

## Microalbuminuria as an Early Marker for Cardiovascular Disease

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Excretion of albumin in the urine is highly variable, ranging from nondetectable quantities to milligrams of albumin and even grams of albumin. Microalbuminuria is defined as low levels of urinary albumin excretion of 30 to 300 mg/d. Microalbuminuria is highly prevalent; in hypertensive and diabetic populations, its prevalence varies from 10 to 40%. It is interesting that microalbuminuria also is found frequently in seemingly healthy individuals (5 to 7%). The variable excretion of albumin in the urine is related to the risk for the individual to develop cardiovascular (CV) disease: Absence or very low levels of albuminuria is associated with low CV risk, whereas the CV risk increases markedly with increasing amount of albumin in the urine (even within the now considered normal range). The predictive power of urinary albumin levels for CV risk is independent of other CV risk factors and not only is present in individual with diabetes and/or hypertension but also in healthy individuals. Treatments that lower albuminuria are associated with CV protection, as demonstrated in randomized, controlled trials of patients with diabetes as well as in patients with hypertension. There is preliminary evidence that albuminuria lowering is CV protective in healthy individuals with an elevated albumin excretion rate. Differences between individuals in their level of albumin excretion are already observed at a very early age (just after birth). In fact, the interindividual variability seems to be relatively constant in the first 5 decades of life, indicating that microalbuminuria is not necessarily a consequence of vascular damage at later age. Higher levels of urinary albumin seem to reflect the ordinary interindividual variability in (renal and systemic) endothelial function. Experimental data show that between strains and even within strains, rats at young age show a remarkable difference in individual endothelial function, and this is strongly related to the susceptibility of that rat to organ damage. In conclusion, albuminuria seems to be a sensitive marker very early in life for the susceptibility of an individual to CV disease. It therefore may be an ideal target for early primary prevention using CV-protective therapy regimens.

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**M**icroalbuminuria is defined as small quantities of albumin in the urine, ranging from 30 to 300 mg/d. The term is confusing, because it does not reflect small albumin molecules but rather little more than normal quantities of the molecule. A better term would be *hyperalbuminuria*. The definition of microalbuminuria is complicated further by three factors: Different sampling techniques (including consequent corrections for sampling errors), different albumin detection techniques, and difference in albumin quantity ranges (for references, see [1]).

First, the collection of urine is not standardized among our profession. Four different sampling methods are used: 24-h urine collection, overnight-timed urine collection, spot morning urine collection (first void), and finally random spot sampling. The best standard would be 24-h collection, because this over-

comes the influence of diurnal variation in albumin excretion. However, daily collections are cumbersome and subject to collection errors. The other end of the spectrum is spot random sampling, because it is subject to both incidental diurnal variation and the prevalent concentration/dilution of that urine sample, giving an overestimation and underestimation, respectively, of the true albumin excretion. To overcome the latter, urinary albumin/creatinine ratio is used. However, this again is biased by the fact that creatinine excretion varies between gender and within gender and introduces an extra measurement error.

The standard techniques of measuring urinary albumin vary. They all apply an antibody that forms a complex with the albumin to be detected. It is interesting that the antibody used is raised against serum albumin and is applied in the detection of both serum and urinary albumin. This assumes that the antigenicity of urinary albumin is similar to serum albumin. Use of HPLC techniques to measure urinary albumin indeed revealed that there are urinary albumin molecules that are not detected by the standard antibody techniques.

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Finally, the term *microalbuminuria* is defined by a lower limit and a higher limit for the urinary albumin level. Below 30 mg/d (or 20 mg/L) is considered normal, and above 300 mg/d (or 200 g/L) is considered to be macroalbuminuria (also called overt albuminuria). Although one should recognize the necessity for a clear definition of the term *microalbuminuria*, one should interpret the term with caution, because albuminuria is a continuous variable. This is particularly relevant for the often-used end point in trials nowadays, such as the transition of an individual from normal to microalbuminuria or from microalbuminuria to overt albuminuria.

From this, one may conclude that the definition of microalbuminuria is far from being standardized, with all of the confusing consequences. Currently ongoing guideline discussion within the renal community (Kidney Disease: Improve Global Outcomes [KDIGO]) should reach out to guidelines committees in the diabetes, hypertension, and cardiovascular (CV) societies to address these issues and propose one urine sampling technique, one detection method for albuminuria, and a clear upper and lower limit definition for microalbuminuria.

## Prevalence and Incidence of Microalbuminuria

Microalbuminuria is highly prevalent in several disease states. Widely known is the high prevalence in individuals with diabetes. A recent worldwide survey (2) showed that in 40% of the patients with diabetes and without known kidney disease, the levels of urinary albumin were in the microalbuminuric range. Similar data (20%) were found in a large population study (Australian Diabetes, Obesity, and Lifestyle Study [AusDiab]) (3). The transition from normo- to microalbuminuria is frequent despite adequate treatment: 2 to 2.5% per year (4,5).

