



Microalbuminuria: So What's a Little Protein?

By Judith T. Klassen, BSc, MD, FRCPC

*University of Saskatchewan Practical Management of
Common Medical Problems Conference.*

We are in the midst of an epidemic: the epidemic of diabetes and its microvascular and macrovascular complications. Without aggressive intervention, morbidity, mortality, and health care costs will be devastating to millions of Canadians predicted to be affected by diabetes over the next decades. Primary prevention of diabetes is the ideal. However, if a patient becomes diabetic, various secondary preventative measures need to be instituted. If not, inexorable disease progression will result in blindness, amputations, coronary artery disease, and renal failure.

One of the early markers of not only diabetic nephropathy, but also vascular disease in patients with diabetes, is the presence of microalbuminuria. Once identified, risk factor modification can be more intensively addressed. The family physician and the internist (who will see these patients early in the course of the disease when intervention can be critical to long-term outcome) are ideally positioned to modify treatment.

How much is too much?

It is normal for all of us to lose some protein—up to 150 mg daily—through our urine. Of that amount, less than 30 mg should be albumin. Microalbuminuria may be transient due

Malcolm's diabetes

Malcolm, 55, has had Type II diabetes for the last 10 years. Medications include insulin and acetylsalicylic acid. He has early diabetic retinopathy. His blood pressure is in the 130/80 mmHg range.

How should Malcolm be investigated and, if need be, treated for diabetic nephropathy?

For the answer, please see page 73.



to a variety of factors and may resolve with no specific treatment.

Persistent albuminuria, however, is abnormal. When present in amounts between 30 mg and 300 mg daily, it may be predictive in people with diabetes of eventual diabetic nephropathy, and end-stage renal failure. The greatest value of microalbuminuria is as a screening tool in early

Pr BEXTRA™

Find out more on page 60

Microalbuminuria

Frequently Asked Questions on: Microalbuminuria

Questions:

What is microalbuminuria?

What is the significance of microalbuminuria in diabetic patients?

Is microalbuminuria always predictive of progressive diabetic nephropathy?

How is treatment monitored?

What is the significance of urine microalbumin being positive for 3,000 mg daily?

Answers:

Microalbuminuria is probably a misnomer. It is not a "small" albumin molecule found in the urine, but simply albumin present in low amounts, below the level of detection of the standard office multi-test urine dipstick.

In Type I and Type II diabetes, the presence of microalbuminuria on repeat specimens collected in the basal state may signify early diabetic nephropathy. It is a marker, in patients with or without diabetes, for cardiovascular mortality.

No. Microalbuminuria may be seen transiently during pregnancy, after exercise, with protein loading, hyperglycemia, fever, and urinary tract infections. There is also day-to-day, as well as diurnal, variation in albumin excretion. Hence, it is important to base treatment on the results of several tests.

Treatment involves either an ACE-I or an ARB. Once started on either one, the serum creatinine and potassium should be checked in 7-10 days. A rise in the serum creatinine of up to 30% is acceptable. If the rise is greater, the ACE-I or ARB should be discontinued, and investigations for renal artery stenosis should be initiated.

There is frequent confusion about this. This is not microalbuminuria, but in fact overt proteinuria in the nephrotic range (*i.e.*, 3 grams/24 hours), and would have been simply detected by the standard multi-test stick. Checking for microalbumin adds nothing. This degree of proteinuria signifies the presence of either advanced diabetic nephropathy, or another glomerular disease and the patient should be referred to a nephrologist.

Microalbuminuria

Table 1

Methods of testing for microalbumin

Test	Advantages	Disadvantages
Office microalbumin test strip (i.e., Micral-II®)	<ul style="list-style-type: none"> • rapid • results available in office 	<ul style="list-style-type: none"> • semiquantitative only • cost borne by office
First morning urine for microalbumin:creatinine ratio	<ul style="list-style-type: none"> • simple • corrects for differences in concentration of urine • less concern for diurnal variation 	<ul style="list-style-type: none"> • has to be sent to the lab
24-hour urine	<ul style="list-style-type: none"> • accurate • volume of urine is irrelevant 	<ul style="list-style-type: none"> • cumbersome for patient • error prone
Timed overnight void	<ul style="list-style-type: none"> • accurate 	<ul style="list-style-type: none"> • cumbersome for patient • error prone • requires extrapolation to 24 hours

diabetes (Figure 1), such that treatment can be initiated or intensified to slow or stop the progression of kidney disease.

