DCs are the equivalent of inflammatory DCs.4 Thus, the co-culture systems developed by Huang et al. more closely mimic a resolving state of renal inflammation, in which recruited inflammatory renal DC precursors are modulated by kidney MSCs toward a more regulatory phenotype. Indeed, inflammatory GM-CSF-derived DCs can be induced into regulatory DCs in the presence of IL-10 and TGF-β.10

If the latter scenario holds true, then one can envision that niches of kidney MSCs play an important role in returning the injured kidney to a state of immunologic homeostasis and repair. Kidney MSCs may be recruited locally to replace damaged and dying kidney stroma after renal injury. In the process, these recruited MSCs may also contribute to microenvironments that favor the development of regulatory, not inflammatory, renal DCs, thereby promoting resolution of renal inflammation. These are exciting questions for future inquiry, and the groundbreaking studies by Huang et al. provide the rationale to move forward.

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DISCLOSURES

None.

REFERENCES


Are We Ready to Screen the General Population for Microalbuminuria?

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The United States Preventive Services Task Force does not recommend screening for proteinuria in adults; however, this recommendation has not been reviewed since 1989 and therefore cannot take into consideration newer information on benefits of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in slowing the progression of kidney disease. It is already accepted practice to screen all individuals with diabetes for microalbuminuria.2 The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends screening with standard urine dipstick for individuals not at increased renal risk and screening for microalbuminuria for individuals who are at increased risk.3 Standard risk factors to identify individuals at increased risk for kidney disease include diabetes, hypertension, older age, family history of kidney disease, and possibly race/ethnicity. The recommendation to screen healthy adults with dipstick proteinuria was opinion not evidence based. Is there enough new data since these recommendations were made to justify screening the general population without risk factors for microalbuminuria?

In this issue of JASN, van der Velde et al., analyze outcomes in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a cohort study designed to evaluate the association of albuminuria with cardiovascular disease (CVD) and ESRD in the general population of Groningen, Netherlands. They found that a urine albumin concentration >20 mg/L predicted initiation of renal replacement therapy (RRT) over 10 yr, although risk was modest in individuals with levels 20 to 100 mg/L (hazard ratio 3.0 versus 47 for urine level 100 to 200 mg/L). Approximately half of the individuals who ultimately required RRT had microalbuminuria. They used the data from this cohort to evaluate albuminuria as a screening test in both high-risk individuals (known CVD, diabetes, or hypertension or age >55) or the general population. Screening only high-risk individuals identified 55% of individuals with
microalbuminuria, although it identified 87% of individuals who progressed to RRT. Because 40 to 50% of individuals with microalbuminuria did not have one of the listed risk factors, the authors advocate screening of the general population rather than targeted screening to those at increased risk and suggest a cutoff of 20 mg/L. This conclusion requires a closer look.

The presented data make it clear that microalbuminuria is a risk factor for renal events. Knowing this does not necessarily mean that we should start screening the general population for microalbuminuria. In PREVEND, 25,597 individuals did not have one of the renal risk factors. Of this number, 5.8% had microalbuminuria defined as urine concentration >20 mg/L, but there were only six cases of RRT and only two of the six had microalbuminuria (0.008% of the population without risk factors); therefore, a large number of individuals would need to be tested to identify and treat to prevent one case of RRT. In these days of expanding medical care costs, can we justify this?

The test for microalbuminuria is relatively inexpensive, which is a factor in favor of screening, but, as the authors discuss, the costs of screening are more than just the cost of the test. The total cost includes the cost of the test, time and effort to collect specimens, any confirmation tests for treatment of positive test, and costs of monitoring and treatment of complications of interventions. Given the small number of cases, screening the general population is unlikely to be cost-effective, which is supported by an analysis that modeled annual urine dipstick proteinuria screening. Furthermore, to support screening, there needs to be an effective therapy if an abnormality is found.

ACEIs and ARBs are effective in slowing the progression of proteinuric kidney disease, but, in these cases, the benefit is seen in those with overt proteinuria. In individuals with diabetes, treatment with ACEIs or ARBs can slow the development of overt nephropathy and decline in GFR. What are the data to support that treatment with ACEI or ARB in individuals with microalbuminuria but without other risk factors decreases the risk for RRT or clinically significant loss of GFR? Although it is appealing to think it would be effective, this has not been demonstrated. Given the low risk for kidney disease progression in individuals without risk factors, it is unlikely that a study will be conducted to answer this question.

