



Recent Developments in Urine Albumin

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Chronic Kidney Disease (CKD)

- Ausdiab data show ~2 million Australians have CKD
 - 57% of subjects with albuminuria and/or proteinuria did not have eGFR <60
- Last 20 years Australian population has grown by 40%, CKD grown by 400%.
- Often not associated with significant symptoms; unrecognised in 80-90% cases
- Primary Care sub-optimal.
 - Only 29% high risk patients tested for proteinuria in preceding 12 months

Urine Albumin Increases Risk for CVD and All Cause Mortality

- Risk commences at levels below current decision thresholds
- WHI: ACR top of the normal range 75% greater risk for developing hypertension at median age 65y and 35% higher risk for median age 44 compared to ACR at the low end of the normal range
 - Forman et al; J Am Soc Nephrology,2008

Diagnosis of microalbuminuria is important because it can be treated.

- Mono - or dual blockade of the renin-angiotensin system decreases microalbuminuria.
- Non-diabetic proteinuric patients treated with ACEi and ARB retarded progression to end-stage renal disease (ESDR).
Nakao et al. Lancet 2003; 361: 117-124.
- Meta-analysis of data from treatment of Type 2 diabetic patients with ACEi and ARBs indicated protection of kidneys and ACEi's reduced all cause mortality
Strippoli et al J Am Soc Nephrol 2006; 17: S 153-155.

UA Standardization – where are we now?

- Measurand is not defined
- No urine reference material
 - Most manufacturers use CRM470 (serum)
 - preparation methods not standardised
 - Candidate SRM Japan: JSCC and JCCTLM purified human albumin. CRM and SRM 470 showed identical immunoreactivity in 13 routine measurement systems. Plan to submit to JCTLM.
- Possible reference method UA
 - LC-MS, BSA internal standard. Mayo clinic
 - N terminal 24 amino acid fragment
 - JCTLM: ID-GC-MS for urine creatinine. Pure creatinine RM, but no urine matrix for a secondary RM

Major Sources Variation are Pre and Post analytical

- Recommended test and collection
- Patient variables
- Units
- Reference intervals
- Interpretation and advice

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- We can act now to reduce these variables!

Australia & New Zealand Laboratory Practice Surveys

- 2006 and 2009
- 2009 - 52 responses

Sample type recommended by laboratory				
Sample	24 hour	Other timed sample	Random Spot sample	First morning spot sample
Total (NZ)	17 (0)	16 (1)	25 (8)	16 (0)

Received sample type (number of laboratories receiving half or more of their samples of the type shown)				
Sample	24 hour	Other timed sample	Random Spot sample	First morning spot sample
Total (NZ)	5 (0)	7 (0)	35 (7)	11 (1)

AACB survey 2009, Jones

Spot Urine Samples - Reporting units					
Quantity	Concentration			Albumin / creatinine ratio	
Units	mg/L	g/L	ug/mL	mg/mmol	g/mol
Total (NZ)	38 (6)	1 (0)	1 (0)	21 (1)	5 (1)

Timed Urine Samples - Reporting units							
Quantity	Conc.		Excretion rate			Albumin / creatinine ratio	
Units	mg/L	g/L	mg/day	ug/min	g/day	mg/mmol	g/mol
Total (NZ)	33 (5)	1 (0)	12 (2)	20 (1)	2 (0)	1 (0)	2 (0)

AACB survey 2009, Jones

UA upper reference limit ug/min

Limit	15	20	30	34
Number Total(NZ)	4(0)	20(0)	1(0)	2(1)

UACR upper limit (mg/mmol)

Limit	1.0	2.0	2.5	2.5/3.0	2.5/3.5	3.0	3.5
Total (NZ)	3 (0)	2 (0)	5 (1)	1 (0)	7 (0)	1 (0)	10 (3)

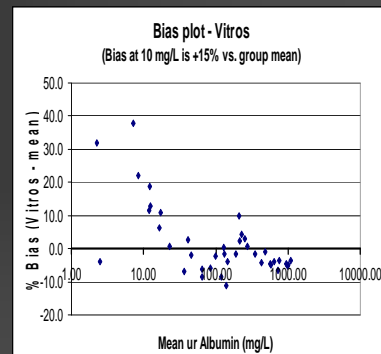
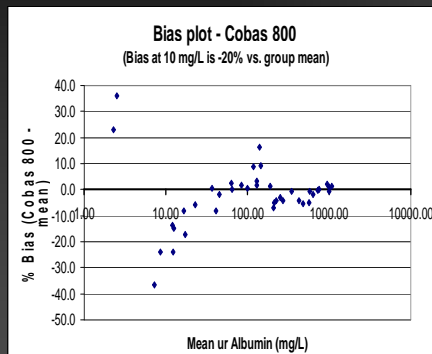
AACB survey 2009, Jones

Assay performance

- Precision
 - 90% (164/182) labs achieve CV <10%
- Accuracy is a major issue because current clinical practice guidelines recommend cut-off values for microalbuminuria.
 - Method median values vary between 3 to 16 mg/L and 142 to 182 mg/L for Low and High levels resp.

RCPA QAP End-of-Cycle 53 Report Jan-Jul 2011

Method comparability: accuracy



40 urines, conc. 5.5-945 mg/L. 4 methods

Tate et al AACB 2009

Clinical comparability and commutability studies

- 40 individual urines, 4 pooled urines, CRM470, RCPA QAP 2008, Bio-Rad Lyphocheck and Liquicheck urine QC
- 18 labs (10 methods)
 - 90% clinical concordance using recommended cut-offs.
 - Imprecision generally below 10%
 - Acceptable agreement down to 20 mg/L
 - RCPA QAP commutable

Tate et al AACB 2011, P7 and P9

Proteinuria Albuminuria Working Group

- Formed in response to primary care and laboratory issues.
- Sponsored by
 - Australasian Association of Clinical Biochemists (AACB)
 - Australian and New Zealand Society of Nephrology (ANZSN)
 - Kidney Health Australia (KHA)
 - Royal College of Pathologists of Australasia (RCPA)
 - Royal Australian College of General Practitioners (RACGP)
 - Australian Diabetes Association.

