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Review

Testing for Albuminuria in 2014

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ABSTRACT

Routine quantification of urinary albumin levels is recommended for all Canadians with diabetes, yet many controversies remain when interpreting these tests. Elevated levels of albuminuria have traditionally been labeled as either microalbuminuria, representing 30 to 300 mg of albuminuria per day (a range not reliably picked up by conventional urine dipsticks), or as overt nephropathy, representing more than 300 mg per day and usually identifiable by dipstick. The random urine albumin-to-creatinine ratio is a convenient test that can predict reliably the total daily protein excretion. The 30 mg per day upper limit of normal was selected to be a threshold far above the normal albumin excretion seen in healthy people. However, recent studies have shown that elevations of albumin excretion below the microalbuminuria threshold are associated with increased cardiorenal risk, suggesting that the 30 mg per day level may be set too high. Recently, the Canadian Diabetes Association Clinical Practice Guidelines changed the threshold for abnormal urine albumin-to-creatinine ratios to be 2.0 mg/mmol for both men and women. As a result, more women will be identified as having abnormal levels of albuminuria. However, these women will be correctly identified as having increased cardiorenal risk. It is important to note that people with diabetes who have abnormal levels of albuminuria are among patients at the highest risk for cardiorenal disease. These risks can be reduced by using the strategies outlined in the guidelines put forth by the Canadian Diabetes Association.

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RÉSUMÉ

La quantification systématique des concentrations d'albumine dans les urines est recommandée aux Canadiens souffrant de diabète. Cependant, l'interprétation de ces analyses fait encore l'objet de plusieurs controverses. Les concentrations élevées d'albumine ont traditionnellement été étiquetées comme une microalbuminurie, qui correspond à une albuminurie de 30 à 300 mg par jour (un intervalle détecté de manière non fiable par les bandelettes réactives traditionnelles pour analyse d'urine), ou comme une néphropathie manifeste, qui correspond à une albuminurie de plus de 300 mg par jour, habituellement décelable par la bandelette réactive. Le rapport albuminurie/créatininurie dans un échantillon d'urine aléatoire est une analyse appropriée pour prédire de manière fiable l'excrétion quotidienne totale des protéines. La limite supérieure de la normale de 30 mg par jour était choisie comme un seuil nettement supérieur à l'excrétion normale d'albumine observée chez les personnes en bonne santé. Cependant, de récentes études ont montré que les augmentations de l'excrétion d'albumine inférieures au seuil définissant la microalbuminurie sont associées à l'augmentation du risque cardiorénal, ce qui suggère qu'une concentration de 30 mg par jour serait trop élevée. Récemment, les lignes directrices de la pratique clinique de l'Association canadienne du diabète ont modifié le seuil des rapports albuminurie/créatininurie dans un échantillon d'urine anormal à 2,0 mg/mmol tant chez les hommes que chez les femmes. Par conséquent, plus de femmes seront considérées comme ayant des concentrations anormales d'albumine. Cependant, ces femmes seront pertinemment considérées comme étant exposées à une augmentation du risque cardiorénal. Il est important de noter que les personnes souffrant de diabète qui ont des concentrations anormales d'albumine sont parmi les patients étant davantage exposés à un risque de maladie cardiorénale. Ces risques peuvent être réduits en utilisant les stratégies exposées dans les lignes directrices mises de l'avant par l'Association canadienne du diabète.

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Introduction

Testing the urine for albumin is a common clinical practice, particularly in people with diabetes. However, there are often questions regarding how to interpret these tests, and recently the normal value ranges for urinary albumin tests have changed. In this article, I review the history of urinary albumin testing, the clinical significance of microalbumin, and the rationale behind changing the threshold for microalbuminuria in women with diabetes.

The History of Microalbuminuria

In early studies of people with type 1 diabetes and nephropathy, kidney disease could be identified even when the serum creatinine level was normal. This disease was evident by the presence of significant proteinuria (1). In decades past, the most common way of testing for urinary protein was through the use of a urine dipstick. However, conventional urine dipsticks are not particularly sensitive and become reliably positive only when the urinary albumin concentration exceeds about 200 mg/L (equivalent to roughly 300 mg/day). This is much higher than the normal amount of albumin in the urine, and the result was a situation in which there was a range of albuminuria that was clearly abnormal but was below the threshold that could be picked up easily by a urine dipstick and would be identified only if the patient performed a 24-hour urine collection.

Terms were developed to describe these ranges of albuminuria. *Microalbuminuria* refers to a urinary albumin concentration that is abnormally high but not high enough to be picked up by a simple dipstick. *Overt nephropathy* refers to a range of albuminuria that is high enough to be detected by a dipstick (2). More recently, it has been suggested that these terms be changed to *moderately increased* and *severely increased* albuminuria, respectively (3).

