Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Measurement of Urinary Albumin

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Slide 1:
Hello, my name is Lorin Bachmann. I am an Assistant Professor in the Department of Pathology and Co-Director of Clinical Chemistry at Virginia Commonwealth University. Welcome to this Pearl of Lab Medicine on Measurement of Urinary Albumin.

Slide 2:
Chronic kidney disease (CKD) is a significant global health problem. Data from National Health Surveys indicates that the prevalence of CKD in the US is approximately 10-12%. CKD is of particular concern in diabetes where the prevalence of CKD in the diabetic population is estimated at 20-40%, and diabetic nephropathy is the single most common cause of kidney failure. In addition to increased risk of kidney failure and all-cause mortality, CKD is a significant risk factor for cardiovascular disease and cardiac mortality.

Slide 3:
Urinary albumin is an important biomarker for evaluation of kidney disease. Abnormal excretion of urine albumin is an indicator of early kidney damage and is used in combination with glomerular filtration rate (GFR) to screen, evaluate, and classify chronic kidney disease (CKD), according to guidelines issued by the National Kidney Foundation (NKF)-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and the Kidney Disease: Improving Global Outcomes (KDIGO) group. The goals for these guidelines include improvement of CKD detection, therapy, and ultimately, improvement of patient outcomes.

Routine measurement of urine albumin excretion is also recommended by the American Diabetes Association (ADA) for assessment of diabetic nephropathy. Excretion of urine albumin is not only used for diagnosis and classification of kidney disease in diabetic and nondiabetic individuals, but is also used for prognosis of CKD progression and cardiovascular risk. Albuminuria has been associated with increased risk of myocardial infarction, stroke, and cardiac mortality.

In addition to its use as a diagnostic and prognostic tool, excretion of urine albumin is used to guide kidney disease therapy and to monitor the effectiveness of therapy for slowing the progression of kidney disease.

Slide 4

The normal concentration of albumin in plasma is approx 4.5 g/dL or 45 g/L. In the healthy kidney, loss of plasma albumin into the urine is prevented by the glomerular filtration barrier. However, a small concentration of albumin, approximately 10 mg/L, is filtered through the barrier and is normally present in the glomerular ultrafiltrate. 99% of this albumin is subsequently reabsorbed into the proximal tubule. The excretion of urine albumin may be increased by either glomerular injury, increased permeability of the glomerular vasculature, such as that due to inflammation, or damage to the proximal tubules.

Slide 5:

Historically, the urine albumin excretion rate (AER), expressed as the albumin concentration per unit time, was the gold standard method for measurement of albuminuria. The AER was traditionally measured using a 24-hr urine specimen. However, due to the difficulties involved in accurate collection of a 24-hr urine sample, the use of the ratio between the urine albumin concentration and the creatinine concentration, also called the albumin-to-creatinine ratio (ACR), is recommended as a surrogate marker for the AER. The ACR has been shown to correlate well with the albumin excretion rate, a finding which will be discussed further in the next few slides. Inclusion of the creatinine concentration component in the ACR corrects for variability in urine volume due to hydration status. In clinical practice, several urine sample collection types may be obtained including the 24-hr timed urine sample, the first morning void sample, or a random urine sample. The next 2 slides show data comparing the ACR measured from these different urine collection types.

Slide 6:

This study included 1,513 patients with diabetic nephropathy. The receiver operating characteristic curve was generated for the combined endpoints of kidney failure or doubling of serum creatinine. As can be seen from this data, the diagnostic accuracy of the ACR from a first morning void (FMV) specimen performs similarly, or even slightly better, than that using the urine albumin excretion rate obtained from at 24-hr urine sample.

Slide 7:

These two graphs show box and whisker plots for ACR from a study that included urine samples collected from 241 subjects with stable hypertension. This data is representative of the findings from numerous other studies on performance of ACR for different urine collection types. As can be seen from the first graph, the ACR from the first morning void sample correlated more closely with the 24-hr timed sample, as compared to the random sample. The second graph shows the intraindividual coefficients of variation obtained for each collection type. This data demonstrates that the intraindividual CVs for the first morning void specimen better approximate the results obtained from the 24-hr urine sample. The random sample had substantially more variability, which would adversely affect the ACR interpretation when fixed clinical decision thresholds are applied.

Slide 8:

Based on the types of studies illustrated in the previous slides and the difficulty of collection for a timed urine sample, use of the ACR is universally recommended by clinical practice guidelines. The use of urine

albumin concentration in the absence of creatinine is not recommended. In addition, the NKF-KDOQI guidelines recommend use of the first morning void sample whenever possible. In the event that a first morning void is not available, the use of a random urine specimen is considered "acceptable." However, an elevated random urine albumin should always be confirmed by a FMV sample.

Slide 9:
The ACR is expressed in different measurement units among different clinical practice guidelines. Appropriate unit conversions are shown in this slide. A joint National Kidney Disease Education Program/International Federation of Clinical Chemistry (IFCC) Laboratory Working Group on Standardization of Urine Albumin Measurement has recommended that the ACR should be expressed in SI units; however, no consensus on reporting units has been established to date.

