Albumin:Creatinine Ratio – A Flawed Measure? The Merits of Estimated Albuminuria Reporting

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Key Words

Albuminuria · Proteinuria · Glomerular filtration rate

Abstract

Current guidelines illogically recommend that a different approach is taken to the correction for creatinine generation rate when estimating glomerular filtration rate (GFR) and when interpreting urine albumin:creatinine ratio (ACR). Age, gender and race are routinely used to adjust for predicted muscle mass in GFR estimation, even though estimated GFR is expressed per unit body surface area. Conversely, ACR is at most adjusted with the use of gender-specific classification thresholds. This difference is surprising since the proportional effect of muscle mass on serum and urine creatinine is identical. Failure to adjust for creatinine generation rate compromises ACR, potentially adversely affecting management decisions and mislabelling individuals as having/not having CKD. A greater ACR is also a marker of low muscle mass, which has confounding prognostic effects. Determination of the optimal method to adjust ACR for estimated muscle mass should improve its performance. Routine reporting of the resulting 'estimated albumin excretion rate', as for routine eGFR reporting, would remove the need for gender-specific thresholds.

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Introduction

The quantification of urine protein excretion plays a key role in the detection, diagnosis and management of kidney disease. Recently, an increasing recognition of its prognostic significance has led to calls for a greater emphasis on proteinuria in the classification of chronic kidney disease (CKD) [1]. Ensuring the optimum measurement of this biomarker is clearly of fundamental importance for nephrology. Most of the evidence on which current proteinuria thresholds are based comes from studies where 24-hour urine collection was performed, considered the gold standard. In clinical practice, however, 24-hour urine collections are burdensome for patients to perform repeatedly and are subject to errors resulting from incomplete collection. The use of spot urine samples for measurement of either the total protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) is now recommended in national and international guidelines [2, 3]. There are, however, potential problems with the current use of ACR and PCR as a consequence of a failure to consider the influence of creatinine excretion. For simplicity, the implications of this will be discussed with reference to ACR, since albuminuria quantification is recommended for measurement from the lowest levels of proteinuria. The effects of creatinine excretion will of course be identical for PCR and evidence relating to PCR will also be considered.

Creatinine as the Denominator in ACR Measurement

The measurement of urine albumin excretion by spot urine sampling rather than timed collection requires that a correction be made for the degree of urine concentration. Creatinine is the natural denominator of choice for this since it is excreted at a fairly constant rate in a given individual and is readily measured. However, creatinine generation and (hence excretion in the steady state) is dependent on muscle mass. It would therefore be anticipated that if creatinine is to be used to correct for urine concentration then some estimate of muscle mass will need to be taken into account. There is an extensive literature on the optimum correction for muscle mass when using serum creatinine to derive estimates of creatinine clearance or glomerular filtration rate (eGFR). It should be noted that muscle mass variation will have the exact same proportional effect on urine creatinine excretion as it does on serum creatinine level.

The Cockcroft-Gault equation is the best known formula relating creatinine generation rate to factors predicting muscle mass [4]. Rearranging this equation gives [5]:

$$\text{24-hour creatinine excretion in grams} = (140 - \text{age}) \times \text{weight in kg} \times 0.0002 (\times 0.85 \text{ for women})$$

The anticipated effect of age and weight on ACR as predicted by this is illustrated in figure 1. It can be seen that a substantial change in ACR due to muscle mass variation is expected. The Cockcroft-Gault equation, though widely used, was derived in a relatively small population of male inpatients and so does not provide sufficient evidence to justify routine application to ACR measurement. When it comes to estimating GFR from serum creatinine, formulae have been produced based on studies involving much larger patient populations and considering a number of predictor variables [6, 7]. These formulae also account for the effects of tubular creatinine secretion, which is not a concern for estimating total creatinine generation/excretion rate. Similar formulae to predict urinary creatinine excretion rate have not been pursued to anything like the same extent. This is surprising given the greater ease of measuring urine creatinine excretion than clearance of an infused glomerular filtration marker. Consequently, ACR measurement guidelines apply creatinine as the denominator with the only adjustment made for muscle mass being gender-specific thresholds. How has this happened? Does it matter?