Microalbuminuria is also predictive of cardiovascular mortality in diabetic and nondiabetic patients.¹ It is representative of the endothelial dysfunction. In the early phases of a variety of renal diseases, patients may also have microalbuminuria.

How do you screen for microalbuminuria?

Microalbuminuria cannot be detected by the standard office multi-test dipstick. These



Dr. Klassen is an associate professor of medicine, University of Saskatchewan, and staff nephrologist, St. Paul's Hospital, Saskatoon, Saskatchewan.

THE FIRST CHOLESTEROL ABSORPTION INHIBITOR

BEFORE PRESCRIBING EZETROL™, PLEASE CONSULT THE ENCLOSED PRESCRIBING INFORMATION. WHEN EZETROL™ IS TO BE ADMINISTERED WITH A STATIN, PLEASE ALSO CONSULT THE PRODUCT MONOGRAPH FOR THAT STATIN.

FOR EFFICACY
EZETROL
ezetimibe

and a Statin
BETTER TOGETHER!



WETZEL PROSST | Schering
Pharmaceuticals
Merck Frosst-Schering Pharma, S.P.
Orléans, Québec

™ Trademark used under license.
EZE-03-CDN-44201184-JA

Microalbuminuria

Table 2

Results of microalbuminuria testing

Results	Normal	Microalbuminuria	Overt proteinuria
Standard office multi-test stick for protein	Negative	Negative or trace	Positive
Albumin to creatinine ratio		Males: > 2.0 mg/mmol Females: > 2.8 mg/mmol	
24-hour urine albumin	< 30 mg/day	30-300mg/day	> 300 mg/day

tests are too insensitive, and special dipsticks or other urine testing must be employed. If, however, the urine by standard dipstick is positive for protein, the diabetic patient is unlikely to have microalbuminuria but rather overt proteinuria and more advanced kidney disease.

Practice Pointers

When to refer a diabetic patient to a nephrologist

- Creatinine increases by > 30% on an ACE-I or an ARB
- Renal insufficiency
- Diabetic with more than 300 mg protein in 24 hour specimen
- Hematuria
- Time course for diabetic nephropathy does not "fit"

ARB:adrenergic receptor binder
ACE-I: angiotensin-converting enzyme inhibitor

There is no further value at that time in testing the urine for microalbuminuria.

There are different means of testing urine for microalbumin (Table 1).

There is debate as to what is the best test for identifying microalbuminuria (Table 2). Many physicians favour screening with the first morning microalbumin/creatinine ratio, as it is simple. There is a good correlation

