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Albuminuria, not only a cardiovascular/renal risk marker, but also a target for treatment?

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Albuminuria, not only a cardiovascular/renal risk marker, but also a target for treatment? Albuminuria has been identified as a marker for predicting both cardiovascular and renal risk. From normal to overt proteinuria levels, albuminuria shows a continuous marked increase in risk. This is independent of other well-known cardiovascular and renal risk markers and factors, such as blood pressure, cholesterol, smoking, overweight, and others. The predictive power is not only present in already diseased populations with either nondiabetic or diabetic renal disease, but also in hypertensive and even in otherwise healthy populations.

New antihypertensive intervention strategies, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor-antagonists are claimed to have cardioprotective and renoprotective benefits that go beyond blood pressure control. Interestingly, these new therapeutic classes share the ability to lower urinary albumin excretion by an average of 40%, a characteristic that is not observed with the other antihypertensive drug classes. This short-term–induced antiproteinuric effect appears to predict the long-term cardiovascular and renal protection: the more albuminuria is lowered, the more that individual (or group) is protected.

These data suggest that albumin is not only a risk marker for cardiovascular and or renal disease, but it may also be a useful target for therapy. Monitoring of albuminuria should be daily practice in subjects at risk for cardiovascular and renal disease. In addition to new clinical trials that prove that albumin can be targeted to obtain cardiovascular protection, guidelines should be made to help the physician in deciding how to measure albumin in the urine, what are normal levels, how to target "abnormal" levels, and how low we should go.

The fact that proteinuria can be used as a predictor for renal outcome has been known for many years. Williams and Bone showed an elegant correlation between a given level of proteinuria and the renal outcome [1]. Remuzzi and Bertani [2] summarized the evidence for a pathophysiologic link between proteinuria and progressive renal function loss. In patients with diabetes it has been clearly demonstrated that albuminuria is a bad sign, heralding an increased chance for diabetic nephropathy. Recently, more and more data show that the link is not restricted to the diabetic kidney, but that albuminuria also is involved in marking the risk for cardiovascular and kidney disease in the general population. This short overview summarizes the currently available data that have evaluated the role of urinary albumin or protein as a marker of renal and cardiovascular risk. In addition, it tries to identify the role that reducing albuminuria can play in therapy guidance.

Key words: albuminuria, end-stage renal disease, cardiovascular disease, treatment.

Overt albuminuria or proteinuria as risk marker for cardiovascular and renal disease

Several studies have demonstrated that high levels of urinary albumin (for practical purposes defined as >300 mg/day) are associated with both an increased risk of progressive renal function loss, as well as cardiovascular (CV) risk [1–7].

As far as the general population is concerned, initial data from the Framingham group showed that the mere presence of proteinuria determines the cardiovascular outcome [6]. Iseki et al [3] showed in a 16-year follow-up of the general population that dipstick positive for urinary albumin gives a considerable higher chance of end-stage renal disease (ESRD) at later life. Similar data were obtained in a group of hypertensive individuals. Samuelsson et al [7] showed that there is an increased cardiovascular risk in those with proteinuria versus nonproteinurics, even if one treats the blood pressure. Effects of proteinuria on the kidney in hypertensive subjects have also been claimed [8]. In advanced diabetes, it was recently shown in post-hoc analyses of the RENAAL and other studies that proteinuria not only determines renal outcome [9, 10], but also cardiovascular outcome [11, 12]. Similar data were obtained in the IDNT study [13].

Normal albuminuria or microalbuminuria as risk marker for CV and renal disease

The definition of normal albuminuria was set years ago, suggesting that levels above 30 mg/day (or in concentrations >20 mg/L) are abnormal. Levels between 30 and 300 mg/day are called microalbuminuria,

suggesting that this is a modestly elevated level of urinary albumin. Interestingly, we learned from the diabetologists that slightly increased levels of albumin form a great risk for the diabetic patient to develop nephropathy [14, 15].