The prevalence of microalbuminuria in patients with hypertension is less consistent in large population or cohort studies, varying from 8 to 23%. In 1974, Parving *et al.* (6) demonstrated the presence of microalbuminuria in patients with untreated essential hypertension. General population studies such as AusDiab and Prevention of Renal and Vascular End Stage Disease (PREVEND) show an 8 to 11.5% prevalence of microalbuminuria in individuals with hypertension (7,8). The Losartan Intervention for Endpoint Reduction (LIFE) trial in hypertensive patients with electrocardiographic signs of left ventricular hypertrophy (LVH) showed a 23% prevalence (9). No large population studies have studied the incidence of microalbuminuria in a specific hypertensive cohort of patients.

The prevalence of microalbuminuria in the general population is in the range of 5 to 7% according to several large cohort studies: PREVEND, Nord-Trøndelag Health Study (HUNT), AusDiab (7,8,10). Recent data from PREVEND show that the incidence of an individual's moving from a normoalbuminuric to a microalbuminuric classification occurs at a rate of approximately 8% in 4 yr, which is surprisingly close to that of treated diabetes. Most frequently, the individuals moved from high-normal albumin levels to microalbuminuria (11).

## Microalbuminuria and CV Risk

Mogensen (12) wrote a seminal paper in 1984, describing the importance of microalbuminuria not only as a renal risk factor but also as a CV risk factor in patients with diabetes. This has led to many subsequent studies' confirming the importance of microalbuminuria in estimating risk for patients with diabetes (reviews [13,14]). Yuyun *et al.* (15) showed recently that the CV predictive effect was comparable for type 1 and type 2 diabetes, although at a lower risk for type 1.

Despite that the Framingham study also established in 1984 that proteinuria is an important risk marker of (CV) mortality in the general population (16), this has never led albuminuria to be added to the list of important CV risk factors/markers or incorporated in CV risk engines. It lasted 20 yr before the topic got proper attention again. Several important studies followed each other, the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, PREVEND, HUNT, and European Prospective Investigation into Cancer (EPIC) (10,17–19). They all showed that, like in diabetes, microalbuminuria is predictive for CV events. Hillege *et al.* (18) showed clearly that urinary albumin is in this respect a continuous risk marker with no lower limit, which was confirmed and stressed again in a recent study by Klausen *et al.* (20) that showed that only slightly raised levels of albumin well in the normoalbuminuric range relate to increased CV risk.

In the patient with hypertension, microalbuminuria has been discovered as an important factor, although it has not penetrated all guidelines. The groups of Bigazzi and Campese *et al.* reviewed the importance of microalbuminuria as a CV risk predictor (21). Larger cohort studies confirmed this to be independent from other risk markers in the general hypertensive population (MONICA) (22), a hypertensive cohort with LVH (LIFE) (23), and in individuals with already increased CV risk (Heart Outcomes Prevention Evaluation [HOPE]) (24).

In the above studies, microalbuminuria was associated and clustered with other widely known CV risk factors (age, diabetes, hypertension, LVH, overweight, metabolic syndrome, etc.) that could explain the increased CV risk. Careful correction for such factors and *post hoc* selection of "healthy" individuals in the large general population cohorts did still reveal the marked and overwhelming independent predictive power of microalbuminuria. This was confirmed by the recent Framingham publication of Arnlov *et al.* (25) that showed elegantly that in normotensive individuals without diabetes and with normal renal function, microalbuminuria remains a strong predictor for CV outcome.

Finally, microalbuminuria not only predicts CV risk but also seems to be a sensitive marker for detecting new onset of other CV risk factors, such as hypertension and diabetes. Brantsma *et al.* (26) showed that individuals with microalbuminuria had an approximately four-fold increase in the risk for developing subsequent new-onset diabetes than those with low normal urinary albumin levels, even after correcting for baseline glucose and insulin levels or after excluding those with impaired fasting glucose or metabolic syndrome. Brantsma *et al.* (27) similarly found that microalbuminuria increased the risk for *de*

*normo* hypertension by two-fold as compared with normal albuminuria levels.