Fig. 1. Actual 24-hour albuminuria required to reach the K/DOQI ACR threshold for microalbuminuria in males (17 mg/g), according to age and weight. Based on Cockcroft-Gault predicted creatinine excretion.

Body Surface Area and the 'Fortuitous' Finding of 1 g/1.73 m² Creatinine Excretion

The early description of PCR measurement by Ginsberg et al. [5] correlated PCR with 24-hour proteinuria per 1.73 m² body surface area (BSA). It is unclear why BSA was chosen as a denominator here. BSA estimated by formulae based on height and weight does indeed correlate with muscle mass [8] but is not in itself a determinant of creatinine generation. Subsequently produced GFR estimation formulae (e.g. MDRD [6] and CKD-EPI [7]) incorporate demographic variables considered to adjust for muscle mass, despite reporting eGFR per 1.73 m² BSA. This indicates that BSA is not an adequate surrogate for muscle mass. Nevertheless, on the basis of the good correlation reported between PCR and 24-hour proteinuria per 1.73 m² BSA, it became accepted that creatinine generation rate is 1 g per 1.73 m² per day. This has been considered 'fortuitous' [9] in simplifying albuminuria estimation. However, in clinical practice, BSA estimation is not performed to adjust ACR interpretation and so ACR is often interpreted to be 'about the same' as 24-hour albumin excretion. Few clinicians probably have much of an idea of the size of a patient corresponding to a BSA of 1.73 m², which is a standard reference with questionable justification anyway [10]. Further error is introduced if creatinine is measured in millimoles and ACR multiplied by 10 for convenience [2] rather than 8.8 (since 1 mmol creatinine is 8.8 g).

Given that height and weight measurements are required for the Dubois formula estimation of BSA, it is just as easy to perform a Cockcroft-Gault-based estimation of predicted creatinine generation as it is to index for BSA. Ginsberg et al. [5] did also correlate PCR with 24-hour proteinuria indexed according to Cockcroft-Gault-predicted 24-hour creatinine excretion. This gave a similarly strong correlation, as expected, but the benefits of this approach have not been validated in larger populations.

Correlations of PCR/ACR with Unadjusted 24-Hour Proteinuria/Albuminuria

Schwab et al. [11] studied the correlation between PCR and 24-hour proteinuria in a population of 101 patients of both genders with a range of age and weight. Despite making no adjustment for any estimate of muscle mass a strong correlation ($r = 0.96$) was found, leading the authors to conclude the PCR 'reliably corresponded with 24-hour urinary collection in men and women independent of renal function, age or body size'. Whilst this statement may be consistent with the data reported, no explanation was offered for the independence from gender, age and body size. For this to be the case would require that the creatinine excretion in this population varied very little according to these variables. This is obviously in conflict with the wider literature relating muscle mass to these variables, such as the Cockcroft-Gault equation.

Following the report of Schwab et al. [11], a large number of publications have reported a correlation between ACR/PCR and 24-hour proteinuria/albuminuria, respectively, without adjusting for indices of muscle mass [2]. These reports have perhaps given the false impression that it is quite acceptable to interpret ACR/PCR without consideration of muscle mass. Reports of the utility of ACR/PCR cut points for detecting thresholds of 24-hour albuminuria/proteinuria have given further reassurance that unadjusted ACR/PCR is acceptable. This is the evidence on which ACR/PCR measurement is advocated in guidelines with no adjustment other than for (at best) gender [2, 3].

How can the reported correlations of unadjusted ACR/PCR with 24-hour measures be reconciled with the requirement to adjust for muscle mass in estimating GFR – even eGFR per 1.73 m^2 BSA? Reporting the correlation for a population may fail to capture the impact of creatinine generation in subsets of patients. For example, Methven et al. [12] studied the performance of PCR and ACR in predicting 24-hour proteinuria. Despite a predic-

tive performance of PCR considered reasonable (correlation coefficient: 0.91, area under ROC curve for 1 g proteinuria prediction: 0.968), there was an almost threefold difference in the PCR threshold required to predict 1 g proteinuria with the same sensitivity in a young man or an elderly woman. Notably, not all studies have reported such strong correlations between ACR/PCR and timed urine protein excretion [13, 14].

