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REVIEW ARTICLE

Microalbuminuria, is it so important?

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Abstract

Microalbuminuria (defined as urinary albumin excretion of 30-300 mg/day, or 20-200 μg/min) is an earlier sign of vascular damage. It is a marker of general vascular dysfunction and nowadays is considered a predictor of worse outcomes for both kidney and heart patients. There is a significant correlation between blood pressure and microalbuminuria. Even high normal blood pressure is associated with significant higher frequency of microalbuminuria and this way may be a biomarker of increased cardiovascular risk. Microalbuminuria could be taken also, as an indicator of insulin resistance and of the increased renal and cardiovascular risk associated with metabolic syndrome. Renal involvement is a pivotal development in diabetes and microalbuminuria is generally the first clinical sign of renal dysfunction in diabetics. It is demonstrated that cardiovascular and renal risk is elevated even in the high normal range of microalbuminuria (below 30 mg/day). There is no doubt that therapies that prevent or delay the development of microalbuminuria and all measures that reduce it, may help to prevent or delay end organ damage. *Hippokratia 2007; 11 (3): 105-107*

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The urinary protein called albumin is increasingly recognized as the earliest sign of vascular damage in both the kidney and the heart. The phenomenon of albuminuria has been recognized for more than 200 years, and its association with kidney disease dates to the epochal insights of Richard Bright in 1827[1].

Currently, 20 million Americans —around one in nine adults— have chronic kidney disease. More than 20 million people are at increased risk for developing kidney disease, and most don't even know it. Kidney disease is the ninth cause of death[2].

Kidney disease is strongly linked to heart disease and the presence of microalbuminuria (defined as urinary albumin excretion 30 - 300 mg / day, or 20-200 μg/min)[3] is a predictor of worse outcomes for both kidney and heart patients. In the US, approximately 6% of men and 9.7% of woman have microalbuminuria[4].

Microalbuminura does not directly cause cardiovascular events, it serves as a marker for identifying those who may be at increased risk. Microalbuminuria is caused by glomerular capillary injury and so may be a marker for diffuse endothelial dysfunction[4]. According to Steno hypothesis, albuminuria might reflect a general vascular dysfunction and leakage of albumin and other plasma macromolecules such as low density lipoproteins into the vessel wall that may lead to inflammatory responses and in turn start the atherosclerotic process[5].

There is positive link between high blood pressure and microalbuminuria. High blood pressure may cause microalbuminuria by increasing glomerular filtration pressure and subsequent renal damage. It is possible that the development of microalbuminuria is a marker for pathophysiologic events that aggravate BP or impair the response to the BP-lowering effects of antihypertensive drugs or, alternatively, that the increasing systemic arterial BP transmits a higher pressure to the glomerular and peritubular capillaries (in the presence of afferent arteriolar dilation), thereby promoting abnormal glomerular permselectivity or changes in tubular albumin processing[1]. Even high normal blood pressure is associated with significant higher frequency of microalbuminuria and this way may be a biomarker of increased cardiovascular risk[6]. There may be also common genetic factors that predispose to both high BP and microalbuminuria[7,8].

It is established that microalbuminuria is an independent risk factor for stroke, myocardial infarction and congestive heart failure. The risk for major cardiovascular events increased at every level of urinary albumin excretion, including levels within the normal range[9].

Albuminuria is often associated with metabolic syndrome, a syndrome of insulin resistance, obesity, hypertension, dislipidemia, and increased renal and cardiovascular morbidity. Several evidence suggest that insulin resistance precedes and probably contributes to the development of microalbuminuria in diabetic patients as well as in non diabetic subjects[10]. It has been shown that subjects with microalbuminuria are more insulin resistant than those with a normal urinary albumin excretion, and that the magnitude of insulin resistance is independently associated with microalbuminuria[11]. Thus

increased albuminuria could be taken as an indicator of insulin resistance and of the increased renal and cardiovascular risk associated with the metabolic syndrome.