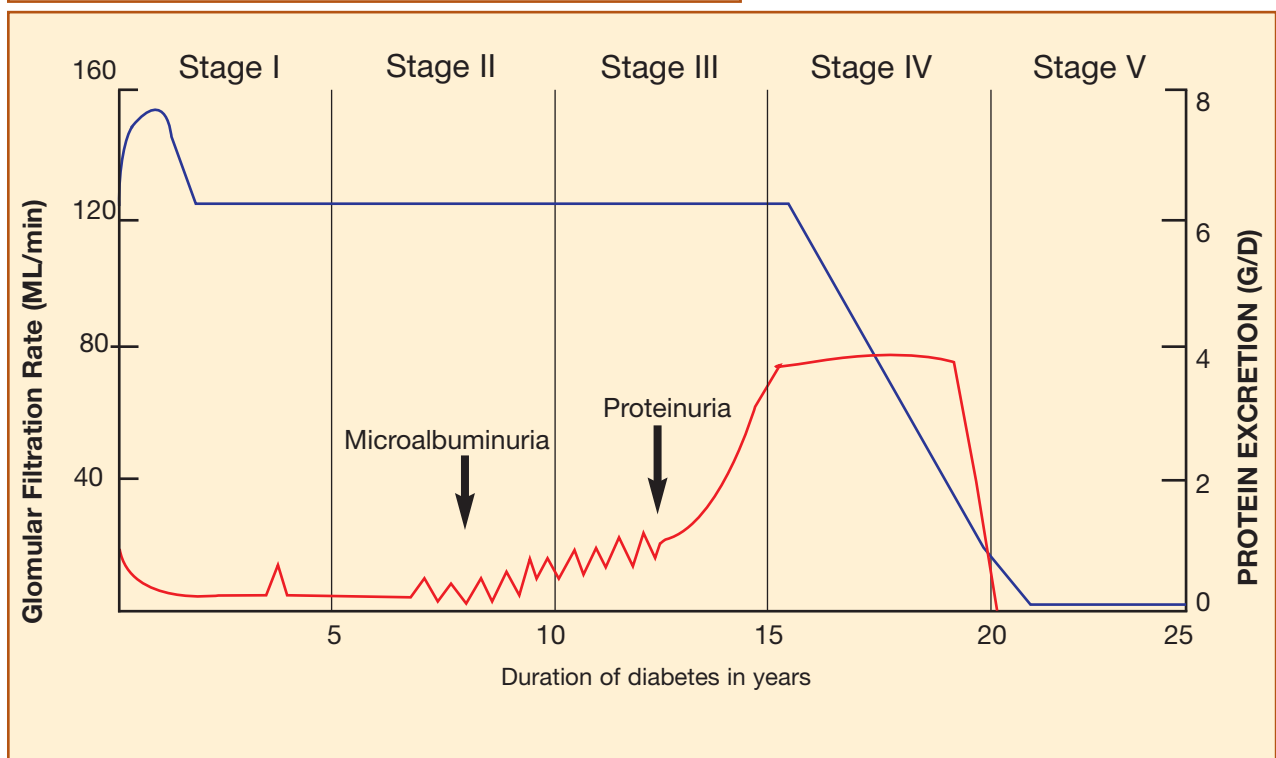


Figure 1. Stages of diabetic kidney disease.

Microalbuminuria

between the 24-hour urine protein and protein/creatinine ratio, and this likely holds true for albumin as well.²

While microalbuminuria reflects endothelial dysfunction and premature cardiovascular events, routine screening is not recommended as yet in non-diabetic patients.

Table 3

Treatment targets

Risk Factor	Treatment/objective
Hyperglycemia	Hemoglobin A _{1c} of 7% or less
Hypertension	Blood pressure of < 130/80 mmHg
Microalbuminuria	Angiotensin-converting enzyme inhibitor or adrenergic receptor binder

Adapted from: The DCCT Trial Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the DCCT trial. *KI* 1995; 47(6):1703-20.

UK Prospective Diabetes Study Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type II diabetes. *Lancet* 1998; 352(9131):837-53.

Malcolm's case continued

Investigations:

1. Urinalysis negative for both blood and protein.
2. Hemoglobin A_{1c} (Hgb A_{1c}) is 7%.
3. Urea and creatinine are 6 mmol/L and 85 umol/L respectively.
4. The 24-hour urine for protein is "below detectable limits," but is positive for 45 mg of microalbumin daily.

What is the next step?

1. First morning urine for microalbumin:creatinine ratio should be sent on several occasions. If greater than 2.0, an AC-I or ARB should be initiated.
2. The serum potassium and creatinine are checked within 7-10 days of starting the above medication.
3. The first morning urine microalbumin:creatinine ratio should be rechecked in 6 months and if still greater than target the medication dose increased or the other agent started.
4. Target Hgb A_{1c} is 7% or less and blood pressure < 130/80 should be maintained.

EZETROL™: A UNIQUE MECHANISM OF ACTION COMPLEMENTARY TO STATINS

BEFORE PRESCRIBING EZETROL™, A CHOLESTEROL ABSORPTION INHIBITOR, PLEASE CONSULT THE ENCLOSED PRESCRIBING INFORMATION. WHEN EZETROL™ IS TO BE ADMINISTERED WITH A STATIN, PLEASE ALSO CONSULT THE PRODUCT MONOGRAPH FOR THAT STATIN.

