Microalbuminurin in diabetes mellitus

Sheldon W. Tobe, Philip Alan McFarlane, David Malcolm Naimark

The incidence of diabetes mellitus in North America is reaching epidemic proportions and is expected to double by 2025.1 Over 5% of the population is known to have diabetes, and as many as another 2.5% are estimated to have the disease without knowing it.2 The prevalence of diabetes is increasing faster in the First Nations population than in the general population, and the onset is occurring at ever earlier ages.3 Diabetes is the most common cause of end-stage renal disease (ESRD) in Canada and is a major risk factor for cardiovascular disease and blindness.4

Microalbuminuria represents an abnormally elevated urine albumin level that cannot be detected with the use of a urinalysis dipstick. The presence of microalbuminuria predicts worsening of renal disease to overt diabetic nephropathy and an elevated risk of cardiovascular disease.6–9 Up to 30% of people with newly diagnosed type 2 diabetes will already have abnormally high urine albumin levels; about 75% of these people will have microalbuminuria and about 25% will have overt diabetic nephropathy.10–14 Patients with type 2 diabetes who were enrolled in the MICRO-HOPE study, for example, had a risk of progression from normal to diabetic nephropathy of 2% and a risk of progression from microalbuminuria to diabetic nephropathy of 20% over 5 years.15 These rates are similar for type 1 and type 2 diabetes.16–21

Early detection of microalbuminuria through screening allows interventions aimed at preventing diabetic nephropathy. In this article we review strategies for microalbuminuria screening in diabetic patients and for introducing therapies to prevent the progression of renal disease.

Diagnosis

Patients with diabetes are at risk of microalbuminuria if they have any of the following factors:

- the urine albumin excretion is in the upper range of normal (20–30 mg/d);
- the systolic blood pressure is greater than 130 mm Hg;
- the glycosylated hemoglobin level is greater than 0.09; or
- the total cholesterol level is greater than 5.24 mmol/L.

Several methods for screening for microalbuminuria are available, including timed urine collections (over 24 hours or overnight) to measure protein levels and random urine tests using laboratory tests, dipsticks or special devices (e.g., automated urine analyzers) to measure microalbumin levels or to calculate the microalbumin:creatinine ratio (MACR). Regular urinalysis dipsticks are not sensitive enough to detect early microalbuminuria.

Microalbuminuria is diagnosed when the urine albumin level is 30 mg/d or greater (Table 1). This can be expressed either as a quantity of albumin excreted per time (≥ 20 µg/min) or as a concentration (≥ 20 mg/L urine). The Canadian Diabetes Association recommends the calculation of the MACR from a random urine sample (Fig. 1). The MACR is preferable to a simple measure of albumin excretion.
creted in urine because the latter can be distorted by the effects of urine concentration. The MACR is more convenient to perform than a 24-hour urine collection, and the results of these 2 tests have been shown to correlate highly. Given that there is significant variability in the daily amount of albumin excreted in urine, the Canadian Diabetes Association recommends that microalbuminuria be diagnosed only if the MACR is abnormal in 2 out of 3 tests.

Because urine albumin excretion is a continuum, we have indicated ranges that define normal, microalbuminuria and overt diabetic nephropathy (Table 1). Higher albumin excretion within each range is predictive of the risk of progression to the next. Worsening of renal disease in people with diabetes is also predicted by the severity of other traditional cardiovascular risk factors, including blood pressure, cholesterol level and blood glucose level.

Management

Glycemic control can prevent progression to microalbuminuria. Preventing the progression of each step of renal disease in patients with diabetes — microalbuminuria, diabetic nephropathy, and ESRD or death — can be achieved with blood pressure control and the use of antihypertensive therapies such as angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (Fig. 2, Table 2). Primary prevention (preventing microalbuminuria) can be achieved through good glycemic and blood pressure control and through the use of an ACE inhibitor in both type 1 and type 2 diabetes (Table 2).

Secondary prevention (preventing the progression from microalbuminuria to diabetic nephropathy) can be achieved with an ACE inhibitor in both type 1 and type 2 diabetes and with an angiotensin II receptor blocker in type 2 diabetes (Table 2). In the study by Parving and associates antiangiotensin therapy with irbesartan was found to reverse microalbuminuria in up to one-third of patients. Of interest, in that study, the higher dose of irbesartan (300 mg) was significantly more protective than the lower dose (150 mg) against progression from microalbuminuria to diabetic nephropathy (59% v. 10%).

