Key opinion update: Microalbuminuria test methods

Perspectives spoke with Chris Price about the recent changes around microalbumin testing found within the 2008 American Diabetes Association recommendations, Standards of Medical Care in Diabetes.

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Christopher Price, MD, is a Visiting Professor in Clinical Biochemistry at the University of Oxford, UK, with primary interests in point-of-care testing and evidence-based laboratory medicine.

In addition, Dr. Price is a Fellow of the Royal College of Pathologists, the Royal Society of Chemistry, and the National Academy of Clinical Biochemistry.

Based in Oxford, Dr. Price has researched and authored several articles on the use of albumin testing to monitor the risk of kidney disease in high-risk individuals.

What is microalbuminuria?

PRICE: Microalbuminuria is a small, but significant, increase of albumin excretion into the urine. It differs from macroalbuminuria, which means a large increase of albumin in the urine.
The expected range for microalbuminuria is 30 to 300 mg per 24 hours. People with normal levels of urinary albumin have less than 30 mg per 24 hours. People with macroalbuminuria have more than 300 mg per 24 hours of urinary albumin.

Is microalbumin a protein?

PRICE: No. Actually the term microalbumin is a misnomer. There is no such thing as "microalbumin". We are always measuring albumin but when performing a microalbumin test, we are looking for levels that fall above normal or 30 mg per 24 hours. We call it microalbumin because we are trying to determine if the albumin is there in small or micro levels above that expected in a non-kidney-diseased healthy individual.

How does albumin get into the urine?

PRICE: There are two ways that this can occur. A small amount of albumin is normally filtered into the urine through the kidney glomeruli but most of it is then reabsorbed by the kidney tubules. The second situation is one where there is increased vascular permeability. In this situation, albumin can leak through the walls of the kidney tubules into the urine.

What types of disease stages does the microalbuminuria test detect?

PRICE: The test detects any condition where there is damage to the glomeruli of the kidney. This includes classical hypertension, pre-eclampsia, diabetes, and nephrotic syndrome, a situation where there is an increase in the porosity of the glomerulus.
Any condition that causes an acute phase response will increase vascular permeability causing albumin levels to increase in the urine. This is why microalbuminuria is believed to be a cardiac risk factor.

Why is this test so important?

PRICE: Because it is one of the best markers to show an early indication of deteriorating renal function and increased vascular permeability. It may also have an interesting potential for monitoring blood pressure treatment. Blood pressure measurements can vary widely and hence do not always give an accurate representation of what is happening with the patient.
It is known that patients with high blood pressure levels have increased levels of albumin, or microalbuminuria, and this in itself can be toxic to the kidneys. Hypertension medications decrease albumin levels in the urine and, hence, may be good monitors of their efficacy.

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Early detection is key

Diabetes is the most common cause of kidney failure in Europe and the US. With prompt detection the key to prevention, elevated urine albumin levels are providing an early warning sign for physicians.

There are more than 200 million diabetics worldwide. By 2030, this number is predicted to double.[1] In the US alone, 23.6 million people, or 7.8 percent of the population, have diabetes. Approximately 18 million (76 percent) have been diagnosed, with the other 24 percent of diabetics going undiagnosed.[2]

There are several different types of diabetes with the most prevalent being type 1 and type 2. Type 1 diabetes develops when the body's immune system destroys the pancreatic beta cells which produce insulin, the hormone that regulates blood glucose. Type 1 diabetes must have insulin delivered by injection or a pump. Type 2 diabetes typically begins as insulin resistance, a disorder where cells increasingly stop using insulin properly, ultimately ending in the inability of the pancreas to produce insulin. It is important to note that type 2 diabetes accounts for approximately 90 percent of all diagnosed cases.[2] The estimated prevalence of diabetes (diagnosed and undiagnosed) according to age is shown in Figure 1. The differentiation of type 1 vs. type 2 diabetes is important as we move onto discussing kidney disease as a comorbidity of diabetes.

Managing diabetes is tough, especially for children and young adolescents. There is the constant monitoring of food intake, weight, and exercise programs. Adults are cautioned to restrict alcohol and tobacco use. One hundred percent of type 1 diabetics and a smaller proportion of type 2 diabetics require insulin injections throughout the day to survive. Many diabetics also need to take medication to reduce cholesterol and/or blood pressure levels, two very strong contributors to the onset or worsening of their disease. Diabetics are also at increased risk of other serious issues, such as blindness, kidney damage, cardiovascular disease, and lower-limb complications.

