Invited Commentary

Invited Commentary: Evaluation of Measures of Urinary Albumin Excretion in Epidemiologic Studies

Alan R. Dyer

From the Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL.

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Abbreviations: INTERMAP, International Study of Macronutrients and Blood Pressure; PREVEND-IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial.

In the current issue of the Journal, Gansevoort et al. (1) raise concerns about our paper (2) that compared the strengths and weaknesses of the urinary albumin concentration and the albumin:creatinine ratio as alternatives to the “gold standard” 24-hour urinary albumin excretion in the International Study of Macronutrients and Blood Pressure (INTERMAP). In that report, which used albumin excretion measures from two 24-hour urine collections, we found that 1) the median within-person coefficient of variation ranged from 25.3 to 81.3 percent for the three measures, with the albumin concentration generally having slightly smaller within-person coefficients of variation; 2) the albumin:creatinine ratio had larger rank-order correlations with 24-hour excretion than did the urinary albumin concentration (0.949 for men and 0.942 for women vs. 0.881 and 0.816 for the albumin concentration); and 3) the average correlations with blood pressure were similar for the three measures, but the correlation with body mass index was lower for the albumin:creatinine ratio (0.118 vs. 0.188 for the albumin concentration and 0.211 for 24-hour excretion), because of high correlation between body mass index and the creatinine level. On the basis of these findings and the lower costs associated with the albumin concentration, we concluded that both the albumin concentration and the albumin:creatinine ratio appeared to be reasonable alternatives to 24-hour albumin excretion for epidemiologic studies. We also suggested that the albumin concentration was the better alternative to 24-hour excretion for studies in which measures of body size and obesity were key variables or the cost of creatinine measurement was an important consideration. When these concerns did not apply, we suggested that the albumin:creatinine ratio was the better alternative to 24-hour excretion.

Gansevoort et al. indicate that, for INTERMAP, “the coefficients of variation for all the variables are so high that they in fact disqualify the use of urinary albumin measures as a reliable risk marker for future cardiovascular events” (1, p. 726). Their statement suggests that the within-person coefficient of variation determines whether or not a variable is reliable. However, the within-person coefficient of variation is but one measure that can be used to assess the reliability/reproducibility of a measurement. The generally accepted measure is the intraclass correlation (3). However, the intraclass correlation is typically not suitable for use with albumin excretion measures, because of their highly skewed distributions in most studies, including INTERMAP (2). In addition, most studies on the reproducibility of albumin excretion have used the within-person coefficient of variation (4–7). Hence, for INTERMAP, we reported the mean and median within-person coefficient of variation, as well as the Spearman rank-order correlation between the first and repeat measurements of each albumin measure as an alternative to the intraclass correlation. In the total sample, rank-order correlations for the three albumin measures ranged from 0.624 to 0.658 in men and from 0.562 to 0.609 in women. These values were larger than those for urinary urea, which had rank-order correlations of 0.593 in men and 0.553 in women, although the median within-person coefficients of variation for urinary urea were 12.5 percent in both men and women, that is, values approximately 75 percent smaller than those for the albumin measures.

Correspondence to Dr. Alan R. Dyer, Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 N. Lake Shore Drive, Suite 1102, Chicago, IL 60611-4402 (e-mail: adyer@northwestern.edu).
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Gansevoort et al. also suggest that “it may well be that these coefficients of variation for the various albumin measures are unrealistically high” (1, p. 726). In their report, they provide estimates of the within-person coefficient of variation for each of the three measures for participants on placebos in the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT) study based on 24-hour urine samples collected on consecutive days and samples collected 3, 6, and 15 months apart. The reported coefficients of variation are lowest for the samples collected on consecutive days and largest for those collected 15 months apart. However, regardless of the time difference between collections, the reported coefficients of variation are substantially lower than those reported by us (2). Further, the reported coefficients of variation for the albumin:creatinine ratio and 24-hour excretion are typically 5–8 percent lower than those for albumin concentration, which is in contrast to our results, where the coefficients of variation for albumin concentration were generally lower.

Gansevoort et al. (1) suggest that the higher values reported by us may be due to problems in sample handling, loss of albumin because of use of samples frozen at $-20^\circ$C for approximately 3 years, and the timing of the repeat urine collection, that is, 3–6 weeks after the first collection.

With respect to sample handling, Daviglus et al. (8) reported that the INTERMAP samples were hand inverted prior to being analyzed for albumin. Hence, it is unlikely that sample handling had an influence on our reported coefficients of variation. Although we acknowledged the potential impact of freezing on our findings and suggested that the coefficients of variation might be somewhat larger than they would have been if albumin had been measured in fresh urine samples, the mean and median coefficients of variation reported by us are consistent with those reported in the literature, which generally range from approximately 30 percent to 60 percent (4–7).