Proteinuria Albuminuria Working Group

- Inaugural meeting September 2009
- 3 further meetings 2010
- Large stakeholder meeting held Feb 2011
- Consensus reached on all recommendations
- Publication expected in MJA early 2012

PAWG Recommendations

- “Preferred method for screening for CKD in both diabetic and non-diabetic patients is urinary albumin/creatinine ratio (UACR) in a first morning spot collection”.
 - Random spot collections are acceptable if first void specimen is not possible or practical.

Recommendation

- “Repeat positive tests on 1-2 occasions over 3 months to confirm persistence of albuminuria. If the first positive UACR was on a random sample, repeat testing should ideally be on first am void samples”.
 - Multiple variables affect UACR transiently
 - High CVi requires confirmation to correctly categorise the albuminuria.

Recommendation

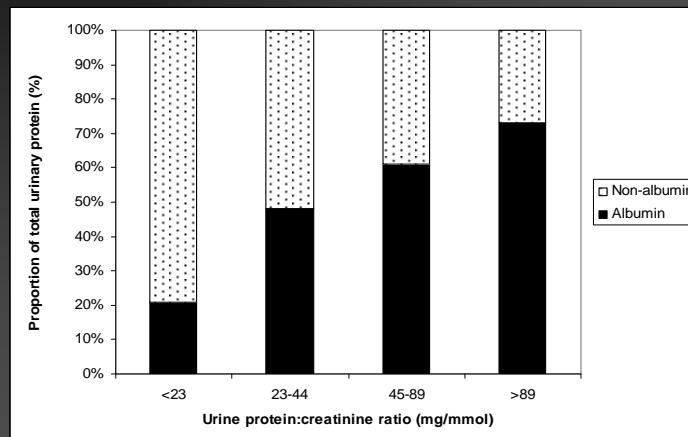
- “Adults with one or more risk factors for CKD should be screened with UACR and serum creatinine/eGFR every 1-5 years depending on their risk factor profile”
 - All adults should be assessed for risk factors when visiting their primary care physician.
 - Recommendations are not made for paediatric populations.
 - Little evidence for cost effectiveness

Who is at higher risk for CKD?	How often to test?	What should be done?
Age >50 yrs	Every 5 years	UACR on first am void.
Smoker		
Diabetes	Every year	Creatinine/eGFR BP
Hypertension		
Obesity		
FHx CKD		
ATSI		

PAWG Recommendations

- “Urine protein excretion cannot be estimated from urinary albumin measurements or vice versa”.
- AusDiab showed as urine total protein increases, the proportion that is accounted for by albumin also increases.

Proportion of UTP that is albumin



Atkins et al; Neph Dial Transplant 2003; 18: 2170-2174

Recommendations

- “UACR is recommended as the initial screening strategy for CKD, however urine protein measurement should be considered where patients are at risk of tubular proteinuria”.
 - Fanconi’s syndrome
 - Myeloma

PAWG Recommendations Pathology Section: Collection

Sample collections and handling should be performed in a standardised manner

- UACR ideally performed on a first morning spot collection.
- Samples not able to be delivered to the lab within 8 hours of collection should be refrigerated.
- Samples should ideally be analysed on the day of receipt but can be stored at 4 degrees C for 7 days if necessary.
- Longer term storage should be at -70 degrees C. Storage at -20 degrees C can cause significant reduction in measured albumin and is not recommended.
- Samples should be visually inspected and centrifuged if necessary to remove any cloudiness.

PAWG Recommendations Pathology Section: Patient

- Patient will ideally be at well baseline
 - No UTI
 - No acute febrile illness
 - No intense exercise within 24 hours of test
 - Not menstruating
- Other factors of influence
 - Dietary protein intake
 - Congestive cardiac failure
 - Drugs (NSAID's, ACEi)

PAWG Recommendations Pathology Section: Analysis

- CVi for UACR is at least 20%.
- Assays require CV <10%
- Assay bias of +/- 10% leads to a misclassification of ~2% of samples at a decision limit of 2.5 mg/mmol.
- Accuracy issues limit commutability between labs, especially within the normal range.
- Improvement requires standardisation.

Recommendations

- “All Australasian laboratories should report cut-points for normoalbuminuria, microalbuminuria, and macroalbuminuria according to the standard definitions”
“Gender-specific cut-points for UACR measurements are recommended”.

Recommended cut-offs

	Gender	Normo-albuminuria	Micro-albuminuria	Macro-albuminuria
UACR mg/mmol	Male	<2.5	2.5 - 25	>25
	Female	<3.5	3.5 - 35	>35
AER mg/day	Either	<30	30-300	>300

PAWG Recommendations Pathology Section: Reporting

- Report UACR in mg/mmol to one decimal place.
- Report gender specific cut-offs
- UAER report in mg/day
- Optional reporting parameters
 - Urine albumin concentration
 - mg/L to nearest whole number
 - No reference interval
 - Urine creatinine concentration
 - mmol/L to one decimal place
 - Reference range in place
 - Interpretative comments

Conclusions

- CKD is a major health issue and early detection is beneficial for society and the individual.
- Assay performance for urine albumin in Australasian labs is generally acceptable
- Standardising laboratory practice in this area will assist clinicians and may improve patient outcomes.
- PAWG have formulated recommendations to facilitate this.