Lifestyle and medication self-management is a key step towards maintaining and improving health outcomes and quality of life.[2]

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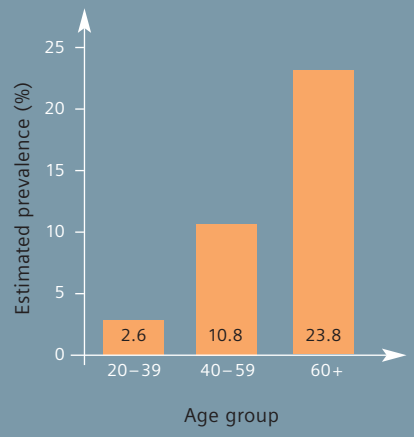

1 Estimated prevalence of diagnosed and undiagnosed diabetes in people aged 20 years or older, by age group, in the US (2007).

The link between diabetes and kidney disease

As mentioned above, kidney disease, otherwise known as renal disease, can occur as a direct result of diabetes. According to the American Diabetes Association (ADA), 20 to 30 percent of diabetics eventually develop renal disease. Diabetes is the most common single cause of kidney failure, also called end-stage renal disease (ESRD), in the US and Europe.[3]
As we eat and digest protein, our body creates waste which is eliminated through the blood stream and then through urine. The kidney acts as a filter to prevent essential substances (e.g. proteins) from moving into the urine. In diabetes, high blood sugar levels can cause damage to the filters, putting extra strain on the kidneys. After many years of strain, the kidneys will start to leak protein into the urine eventually resulting in ESRD.

Monitoring albumin levels in urine as a method to prevent kidney disease

Early detection is the key to preventing kidney disease. There are no symptoms in the earliest stages, so it's vital to test for microalbuminuria on a regular basis. Kidney disease can be prevented and/or reversed with treatment if detected early. The best way to assure early detection is to measure the levels of the protein, albumin, in urine. In non-diseased individuals, the level of albumin should be less than 30 mg per 24 hours. When levels fall between 30 and 300 mg per 24 hours, this is called microalbuminuria. Concentrations in this range are a warning sign to the physician that

albumin is spilling into the urine at a level that may place a diabetic patient at risk for kidney disease.

Testing for microalbuminuria

The American Diabetes Association guidelines recommend annual testing for microalbuminuria in patients with type 1 diabetes starting five years after diagnosis.[4]

Because of the difficulty in determining type 2 diabetes onset, annual testing for these patients should begin at diagnosis. There are three methods of microalbuminuria testing:

1) Measurement of the albumin/creatinine ratio in a random spot collection
2) 24-hour collection with creatinine, allowing the simultaneous measurement of creatinine clearance
3) Timed collection (e.g. four-hour overnight).

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Collection method	Non-disease	Microalbumin	Macroalbumin
Random spot collection	< 30 mcg/mg	30 – 299 mcg/mg of creatinine	> 300 mcg/mg of creatinine
24-hour collection	< 30 mg/24 hours	30 – 299 mg/24 hours	> 300 mg/24 hours
Timed collection	< 20 mcg/minute	20 – 199 mcg/minute	> 200 mcg/minute

2 Albumin level ranges by collection type in diseased and non-diseased individuals[4, 5]

The first method is often preferred because it is the easiest to perform in an office or clinic setting and generally provides accurate information.

Differences in method collection can cause confusion regarding expected ranges for each method and the units of measurement. Figure 2 defines the most common ranges for each collection type.

Standards of Medical Care in Diabetes – 2008 recommendations for prevention and management of kidney disease in diabetics[5]

In January 2008, the American Diabetes Association published new recommendations detailing actions for testing, diagnosis, and therapy to improve the health outcomes of patients with diabetes. These recommendations included treatment goals and other tools by which healthcare professions can evaluate the quality of diabetic care.

Does the microalbuminuria test offer any advantages to estimated glomerular filtration rate (eGFR) testing for kidney disease?