The performance of unadjusted ACR will clearly depend on the distribution of muscle mass in the population studied. Younes et al. [13] reported that in young diabetics ACR (in mg/g) was systematically lower than measured timed albumin excretion, particularly in men. In contrast, in a middle-aged population the prevalence of microalbuminuria based on ACR was 8.5%, whereas the prevalence on timed urine collection was only 4.3% [15]. An association was reported between low non-fat mass and the presence of high ACR with normal albumin excretion. In persons of low muscle mass, a raised ACR thus might often be a marker of low muscle mass rather than of increased urine albumin excretion.

The available evidence therefore does not provide sufficient reassurance that adjusting for muscle mass is unnecessary, or any explanation of how it could be justifiable.

Adjustment for Gender, Age and Race

Since BSA estimation incorporates height and weight (which relate to muscle mass), the expression of eGFR as per 1.73 m^2 BSA partially indexes for muscle mass. Weight is thus not included in the MDRD equation since as a component of BSA estimation it did not independently relate eGFR per 1.73 m^2 BSA to serum creatinine [6]. Estimation equations deriving eGFR from serum creatinine are consequently only correcting partially for the effects of muscle mass. The estimation of absolute urine creatinine excretion (for ACR interpretation) would therefore be expected to require a *greater* muscle mass adjustment than is performed for eGFR by the MDRD and CKD-EPI equations. This emphasises the potential error in current ACR interpretation on the basis of the different approach to muscle mass adopted for ACR versus eGFR. The demographic coefficients applied for gender and age in eGFR equations cannot be translated directly to ACR interpretation due to the indexing of eGFR for BSA and due to the adjustment for tubular creatinine secretion in eGFR estimation.

Table 1. Studies examining the effects of gender on creatinine excretion rate and ACR

Reference	Population	Coefficient for female relative to male	Notes
Cockroft [4]	Coefficient not based on population studied	0.85	Coefficient of 0.85 chosen based on previous studies reporting 10–20% less muscle mass in females
Jafar [16]	(n = 577) over 40 years, South Asian general population	0.81 ¹	Based on mean measured 24-hour creatinine excretion per unit weight
Younes [13]	(n = 1,186) type 1 diabetics, 13–39 years, normal excretory function	0.66	Derived gender coefficients based on comparison of ACR with timed albumin excretion
Jacobs [17]	(n = 839) healthy individuals, 28–40 years	0.67, 0.68 (for black and white subpopulations)	Studied determinants of measured 24-hour creatinine excretion
James [18]	(n = 2,059) normal subjects	0.63	Measured 24-hour urine creatinine
Warram [19]	(n = 218) healthy controls, (n = 1,613) subjects with diabetes	0.68 (ratio of the cut-points 17 and 25 mg/g)	Cut-points reflect the 95th percentile for healthy controls and most reproducible cut-points on repeat testing in diabetic subjects
Cirillo [20]	(n = 1,567) normal population 45–64 years	0.67	Measured timed overnight creatinine excretion

¹ Since males tend to have greater weight, a coefficient derived for creatinine excretion already adjusted for body weight will be expected to be closer to 1.

Those studies that have examined the effect of gender on measured creatinine excretion or the performance of ACR have given results that are consistent and substantial (table 1) [13, 16–20]. Warram et al. [19] reported the 95th centiles of ACR in healthy men and women to be 17 and 25 $\mu\text{g/g}$, respectively, levels which also corresponded to cut points maximizing reproducibility of classification on repeat sampling. On this basis, gender-specific definitions of microalbuminuria and also albuminuria were included in the K/DOQI CKD guidelines [3]. The UK NICE guidelines recommend gender-specific ACR thresholds for the classification of microalbuminuria, but not for the definition of albuminuria or for thresholds determining nephrology referral and preferential use of renin-angiotensin system inhibitors [2]. No justification is given for this selective approach. Other guidelines make no effort to adjust for gender [21], and the majority of publications considering the performance of ACR/PCR also have not done so.

