Early Detection of Progressive Chronic Kidney Disease: Is It Feasible?

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The Multiple Risk Factor Intervention Trial (MRFIT) Research Group presents in this issue of *JASN* data on the value of a single measurement of dipstick proteinuria and estimated GFR for prediction of end-stage renal disease (ESRD) over a 25-yr period (1). These data were obtained in middle-aged men, predominantly of Caucasian descent, and show that only a baseline GFR <60, but not of 60 to 75 ml/min per 1.73 m^2, indicates a poor renal prognosis. The presence of a dipstick test 1+ or ≥2+ for proteinuria was more strongly associated with renal risk. Because only subjects with a baseline serum creatinine <2.0 mg/dl were included, the risk attributable to impaired baseline GFR may be underestimated. These findings extend earlier observations by Iseki *et al.* in a more general population of Japanese subjects, which had notably shorter follow-up (2). In the Japanese study, no limitation was set on baseline GFR. These authors showed that the prevalence of impaired renal function at baseline was relatively high in the elderly population, resulting in an equivocal clinical significance in predicting ESRD. Subjects that were dipstick-positive for proteinuria were also found to be at higher risk for ESRD, especially in combination with a low baseline GFR (2).

Even though these data are, at present, the best available evidence arguing for routine testing for renal risk markers, the benefit seems disappointing. As the MRFIT Research Group points out, testing for an impaired GFR detects only 13% of the patients who later develop ESRD, screening for proteinuria detects only 19%, and screening for the combination of both detects no more than 27% (1). These data, in combination with a recent study by Boulware *et al.*, in which it was suggested that screening for dipstick proteinuria by general practitioners is not cost-effective when evaluated with respect to prevention of ESRD (3), make it unlikely that such screening programs will be endorsed by health care authorities. The question then becomes whether it is possible to improve the yield and cost-effectiveness of screening.

At least two possibilities are worth considering. The first would be the development and application of an integrated renal risk score for prediction of ESRD. Besides GFR and proteinuria, this risk score should take into account other renal risk factors, such as age, smoking status, BP, (HDL) cholesterol, and race. Such an approach would likely increase the sensitivity and specificity of screening. However, many subjects would have to be seen by health care professionals for BP measurement, venapuncture, and urine examination. Consequently, such a screening approach can only be achieved at high cost. Whether this option is feasible at a population level is therefore questionable. The second and, in our opinion, more promising scenario would be to screen for lower levels of proteinuria. The traditional dipstick method is only positive when albuminuria exceeds 200 mg/L. Given the documented impact of proteinuria in chronic kidney disease (CKD) progression (4) and considering the stepwise increase in risk with increasing dipstick proteinuria (1,2), it is not unexpected that lower levels of albuminuria (20 to 200 mg/L, defined as microalbuminuria) have also been shown to predict progressive CKD, not only in diabetic (5) and hypertensive patients (6) but also in the general population (7). This suggests that screening for lower levels of albuminuria than can be done by traditional dipstick methodology may result in a better diagnostic yield. Population screening for albuminuria can also be carried out at a lower cost than screening for an impaired GFR or abnormal integrated renal risk score. Albuminuria testing can, for instance, be done by "postal survey." This procedure has been used in the Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND-IT) study (8). In this study, subjects were asked to return by mail a vial containing a portion of a spot morning urine sample to a central laboratory where albumin concentration was determined by nephelometry. Those subjects with albuminuria in excess of 20 mg/L were invited to confirm the presence of microalbuminuria, and to perform more extensive risk profiling in case of positive confirmation (9). Another option would be to use newly developed antibody-based dipstick tests for albuminuria (10,11). Although only semiquantitative, these new tests have the advantage that they are more sensitive than traditional proteinuria-based dipsticks and that they can easily be applied, even by subjects at home.

Lowering the cut-off value for albuminuria will of course increase the number of subjects found positive, and consequently the specificity of albuminuria predicting ESRD will decrease. It is important to note, however, that albuminuria in

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the range of 20 to 200 mg/L has also been shown to predict future cardiovascular (CV) events, again not only in diabetic (12) and hypertensive subjects (6), but also in the general population (13). Microalbuminuric subjects will therefore benefit from early cardioprotective treatment, such as BP lowering. There is even evidence that agents that interfere with the renin-angiotensin system may be of superior benefit in microalbuminuric subjects compared with other BP-lowering agents. In the Heart Outcomes Prevention Evaluation (HOPE) study, subjects who had a high risk for CV events were included (14). Subgroup analysis showed that in subjects with higher baseline levels of albuminuria, intervention with an angiotensin-converting enzyme (ACE) inhibitor is of particular value (14). A similar observation has been made in the Losartan Intervention for Endpoint Reduction (LIFE) study, which included subjects with hypertension and left ventricular hypertrophy (15), and the PREVEND-IT study, which included subjects without a history of cardiovascular disease and with (near-)normal BP and cholesterol (16). Based on the latter study, we calculated that screening for microalbuminuria and subsequent treatment with an ACE inhibitor of subjects found positive is cost-effective for prevention of cardiovascular events (17). Of note, BP lowering, especially with ACE inhibitors, is expected to also lower the rate of decline in renal function in subjects with atherosclerosis-related CKD. This disease entity is at present the most significant cause for ESRD (18).

Before albuminuria-based screening programs to prevent ESRD can be implemented, additional questions need to be answered that could not be addressed in the reports of the MRFIT Research Group and Iseki *et al.* (1,2). It is, for instance, not known how many of the subjects that are found positive for proteinuria were already known to have this abnormality, or overt renal disease, before screening took place. Moreover, critics doubting the value of screening for albuminuria state that many subjects will develop ESRD without having had albuminuria in excess of 20 mg/L. It is important to realize, however, that the available evidence regarding the value of renal risk markers concerns one-time population screenings. It may well be that subjects at risk for ESRD who were initially albuminuria-negative will develop albuminuria at a later stage. Such subjects can still be picked up by repetitive population screening. These questions and concerns can only be addressed in studies especially designed for this purpose, in which subjects are screened on a regular basis and specific information on renal morbidity is obtained.

It is clear that there are several unresolved issues, but the data establishing the predictive value of even dipstick screening is important. We believe, based on the presently available evidence, that screening for albuminuria (instead of dipstick proteinuria), with subsequent treatment of those found positive, may well be even more cost-effective for prevention of cardiovascular events in the short term (17), and as a consequence may help prevent ESRD in the long term. The benefits of such an approach would almost certainly increase when such screening programs are not limited to a single assessment, but when screening is repeated every few years (as advocated for diabetic patients by the American Diabetes Association) (19). The possibility of developing widely available and cost-effective screening programs that could reduce the rapidly expanding burden of both renal and cardiovascular disease offers the real possibility of controlling these major health care problems and their associated economic burden through prevention strategies in the decade ahead.

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See related article, "Association of Single Measurements of Dipstick Proteinuria, Estimated Glomerular Filtration Rate, and Hematocrit with 25-Year Incidence of End-Stage Renal Disease in the Multiple Risk Factor Intervention Trial," on pages 1444–1452.