PRICE: The strength of eGFR testing is that the calculation includes a serum creatinine level, which is needed to confirm the stage of kidney disease. It is a tried and true test that has been in place for many years. Utilizing an albumin/creatinine ratio test provides earlier detection of kidney disease and is much easier to conduct for the patient and the healthcare provider in that you can use a single void vs. a 24-hour collection.
eGFR testing levels can be affected by decreased creatinine levels in patients with decreased muscle mass (children and the elderly), leading to less than accurate results.

If the microalbuminuria test is positive for kidney disease, is follow-up testing suggested and, if yes, why?

PRICE: If a semi-quantitative method is being used, it is suggested that a positive ratio result be followed with another test in four to six weeks to assure that the microalbuminuria is persistent. After another positive result, the sample should be fully quantitated via another method. If the test measures albumin alone using a single-void of urine, a follow-up test should be performed to assess the albumin/creatinine ratio. The alternative follow-up would be to collect a 24-hour specimen but this approach is known to have limitations.
The American Diabetes Association (ADA) 2008 position statement on the Standards of Medical Care in Diabetes[1] recommends that due to the variability in urinary albumin excretion, an albumin/creatinine ratio test is preferred and that two of three specimens collected within a three- to six-month period should be abnormal before a patient is considered to have diabetic nephropathy. The variability seen is typically associated with rises and fall in blood pressure. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension can all be causes of elevated urinary albumin excretion over baseline values.

When should a physician start testing a diabetic patient for renal disease?

PRICE: This depends upon whether they have type 1 or type 2 diabetes. With type 1 diabetes, recommendations indicate testing five-years post diagnosis. With type 2 diabetes, testing should start

In this ADA publication, recommendations are also made concerning the prevention of nephropathy, a progressive form of kidney disease affecting the capillaries of the glomeruli – one of the key components needed for effective filtration of blood within the kidney.

The following is a summary of several of the key points on this subject:

Testing for nephropathy

- Perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of greater than five years and in all type 2 diabetic patients, starting at diagnosis.
- Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate glomerular filtration rate (GFR) and stage the level of chronic kidney disease, if present.

Assessment of albuminuria status and renal function

- Testing for microalbuminuria can be performed by measurement of the albumin/creatinine ratio in a random spot collection (preferred method). 24-hour or timed collections are more burdensome and add little to prediction or accuracy.
- Measurement of a spot urine for albumin only, whether by immunoassay or by using a dipstick test specific for microalbumin, without simultaneously measuring urine creatinine, is somewhat less expensive but susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors.
- Because of variability in urinary albumin excretion, two of three specimens collected within a three- to six-month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds. Exercise within 24 hours, infection, fever, congestive heart failure (CHF), marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values. Information on presence of abnormal urine albumin excretion in addition to level of GFR may be used to stage chronic kidney disease.

Conclusion

Diabetic patients are at increased risk for kidney disease due to the damage by increased levels of blood glucose. The presence of microalbuminuria is an indicator of the early stages of kidney disease and should be performed on type 2 diabetics upon diagnosis and type 2 diabetics five years after diagnosis. The benefits of early microalbuminuria testing, identification, and treatment can be linked to early detection and treatment of kidney disease ultimately resulting in improved health outcomes for diabetic patients.

Although many microalbuminuria tests offer rapid results in a simple-to-use format, testing is not utilized by many

immediately. This is due to the fact that by the time most type 2 diabetics are diagnosed, they most likely have had the disease for some period of time and hence are at a greater risk for renal disease also.

What action might a physician take once a patient is confirmed for kidney disease?

PRICE: Once again, this is quite dependent upon the patient and the etiology of their condition. In patients with hypertension or high blood pressure, a physician might use a combination of ACE inhibitors and diuretics. In other patients, they may use calcium channel blockers. In either case, urinary albumin levels should continue to be monitored as a mechanism of determining the efficacy of the medication. For this purpose, a quantitative measurement, such as that given with the Siemens DCA analyzer, should be used.

The most recent ADA recommendations have been updated in regards to microalbuminuria testing. What are the major points?

