3 months indicates chronic kidney disease [22], in the current publications [37] and its definition are maintained in medical books [24].

It was demonstrated that the risk for future diabetic nephropathy over the next decade is markedly higher (about 80%) in the presence of microalbuminuria in persons with diabetes type 1, compared with patients with completely normal UAER (about 5%) [14]. The prevalence of persistent albuminuria in microalbuminuria is an early predictor of progressive renal function loss in type 1 [20,25] and type 2 diabetes [18,21]. Recently the results of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study demonstrated that microalbuminuria is common, also in nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascu- lar morbidity [11]. In the PREVEND study postal questionnaires and morning urine samples from more than 40,000 residents of the city of Groningen were collected. Urinary concentration of albumin of 20 to 200 mg/L (corresponding to microalbuminuric range) was found in 7.2% of residents and a further 16.6% had “high-normal” albuminuria (albumin excretion rate 20-200 mg/L). These results indicated that 23.8% of the population had increased UAE, despite the fact that in this population the prevalence of diabetes was only 2.6% and that of hypertension was 11.2%. The follow-up observations indicated that microalbuminuria was independently associated with increased risk for cardiovascular morbidity [11]. The results of other studies demonstrated also that persons with only slightly elevated urinary albumin-to-creatinine ratio (UACR) of 0.65 to 2.0 mg/mmol (5.8-17.7 mg/g) had more than twice the risk for cardiovascular events, compared with persons with lower UACR values [9,29].

All these data indicate that microalbuminuria, not only in patients with diabetes or hypertension, but also in general population is a strong and independent marker of increased cardiovascular risk. Once microalbuminuria is present, cardiovascular risk factor reduction should be aggressive, including the maximal reduction of microalbuminuria as an additional, new target for treatment.

The nature of link between microalbuminuria and cardiovascular risk remains poorly understood. The possible mechanisms involved in this link have been recently reviewed (30). It was concluded, that at present, the most likely possibility is that a common pathophysiologic process, such as endothelial dysfunction, chronic low-grade inflammation, or increased transvascular leakage of macromolecules, underlies the association between microalbuminuria and cardiovascular disease [30].

Reversibility of microalbuminuria

Perkins et al. [26] analyzed the frequency of a significant reduction in UAE and factors affecting such reduction in patients with type 1 diabetes and microalbuminuria followed-up during six years. It appeared that the regression of microalbuminuria (defined as a 50% reduction in UAE from one two-year period to the next) had a six-year cumulative incidence of 58% and with the cumulative proportion of subjects whose UAER at six years had decreased into the normal range (<30 mg/min) of 59%. Microalbuminuria of short duration, the levels of glycosylated hemoglobin (less than 8%) and low systolic blood pressure (less than 115 mmHg) and low levels of cholesterol and triglycerides (less than 198 mg/dl and 145 mg/dl, respectively) were independently associated with the regression of microalbuminuria. The patient with all these "salutary" levels had a hazard ratio for regression of 3.0 as compared with patients with "non-salutary" levels. It was concluded that multifactorial intervention in type 1 diabetic patients with microalbuminuria results in frequent its regression which is associated with marked reduction of the risk of progression toward overt diabetic nephropathy. Surprisingly, in this study the use of angiotensin-converting enzyme inhibitors or a beta-blocker was not associated with the regression of microalbuminuria, but additional nephroprotective effect of ACEI could not be excluded [26].

In the Steno-2 study, the effect of a targeted, intensified multifactorial intervention was compared with conventional therapy and treatment on modifiable risk factors for cardiovascular disease and progression toward overt diabetic nephropathy, in patients with type 2 diabetes and microalbuminuria [8]. The intensive treatment was composed of the stepwise implementation of behavior modification and pharmacological therapy that targeted hyperglycemia, hypertension, dyslipidemia and microalbuminuria (by use of ACEI irrespective of blood pressure values), along with secondary prevention of cardiovascular disease with aspirin. It was demonstrated that intensified intervention during the mean follow-up period of 7.8 years reduced the risk of cardiovascular events by about 50% and the relative risk of the
minuria toward normal values results in signif-
ificant diminution of the risk for progres-
sion of kidney function impairment and for
the prevention of cardiovascular events.
Further studies are needed to confirm the
reasonable suggestions that systematic
screening for albuminuria in the general
population is important for the detection of
the persons at risk of renal and cardiovas-
cular complications and is cost effective.