The few studies reporting differences in urine creatinine excretion attributable to ethnicity are shown in table 2 [16–18]. More evidence is needed to clarify this issue, as for other factors.

Table 2. Effects of ethnicity on creatinine excretion rate

Reference	Ethnicity coefficient for creatinine excretion rate
Jacobs [17]	white = $0.89 \times$, $0.9 \times$ black (in men and women, respectively)
James [18]	white = $0.88 \times$ black
Jafar [16]	South Asian = $0.92 \times$, $0.87 \times$ white (in men and women, respectively) values for matched white individuals were predicted by the Cockcroft-Gault equation, not measured

The benefit of adjusting for age and weight has not been clearly demonstrated for ACR/PCR. Both increasing age and lower non-fat mass are associated with increasing risk of false positive ACR, suggesting that adjustment for these factors would improve the accuracy of albuminuria estimation by ACR [15, 20]. The Cockcroft-Gault equation reported creatinine generation to be proportional to weight, though (like other readily obtained

demographic data) this is an imperfect surrogate for lean muscle mass. It would nevertheless be important to determine the extent to which weight adds accuracy to the prediction of albumin excretion rate by ACR.

The Consequences of Failing to Adjust

The current failure to adjust for creatinine excretion rate may be resulting in the misclassification of a large number of individuals. At heavier degrees of proteinuria (>1 g/24 h) the absolute level is less important to measure precisely, since patient management will not be altered. However, when it comes to detection of microalbuminuria and labelling patients as having CKD, there is clearly a potential problem. The greater prevalence of microalbuminuria reported in the elderly [22] may be due at least partly to lower muscle mass and creatinine excretion. Similarly, unadjusted ACR comparisons of microalbuminuria prevalence on the basis of gender or race will over- or underestimate the effect of these variables [23]. Of more concern, referral, investigation and treatment decisions based on ACR thresholds are also confounded by creatinine excretion rate (as illustrated in figure 1).

Other Problems with Spot Urine Sampling

Spot urine samples for ACR are more vulnerable to transient changes in excretion of creatinine and albumin than timed collections that average such changes over a longer time period. For example, ingestion of creatinine in cooked meat potentially changes the urinary creatinine excretion rate substantially [24]. Urinary albumin excretion follows a circadian rhythm with lower excretion rates overnight. A first morning void ACR consequently classifies fewer individuals as microalbuminuric than an ACR from a random spot urine; 7.5 vs. 24% in one study [25]. It is not surprising therefore that random spot urine ACR results are less consistent than timed urine samples. Reported intraindividual coefficients of variation for 24-hour urine albumin excretion and spot urine ACR were 19 and 36%, respectively, in the same study [25]. Reports of microalbuminuria prevalence based on single random ACR measurement are consequently potentially misleading. Use of a first morning void is recommended for ACR/PCR measurement where possible [3] and for confirmation of albuminuria detected on a random sample [2]. In practice this may not happen if the degree of circadian variation is not appreciated.

These concerns do not outweigh the benefits of avoiding the requirement for timed urine collection, but emphasise the need for a cautious approach to the interpretation of spot urine results.

Evidence to Support ACR?

Justification for the use of ACR does not come solely from the reported correlations with timed urine measurement results. Albumin/protein:creatinine ratios have themselves been shown to be powerful predictors of adverse cardiovascular [26] and renal [27–29] outcomes. In particular, ACR has been used to demonstrate an association of even low (submicroalbuminuria) levels of albuminuria with renal [30] and cardiovascular events [31]. Incorporation of ACR into risk stratification algorithms would thus seem justified. This does not mean, however, that unadjusted ACR is a satisfactory measure of urinary albumin leak. The leak of even small amounts of albumin into the urine is clearly of profound biological significance. Therefore, even flawed methods of albuminuria quantification may generate impressive prognostic data. A morning void urine albumin concentration – i.e. unadjusted for urine concentration and thus theoretically sub-optimal – also demonstrates the association of even small albuminuria increments with cardiovascular mortality [32]. It has in fact been reported that urine albumin concentration and ACR have similar areas under ROC curves for microalbuminuria detection [33], with urine albumin concentration considered a potential alternative to ACR for albuminuria screening. This would suggest that the use of unadjusted creatinine as the denominator to correct for urine concentration does not contribute very much to the accuracy of albuminuria quantification by ACR. Within patient, reproducibility is nevertheless improved when urine albumin concentration is indexed for urine creatinine concentration [17, 19], an important issue when assessing response to treatment.

