Albuminuria: A Great Risk Marker, but an Underestimated Target in Diabetes

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Diabetes is a growing disease with a potentially devastating outcome. Diabetic patients run a great risk of developing multiple organ dysfunction and ultimately organ failure. The current approach of patients with diabetes is first to assess their risk profile by measuring risk factors such as glucose level, systemic blood pressure, blood lipids, body weight, and smoking. Second, to reduce the risk, the patient is advised to make a lifestyle change (lose weight and stop smoking) and to take medication that regulates glucose and lowers blood pressure and cholesterol. This approach has indeed resulted in a slowing of progressive organ dysfunction and has substantially prolonged life.

However, the residual risk of diabetic patients, despite "optimal" treatment of these risk factors, is still extremely high, and the number of patients is dramatically growing. This has urged the medical profession to improve risk profiling and design new therapeutic strategies to further reduce existing risk. In addition, the search for early disease markers was intensified with the goal to apply preventive therapeutic measures in early stages of disease, instead of waiting until the disease had fully developed.

The next paragraphs will address the status of a "new" cardiovascular and renal risk marker: increased levels of albumin in the urine. This so-called albuminuria not only marks risk in advanced stages of diabetic disease, but also indicates risk in the very early stages of the disease. Moreover, new antihypertensive therapies not only lower blood pressure, but also reduce albuminuria. We will address the need of not only measuring the risk marker, but also targeting therapies to lower albuminuria. Finally, the individual response to such therapies appears to be highly variable, offering us opportunities to optimize organ protection by individualizing therapies with the goal to overcome therapy resistance.

Clearly, diabetes constitutes a multifactorial disease in its organ damage (and maybe even in its cause). This forms a sound reason to look for multiple targets (next to optimization of treating existing targets).

ALBUMINURIA AS A RISK MARKER

— Large amounts of albumin in the urine (>300 mg/day) indicate a late stage of diabetic renal disease and indicate, next to loss of filtration rate, the degree of kidney damage. In addition, however, the degree of increased albumin loss also heralds an increased chance of losing kidney function. In fact, the more albumin is lost in the urine, the more chance the individual has on reaching end-stage renal disease (1). Intriguingly, this predictive power of increased albumin excretion does not only predict renal progressive disease, but it also predicts an increased risk for cardiovascular disease (2). Although classical risk factors such as hypertension play a major role in renal and cardiovascular disease progression in advanced diabetes, increased urinary albumin levels have their separate predictive power for risk of organ failure (3).

An increased renal and cardiovascular risk profile is also observed even when smaller amounts of albumin are present in the urine (microalbuminuria: 30–300 mg/day). Microalbuminuria heralds diabetic nephropathy as well as cardiovascular risk (4,5). Although other risk factors (mainly increased blood pressure) already play a major role in this stage, microalbuminuria also has important independent value in estimating the cardiovascular and renal risk of a diabetic patient.

Despite the clear power of using the level of albumin for marking renal and cardiovascular risk, the measurement if still markedly underused in worldwide practice (6). One of the reasons for this under use may be the fact that there is not yet a specific therapy that lowers albuminuria specifically. For other risk factors, such as high glucose and hypertension, drugs are available to lower these risk markers, with associated reduction of risk. Currently, increased levels of albumin are reduced by antihypertensive drugs that intervene in the renin-angiotensin-aldosterone system (RAAS) (7,8). Because such drugs are the recommended therapy in diabetes, most doctors thus see no additive value in measuring urine albumin. The following paragraphs will give reasons for measuring urine albumin in all individuals with diabetes.

ORGAN-PROTECTIVE PROPERTIES OF ALBUMINURIA LOWERING

— As mentioned above, intervention in the RAAS using antihypertensive drugs like ACE inhibitors or angiotensin II receptor blockers (ARBs) are proven to be associated with substantial reductions of ~50% in albuminuria both in microalbuminuric and macroalbuminuric patients. Several studies have demonstrated that this lowering of albuminuria is associated with reduction of renal risk, independent of the blood pressure–lowering effect of these drugs (9,10). Recently, three important large trials were published that specifically targeted renal risk in type 2 diabetic patients using ARBs. The results of these

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Abbreviations: ARB, angiotensin II receptor blocker; RAAS, renin-angiotensin-aldosterone system.

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trials showed that ARBs are indeed effective in lowering blood pressure as well as albuminuria. In the long term, ARB treatment resulted in renal protection both in advanced diabetic nephropathy (11,12) and early diabetic renal disease (13). This renal protection goes beyond the blood pressure–lowering capacity of ARBs, since the blood pressure in the comparator arms of these trials (using conventional antihypertensive drugs) was the same as in the ARB arms. Intriguingly, albuminuria was only lowered in the ARB arms of these trials. Although these clinical trials cannot give an answer to the question whether this lowering of albuminuria is the "cause" of the renoprotective effect of ARBs, post hoc analysis of both the Irbesartan Diabetic Nephropathy Trial and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial clearly showed that the more one reduces albuminuria, the more patients are protected against progressive renal disease (1,14). This appears not only to be applicable to renal protection, but also to cardiovascular protection, since the level of albuminuria reduction was also associated with the level of cardiovascular risk (2).