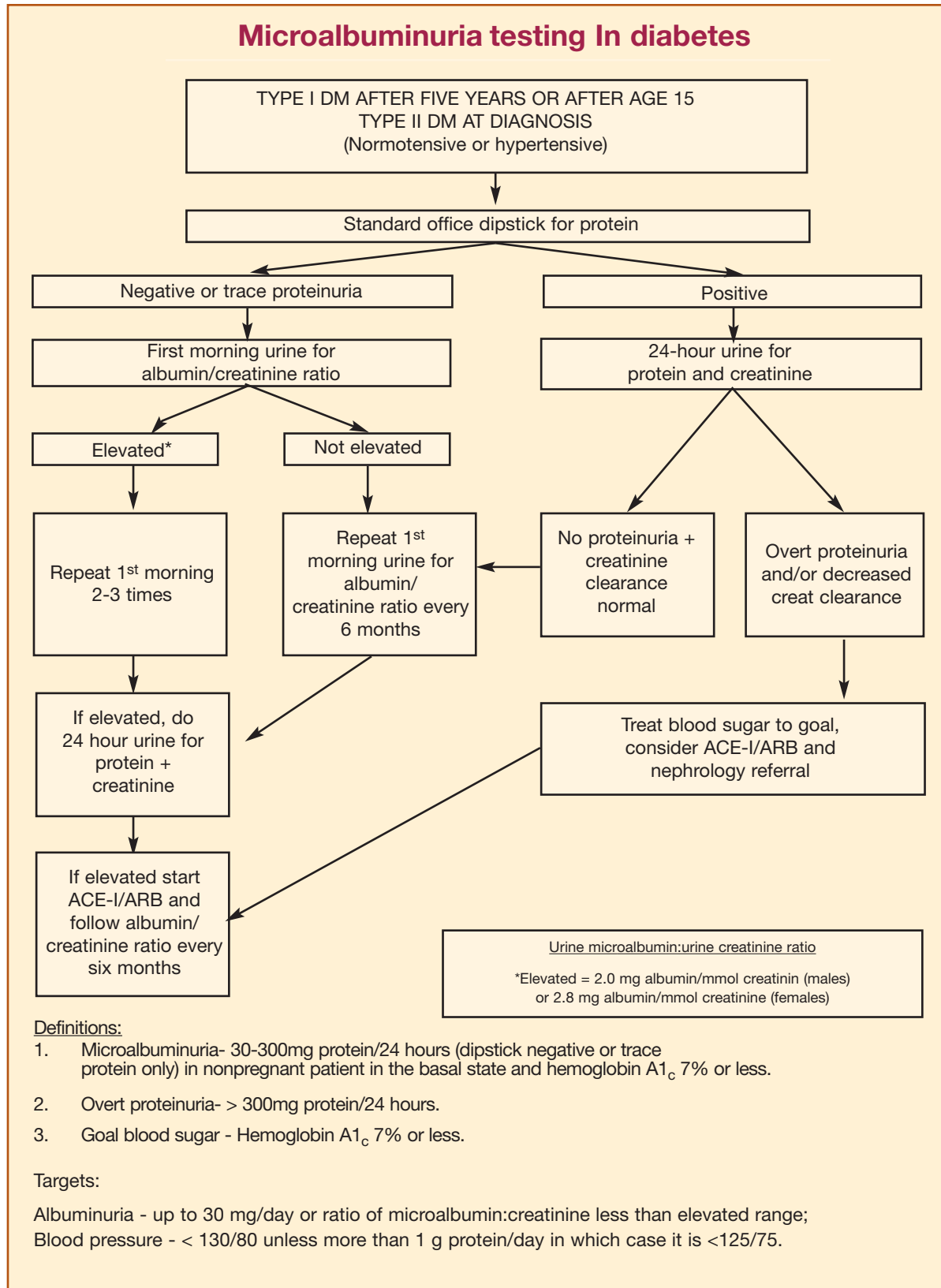
FOR EFFICACY
EZETROL™
ezetimibe
and a Statin
BETTER TOGETHER!



BIOMERK PRODUKT / Schering
Pharmaceuticals
Kenilworth, NJ, USA
Kenilworth, NJ, USA

™ Trademark used under license.
EZE-03-CDN-44208185-3A

Microalbuminuria



Microalbuminuria

What are the treatment goals?

Once a patient with diabetes has been identified to have persistent microalbuminuria, treatment is either initiated or intensified (Table 3). Both angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) reduce microalbuminuria, which is a marker of renal disease.

Hyperglycemia alone can result in increased microalbuminuria. Reducing hemoglobin A_{1c} to target can reduce microalbuminuria. It is unclear for what period of time normoglycemia must be maintained, however, to achieve this end.

Achieving optimal blood pressure (BP) control is critical to slowing the progression of diabetic kidney disease. The target blood pressure for patients with > 1 g of proteinuria are even more aggressive.

