Microalbuminuria: An increasingly recognized risk factor for CVD

Long known to be associated with kidney disease, the importance of protein in the urine is now becoming recognized as a sensitive, accessible predictor of cardiovascular risk

Microalbuminuria—abnormally high amounts of albumin in the urine—is commonly thought of as an important risk factor for kidney disease. But recently, studies have emerged highlighting microalbuminuria as an important, independent marker for endothelial dysfunction and CVD.\(^1\)\(^-\)\(^5\) Heightened awareness of microalbuminuria as an early prognostic indicator of CVD risk, knowing when, how, and in whom to screen for it, and finally, knowing the strategies to manage it, are therefore essential prerequisites for cardiologists and other healthcare providers.

“We have to acknowledge that microalbuminuria is a new marker for cardiologists. Nephrologists and diabetologists have traditionally measured microalbuminuria in their patients to monitor the development and progression of kidney disease, but now studies such as the HOPE trial,\(^6\) have shown a clear relationship between microalbuminuria and cardiovascular events. The good news is that we have drugs that can impact microalbuminuria and have a beneficial effect on the cardiovascular system,” commented Dr Gilles Montalescot of Pitié-Salpêtrière Hospital, Paris.

Defined as an albumin-to-creatinine ratio of 10-25 mg/mmol on the first morning urine sample, or an albumin excretion rate of 20-200 µg/min on a timed collection,\(^3\) microalbuminuria is present in several populations known to be at risk for CVD, including people with type 1 and type 2 diabetes, hypertension, endothelial dysfunction, and other features of insulin resistance.\(^3\)
The prevalence of microalbuminuria has been most often studied in patients with diabetes, and large trials have found the incidence to range between 20% and 40%. Studies have also found that approximately 40% of poorly controlled hypertensive individuals have microalbuminuria, and that its prevalence increases with the duration and severity of hypertension. Hypertensive patients who also have microalbuminuria more frequently have left ventricular hypertrophy, carotid artery thickening, and other end-organ damage.

Microalbuminuria can also signify a deleterious cardiovascular prognosis in other individuals, such as patients with dyslipidemia or the cluster of risk factors that make up cardiometabolic risk, also known as the metabolic syndrome: abdominal obesity, elevated triglycerides, and elevated fasting blood glucose.

**The microalbuminuria-CVD link**

Although studies have shown that small increases in urinary excretion of albumin predict adverse renal and cardiovascular events in patients with diabetes, hypertension, or both, the exact mechanism of action is unknown, particularly with regard to CVD. Many researchers have hypothesized that microalbuminuria is associated with generalized endothelial dysfunction. However, which condition precedes the other is still uncertain.

The current consensus among researchers is that somehow, albumin passes through the vascular walls, and this increased permeability is a marker of endothelial dysfunction. Studies in diabetic and hypertensive patients with microalbuminuria have shown that increased albumin leakage in the glomerulus is linked to enhanced capillary permeability for albumin in the systemic vasculature.

Researchers hypothesize that such leakage might lead to hemodynamic strain and instability, which could then start the atherosclerotic process, and eventually lead to adverse cardiovascular events, such as congestive heart failure, acute coronary syndromes, myocardial infarction and stroke. “Whatever the mechanism, the evidence linking the presence of microalbuminuria to cardiovascular disease has been well established in many large studies. In addition to HOPE, there have been the LIFE and the PREVEND studies,” commented Montalescot.

Increased cardiovascular mortality associated with microalbuminuria, as well as gross proteinuria, has also been established in a population-based study of people with older-onset diabetes (diagnosed after the age of 30). Of the 840 older-onset diabetic persons, 54.8% had normoalbuminuria, while 24.8% had microalbuminuria and 20.5% had gross proteinuria. During the 12-year follow-up, the investigators identified 364 deaths from CVD, with those individuals who had microalbuminuria and gross proteinuria having significantly higher risks of cardiovascular mortality (relative risk 1.84 for those with microalbuminuria, and 2.61 for those with gross proteinuria).
Table 1: Mortality rate according to urine albumin and proteinuric status

<table>
<thead>
<tr>
<th></th>
<th>Normoalbuminuria (n=460)</th>
<th>Microalbuminuria (n=208)</th>
<th>Gross proteinuria (n=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths from CVD</td>
<td>146</td>
<td>113</td>
<td>105</td>
</tr>
<tr>
<td>CVD mortality rate/1000 person-years*</td>
<td>36.9</td>
<td>85.5</td>
<td>123.0</td>
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</tbody>
</table>

*Overall CVD mortality rate: 59.4/1000 person-years
Adjusted from Valmadrid et al

When death from coronary heart disease, stroke, or all causes was used as the study end point, the increased risks were also significant for both microalbuminuria and gross proteinuria, (1.96 and 2.20, respectively). The investigators concluded that microalbuminuria and gross proteinuria were significantly associated with subsequent mortality from all causes and from cardiovascular, cerebrovascular, and coronary heart disease, independent of known cardiovascular risk factors and diabetes-related variables.