In the general population, Hillege et al have previously shown in the PREVEND study that at each higher level of albuminuria from normal to overt proteinuria cardiovascular risk is predicted to increase in a continuous fashion [16, 17]. These data were corroborated by the HUNT and EPIC studies [18, 19]. The predictive power of microalbuminuria on cardiovascular risk is present irrespective of other risk markers. New and presented in this supplement are the data from Asselbergs et al, who show that microalbuminuria might indeed add to the overall Framingham score as an additional tool to optimize therapy [20]. For renal risk to be assessed in the general population, time to event takes obviously too long for many studies. The above mentioned Japanese study by Iseki et al is, however, long enough, and indeed shows that a single "+" dipstick is already associated with increased ESRD [3]. Verhave et al show in this supplement in the PREVEND study, that high normal levels of albumin, as well as microalbuminuria, are associated with renal risk [21]. Also, in the hypertensive population, at low levels of albuminuria (even in the normal range), patients with hypertension in both the LIFE and the AASK trials showed an increased cardiovascular risk with each increase in albumin levels [22, 23]. In patients with several cardiovascular risk factors present, albuminuria is also a predicting outcome, as shown by the data from the HOPE trial [24]. In diabetes, it has been long known that microalbuminuria is a predictor of renal as well as cardiovascular risk [14, 15, 25, 26].

Mechanism of albuminuria linking it to CV and renal risk

Why is albuminuria an independent risk marker for both cardiovascular as well as renal disease? The most likely current explanation is that urinary albumin leakage, in fact, reflects a generalized vascular dysfunction, in particular endothelial dysfunction. Endothelial dysfunction may be the cause for accelerated atherosclerosis, and thus, CV and renal risk. Alternatively, albumin leakage itself may cause vascular inflammation, thus, further damaging the microvessels. Indeed, there is a lot of evidence that microalbuminuria is associated with endothelial dysfunction [27], but much work needs to be done to really prove how this link plays a pathophysiologic role in CV disease [28]. Although the above mechanism may be in play with the kidney, as well, a lot still has to be explained. The fact that microalbuminuria would reflect endothelial dysfunction is hard to explain in the kidney, given the different vascular architecture of the glomerular vasculature. However, the subsequent pathway that leaked albumin, after (proximal) tubular uptake, brings an inflammatory circle into play, and could be similar to the mechanism of damage in other tissues [29].

Albuminuria reduction as measure of CV and renal protection

The important question whether albuminuria should be an individual target for therapy can clearly not be answered by overwhelming pathophysiologic evidence. However, another way of proving that albuminuria should be targeted is bringing forward evidence that albuminuria lowering by itself proves to be CV and renal protective.

Several measures are at our disposal to lower albuminuria, such as dietary protein restriction [30], nonsteroidal anti-inflammatory drugs [31], angiotensin-converting enzyme (ACE) inhibitors [32], and angiotensin II (Ang II) receptor antagonists [33]. The latter two options are particularly effective in cases of dietary sodium restriction and/or addition of diuretics [34, 35]. Interestingly, all of these measures are by themselves renal protective, and for those properly studied, also CV protective [5, 36–40]. To start proving that this renal/CV protection is actually related to the antiproteinuric or antialbuminuric effect, one should at least establish that those who do not show a decrease in albuminuria upon start of treatment do not show renal/CV protection, whereas protection was afforded in those where the intervention induced an albuminuria reduction.

In patients with high levels of albuminuria or proteinuria, Apperloo et al, as well as Rossing et al, showed that the degree of albuminuria/proteinuria reduction is associated with a more beneficial renal outcome in the long run [41, 42]. These data showed that the degree of early reduction in high levels of urinary albumin is associated with the long-term renal prognosis of the individual patient. This is similar to what one has demonstrated with other risk factors, such as hypertension or hypercholesterolemia, in which cases short-term reduction of the risk markers (or in this case factors) is associated with CV risk reduction. Meta-analysis of some of the larger renal protection trials with ACE inhibitors showed that reduction in albuminuria is indeed associated with renal protection in nondiabetic renal disease [4]. Recently, we showed that in diabetes a similar phenomenon is true. The more one reduces albuminuria in patients with type 2 diabetes with nephropathy the more these patients were protected against development of ESRD [10]. This was irrespective of changes in all other risk markers/factors. In fact, the enhanced protective effect of the Ang II receptor antagonist losartan (compared to conventional antihypertensives) was nearly fully explained by its antiproteinuric effect. Similar data were obtained in the IDNT trial with irbesartan, although the authors raise a caveat with

respect to the interpretation of such data [13]. Recently, the first data were gathered showing that this antialbuminuric response is not only predicting the renal but also the CV protection in these diabetic patients [11].

Not only in advanced (non)-diabetic renal disease, one may find that lowering of albuminuria is predictive of CV/renal protection. Also, in incipient diabetes with hypertension, Parving et al showed in the IRMA-2 trial that lowering of albuminuria with Ang II receptor antagonist irbesartan is associated with less progression to diabetic nephropathy [43].