The Canadian Diabetes Association (CDA) 1998 guidelines recommend ACE-I for patients with Type I and Type II diabetes with microalbuminuria.³ New guidelines will be published this year. The American Diabetes Association Guidelines, published in 2002, recommend the use of an ACE-I for people with Type I diabetes even in the absence of hypertension, and ARBs for people with Type II diabetes with microalbuminuria.⁴ This discrepancy is likely because of the publication of the various ARB trials after the release of the CDA guidelines.^{5,6}

What about the combination of ACE-Is and ARBs?

Many people with diabetes are hypertensive and many hypertensive patients require more than one agent to obtain proper BP control. There is evidence that the addition

of an ACE-I to an ARB may improve blood pressure control, but the combination will possibly also reduce microalbuminuria.⁷

If neither an ACE-I or ARB can be tolerated, a nondihydropyridine calcium channel blocker can be instituted.⁴

Take-home message



How to diagnose and treat

- Use urine microalbumin screening for early diabetic nephropathy.
- Screen appropriately (basal conditions, request microalbumin and not protein).
- Intervene early and aggressively with risk factor modification.

CAN YOU ACHIEVE SUPERIOR EFFICACY THROUGH DUAL INHIBITION?

BEFORE PRESCRIBING EZETROL™, A CHOLESTEROL ABSORPTION INHIBITOR, PLEASE CONSULT THE ENCLOSED PRESCRIBING INFORMATION. WHEN EZETROL™ IS TO BE ADMINISTERED WITH A STATIN, PLEASE ALSO CONSULT THE PRODUCT MONOGRAPH FOR THAT STATIN.

FOR EFFICACY
EZETROL™
ezetimibe
and a Statin
BETTER TOGETHER!



BIETEC PROJECT / Schering
Pharmaceuticals
Kenilworth, NJ, USA
© 2003 Schering-Plough

™ Trademark used under license.
EZT-03-CDN-4420186-JA

Microalbuminuria

Hyperlipidemia and smoking are also risk factors for microalbuminuria and diabetic nephropathy, and should be aggressively modified.¹⁰⁻¹²

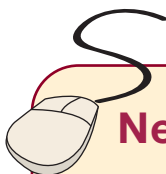
The role of annual microalbuminuria testing is less clear after diagnosis and institution of ACE-I or ARB therapy, blood sugar and BP control. Most physicians recommend continued surveillance to assess response to treatment and the progression of disease.

So, what's a little protein?

It is microalbuminuria; a marker, if persistent, of eventual diabetic kidney disease and of cardiovascular death. It is measurable early in diabetes and modifiable to slow and hopefully halt the progression to end-stage renal failure. CME

References

1. Gerstein HC, Mann JF, Yi Q, et al: Albuminuria and risk of cardiovascular events, death and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286(4):421-6.
2. Ginsberg JM, Chang BS, Matarese RA, et al: Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 1983; 309(25):1543-6.
3. Meltzer S, Leiter L, Daneman D, et al: 1998 Clinical practice guidelines for the management of diabetes in Canada. *CMAJ* 1998; 159(Supplement 8):S1-29.
4. American Diabetes Association: Standards of care for patients with diabetes mellitus. *Diab Care* 2002; 25:S33-49.
5. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to Type II diabetes. *N Engl J Med* 2001; 345(12):851-60.
6. Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with Type II diabetes and nephropathy. *N Engl J Med* 2001; 345(12):861-9.
7. Mogensen CE, Neldam S, Tikkanen I, et al: Randomised controlled trial of dual blockage of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: The candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; 321(7274):1440-4.
8. Sinzinger H, Kritiz H, Furberg CD: Atorvastatin reduces microalbuminuria in patients with familial hypercholesterolemia and normal glucose tolerance. *Med Sci Monit* 2003; 9(7):PI88-92.
9. Eliasson, B: Cigarette smoking and diabetes. *Prog Cardiovasc Dis* 2003; 45(5):405-13.
10. Hovind P, Tarnow L, Rossing K, et al: Decreasing incidence of severe diabetic microangiopathy in Type I diabetes. *Diab Care* 2003; 26(4):1258-64.



Net Reading

1. Hypertension, Dialysis & Clinical Nephrology: www.hdcn.com

www.stacomcommunications.com



For an electronic version of this article, visit:
The Canadian Journal of CME online.