Tertiary prevention (preventing the progression from diabete nephropathy to ESRD) independent of the blood pressure effect can be achieved with an ACE inhibitor in type 1 diabetes and with an angiotensin II receptor blocker in type 2 diabetes. It is unknown whether ACE inhibitors and angiotensin II receptor blockers are equally effective or whether they are more effective when combined.

Once microalbuminuria is diagnosed in a patient with diabetes, it is time to stress to the patient the need to manage multiple risk factors for cardiovascular disease. The target blood pressure should be below 130/80 mm Hg, the target low-density lipoprotein cholesterol level should be below 2.5 mmol/L, and smoking cessation should be mandatory.

Fig. 3 outlines a potential algorithm for controlling blood pressure in people with diabetes. Combinations of antihypertensive drugs are often needed to achieve the target blood pressure. The algorithm represents an extrapolation from existing evidence; however, evidence concerning the most ef-

Table 1: Definitions of microalbuminuria (MAU) and diabetic nephropathy according to urine dipstick test results, daily urine albumin levels and albumin:creatinine ratios

<table>
<thead>
<tr>
<th>Condition</th>
<th>Result of urine dipstick test for protein</th>
<th>Daily urine albumin level, mg/d</th>
<th>Urine albumin:creatinine ratio (mg:mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>&lt; 30</td>
<td>Males: &lt; 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females: &lt; 2.8</td>
</tr>
<tr>
<td>MAU</td>
<td>Negative</td>
<td>30–300</td>
<td>Males: 2.0–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females: 2.8–28</td>
</tr>
<tr>
<td>Overt diabetic nephropathy</td>
<td>Positive</td>
<td>&gt; 300</td>
<td>Males: &gt; 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females: &gt; 28</td>
</tr>
</tbody>
</table>

Fig. 1: Guidelines for screening microalbuminuria in patients with diabetes mellitus. BP = blood pressure, ACE = angiotensin-converting-enzyme, CDA = Canadian Diabetes Association.
Fig. 2: Prevention of progression of renal disease in people with diabetes mellitus. ARB = angiotensin II receptor blocker, ESRD = end-stage renal disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of diabetes studied</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCCT study, 1995<strong>26</strong></td>
<td>Type 1</td>
<td>Glycemic control</td>
<td>Intensive diabetes treatment delayed onset of MAU by 43% and progression to renal disease by 56%</td>
</tr>
<tr>
<td>Euclid study, 1997<strong>27</strong></td>
<td>Type 1</td>
<td>Lisinopril v. placebo</td>
<td>Lisinopril delayed onset of MAU (6% v. 8% over 2 yr)</td>
</tr>
<tr>
<td>Ravid et al, 1998<strong>28</strong></td>
<td>Type 2</td>
<td>Enalapril v. placebo</td>
<td>Enalapril protected against development of MAU (6.5% v. 19% over 6 yr)</td>
</tr>
<tr>
<td>UKPDS-39, 1998<strong>29</strong></td>
<td>Type 2</td>
<td>Captopril v. atenolol</td>
<td>Development of MAU at 9 years was 31% in captopril group v. 26% in atenol group; progression to nephropathy was 5% v. 10%</td>
</tr>
<tr>
<td>Stratton IM (UKPDS-35), 2000<strong>30</strong></td>
<td>Type 2</td>
<td>Glycemic control</td>
<td>1% reduction in Hb\textsubscript{a1c} was associated with 21% reduction in incidence of diabetes complications, including diabetic nephropathy</td>
</tr>
<tr>
<td>Adler et al (UKPDS-36), 2000<strong>31</strong></td>
<td>Type 2</td>
<td>BP control</td>
<td>Each 10 mm Hg of reduction in systolic BP was associated with a 12% reduction in incidence of diabetic complications</td>
</tr>
<tr>
<td>MICRO-HOPE study, 2000<strong>32</strong></td>
<td>Type 2</td>
<td>Ramipril v. placebo</td>
<td>Ramipril reduced progression to diabetic nephropathy (6.5% v. 8.4% over 5 yr)</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ravid et al, 1993<strong>33</strong></td>
<td>Type 2</td>
<td>Enalapril v. placebo</td>
<td>Enalapril reduced progression to diabetic nephropathy and renal disease by 30% over 5 yr</td>
</tr>
<tr>
<td>Laffel et al, 1995<strong>34</strong></td>
<td>Type 1</td>
<td>Captopril v. placebo</td>
<td>Captopril reduced progression from MAU to diabetic nephropathy (6% v. 18% over 2 yr)</td>
</tr>
<tr>
<td>MAU Captopril Study Group, 1996<strong>35</strong></td>
<td>Type 1</td>
<td>Captopril v. placebo</td>
<td>Captopril reduced progression from MAU to diabetic nephropathy (7% v. 22% over 2 yr)</td>
</tr>
<tr>
<td>Sano et al, 1996<strong>36</strong></td>
<td>Type 2</td>
<td>Enalapril v. placebo</td>
<td>Enalapril reduced incidence of MAU at 1 yr and slowed progression to diabetic nephropathy</td>
</tr>
<tr>
<td>Mathiesen et al, 1999<strong>37</strong></td>
<td>Type 1</td>
<td>Captopril v. placebo</td>
<td>Captopril reduced progression to diabetic nephropathy</td>
</tr>
<tr>
<td>Estacio et al (ABCD Trial), 2000<strong>38</strong></td>
<td>Type 2</td>
<td>Enalapril v. nisoldipine</td>
<td>Both agents prevented progression to MAU (20% and 23%) and diabetic nephropathy (19% and 20%)</td>
</tr>
<tr>
<td>Schrier et al, 2002<strong>39</strong></td>
<td>Type 2</td>
<td>Intense (125/75 mm Hg) v. moderate (117/81 mm Hg) BP control</td>
<td>Lower BP associated with reduced incidence of diabetic nephropathy (25% v. 54%)</td>
</tr>
<tr>
<td>Lacourciere et al, 2000<strong>40</strong></td>
<td>Type 2</td>
<td>Enalapril v. losartan</td>
<td>Both drugs were associated with 30% reduction in urine albumin level</td>
</tr>
<tr>
<td>Parving et al (IRMA II), 2001<strong>41</strong></td>
<td>Type 2</td>
<td>Irbesartan v. placebo</td>
<td>Irbesartan delayed progression to diabetic nephropathy (5% with high dose and 10% with lower dose v. 15% with placebo over 2 yr)</td>
</tr>
<tr>
<td>ACE Inhibitors in Diabetic Nephropathy Trialists Group, 2001<strong>42</strong></td>
<td>Type 1</td>
<td>ACE inhibitors v. placebo</td>
<td>ACE inhibitors reduced progression to diabetic nephropathy by more than 50% and more than doubled regression to normoalbuminuria</td>
</tr>
</tbody>
</table>