## Lowering Microalbuminuria and CV Protection

Albuminuria seems to be an independent and strong predictor for CV disease. However, for albuminuria to be a target for therapy, one needs to prove that lowering of albuminuria *per se* is cardioprotective. Several strategies are available to lower urinary albumin excretion in the microalbuminuric range. Widely known is the albuminuria-lowering effect of antihypertensive agents, in particular those that intervene in the renin-angiotensin-aldosterone system. However, statins and glucose-aminoglycans also have been proved to lower albuminuria (28–30). Some of these strategies have been proved in randomized, controlled trials to be cardioprotective. However, few have been directed at albuminuria lowering *per se* to evaluate the effect on CV outcome. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study, evaluating the effect of the angiotensin II antagonist irbesartan, shows that albuminuria can be substantially lowered in microalbuminuric hypertensive patients with type 2 diabetes, and this is associated with renal protection and some degree of CV protection (31). However, this study was not powered to address the effect on CV events. The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT) is the only randomized trial to study the effect of albuminuria lowering in microalbuminuric “healthy” individuals (other CV risk factors were excluded). Asselbergs *et al.* (32) indeed showed that the lowering of albuminuria with the angiotensin-converting enzyme inhibitor fosinopril tended to be cardioprotective. A recent *post hoc* analysis of the LIFE trial found similar results in hypertensive patients: The more the angiotensin II antagonist losartan lowered albuminuria, the more the patient was cardioprotected, irrespective of the effect on other CV risk factors (33). Future CV trials involving drugs that target albuminuria more specifically are needed to resolve the issue of whether specific lowering of albuminuria results in CV protection and whether this is a cost-effective health care approach. In this issue’s *Frontiers in Nephrology*, De Jong and Curhan (34) review the public health perspectives of screening and monitoring of urine albumin excretion in relation to CV disease prevention.

## Microalbuminuria: Consequence or Cause of Organ Damage

The classical view on the cause of microalbuminuria and proteinuria is that these are the consequence of renal damage. Under physiologic circumstances, the glomerular filter forms a barrier to prevent macromolecules such as albumin from reaching the urinary space. However, large quantities of albumin may reach the primary filtrate according to several experimental studies. That the final urine contains no or only small quantities of albumin is because the proximal tubule is equipped with an effective albumin reabsorption system that subsequently metabolizes albumin to fragments and amino acids. Damage to the glomerular barrier and/or damage to the

reabsorptive or metabolizing capacities of the proximal tubule therefore should lead to increased excretion of albumin or its fragments in the urine. The pathophysiology of renal albumin leakage includes that this albumin leak may damage the glomerulus through increased mesangial protein trafficking. In addition, an increased tubular burden of albumin reabsorption may damage the proximal tubule, leading to interstitial inflammation and loss of functioning kidney tissue (35). Indeed, this process seems to be reflected in the loss of filtration power that one observes with increasing levels of urinary albumin, such as in patients who have diabetes and show transition from normo- to micro- and macroalbuminuria.

Assuming that excess urinary albumin loss is a consequence of renal damage, one wonders how, particularly in the low albuminuria ranges, microalbuminuria is such a powerful predictor of CV disease. Could it be that even small changes in kidney function offset a (neuro)humoral cascade that influences the CV system? In this issue’s *Frontiers in Nephrology*, Amann *et al.* (36) describe the potential relation between changes in kidney function and the potential consequences for the CV system. There may be an alternative explanation, however; microalbuminuria reflects impaired vascular function in general and is associated with a higher susceptibility to CV and renal events. Indeed, Deckert *et al.* (37) proposed in the Steno hypothesis that albumin leakage is a result of widespread vascular damage. This hypothesis links impaired vascular endothelial function with vascular leakage of albumin. The kidney thus would become a window to the vasculature: Leaky renal vessels reflecting the permeability of the vasculature in general. Several studies have shown that microalbuminuria indeed is associated with increased permeability to macromolecules of peripheral vascular beds (38,39). In addition, microalbuminuria is associated with changes in vasomotor tone regulation of peripheral vessels, although this remains controversial (40–42). This hypothesis indeed unifies the idea that damage to the renal vasculature could lead to glomerular barrier changes or even proximal tubular changes that would explain leakage of albumin into the urinary space and subsequent renal risk, whereas damage to the systemic vasculature leads to increased CV risk. In this issue’s *Frontiers in Nephrology*, Stehouwer and Smulders (43) review the potential relation among endothelial function, microalbuminuria, inflammation, and the consequences for the CV system.