It is also well established that microalbuminuria is an adverse prognostic indicator in people with hypertension. In the MONICA study, one of the largest longitudinal studies to investigate a predictive role of microalbuminuria, hypertensive subjects with albuminuria showed almost a four-fold increased risk of ischemic heart disease as compared with hypertensive subjects without albuminuria.

Screening for microalbuminuria

Awareness of the cardiovascular danger posed by microalbuminuria in patients with hypertension and/or diabetes is the first step in managing these patients; the next is screening for microalbuminuria. According to the American Diabetes Association, screening for microalbuminuria can be done three ways. The first is to measure the albumin-to-creatinine ratio in a random spot collection. The second is to do a 24-hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance. The third is a timed urine collection, either over four hours, or overnight. The ADA further advises that the first method is often the easiest to carry out in an office setting and generally provides accurate information. The first-void urine or other morning collections are best because of diurnal variations in albumin excretion. However, if this is not possible, different collections in the same individual should be performed at regular intervals.

ADA recommended methods for measuring microalbuminuria
- Albumin-to-creatinine ratio in a random spot collection
- 24-hour collection with creatinine
- Timed urine collection over four hours or overnight
Factors that can cause transient elevations in urinary albumin excretion include short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness. The use of reagent tablets or dipsticks is acceptable, as they show acceptable sensitivity (95%) and specificity (93%) if done by trained personnel. However, reagent strips indicate albumin concentration only and do not correct for creatinine, as does the random spot collection of the albumin-to-creatinine ratio. If reagent strips or tablets do indicate that albumin is present in the urine, more specific tests should be used to confirm the results.

“Unfortunately, the reality is that measuring microalbuminuria is often difficult and time consuming for the busy practitioner,” commented endocrinologist Dr David CW Lau, University of Calgary, Calgary, AB. “Such testing is cumbersome to do for many clinicians, whether in primary care or specialist settings,” he said.

The dipstick method of measuring albumin in the urine, although convenient to do in the office, only detects protein excretion that exceeds 300 mg per 24 hours, which is a range that is currently denoted as macroalbuminuria, or gross proteinuria. Nevertheless, this method can be used as an initial screen to determine whether further testing is necessary, said Lau.

“If the dipstick for protein is negative, the next step would be to request a random urine specimen to measure the albumin-to-creatinine ratio. Of course the gold standard is a 24-hour urine collection for albumin, or a timed collection over a minimum of four hours, but that is often very difficult to do. In general, it is a lot easier in the office setting to get a random specimen and ask for an assay for the albumin-creatinine ratio, which is a very simple test,” he said.

Because of the importance of microalbuminuria as a marker of risk in diabetic and hypertensive individuals, the Canadian Diabetes Association and the Canadian Hypertension Education Program both recommend screening for microalbuminuria in such subjects, said Dr Ernesto L Schiffrin, of the Clinical Research Institute, University of Montreal, Montreal, QC. He suggests that the examination for microalbuminuria should be performed at least three times within a three-month period in this at-risk population, and that repeat examinations for microalbuminuria should be performed in diabetic individuals every six months, and in hypertensive individuals every year.

**The role of the renin-angiotensin-aldosterone system**

The renin-angiotensin-aldosterone system (RAAS) plays an important role in modulating the effects of microalbuminuria, noted Schiffrin. RAAS-directed antihypertensive agents, including both angiotensin-
converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), have been demonstrated to have renoprotective effects, he said.

“Angiotensin II activates the AT1 receptor, thereby resulting in a stimulation of oxidative stress, inflammatory mediators, proliferation, and other mechanisms that contribute to the progression of renal disease. It is clear that blockade of the renin-angiotensin system should result in decreased progression of renal disease in both experimental models and in humans,” Schiffrin added.

Montalescot agrees: “A critical driving factor within both renal and wider cardiovascular pathologies is overactivation of the renin-angiotensin-aldosterone system. Agents that delay the progression of renal disease, therefore, are also likely to be cardioprotective ... These agents not only lessen the systemic consequences of renal dysfunction, but may have other cardioprotective effects by exerting beneficial effects on endothelia elsewhere in the body and within the heart.”

Endocrinologist Dr Lawrence A Leiter, of St Michael’s Hospital and the University of Toronto, Toronto, ON, also acknowledges the importance of the RAAS: “We know that the renin-angiotensin-aldosterone system is very important in the pathogenesis of diabetic nephropathy. We know that angiotensin II is a vasoconstrictor and is proatherogenic, and there is now a lot of evidence that drugs which inhibit the renin-angiotensin-aldosterone system can have beneficial effects, both in terms of the kidney as well as the cardiovascular system.”

**Interventions to reduce microalbuminuria**

Since endothelial dysfunction occurs early in patients with microalbuminuria, it may be possible to slow or reverse this dysfunction by modulating microalbuminuria.¹ There are several large studies that show such modulation may have beneficial results, said Leiter.