Thus, albuminuria is not only a good risk marker, but the therapy-induced fall of albuminuria is also predictive of renal and cardiovascular protection.

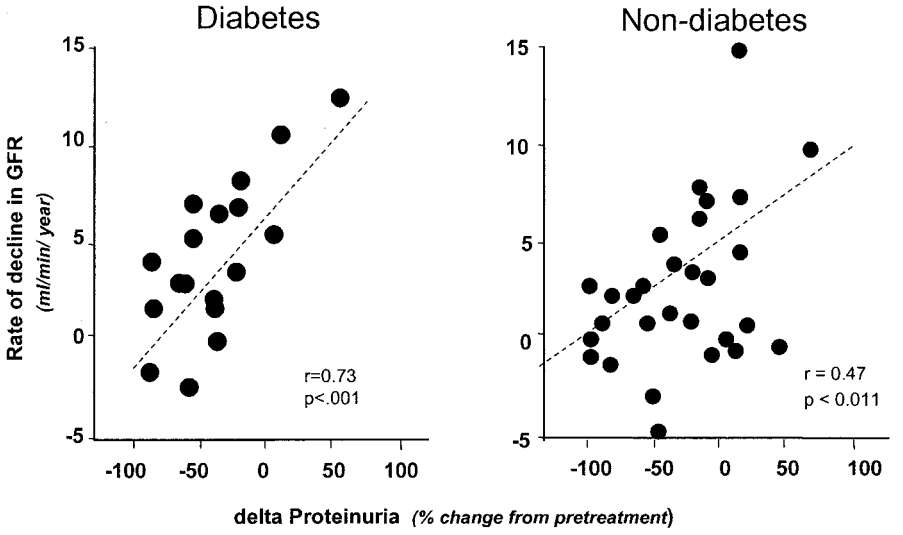

Figure 1—*The individual degree of proteinuria lowering (after several weeks of therapy) is a predictor for long-term (years) renal protection: the more proteinuria is lowered, the less the glomerular filtration rate (GFR) will decline during follow-up, both in diabetic (15) and nondiabetic renal (16) disease patients.*

INDIVIDUAL VARIABILITY IN THERAPY RESPONSE

— Although RAAS intervention is clearly effective in lowering albuminuria, with an average reduction around 50%, the individual variability is high. Some patients show a nearly 100% reduction in albuminuria, whereas others can show no change or even a rise in albuminuria upon RAAS intervention. The important question is, whether this variability in response is related to long-term renal (or cardiovascular) outcome. Rossing et al. (15, diabetes) and Apperloo et al. (16, nondiabetes) have shown that individuals who have a poor albuminuria-lowering response in the first month of ACE inhibition therapy are the individuals who show progressive renal function loss during follow-up, whereas the individuals who show an initial marked reduction in albuminuria upon therapy are protected in the long run (Fig. 1). These data are very similar to data of classical risk factors such as high blood pressure: the more an individual lowers blood pressure with therapy, the more that person is protected against cardiovascular and renal disease progression.

The above findings with albuminuria constitute sound reason to measure albuminuria in each diabetic individual to monitor the effectiveness of RAAS intervention therapy. However, the current guideline tells us that antihypertensive therapy like RAAS intervention is targeted toward high blood pressure (and not to high albumin). In fact, one could argue that the variability in albuminuria reduction is likely paralleled by a similar variability in blood pressure–lowering response. If true, than one would not need to measure albuminuria, but just measure and target for effective blood pressure lowering.

Although albuminuria is usually accompanied by increased blood pressure, recent new data from a post hoc analysis of the RENAAL study give us a clear reason to measure and target not only blood pressure but also albuminuria. Eijkelkamp et al. (17) found that the response to the ARB losartan was indeed highly variable both for blood pressure lowering as well as albuminuria lowering: roughly 60% showed a lowering for both variables, whereas 40% showed no change or even a rise after the first months of therapy. However, an important new finding was that, in nearly 40% of the patients, blood pressure response and albuminuria response were nonconcordant: either blood pressure fell and albuminuria rose, or albuminuria fell and blood pressure rose. Most importantly, the patients who had a drop in albuminuria in the first months of therapy showed a clear renal protection during follow-up despite a rise in the blood pressure. In other words, monitoring therapy-induced changes in albumin in individual patients is important independent of blood pressure changes, since it predicts the effectiveness of renal protection.

FUTURE THERAPIES FOR (FURTHER) ALBUMINURIA REDUCTION

— Despite the fact that we are able to reduce renal (and cardiovascular) risk in diabetic patients with treatments that reduce high levels of risk factors, recent trials have shown that the residual risk (even when there is optimal treatment applied) is extremely high.