Assuming that the Steno hypothesis is valid, the important questions remain: What is the cause of the vascular damage? What is the cause of endothelial dysfunction? The underlying cause of the endothelial dysfunction and thus microalbuminuria still could be a parameter or a condition that directly causes CV and/or renal risk. An alternative may be that there is no pathologic vascular damage but that individuals are born with varying degrees of vascular function (within a physiologic range) and thus excrete variable amount of albumin. Recent experimental data lead us to extend the Steno hypothesis. When one measures endothelial function in renal vessels of young, healthy rats, one finds that there is a marked variability in the capacity of the endothelium to regulate vasomotor tone. This is present within a strain, but there also is a difference

between strains. Striking, this normal variation in endothelial function of healthy rats is associated with their susceptibility to subsequent renal damage in life (Figure 1) (44,45). It is interesting that the vasodilatory capacity of renal arteries that is mediated by nitric oxide (NO) of healthy kidney inversely predicts the subsequent development of focal glomerulosclerosis in both models of 5/6 nephrectomy and Adriamycin nephrosis. Moreover, the vasodilation that is mediated by endothelial hyperpolarizing factor (EDHF) is positively related with the renal damage. The rats with more pronounced endothelial NO-mediated relaxation and the ones with lower EDHF-mediated relaxation seem to be protected against end-organ damage. This is in agreement with the protective role of NO against the development of renal damage and EDHF serving as a backup mediator under the conditions of impaired NO availability.

Can one find this interindividual variability in the human situation? Urinary albumin levels vary considerably between individuals already at young age. PREVEND data show that the median and 97.5th percentile of albuminuria are relatively similar throughout life, at least below the age of 50 (Figure 2) (46). This could mean that the difference in albuminuria levels reflects a different physiologic state. However, this reasoning may be biased because the analysis is a cross-sectional approach starting at the relative age of 27. However, if one looks at the pediatric literature, one may find several publications showing that the level and the interindividual variation of albuminuria are very similar from birth to adolescence (47,48) (Figure 2). It seems that one is endowed at birth with a level of albumin excretion that may represent a vascular state and that in turn may be associated with increased or reduced susceptibility to organ damage. This would explain why albuminuria is such a powerful predictor of CV and even renal disease but also why it predicts new-onset hypertension and diabetes. Obvi-

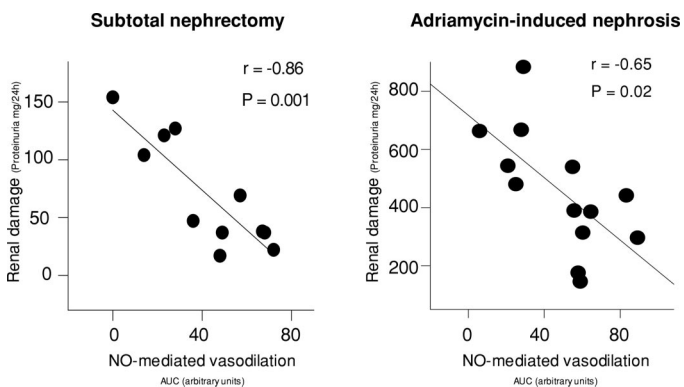


Figure 1. Individual variation in endothelial function of healthy rats predicts individual development of renal damage. Nitric oxide (NO) endothelium-dependent relaxation measured in small renal arteries of healthy animals (in arbitrary units of area under dose-response curve to acetylcholine [AUC]) predicts the development of renal damage (proteinuria in mg/24 h) after induction of chronic renal disease either by subtotal nephrectomy (A) or Adriamycin injection (B). Adapted from references (44,45).

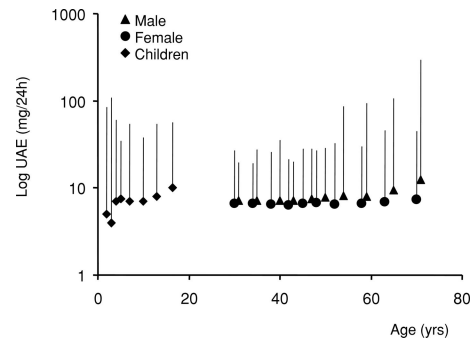


Figure 2. Individual variation of urinary albumin excretion is relatively constant with aging. Median and 97.5th percentile of albuminuria (mg/d) according to different age classes in a random adult cohort of the general population (PREVEND data modified from reference [46]) and in a cohort of children. Adapted from reference (48).

ously, this extension of the Steno hypothesis will need further experimental and clinical testing. A particular challenge will be to appreciate the weight of genetic and environmental factors that determine the vascular state at birth. There is ample evidence pointing to involvement of genetic factors, such as that renal disease of patients with diabetes clusters in families (reviewed in [49]). However, uterine life is known to exert a major impact on development of the kidney (50) and the vascular tree in the fetus (51,52).

### Conclusion

Microalbuminuria seems to reflect a state of (patho)physiologic vascular dysfunction that makes an individual susceptible to organ damage. High levels of albuminuria may already be found in young children and reflect a normal physiologic variation in endothelial function associated with CV and renal risk at later age. Intervention strategies aimed at repairing this vascular function could be very useful not only in secondary but also in primary prevention. Albumin excretion levels may represent the primary marker for success of such therapies.

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