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Urine Dipstick to Detect Trace Proteinuria: An Underused Tool for an Underappreciated Risk Marker

Related Article, p. ●●●

In the medical evaluations of healthy individuals, urinalysis receives relatively little attention compared to blood work. However, one finding from the urinalysis--proteinuria--carries a risk far higher than many abnormalities identified from blood studies.[1-4] Even small quantities of albumin in the urine (an albumin-creatinine ratio [ACR] of 30-300 mg/g, often termed "microalbuminuria") is not only a sign of kidney damage,[5] but is also associated with an increased risk for cardiovascular diseases,[1] certain cancers.[6,7] and for increased all-cause mortality.[1,3]

Although the 2002 publication of the National Kidney Foundation's KDOQI classification of chronic kidney disease (CKD)[5] established sustained albuminuria as a marker of kidney damage sufficient for the diagnosis of CKD, it is not clear who should be screened for proteinuria and what method of screening should be used. In a healthy population, nearly 9 out of 10 people have ACR <30 mg/g[1], a level traditionally

considered normal. Quantifying albuminuria by ACR is slow, cumbersome, and expensive. In contrast, dipstick screening for proteinuria, is a simple, instantaneous laboratory test that can be easily performed in most medical offices. Because a major challenge for the prevention of CKD complications is limited awareness of CKD (more than 90% of CKD patients are unaware of their condition[3,8,9]), a simpler screening test for kidney damage is an attractive way to improve detection and awareness. However, the dipstick test for proteinuria may be viewed as inadequate by many nephrologists, who prefer having ACR results. This reluctance to rely on urine dipstick testing for proteinuria is understandable given that few studies have evaluated urine dipstick testing in comparison with the gold standard of ACR.[10-12]

In this issue of the *American Journal of Kidney Diseases*, White et al[13] studied the relationships between urine dipstick and urine ACR by analyzing urine collected in 1999 and 2000 from 10,944 randomly selected Australian healthy adults from AusDiab (Australian Diabetes, Obesity and Lifestyle Study) designed to examine diabetes, heart disease and kidney diseases) with. They report that a dipstick reading of 1+ or more was seen in nearly all of those with larger quantities of albumin in the urine (ACR above 300 mg/g, termed "macroalbuminuria"). However, the investigators did not find the 1+ cutoff in dipstick urinalysis sufficiently sensitive to detect urine ACR 30-300 mg/g. Although

the sensitivity of screening by dipstick urinalysis can be improved by decreasing the threshold for a positive test to a trace proteinuria reading, the authors caution that this increases the false-positive rate for detection of ACR 30-300 mg/g to nearly 73%. Although this point is important, the lack of outcome data for various dipstick results may have obscured the value of findings in the range of proteinuria equivalent to an ACR less than 30 mg/g.

Previous studies have shown that trace proteinuria by urine dipstick is a powerful predictor of mortality risk.[1] In a pooled meta-analysis of 1.1 million individuals with normal GFR, the hazard ratios for cardiovascular mortality for those with trace proteinuria by dipstick test were reported to be at 1.78 and for all-cause mortality, 1.44.[1] The risks associated with trace proteinuria at normal level of GFR were more similar to those for ACR of 10-29 mg/g than ACR of 30-300 mg/g. **(Fig 1)** shows the relationship between all-cause mortality risk and proteinuria in a cohort of approximately 500,000 Taiwanese individuals.[3] This analysis, which was adjusted for 12 risk factors, fit a curvilinear line through hazard ratios associated with negative, trace, 1+, 2+, and 3+ dipstick results. The magnitude of the increased risk due to trace proteinuria (1.70) is approximately equivalent to the risk from smoking (1.55).[14] It is intriguing that detecting trace proteinuria in the office obtaining history about smoking yield similar information

about health risk. When trace and 1+ were considered together as mild proteinuria in a study investigating mortality risk in a Canadian cohort of nearly 1 million individuals, the all-cause mortality risk became approximately two-fold (2.1),[15] a result similar to the large Taiwan study.[3]

Three mechanisms may explain why the risks of trace proteinuria were so high in these studies. First, the median ACR corresponding to trace proteinuria was 65 mg/g from healthy adults in the Taiwan data[3] and 48 mg/g in 2,321 community based, healthy participants in Takahata, Japan.[11] Given that the hazard ratio of 1.40 and 1.78 for ACRs of 10-29and 30-299 mg/g, respectively,[1] the relative mortality risk of proteinuria of 1.44 (or 1.70 in Taiwan study, Fig 1) reflects the weighted average of the two groups. Second, those with trace proteinuria are concentrated among those of lower socioeconomic status,[3] who tend to have additional cardiovascular diseases and more life style risks. Third, proteinuria is hypothesized to be linked to cardiovascular disease via endothelial dysfunction [16] and to occult cancer via immunological reaction.[6,7]

Semi and fully automated reading of dipsticks reveals a higher proportion of trace readings compared to visual readings, and 6-7 times more frequently than the number of 1+ or more.[1, 3, 8 11] Inconsistent and poor-quality results from visual readings may have left many physicians, including nephrologists, with the impression that a finding of trace

proteinuria is unreliable, and therefore, the result is often dismissed as negative.[10,17-19] The automated reading of trace is critical, as it constitutes the bulk of patients in the ACR range associated with increased risk, including 10-29 mg/g and 30-300 mg/g.

