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ORIGINAL ARTICLE

Urine albumin: Recommendations for standardization

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A joint working group of the National Kidney Disease Education Program (NKDEP, USA) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has the objective of improving the standardization of sample collection, measuring and reporting for urine albumin concentration. The group held a conference in March 2007 to frame the issues and identify solutions for standardization. A full manuscript is in development reporting on the proceedings and recommendations from that conference. A brief summary is provided in this report.

Current routine measurement procedures use immunoassay with nephelometric, turbidimetric or enzyme-linked measurements. External quality assessment programmes in several countries have shown a lack of agreement in results and in the units used to report results among different methods and laboratories. Surveys of clinicians and clinical laboratories have identified a lack of uniformity in sample collection, result-reporting and interpretation practices. Diabetes and kidney disease professional societies have developed clinical practice guidelines for interpreting urine albumin results. Consequently, the clinical laboratory profession is challenged to standardize the sample collection, albumin and creatinine measurements and reporting practices.

Most professional society guidelines recommend either a random or first morning sample, rather than a 24-h collection. It is generally accepted that a random sample is more variable than a first or second morning sample, but it is not clear which of the latter two samples is preferred. The most common practice is to report the albumin:creatinine ratio (ACR), because this value is more consistent, regardless of the sample collection conditions, and correlates well with the albumin excretion rate. However, there are different units used for the ACR {(mg albumin)/(g creatinine) and (mg albumin/mmol creatinine)} that can complicate implementation of clinical guidelines for interpretation.

Current professional society guidelines use fixed cut-points for classification of positive albuminuria and its relationship to kidney damage and risk for

cardiovascular complications. However, the relationship between albumin excretion, kidney damage and cardiovascular disease is a continuum that is also influenced by factors such as age and gender. Additional investigation is needed to clarify the appropriate decision thresholds.

Albumin is known to exist in a number of different molecular forms in both plasma and urine, including fragmented and glycosylated molecules, conformation changes due to ligand binding and a relatively wide range of matrix (e.g. pH, ionic strength) conditions. The influence of molecular forms and matrix conditions on quantitation by routine immunoassays is not well understood, but is a factor in standardizing measurements. Albumin in urine undergoes polymerization and fragmentation on storage and during freeze–thaw cycles. In addition, albumin is adsorbed to the surface of some plastic containers.

There is no Joint Committee for Traceability in Laboratory Medicine listed reference measurement procedure for urine albumin concentration. An isotope dilution liquid chromatography tandem mass spectrometry procedure has been developed at the Mayo Clinic, USA that quantitates the intact N terminal fragment of urine albumin. This procedure has attributes of a candidate reference measurement procedure.

The most commonly used reference material for routine urine albumin measurement procedures is serum protein reference material CRM 470 (39.7 g/L albumin) distributed by the Institute for Reference Materials and Measurements of the European Commission. This material must be diluted to cover a measuring range of 5–1,000 mg/L for urine measurements. A standard diluent and procedure for dilution has not been developed. For the production of a primary reference material (a “pure substance” reference material), it is important to prepare intact human serum albumin and maintain it intact by setting proper conditions to minimize structural and immuno-reactive alteration.

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A candidate urine albumin reference material has been developed under the auspices of the Japan Society of Clinical Chemistry and the Japanese Committee for Clinical Laboratory Standards and is in the process of validation and credentialing. The candidate reference material is a lyophilized preparation of purified monomeric human albumin in an aqueous buffer. The reference material was value assigned by traceability to dilutions of CRM 470 using a group of routine immunoassays that had uniform antibody binding to albumin in the reference material and in CRM 470.

The NKDEP/IFCC joint work group intends to coordinate investigation of the issues identified above and development of a reference system for urine albumin measurement. The goal is to standardize the laboratory components for urine albumin and creatinine measurements to improve use of urine albumin and the albumin/creatinine ratio in clinical practice.

Key points from the discussion

- The concept of developing a standard related to the albumin:creatinine ratio (ACR), which could vary according to the size of the individual, needs

to be further explored. There could be natural variation in GFR depending on the ratio. It may not be necessary to create an algorithm to convert ACR to anything. Work is ongoing and different patient groups need to be studied.

- There is the possibility of albumin binding to catheter walls, just as it can to plastic containers. A paper is to be published giving data on the different plastics used in their construction.
- ACR results vary depending on the time of day.
- The most variable urine specimen is the first voided morning specimen (EMU). There are data showing that the second specimen voided in the morning is most consistent for urine albumin concentration measurement.

Contributing to the discussion

J. Bonventre, A. Grubb, W. Guder.

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