NKDEP/IFCC Conference to Address Standardization of Urine Albumin/Creatinine Measurement and Reporting

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Minutes on NKDEP/LWG web site

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Objectives: Urine albumin

- Frame the issues
- Develop a path forward to improve standardization
- Impact successful implementation of clinical practice guidelines

Agenda

- Review current status of measurement and reporting
- Discussion groups to address specific issues
  - Define the measurand; what molecule(s) should be measured
  - Standardization of sample requirement and reporting
  - Calibration traceability; reference system
- Reports from discussion groups
- Consensus of current status and path forward

Current status of measurement

PT/EQA suggested:

- A range of results for the same sample
  - Influenced by non-commutability
- Urine dipstick results were highly variable
- A range of imprecision; with most acceptable within a method
- A variety of reporting units for albumin and albumin/creatinine ratio

Current status of measurement

Practice surveys suggested:

- No uniformity in sample type (timed vs. first morning vs. random collection)
- Lab recommendations for sample type were not followed
- Variability in lab provided decision limits for albumin and albumin/creatinine ratio
- Physicians react to differences that are smaller than is analytically justified
- Guidelines for the diagnosis of albuminuria were not followed
- Variation regarding treatment once albuminuria has been diagnosed

Define the measurand

- Fragmented and dimeric forms of albumin are found in urine
  - Unclear if native or due to post collection handling and storage (including freezing)
  - Some polyclonal Ab methods were relatively insensitive to fragmented forms
- Influence of pH, osmolality, contact with sediment and adsorption, centrifugation, and other sample handling factors is not well understood

Sample collection issues

- Physiologic effects that influence a result
  - Diurnal, postural, exercise influences
  - Biological variation of normal vs. impaired kidney function
  - First morning void vs. random void vs. stress condition
  - Applicable restrictions, e.g. physiological steady state, non-menstruating, free of concurrent infections, drugs, dietary supplements
- Sample handling that influences a result
  - Non-specific binding to the collection container
  - Degradation and fragmentation during storage and freeze-thaw

Reporting issues

- Nomenclature
  - Urine albumin excretion rate (UAE) is what is physiologically desired and correlates with CKD and CVD
  - “microalbumin” is confused with a different type/size of albumin rather than detecting a low concentration
  - “urine albumin” is simple and may be preferable
- Urine albumin/creatinine ratio (ACR) is used as a surrogate for UAE
  - A variety of units are used (e.g. mg/g, mg/mol) with different numeric values for decision points
- Time period of collection influences decision point
- Age, gender, race influences decision point

Measurement issues

- Influence of: labels; competitive vs. non-competitive assays; homogeneous vs. heterogeneous assays; polyclonal vs. monoclonal antibodies
- Influence of epitope for the Ab and albumin fragmented forms
- Calibration traceability to diluted CRM 470 (ERM DA470) serum protein reference material
  - Details of traceability design and measurement implementation appear to influence calibration uniformity
- No urine albumin reference material, nor reference measurement procedure at this time
- No urine creatinine reference material; do have a RMP for urine creatinine listed by JCTLM

Reference system

Mayo Clinic LC-MS candidate reference measurement procedure

- Measures N-terminal 24 peptide fragment following digestion
- Internal standards: BSA; 15N-labeled recombinant HSA
- Inter-assay CV is 12-15%
- LOQ is 10 mg/L
- Correlation to immunoassay is better than to HPLC
- Further development and characterization is in progress

Reference system

JCCLS candidate urine albumin reference material

- Purified monomeric human serum albumin (>97.5% pure)
- Characterized by amino acid analysis, SDS-PAGE, MS, HPLC
- Prepared in a buffered aqueous matrix
- Value assignment by traceability to diluted CRM 470 (human serum albumin) using selected routine measurement procedures
- Preliminary evaluation of improvement in uniformity of results among routine methods

Path forward - 1

- Publish a report describing current status and recommendations for addressing the issues
  - Establish clinical requirements for measurement performance
  - Develop recommendations for nomenclature and reporting
- Define specifications for routine method robustness to range of matrix components in urine samples

Path forward - 2

- Understand current method performance
  - Conduct a round robin evaluation of routine and higher order methods using a panel of native urine samples
    - Include: candidate RMs , diluted CRM470, representative EQA samples, urine containing modified albumin forms
    - Evaluate adsorption to collection, storage, and sample containers
    - Evaluate effect of centrifugation of sediment

Path forward - 3

- Develop a reference system for urine albumin
  - Define the measurand
    - What is native in fresh urine
    - Can the N-terminal 24 peptide be used
  - Define a reference material for urine albumin
    - Diluted CRM 470
    - JCCLS candidate material
    - Value assignment
  - Establish a reference measurement procedure
    - Continue development of Mayo LC-IDMS method

Path forward - 4

- Develop a reference system for urine creatinine
  - Reference measurement procedure exists
    - Only 1 lab listed in JCTLM
  - Reference materials in urine matrix are needed
  - Establish performance requirements for routine method result to be used in a ratio with albumin

Path forward - 5

- Investigate relationship between albumin/creatinine ratio (ACR) and albumin excretion rate (AER)
  - Develop an algorithm to convert ACR to AER
  - Consider gender, age and race factors
  - Requires standardization to be accomplished
  - Interpretive criteria related to risk assessment