Note: MAU = microalbuminuria, BP = blood pressure, Hb\textsubscript{a1c} = glycosylated hemoglobin, ACE = angiotensin-converting enzyme.
Drugs in classes referred to in this article

- Angiotensin II receptor blockers: candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan
- Angiotensin-converting-enzyme (ACE) inhibitors: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril
- Dihydropyridine calcium-channel blockers (CCBs): amlo- dipine, felodipine, nifedipine
- Nondihydropyridine CCBs: diltiazem, verapamil
- Thiazide diuretics: hydrochlorothiazide, indapamide
- β-Blockers: atenolol, bisoprolol, metoprolol

Effective combination or order of medications has not yet been established in trials. Diabetic patients with microalbuminuria should have their blood pressure monitored quarterly and their renal function checked annually, or more often if they have risk factors for vascular disease. If renal function deteriorates, referral to a nephrologist is appropriate.

Case revisited

The patient should have a random urine test to determine the MACR. If the ratio is greater than 2.8 the test should be repeated twice. If the ratio is greater than 2.8 in 2 out of 3 tests, microalbuminuria should be diagnosed and antiangiotensin therapy started with an ACE inhibitor or angiotensin II receptor blocker. Because of the patient’s increased risk of cardiovascular and renal disease, her blood pressure and hypercholesterolemia should be closely monitored and managed as necessary.

Comments

Microalbuminuria screening meets the fundamental requirements for a screening test, and because it is cost-effective it will help to relieve some of the burden on our health care system. In our view, the Canadian Diabetes Association practice guideline regarding microalbuminuria screening is an important contribution to the management of patients with diabetes. In conscientiously applying the guideline, physicians may be able to prevent progressive renal disease, and ultimately renal failure, in many patients with diabetes.

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References


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Additional resources

- American Diabetes Association: www.diabetes.org
- Canadian Diabetes Association: www.diabetes.ca
- Canadian Hypertension Society: www.chs.md
- National Institutes of Health diabetes site: www.niddk.nih.gov/health/diabetes
- diabetes.htm

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