According to Barker hypothesis, the reduced number of nephrons at birth might predispose to metabolic syndrome, renal and cardiovascular disease in adult life[12]. This may occur due to aberrant fetal programming by genetic factors, malnutrition and other insults to the pregnant mother and those factors lead to less glomeruli. Reduced nephron number at birth might be the common determinant of hyperfiltration and insulin resistance. Hyperfiltration and insulin resistance may both predispose to the development of albuminuria, hypertension, obesity, or diabetes that may contribute to worsen glomerular dysfunction.

World Health Organization estimates that by 2010, 200 million people will have Diabetes[13]. Diabetes is the fifth cause of death and diabetes is the leading cause of kidney failure in the US, and patients with diabetes are at an increased risk of kidney and cardiovascular disease[2]. Renal involvement is a pivotal development in diabetes, signifying a high risk not only of end-stage renal failure but also and more important of vascular complications. Patients with diabetic ESRD now account for 53% of incident patients and comprise 45% of the prevalent ESRD population[2]. The first clinical sign of renal dysfunction in patients with diabetes is generally microalbuminuria (a sign of endothelial dysfunction that is not necessarily confined to the kidney), which develops in 2 to 5 percent of patients per year[3].

Microalbuminuria has been recommended as reliable marker for early detection even of Balkan Endemic Nephropathy. Recently microalbuminuria was found in 50% of patients with Balkan Endemic Nephropathy[14].

In many cases, the first sign of kidney disease is albuminuria, in which damaged kidneys allow traces of the protein albumin to spill into urine. The condition, which can also serve as an early warning sign of cardiovascular disease, can be detected earlier using a relatively inexpensive urine test, and it is recommended that every diabetic receive the test at least once per year. Albumin excretion rate has been the mainstay for early detection of diabetic nephropathy[15]. Some authors have convincingly argued that microalbuminuria is likely a marker than a predictor of renal structural changes[16]. This argument is based on the finding that in some patients with microalbuminuria renal lesions are quite advanced[17]. Numerous studies show that early detection and treatment of kidney disease can slow, halt or even reverse its progression.

While only few years ago, microalbuminuria was considered as a measurable increase in urine albumin excretion less than a threshold for traditional dipstick assessment of proteinuria, nowadays this concept has been challenged[4]. Although it is declared that microalbuminuria is a predictor of cardiovascular events and of progression to overt nephropathy, it is now recognized that this risk is elevated even in the high normal range of albuminuria, that is below 30 mg/day. Mounting evidence indicate a continuous relationship between albumin excretion rate and risk[11]. The threshold level to define normality is inconsistent with epidemiological data[18]. Different studies corroborate the suggestion that incremental increases in albuminuria within the normal range carry the risk of nephropathy or cardiovascular events. So there is a graded risk that continues into normal ranges[4]. These evidence led Forman and Brenner[18] to suggest that: "Microalbuminuria is another term that should now be eliminated from our lexicon as there are ample data to suggest that albuminuria in the 'normal' range carries significant risk of cardiovascular events". Thus according to Ruggenti and Remuzzi[11], the concept of normal or abnormal albuminuria should be abandoned and the unifying term of albuminuria could be used to describe maeasuarable amounts of albumin in the urine.

Anyway in diabetics, the onset of albuminuria does not irrevocably seal the fate of the patient. Some authors found a 50% reduction in the urinary excretion of albumin between successive two years periods, in a sizable proportion of patients[19]. This lend a note of optimism, since it provides indirect evidence that aggressive treatment has its positive results: regression was seen in patients who had had microalbuminuria for only a short period (and presumably had only incipient renal damage) and in those with low levels of glycosilated hemoglobin, systolic blood pressure and cholesterol or triglycerides. These facts provide documentation that a widely accepted surrogate marker for the progression of renal disease can be favourably influenced[20]. Beyond that, there is evidence of improvement of diabetic glomerulosclerosis after isolated pancreas transplantation[20]. Early intervention started before progressive glomerulosclerosis and scarring is initiated may be important to maximixe reno- and cardioprotection. In diabetes there is no doubt that therapies that prevent or delay the development of microalbuminuria are beneficial. Every halving of albumin exretion is associated with an 18% reduction of cardiovascular events[17]. In general agents that act on the renin angiotensin axis (ARB and ACE-I) slow the progression to overt nephropathy. The data suggest that early intervention prevent the onset of overt nephropathy and subsequent progression to ESRD, as well as reduce cardiovascular risk associated with albuminuria.