Creatinine Excretion as a Predictor of Cardiac Events and CKD Progression

Paradoxically, some of the prognostic power of ACR may actually derive from the failure to adjust for muscle mass. Subjects with lower urinary creatinine excretion are at greater risk of mortality [34], cardiovascular events [35] and graft loss [36]. The impressive prognostic impact of ACR cannot therefore be attributed solely to urine pro-

tein leak quantification. Lower urinary creatinine excretion is also independently associated with kidney disease progression [29]. This may explain the finding that ACR/PCR apparently predicts CKD progression better than 24-hour urine albumin/protein [28, 29]. The relationship between creatinine excretion and adverse outcomes presumably reflects confounding poorer general health, malnutrition or inflammation in individuals with lower muscle mass. Since ACR is thus not simply a measure of urinary albumin leak, extrapolation of treatment thresholds from timed urine collection parameters to unadjusted ACR is not justified; interventions directed by an ACR threshold will inadvertently be targeted towards individuals with lower muscle mass.

The Way Forward

Evidence is needed to define the optimum method for adjusting ACR according to estimated muscle mass. Equations considered acceptable for eGFR calculation in clinical practice are based on the simple demographic variables of age, gender and race. Adjustment using these variables should achieve an improvement in accuracy for ACR interpretation. Further benefits would be anticipated from the incorporation of weight or height measurement; the effort required to perform such measurements may be a small price to pay for accurate albuminuria assessment. Analysis of demographic and laboratory data pooled from previous studies could certainly address these issues. (This would in fact just be a matter of deriving an equation like that of Cockcroft-Gault but validated in a larger population and with the consideration of more variables.) The introduction of multiple ACR thresholds based on age/gender/race etc. would seem unnecessarily complicated and is not recommended. As is the case with eGFR reporting, it would be more logical to incorporate an adjustment for muscle mass into the reported ACR and then have one set of thresholds. Thus, an automatic 'estimated albumin excretion rate' report can be envisaged similar to the automated eGFR reporting that is now routine practice. This is no more complicated than the concept of eGFR and seems physiologically sounder than ignoring the confounding effects of creatinine. Until this is addressed, a tension will remain between current guidelines and the basic tenets of renal (creatinine) physiology as applied to eGFR calculation. Consider if the same approach to muscle mass were adopted for eGFR as is currently applied to ACR; decisions regarding referral and intervention would then be based on serum creati-

nine thresholds, with different sets of thresholds for men and women. Few would consider this satisfactory!

The benefit of using demographic data to adjust for predicted muscle mass will always be limited by individual variation. Patients with extremes of muscle mass resulting from cachexia, amputations or bodybuilding will clearly have urinary creatinine excretion that is not readily predicted by standard demographic data. This is recognised in guidelines for GFR estimation [2], but less appreciated as an implication for ACR interpretation. As with GFR, it may occasionally be necessary to resort to a timed urine collection to quantify albuminuria in cases where the impact of muscle mass is a particular concern.

An alternative and fundamentally different approach is to measure the fractional excretion of albumin relative to creatinine. By considering the values of serum and urine creatinine, this removes concerns relating to muscle mass. Measuring the leak of albumin relative to creatinine clearance also accounts for the size of the functioning nephron mass across which the albumin leak is occurring and may thus give a more physiologically sound measurement, as we have argued [37]. At lower GFR, tubular creatinine secretion becomes a complicating factor. Indexing ACR for eGFR is another option to account for the size of the functioning nephron mass and also provides a degree of adjustment for muscle mass [37].

Conclusion

Determining the best method for muscle mass adjustment in ACR interpretation should be straightforward. Until this is established, it seems prudent at least to consider the potential effect of creatinine excretion rate on ACR results both for patients and study populations.

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