References

1. Bigazzi R., Bianchi S., Baldari S. et al.: Micro-albu-
minuria predicts cardiovascular events and renal
insufficiency in patients with essential hypertension.
J. Hypertension 1998, 16, 1325.
urinary albumin excretion is associated with impaired
artificial arterial capacity in clinically healthy subjects.
Circulation 2001, 103, 1899.
of overnight albumin excretion in insulin-dependent
diabetic and normal subjects. Diabet Med. 1987, 4,
437.
4. Czekalski S.: How to diagnose and how to interpret
microalbuminuria in the diabetic patients. Nephrol.
5. Czekalski S.: Patofizjologiczne i kliniczne znaczenie
7. Dinneen S.F., Gerstein H.C.: The association of
microalbuminuria and mortality in non-insulin-de-
dendent diabetics mellitus. A systematic overview of
intervention and cardiovascular disease in patients
387–394.
and risk of cardiovascular events, death, and heart
failure in diabetic and nondiabetic individuals. JAMA
2001, 286, 516.
10. Heraldsen B., Sorensen J.: Why do we not all
have proteinuria? An update of our current under-
standing of the glomerular barrier. News Physiol.
11. Hillige H.L., Jansen W.M., Bak A.A. et al.: Micro-
albuminuria is common, also in a nondiabetic,
nonhypertensive population, and an independent
indicator of cardiovascular risk factors and cardiovas-
12. Ibsen H., Olsen M.H., Wachtell K. et al.: Reduction
in albuminuria translates to reduction in cardiov-
sascular events in hypertensive patients. Losartan inter-
vention for endpoint reduction in hypertension study.
Hypertension 2005, 45, 198.
definition and monitoring. [In:] Mogensen C.E. (ed).
Microalbuminuria. A marker for organ damage. 2nd
14. Heraldsen B., Sorensen J.: Why do we not all
have proteinuria? An update of our current under-
standing of the glomerular barrier. News Physiol.
15. Keen H., Chlouverakis C.: An immunoaassay method
for urinary albumin at low concentrations. Lancet
1983, 2, 913.
16. Mogensen C.E.: Microalbuminuria predicts clinical
proteinuria and early mortality in maturity-onset dia-
17. Mogensen C.E.: Clinical and epidemiological features
of microalbuminuria: Notes on method, interpretation
and classification. [In:] Clarke W.L., Larner J., Pohl S.L.
(edds), Methods in Diabetes Research, vol. II: Clinical
18. Mogensen C.E.: Microalbuminuria predicts clinical
proteinuria and early mortality in maturity onset dia-
19. Mogensen C.E.: Definition of diabetic renal disease in
insulin-dependent diabetes mellitus based on re-
nal function tests. [In:] Mogensen C.E. (ed), The
kidney and hypertension in diabetes mellitus. 2nd ed. 
20. Mogensen C.E., Christiansen C.K.: Predicting dia-
betic nephropathy in insulin-dependent patients. N.
21. Verhave J.C., Gansevoort R.T., Hillege H.L. et al.: De-
velopment and progression of renal disease in Pima
Indians with non-insulin-dependent diabetes mellitus.
22. NKF-KDOQI Clinical Practice Guidelines on Chronic
renoprotection be extrapolated to cardiovascular pro-
24. Parving H.H., Mauer M., Ritz E.: Diabetic neph-
ropathy. [In:] Brenner B.M. (ed), The Kidney, 7th ed.,
25. Perks B.A., Ficocielli L.H., Silva K.H. et al.: Re-
gression of microalbuminuria in type 1 diabetes.
26. Poulsen P.L.: Microalbuminuria: techniques of meas-
urement. [In:] Mogensen C.E. (ed), Microalbuminuria.
A marker for organ damage. 2nd ed. Science Press,
27. Rachmini R., Levi Z., Lidor M. et al.: Considera-
tions about the threshold value of microalbuminuria
in patients with diabetes mellitus: lessons from an 8-
year follow-up study of 599 patients. Diabetes Res.
Clin. Pract. 200, 19, 47.
and all-cause mortality in 2,089 apparently healthy
individuals: a 4.4-year follow-up study. J. Intern.
Med. 2003, 19, 2100.
29. Wachtell K., Ibsen H., Olsen M.H. et al.: Micro-
albuminuria and cardiovascular risk factors in hypo-
tensive patients with left ventricular hypertrophy: the LIFE study.
30. Wachtell K., Olsen M.H., Dahlöf B. et al.: Micro-
albuminuria in hypertensive patients with electro-
cardiographic left ventricular hypertrophy: the LIFE study.
31. Weir M.R.: Microalbuminuria in type 2 diabetes:
An important, overlooked cardiovascular risk factor.
32. Yuyun M.F., Dinneen S.F., Edwards O.M. et al.: Absol-
ute level and rate of change of albuminuria over 1
year independently predicts mortality and cardio-
vascular events in patients with diabetic nephropa-
33. Zandi-Nejad K., Eddy A.A., Glassock R.J., Bren-
ner B.M.: Why is proteinuria an ominous
biomarker of progressive kidney disease? Kidney Int.
2004, 66, (Suppl. 92), S18.
34. de Zeeuw D., Parving H.H., Hamsten A.: Micro-
albuminuria: an exposure marker for cardiovascular