In the White et al article, the sensitivity for trace or higher proteinuria for detecting ACR>30 mg/g was 69.4% for all participants but higher for high-risk patients, such as those with diabetes, it was 74.1%. Given the test's inexpensiveness and availability, a repeat dipstick screening can improve the sensitivity to even higher, a practical way to enhance the screening results. The aforementioned 73% false positive rate of trace in identifying >30 mg/g, would be much lower elsewhere as the Aus Diab was based on an unusual distribution of 16.9% proteinuria, in contrast to 7-10% in most other populations.[1,3,8] False-negative results, an equally important consideration for the role of urine dipstick testing, were low: 2.4% from the White et al article, when trace or higher was considered for detecting ACR $\geqq$30 mg/g.

Whether dipstick screening should be advocated for the general public hinges on whether it adds value to patients and can prolong life.[18] This article adds a positive voice in the current debate; to date, much of the literature has not been supportive of the practice based on a study using the reduction of kidney failure, not all-cause mortality, as the endpoint.[19] While clinical trials will be required to test the cost effectiveness of

dipstick testing, it may be time to reconsider and shift our old paradigm based on the knowledge gained recently on proteinuria. Through dipstick, both mild and heavy proteinuria can be discovered. Given its grave risk, heavy proteinuria is important to know, regardless of its outcome. Mild proteinuria, on the other hand, may not only treatable, but its progression may also be modified.[20] Given that those with trace proteinuria had more risk factors, trace results can give the general practitioners another important reason to intervene and reduce those risks for cardiovascular diseases or cancer. Finding trace proteinuria may also give greater impetus to smoking cessation, which is one of the most cost-effective health interventions.[21] Increasing physical activity, reducing weight, and properly managing hypertension or diabetes, as advocated for CKD,[20] will be of great value to patients found to have proteinuria, especially among the younger ones.

Current recommendations for proteinuria screening limit testing to the elderly or those with high risk (diabetes or hypertension).[18] Trace proteinuria is a high risk condition for all-cause and cardiovascular mortality, affecting 6%-9% of the adult population,[22] and shortening one's life span by up to 7 years (calculated data not shown).[3] Unlike GFR, the age distribution of trace proteinuria is spread equally across most age groups, hovering around 6% from the early 20s until age 60. As two thirds of CKD

patients have proteinuria, effective prevention of CKD complications can only occur when proteinuria is timely identified and the public is made aware of its implications. Dipstick screening, if used as part of the office routines like checking one's blood pressure, could be an effective way to reach out to the public in improving awareness of CKD. As increasingly more studies call our attention to the importance of proteinuria in CKD,[23-25] more research for the prudent promotion of dipstick screening will go a long way to improve detection and prevention of this emerging epidemic.

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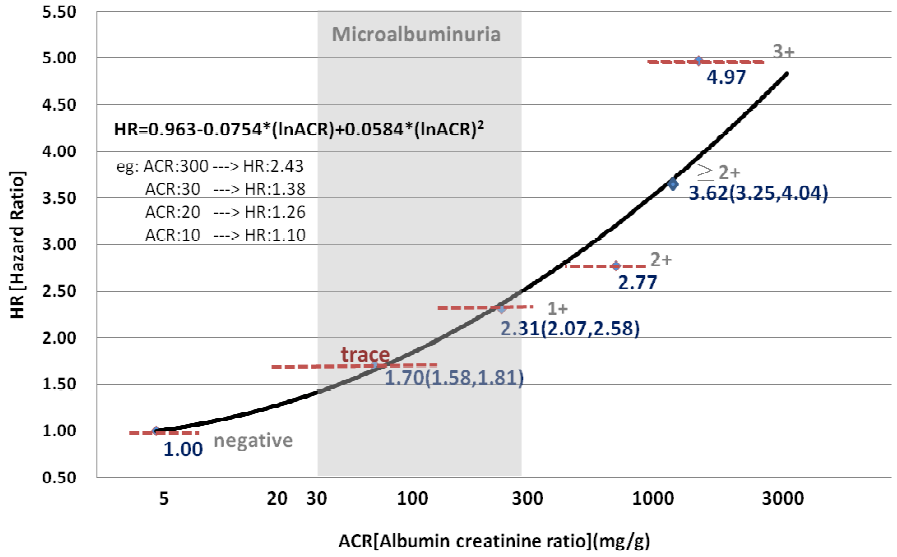
Figure: The dose response relationship between ACR and HR from fitting a curvilinear line through the five levels of all-cause mortality risks identified by dipstick in Taiwan cohort,[3] with inter-quartile (25%-75%) range of ACR shown for different dipstick results.



[Figure Legend]

The hazard ratios, adjusted for 12 risk factors, came from the Taiwan cohort of 464,709 adults recruited since 1994, with ACR values additionally analyzed on a subset consisting of 773 dipstick "negatives", 300 dipstick "trace", 142 dipstick "+", 72 dipstick "++" and 24 dipstick "+++" in 2007. The age, gender and educational distributions of subjects in each dipstick category in this subset have been tested and found to be grossly similar to those in the cohort.