Concluding, screening for albuminuria may be the most effective way to early identify subjects who are at increased risk for both renal and cardiovascular events. Any degree of measurable albuminuria bears a significant risk for renal and cardiovascular events. Only negligible amounts of albuminuria below approximately 2mg/day should be considered as 'normal'[11]. Dipstick for albuminuria is easy and inexpensive, and remains the most practical way to identify subjects at risk. It is particularly important to search for albuminuria (even below 30 mg/day), in patients with increased risk factors such as family history of nephropathy, poor glycemic control, and

increased GFR. All measures that reduce albuminuria as amelioration of insulin sensitivity, weight loss, blood pressure reduction, normalization of blood glucose levels and RAS inhibitor therapy may help to prevent or delay end organ damage.

References:

1. Glassock RJ. Prevention of Microalbuminuria in Type 2 Diabetes: Millimeters or Milligrams. J Am Soc Nephrol 2006; 17:3276-3278
2. Sedor JR. Frontiers in Diabetic Nephropathy: Can we predict who will get sick? J Am Soc Nephrol 2006; 17: 336-338
3. Ruggenenti P, Fassi A, Parvanova Ilieva A, et al. Preventing Microalbuminuria in Type 2 Diabetes. The New Eng J Med 2004; 351:1941-1951
4. Wrone EM, Carnethon MR, Panaliappan LP, et al. Association of dietary protein intake and microalbuminuria in healthy adults: Third National Health and Nutrition Examination Survey. Am J Kid Dis 2003; 41: 580-587
5. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, et al. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989; 32:219-226
6. Knight EL, Kramer HM, Curhan GC. High-Normal Blood Pressure and Microalbuminuria. Am J Kidney Dis 2003; 41:588-595
7. Festa A D, Agostino R, Howard G, et al. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. Kidney Int 2000; 58:1703-1710
8. Pedrinelli R, Gianpietro O, Carmassi F, et al: Microalbuminuria and endothelial dysfunction in essential hypertension. Lancet 1994; 344: 14-18
9. Gerstein HC, Mann JF, Yi Q, et al: Microalbuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286: 421-426
10. Mykkanen L, Zaccaro DJ, Wagenknecht LE, et al. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the insulin resistance atherosclerosis study. Diabetes 1998; 47:793-800.
11. Ruggenenti P, Remuzzi G. Time to abandon microalbuminuria. Kidney Int 2006; 70: 1214-1222
12. Barker DJ, Osmond C, Forsen TJ, et al Trajectories of growth among children who have coronary events as adults. N Eng J Med 2005; 353: 1802-1809
13. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetic epidemic. Nature 2001; 414: 782-787
14. Imamovic G, Trnacevic S, Tabakovic M, et al. Microalbuminuria – The new marker for Balkan Endemic Nephropathy. BANTAO Journal 2006; 4:58-59
15. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin dependent patients. New Eng J Med 1984; 311:89-93
16. Caramori ML, Fioreto P, Mauer M. The need for early predictors of diabetic nephropathy risk: Is albumin excretion rate sufficient? Diabetes 2000; 49: 1399-1408
17. Battlle D. Clinical and cellular markers of diabetic nephropathy. Kidney Int 2003; 63: 2319-2330
18. Forman JP, Brenner BM. Hypertension and microalbuminuria: the bell tolls for thee. Kidney Int 2006; 69: 22-28.
19. Perkins BA, Ficociello, Silva KH, et al. Regression of microalbuminuria in type 1 diabetes. New Eng J Med. 2003; 348: 2285-2293
20. Ritz E. Albuminuria and vascular damage-The vicious Twins. New Eng J Med 2003; 348:2349-2352