With respect to the impact of time between measurements on the estimated coefficients of variation, the goal of computing the within-person coefficient of variation is to assess day-to-day variability in albumin excretion. An accurate estimate of day-to-day variability requires that 1) the individual has a specific mean value around which he or she varies and 2) the variations around the mean are independent. Albumin excretion measured on 2 consecutive days likely violates the second requirement, since the deviations around the mean are likely to be correlated because of common influences on the two measurements. Thus, coefficients of variation calculated from consecutive days would be expected to underestimate day-to-day variation. Albumin excretion measured 15 months apart likely violates the first requirement, since for some individuals the mean around which they vary will have changed during this long a time between measurements. Thus, estimates of the coefficient of variation for collections obtained 15 months apart would be expected to overestimate day-to-day variation because of the inclusion of true change in mean excretion over the time between measurements. Hence, the most appropriate comparison between the results in INTERMAP and PREVEND-IT appears to be the month 3 coefficients of variation reported by Gansevoort et al. (1).

While the month 3 coefficients of variation are lower than those in INTERMAP and are likely lower in part because of use of fresh urine samples for measurement, there are reasons to believe that these results and the lower value for 24-hour excretion compared with albumin concentration were influenced by sample selection for PREVEND-IT. In particular, to be included in PREVEND-IT, individuals had to have an albumin concentration greater than 10 mg/liter in a spot sample and a 24-hour excretion of 15–300 mg in at least one of two consecutive 24-hour urine collections (9). This sample selection essentially requires that two of three measurements be in agreement. When one restricts two measurements to be in the same range or nearly in the same range, one will generally obtain a smaller coefficient of variation than if one allows both to vary and only restricts the mean to be within that range. For example, in INTERMAP, there were 41 women for whom both the first and repeat values of 24-hour albumin excretion were in the range of 30–299 mg. For these women, the median coefficients of variation were 22.6 percent for 24-hour excretion, 29.4 percent for the albumin:creatinine ratio, and 28.9 percent for albumin concentration. These values are substantially lower than the values of approximately 80 percent for all 102 women with mean excretion in this range, where the albumin concentration could be...
below the detection limit for one collection or the 24-hour excretion greater than 300 mg in one. Similarly, if the first and repeat values for 24-hour excretion in INTERMAP are restricted to being between 8.6 and 125.7 mg, the range for the baseline mean in PREVEND-IT, the median coefficients of variation are 19.3 percent, 20.1 percent, and 22.6 percent for 24-hour excretion, the albumin:creatinine ratio, and albumin concentration, respectively, in men and 28.5 percent, 31.8 percent, and 33.4 percent, respectively, in women. What is also noteworthy here is that, in restricting the range for 24-hour excretion, 24-hour excretion has a median coefficient of variation 3–5 percent lower than that for urinary albumin concentration, while the albumin:creatinine ratio has a median 1–2 percent lower.

The low coefficients of variation for the consecutive urine samples may also have been influenced by sample selection, and it is likely that the increase over time is due in part to there being no restrictions on the range for the follow-up measurements.

Gansevoort et al. also suggest that our conclusions “are based on a comparison of the urinary albumin concentration and the albumin:creatinine ratio in relation to a reference standard... In daily practice, the urinary albumin concentration and the albumin:creatinine ratio are assessed from spot morning urine samples” (1, pp. 726–727).

We readily acknowledged that a limitation of our study was whether or not the reported results would be similar for spot or random collections (2). The goal of our study was to assess the strengths and weaknesses of the albumin:creatinine ratio and the albumin concentration as alternatives to 24-hour collections and to help researchers make an informed decision. The results were intended to be useful to those involved in the design and conduct of epidemiologic studies and not necessarily for clinicians involved in the daily practice of medicine. In large-scale epidemiologic studies that involve collection of large amounts of data and in which albumin excretion is but one of many measures being collected, cost can be an important consideration. Hence, although albumin excretion in a 24-hour collection is the gold standard, the costs of such collections may make them unfeasible for some epidemiologic studies. Further, the relatively large day-to-day variability in all measures of albumin excretion suggests the need for at least two urine collections. In this era of cost constraints, would one rather have two assessments of albumin concentration or a single albumin:creatinine ratio, if that is in fact the choice that needs to be made? We would choose two measures of albumin concentration rather than a single measurement of the albumin:creatinine ratio.

Gansevoort et al. also indicate that one reason for using the albumin:creatinine ratio, rather than albumin concentration, is that “urinary albumin and creatinine excretions follow a circadian rhythm” (1, p. 727). Although it is clear that albumin excretion follows a circadian rhythm, two carefully designed studies conducted by our group did not show a circadian rhythm in creatinine excretion, since the average rate of creatinine excretion was the same for daytime and nighttime collections (10, 11).

In summary, we thank Gansevoort et al. (1) for their interest in and comments on our paper (2). We also agree with their assessment that 24-hour urine albumin excretion should remain the gold standard and that carefully designed prospective studies are needed to clarify the issue of which urinary albumin measure to use. Nonetheless, we continue to believe that there are situations in which the albumin concentration is a better alternative to 24-hour albumin excretion than the albumin:creatinine ratio.

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REFERENCES