An important reason for this high residual renal and cardiovascular risk observed in diabetic patients is the fact that the current therapies are not 100% effective. Many patients still suffer from insufficient glucose and blood pressure regulation (particularly in type 2 diabetes). Clearly, we need better medication as well as therapy compliance to battle this residual risk.

The residual risk can also for a large part be explained by the fact that the level of albuminuria is not fully reduced to normal by the current therapy strategies. And indeed the residual level of albuminuria is still a powerful predictor of the residual renal and cardiovascular risk in this population.

Which measures can we take to im-

prove the reduction in albuminuria, with the goal to reduce this high residual renal and cardiovascular risk in the diabetic population? First, addition of a low-sodium diet and/or a diuretic to the RAAS intervention is extremely important for both an optimal blood pressure as well an optimal anti-albuminuric effect (18). Second, dosing of the RAAS intervention drug is important. Several studies have shown that increasing doses of either ACE inhibitors or ARB results in a further decrease of albuminuria in many patients (19,20). Important to note is that a further fall in albuminuria may even be seen at doses far beyond the maximum recommended dose, at which doses there is no additional blood pressure effect. Although it is clear that albuminuria can thus be further lowered, the question whether this is associated with further renal and cardiovascular protection is not yet answered. The only dose response study with RAAS intervention in diabetes is the Irbesartan MicroAlbuminuria in Type 2 Diabetic Subjects study. This study indeed showed that 300 mg irbesartan was significantly more efficient than 150 mg as far as attenuating the transition from microalbuminuria to macroalbuminuria (13). Further dosing studies on hard end points are awaited.

Another way to try to enhance the albuminuria lowering is to switch the patient from ARBs to ACE inhibitors, or vice versa. However, nonresponders to ACE inhibitors (as far as albuminuria lowering) remain nonresponders to ARBs (21). The currently best option to enhance anti-albuminuric efficacy is to combine drugs that inhibit the RAAS. The current strategies available to interfere in the RAAS are as follows: ACE inhibitors, ARBs, aldosterone antagonists (22), and rennin inhibitors (23). All these drug classes have a similar characteristic in lowering blood pressure as well as albuminuria. The most tested combination is ACE inhibitors plus ARBs. This combination not only shows an enhanced effect on albuminuria lowering (24), but it also shows an enhanced effect on long-term renal outcome in non-diabetic renal disease patients (25). The latter combination needs to be confirmed in other trials. With regard to albuminuria, combinations of ACE inhibitors and aldosterone antagonists also have an additive lowering effect; however, no hard end point trials are published.

Finally, currently ongoing or starting studies are looking for new non–RAAS intervention strategies that lower albuminuria (in addition to RAAS intervention). New applications of existing drugs such as statins and Paracalcitol (Abbott Laboratories, IL) (26) are currently under investigation for their additive effect on albuminuria lowering in addition to RAAS intervention. A drug that has been proven to be additive to ACE inhibitors with respect to albuminuria lowering is Sulodexide (Keryx Pharmaceuticals, NY). Gambaro et al. (27) showed that it was very effective in lowering albuminuria. This drug is currently under study for its effect on renal protection both in microalbuminuric as well as macroalbuminuric renal diabetic patients.

CONCLUSIONS — Next to the existing risk factors (mainly increased blood pressure), albuminuria is a valuable tool in further decreasing the risk for progressive organ function loss in patients with diabetes, in particular with respect to the kidney and the cardiovascular system. Albuminuria assesses renal and cardiovascular risk independent of other risk markers both in advanced as well as in early diabetic disease states. Despite the fact that albuminuria is as such mentioned in global guidelines for the diagnosis and treatment of diabetes, albuminuria is still markedly underused in the daily practice of diabetes care.

However, the use of albuminuria as a risk marker in diabetes is clearly needed. First, it helps in stratifying the patient's individual risk for renal and cardiovascular disease and thus the need for "aggressive" therapy using drugs that intervene in the renin-angiotensin system. Second, these antihypertensive drugs have a short-term effect, not only lowering blood pressure but also lowering albuminuria, whereas both renal and cardiovascular protection is seen in the long term. Interestingly, the more albuminuria is lowered after initializing RAAS intervention therapy, the more the individual is protected in the long run. This is independent of the blood pressure–lowering effect of these drugs. Thus, albuminuria is not only a marker of renal and cardiovascular risk, but also a marker of the protective treatment effect of such drugs. The individual effect of RAAS intervention can be different for blood pressure lowering and albuminuria lowering. Because the long-term outcome in these patients is independently determined by the short-term effect on albuminuria (independent from the blood pressure effect), albuminuria needs to be monitored and targeted in each diabetic patient.

New therapies that further lower albuminuria on top of RAAS intervention are currently under investigation and may lead to further curtailing of the abundant risk of patients with diabetes.

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