Recently, trials in hypertensive subjects like the LIFE and AASK have evaluated and found some interesting data on the question of whether CV or renal risk reduction is associated with albuminuria reduction. Needless to say, more trials are needed, specifically those that target albuminuria reduction and analyze whether it is associated with CV/renal protection. The fact that the effect of drugs such as ACE inhibitors as well as Ang II antagonists can be titrated to their antiproteinuric/antialbuminuric effect irrespective of their effect on blood pressure is important for the design of such a trial, as well as later for clinical practice [44, 45]. Recently, Asselbergs et al have indeed shown that ACE inhibitors offer CV protection in subjects that have no other risk factor than increased amount of albumin in the urine [46]. This may well be the lead to a new era, in which albuminuria is by itself a target for treatment.

How, when, and where to measure?

Standard techniques for measuring albumin in urine are nearly all based on antibody interaction with albumin. There are several ways of detecting this complex, varying from radiolabels and coloring of the complex, to precipitation techniques, such as nephelometry. All these techniques have in common that they detect immunoreactive albumin (in urine or serum). Recently, it was found that albumin also appears in urine in a non-immunoreactive form. This can be measured by a novel high-performance liquid chromatography (HPLC) technique (Accumin™; AusAm Biotechnologies, Inc.). Several authors have found that this new technique may pick up microalbuminuria in earlier stages of the disease, and may be even more sensitive in its relation with CV disease [47–49].

All these techniques have in common that they need to be carried out in a standardized laboratory environment. Although albuminuria can be semiquantitatively measured with a urine dipstick technique (Micral™; Roche Laboratories), accurate measurements in the field may be extremely valuable both in a setting of the future practicing physician needing to titrate his medication to albuminuria, but also in the current setting for developing countries. Fortunately, new devices are available that can accurately and rapidly measure albumin with "desktop" machines (Hemocue Urine Albumin™, Bayer DCA 2000®).

When should we test urine for albumin? Certainly in the case of diabetes, urine albumin testing is obligatory according to the guidelines. In the case of hypertension, it is certainly advisable (and according to some guidelines, more than recommendable) that one measures urinary albumin because it enhances the risk profiling of the individual. In the future, it may become standard to test the general population visiting the general physician for the presence of albumin in the urine. However, such a standard use will clearly depend on the outcome of urgently needed prospective, randomized intervention trials targeting albuminuria for cardiovascular protection. An exception may be the use of such urine albumin measurements in the developing countries. As one may appreciate from the work of Correa-Rotter et al [50] derived from the recent ISN-COMGAN Bellagio meeting [51], the need for simple and inexpensive predictors for CV/renal morbidity and mortality is rising dramatically in developing countries. Next to blood pressure, albuminuria and renal function by serum creatinine may be such "easy" markers for risk. In these countries, this may well lead to early (primary) intervention strategies, certainly given the fact that treatment in advanced [52], as well as early stages of albuminuria appears to be cost-effective [53].

Finally, having a measurement of albumin in the urine should lead to action in case the result is "abnormal." The definition of normal is now still based on the historic findings in diabetes, in which microalbuminuria is defined as "abnormal," ranging from 30 to 300 mg of albumin in the urine per day. Because daily collection of urine is very cumbersome, spot urine collections are often preferred. This leaves only concentration of albumin in the urine as a measure, giving normal ranges between 20 and 200 mg/L. Because urine may be diluted or concentrated, correction of albumin concentration values using urinary creatinine is often practiced. However, gender differences in urinary creatinine excretion may further complicate this issue. Until proven differently, the standard for normal urinary albumin levels should thus be <30 mg/day or <20 mg/L. This allows correct interpretation of all of the data from the past. Changing borders will only lead to more confusion. Certainly, just like with the definition of normal blood pressure, boundaries for normal albuminuria will shift in the future [17, 22, 54, 55].

CONCLUSION

Urinary albumin excretion is a powerful independent marker for both CV and renal risk in healthy subjects, as well as in patients with different comorbid conditions. Albuminuria may reflect a generalized vascular

dysfunction. Treatment regimens that lower albuminuria are associated with both CV and renal protection. The more albuminuria is lowered, the better the patient is protected. Future trials may provide us with the data that ensures that albuminuria should be measured in all subjects, and that, in case of abnormal high levels, treatment should be initiated that lowers the albuminuria as much as possible. Albuminuria may thus become a modifiable CV/renal risk factor just like high blood pressure and/or cholesterol.

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