PRICE: The ADA recommendations put a stronger emphasis on the albumin/creatinine ratio for spot samples as the preferred method. Additionally, recognition that without the creatinine ratio, the methods are more prone to false positives and false negatives due to the varying urinary output.
False positives via spot sample testing is typically resolved once the quantitative confirmatory testing is conducted. False negatives are a big problem though, as there is no strategy for dealing with them other than to take another sample at the next check-up and hope that microalbuminuria is detected then. However, since "time is nephrons," this approach is not optimal.

The recommendations indicate that an albumin/creatinine ratio is preferred in the assessment of microalbuminuria. Can you explain why?

PRICE: We have spoken a bit about this already but the major point here is that albumin excretion rates vary during the course of the day. Expressing as a ratio to the urine creatinine level takes this into account and normalizes the albumin in a spot sample. The only way to get around this is to gather a 24-hour urine sample or collect a timed sample (e.g. four hours) and compare the results to a reference range for that exact same time period within the day.

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System	Result Interpretation
CLINITEK® 50	Semi-quantitative
CLINITEK Status® Urine Chemistry Analyzer	Semi-quantitative
CLINITEK Advantus™ Urine Chemistry Analyzer	Semi-quantitative
CLINITEK Atlas® Urine Chemistry Analyzer	Semi-quantitative
ADVIA® 1200/1650/1800/2400 Clinical Chemistry Systems	Quantitative
Dimension® Integrated Chemistry Systems	Quantitative
Dimension Vista® Intelligent Lab System	Quantitative
DCA 2000+® Analyzer	Quantitative
DCA Vantage® Analyzer	Quantitative

3 Microalbumin testing methods offered by Siemens Healthcare Diagnostics

healthcare professionals as a method to monitor the start or progression of kidney disease in their diabetic patients. Education of patients and healthcare providers in regard to the types of microalbuminuria tests available is a primary focus of Siemens Healthcare Diagnostics.

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References

1 www.medicalnewstoday.com/articles/63045.php
2 National diabetes statistics; prevalence of diagnosed and undiagnosed diabetes in the United States, all ages, 2007. National Diabetes Information Clearinghouse. Available at: www.diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#allages. [Accessed 30 December, 2008].
3 American Diabetes Association. Nephropathy in diabetes. Diabetes Care 2004; 27(Suppl 1):S79-83.
4 Iltz JL, Setter MS, Campbell RK. Microalbuminuria screening for patients with diabetes. US Pharm 2005; 5:HS3-7. Available at: www.uspharmacist.com/index.asp?show=article&page=8_1490.htm [Accessed 30 December, 2008].
5 American Diabetes Association Position Statement. Standards of Medical Care in Diabetes – 2008, Diabetes Care 2008; 31(Suppl 1):S12-54.

What microalbuminuria test method is preferred for physicians' offices?

PRICE: The simple dip and read urinalysis strip that is waived in the US under the Clinical Laboratory Improvement Act (CLIA) is ideal for physician's offices. This test is convenient, easy to use, and provides automatic calculation of ratio results when using the strip with a urine analyzer.

The accepted practice for many years has been to do a microalbuminuria test via a 24-hour urine sample. Do you believe this is still the best way to measure microalbuminuria?

PRICE: Utilization of 24-hour urine is not convenient for the patient or for the healthcare professionals managing the patient. Collection is cumbersome leading to poor patient compliance (e.g. missed voids) and storage in the laboratory is not user-friendly. There is also high inter-individual variation. A simple urinalysis strip yielding an albumin to creatinine ratio using a random void eliminates this inconvenience.

Do you have any other comments for our readers?

PRICE: It is important to stress the fact that semi-quantitative methods are best used as a rule-out of kidney dysfunction and not as a rule-in. Semi-quantitative methods should be followed up with a quantitative method which will take care of any false-positive results.
Secondly, laboratorians tend to utilize correlation coefficients when comparing their existing method vs. a new investigatory method. In the case of comparing a quantitative urinary albumin method vs. semi-quantitative point-of-care methods, this type of statistical analysis may not be the best. I recommend focusing on the number of false negatives between the two methods. In this manner, you will see that the semi-quantitative methods yield very few false negatives and that is the most important parameter to assess. In this case, the workflow and patient benefits of the semi-quantitative point-of-care methods can not be overlooked.

Reference

1 American Diabetes Association. Standards of Medical Care in Diabetes – 2008. Diabetes Care 2008; 31:S12-54.