Testing for Albuminuria

The gold standard for quantifying albumin in the urine remains the 24-hour urine collection. However, these collections are inconvenient, unpopular and often done incorrectly. Random urine samples are an appealing alternative; however, the albumin quantification in random urine samples can be inaccurate, primarily because of differences in urine concentration. For example, a highly concentrated urine sample such as the typical first morning urine may make the urine albumin level appear falsely elevated. Conversely, a very diluted urine may wash out an abnormally high urine albumin level and falsely report a normal value. For this reason, methods of measuring urine albumin levels in random specimens through laboratory quantification or the use of special microalbuminuria dipsticks may not predict accurately the actually daily albumin excretion (4).

However, adjusting for the urine concentration in a random urine sample can greatly improve the accuracy of the test (5). The urinary creatinine can be used as a rough measure of urinary concentration. The higher the concentration of creatinine in the sample, the greater the concentration in the urine. Dividing the urinary albumin concentration by the concentration of creatinine greatly improves the accuracy of the random urine measurements. A random urine albumin-to-creatinine ratio (ACR) has a sensitivity and specificity of about 95% when compared against a 24-hour urine collection (4). Because random urine samples are more convenient, the random urine ACR is the test of choice when screening for nephropathy (2).

How normal is "normal" albuminuria?

The normal values for urinary albumin excretion are somewhat arbitrarily selected. In young adult men and women, the usual albumin excretion is less than 10 mg per day, equivalent to an ACR of about 0.7. For example, in the Framingham Heart Study, the median ACR was about 0.5 in men, and about 0.8 in women. Similarly, in the Third Copenhagen Heart Study, the highest quartile of albuminuria had about 7 mg per day of albumin or higher. The 30 mg per day top limit of the normal range was selected to be 3 times higher than the usual maximum albumin excretion, safely distant from normal values (3), but 95% of healthy people have albumin excretions below this level (6).

The validity of this threshold was initially thought to be high because studies demonstrated that the degree of albuminuria is a strong predictor of progressive kidney disease as well as of the risk for cardiovascular events and death and because this risk began in the microalbumin range, with escalating risks as albuminuria increased. For example, the Heart Outcomes Prevention Evaluation (HOPE) study examined almost 10 000 people at high cardiovascular risk over 5 years and found that the presence of microalbuminuria was associated with a 17.5 times greater risk for progressing to overt nephropathy (7) and approximately a doubling of the risk for cardiovascular events and death in people with and without diabetes (8).

However, recent studies have found that both renal and cardiovascular risks begin to increase at levels currently considered to be in the "normal" range. The HOPE study demonstrated that among people with diabetes, the risk for developing overt nephropathy was 20 times higher in those with ACRs above 1.57 than in those with ACRs below 0.21 (7). The risk for death was about 50% higher in those with ACRs above 1.46 than in those with ACRs below 0.22 (relative risk [RR] 1.46; 95%; CI [confidence interval] 1.21 to 1.75) (9). These results were similar in both men and women. The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) study followed 1209 people with diabetes and hypertension who had albumin excretion below the microalbumin level for a median of 3.6 years (10). Remarkably, any urinary albumin excretion above about 2 mg per day was associated with progressively increasing cardiovascular risk (11).

These studies and many other similar results have called into question the appropriateness of setting the upper limit of normal albuminuria as high as 30 mg per day. This level might be "safe," being far from the normal level of albumin excretion, but setting the bar this high appears to under-diagnose people who are at increased risk for renal and cardiac disease. It is important to remember that the random urine ACR cutoffs that we have used were selected based on their ability to predict a urinary albumin excretion of 30 mg per day, so they are also likely to be set too high.

Changing the normal values for women

Prior to the 2013 Canadian Diabetes Association (CDA) Clinical Practice Guidelines, the upper limit of normal for a random urine ACR was 2.0 for men and 2.8 for women (12). These values were selected as having the highest sensitivity and specificity for predicting a 24-hour albumin excretion of 30 mg per day. Muscle mass is the major determinant of daily creatinine production. On average, men have more muscle mass than women and, as a result, have a higher daily urinary creatinine excretion and a higher urinary creatinine concentration in a random specimen. Having a higher value in the denominator of the albumin-to-creatinine ratio means that more muscular people have lower ACRs for the same albumin concentration in a random urine sample. This has been the historical basis for different ACR cutpoints in men and women. Although both sexes had the same albuminuria cutpoint of 30 mg