“We now have evidence that there are a number of interventions that can reduce microalbuminuria and that can be associated with improved renal and cardiovascular outcomes,” Leiter said, adding: “Nonpharmacological measures that are well known to improve insulin sensitivity may improve endothelial function. These include weight loss, exercise, and eating a low-fat diet. Most of the time, however, these are not enough.”

Pharmacological agents such as statins, ACE inhibitors, and ARBs have been shown in several landmark studies to decrease high blood pressure and microalbuminuria.¹ Moreover, there is ample evidence to suggest that specific lowering of microalbuminuria translates into reduced renal and cardiovascular adverse events in several populations.¹
Indeed, data from two large randomized, double-blind, placebo-controlled trials, Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA-2) and the Irbesartan Diabetic Nephropathy Trial (IDNT), showed that irbesartan was renoprotective and inhibited the development of overt nephropathy and the progression of renal disease in hypertensive patients with type 2 diabetes.

IRMA-2, which was conducted in 96 centres worldwide, randomized 590 hypertensive patients with type 2 diabetes and microalbuminuria but normal kidney function to one of three groups: irbesartan 150 mg daily, irbesartan 300 mg daily, or placebo. Patients were followed for two years. The primary outcome was time to onset of diabetic nephropathy, defined as persistent albuminuria in overnight urine specimens, with a urinary albumin excretion rate >200 µg/min and at least 30% higher than the baseline level.

During the 24 months of the study, overt nephropathy developed in 30 patients in the placebo group, as compared with 19 patients in the irbesartan 150 mg group, (p=0.08) and 10 patients in the 300 mg group (p<0.001).

Irbesartan reduced the level of urinary albumin excretion throughout the duration of the study. In patients taking the 150-mg dose, albumin excretion decreased by 24%; in the 300-mg group, albumin excretion decreased by 38%; whereas in the placebo group, albumin excretion decreased just 2% (p<0.001 for comparison between placebo and combined irbesartan groups). The higher dose of irbesartan was significantly more effective in reducing the level of microalbuminuria than the lower dose (p<0.001). In addition, irbesartan was well tolerated, with more patients on placebo than those receiving irbesartan reporting serious adverse events (23% for placebo compared with 15% for irbesartan, p=0.02).

Table 2: Effect of irbesartan vs placebo in the IRMA-2 trial

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>Irbesartan 150 mg</th>
<th>Irbesartan 300 mg</th>
<th>Placebo</th>
<th>p value placebo vs combined irbesartan groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with diabetic nephropathy</td>
<td>19</td>
<td>10</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Decrease in albumin excretion (%)</td>
<td>24</td>
<td>38</td>
<td>2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Serious adverse event rates (%)</td>
<td>15</td>
<td>23</td>
<td></td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Adjusted from Parving et al

The IDNT trial, which studied 1715 hypertensive patients with nephropathy due to type 2 diabetes for a mean duration of 2.6 years, concluded that irbesartan was renoprotective and inhibited the progression of kidney disease. The patients were randomized to 300 mg of irbesartan daily, 10 mg of the calcium-channel blocker amlodipine daily, or to placebo. The primary composite end point was time to doubling of
the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause.\textsuperscript{9}

The investigators found that treatment with irbesartan was associated with a 20% lower risk of the primary composite end point compared to placebo, and a 23% lower risk of the primary composite end point compared to amlodipine. The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group compared with the placebo group (\(p=0.003\)) and 37% lower compared with patients randomized to amlodipine (\(p<0.001\)). Furthermore, irbesartan significantly decreased the risk of progression to end-stage renal disease by 23% (\(p=0.07\)) compared with placebo and amlodipine, and also lowered the rise of serum creatinine more effectively than the other two treatments.\textsuperscript{9}

Table 3: IDNT: Relative risk of the primary composite end point

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted relative risk (95% CI)</th>
<th>p value</th>
<th>Adjusted* relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan vs placebo</td>
<td>0.80 (0.66–0.97)</td>
<td>0.02</td>
<td>0.81 (0.67–0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Amlodipine vs placebo</td>
<td>1.04 (0.96–1.25)</td>
<td>0.69</td>
<td>1.07 (0.99–1.29)</td>
<td>0.47</td>
</tr>
<tr>
<td>Irbesartan vs amlodipine</td>
<td>0.77 (0.63–0.93)</td>
<td>0.006</td>
<td>0.76 (0.63–0.92)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Adjusted for the mean arterial blood pressure during follow-up

Adjusted from Lewis et al\textsuperscript{9}

“The IDNT study is perhaps the more important study because it took patients with type 2 diabetes who had significant proteinuria and showed that treatment with irbesartan over several years reduced the composite end point of doubling of serum creatinine, the requirement for dialysis, and death,” commented Leiter.

The bottom line for clinicians

The growing awareness of the significance of microalbuminuria in CVD is an important and positive step towards utilizing this emerging risk marker in the therapeutic decision-making process. The evidence from large clinical trials attests not only to the renal but the cardioprotective effects of early recognition and reduction of microalbuminuria. But perhaps most importantly, the right tools exist to effectively treat patients who present with this early marker for CVD, thus reducing their CVD risk.

Bibliography