Slide 10:
So what value would constitute an elevated ACR? Numerous practice guidelines, such as the ADA, utilize 2 terms for elevated ACR. "Microalbuminuria" refers to a small elevation of urine albumin. The ADA has defined microalbuminuria as ACR in the range of 30-299 mg/g (3.4-33.9 mg/mmoL) creatinine. Evidence of microalbuminuria in 2-3 specimens within a 3-6 month period marks the early stages of diabetic nephropathy. The ADA guidelines advise immediate implementation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy if microalbuminuria persists.

"Macroalbuminuria" is the presence of ≥ 300 mg/g (33.9 mg/mmoL). The progression from microalbuminuria to macroalbuminuria is associated with increased risk of kidney failure and other complications, and suggests that a more aggressive therapeutic approach is needed to slow the progression of diabetic nephropathy. Therefore, continued monitoring of the ACR to assess response to therapy and to evaluate kidney disease progression is considered "reasonable."

Slide 11:
To avoid confusion regarding the terms "micro-" and "macro-" albuminuria and to reflect the fact that the magnitude of urine albumin excretion represents a continuous scale of kidney damage, the National Kidney Disease Education Program has recommended the use of a single term, "urine albumin." Prior to 2009, the NKF-KDOQI/KDIGO guidelines recommended that the diagnosis of CKD could be confirmed by demonstration of an ACR ≥ 30 mg/g (3.4 mg/mmol) upon repeat analysis or a GFR < 60 ml/min/1.73m2 for a period of ≥ 3 months. Classification of CKD was primarily based on GFR.

Slide 12:
However, in October of 2009, meta-analysis data was presented at a KDIGO conference. This slide shows the hazard ratios for numerous outcomes plotted vs. the ACR. The study found that the hazard ratios for all-cause mortality, cardiovascular mortality, and adverse kidney outcomes were increased with increasing ACR at all levels of GFR.

Slide 13:
The meta-analysis data, presented in a report summarizing the 2009 KDIGO conference, showed an independent, graded increase in risk for CKD with increasing ACR. This report included conference recommendations suggesting that CKD should be classified based on GFR but each stage may be further stratified by ACR.

Slide 14:
Urine albumin excretion may be elevated in conditions other than kidney damage. For example, excretion may be increased with strenuous exercise, illness, inflammation, and Urinary Tract Infection (UTI). For this reason, most guidelines recommend that albuminuria should be confirmed on more than one occasion. The next few slides review several urine albumin measurement and reporting issues that have not yet been resolved.

Slide 15:
Urine albumin is measured using a variety of analytical techniques including immunoassay, colorimetric test strip, and size exclusion chromatography. However, variability among methods has been reported. Improvement of agreement among methods has been limited by lack of an available reference system to enable method standardization. A Joint NKDEP/IFCC Laboratory Working Group has been convened to facilitate the standardization of urine albumin methods. The goals of this working group are to develop a reference measurement procedure for urine albumin, to develop new albumin reference materials and assess their commutability characteristics, to assess the current state of harmonization among methods, and to evaluate the feasibility of utilizing the reference system to standardize methods.

Slide 16:
Another issue that affects interpretation of ACR results is that single decision thresholds may not be appropriate for all patient populations. This slide shows data suggesting that ACR decision thresholds may be influenced by gender. The study measured the albumin excretion rate (AER) and the corresponding ACR for 218, non-diabetic healthy individuals. At equivalent AER values of approximately 30 µg/min, the ACR for males was lower than that for females. This observation is due to the fact that urine creatinine is higher in males vs. females. Therefore, at equivalent AERs, the ACR for men will be lower than the ACR for women. This data, as well as similar data from additional studies, suggests that the ACR clinical decision thresholds for men vs. women may be different.

Slide 17:
In this large study, the relationship of hazard ratio for cardiovascular mortality was plotted vs. ACR. The hazard ratio for cardiovascular mortality increased in a continuous manner with urine albumin concentration, suggesting that single decision thresholds for ACR may not adequately describe cardiac risk.

Slide 18:

This slide shows the results of a meta-analysis including 21 cohorts that represented 1.2 million patient results. In this study, an increase in ACR from 5 to 10 mg/g (0.6-1.1 mg/mmol), which is well below the current recommended threshold of 30 mg/g (3.4 mg/mmol), resulted in a hazard ratio of 1.29 for cardiovascular mortality, suggesting that the current ACR threshold may need to be lowered. However, the current lack of method standardization needs to be addressed before utilization of decision thresholds at lower concentrations will be practical.

Slide 19:

In conclusion, excretion of urinary albumin is an important marker for diagnosis, classification, prognosis, and monitoring of therapy for CKD. For best accuracy, excretion of urine albumin should be measured using the ACR obtained from a FMV specimen. Efforts to accomplish standardization of urine albumin methods are underway to facilitate increased applicability of clinical decision thresholds. Use of single ACR decision thresholds is limited by influences of gender and the fact that the risks of CKD progression and its complications increase in a continuous manner with ACR. Furthermore, the current ACR clinical decision thresholds may not be low enough to identify all patients at increased risk.