Individuals with microalbuminuria are at greater risk for CVD than for RRT, so should we screen for microalbuminuria to prevent CVD rather than need for RRT? Studies do support treatment of high-risk individuals with microalbuminuria. In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Arm (ASCOT-LA), treatment with atorvastatin in individuals with hypertension and microalbuminuria decreased cardiovascular events. The Heart Outcomes Prevention Evaluation (HOPE) study found that treatment with ramipril decreased the risk for CVD and mortality in high-risk individuals, including microalbuminuria. Are there data that treatment of individuals with microalbuminuria but without diabetes, hypertension, or age >55 prevents cardiovascular events? This is a question that analysis of the Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND-IT) could answer. PREVEND-IT recruited individuals from the PREVEND cohort who had microalbuminuria but did not have diabetes or hypertension. The study was a 2 × 2 study of pravastatin and fosinopril with a primary outcome of CVD. Pravastatin was not effective, but fosinopril was effective in decreasing cardiovascular events. A cost-effectiveness analysis using the PREVEND-IT data found that screening followed by treatment of individuals with microalbuminuria with fosinopril was cost-effective. It would be more cost-effective to screen individuals who are older than 60 (cost-effectiveness ratio 6300 €) or cutoff of urine albumin excretion rate >50 mg/d (7000 €) versus 16,500 € for all individuals. What was not presented was the subgroup analysis for individuals who were younger than 55, so we do not know whether the treatment is similarly effective or cost-effective in this group.

In individuals who have kidney disease or are at increased risk for kidney disease, the presence of proteinuria identifies individuals at high risk for CVD, mortality, and ESRD. In addition, there is an effective therapy to decrease this risk. Individuals without renal risk factors are at low risk for progression, and screening for and treatment of microalbuminuria expose them to potential risks without a clear benefit. It is premature at this time to advocate for screening the general population for microalbuminuria. Screening efforts, such as the Kidney Early Evaluation Program (KEEP), should continue to focus on high-risk individuals.

DISCLOSURES
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REFERENCES
The maximum recommended therapeutic dose (MRTD) of a drug is an important limit not only for the manufacturer but also for physicians and their patients. Limits are derived from a dose–response curve that represents the combination of optimal efficacy and highest safety. The MRTD is established during the developmental phase of a drug. An error in that process may be very costly for both the manufacturer and patients. For example, when looking at the development of drugs altering the renin-angiotensin-aldosterone system (RAAS), there are interesting examples of “mistakes.” Captopril was the first practical drug to target the RAAS in the angiotensin-converting enzyme inhibitor (ACEI) class. During initial testing, the drug was given at dosages of 450 mg/d. Although BP was very effectively lowered, these dosages produced adverse effects such as decreases in renal function, increases in albuminuria, and skin rashes. Too high a dosage was later determined as the reason for these unwanted effects. Ironically, subsequent ACEIs, including lower dosages of captopril, were used to reduce albuminuria and provide renoprotection.

When the first drug in a second new class targeting RAAS, the angiotensin II receptor blockers (ARBs), was launched, the manufacturer and regulators did not want to make the same mistake twice, and care was taken in establishing the MRTD for losartan at 50 mg/d. The choice of this dosage may have been too cautious, because, nowadays, the MRTD for losartan is 100 mg/d. First-class drugs seem to suffer from this trial and error. Thus, manufacturers and regulatory agencies have established even more rigorous protocols to establish an MRTD for optimal efficacy at maximum safety for a new drug. Many physician groups are also guiding proper use by implementing best practice guidelines.

Nevertheless, current regulatory protocols for establishing an MRTD are challenged by at least two recent findings. First, the maximum dosage of a drug may not be the same for different targets, and, second, individual patients may show a different dose–response curve and thus need a dosage that differs from the recommended one.

The obvious goal of antihypertensive drugs such as ACEIs and ARBs is to lower BP; however, organ protection is the ultimate goal of the treatment. What now is the MRTD for these two classes of drugs for nephrologists: Is it the optimal dosage for BP control or the optimal dosage for improved long-term renal outcome?

Recent data show that BP response to RAAS intervention may not be the best “surrogate” for estimating the efficacy of renoprotection. In diabetic nephropathy, Eijkelkamp et al. found that long-term renoprotection is related more to the lowering of albuminuria and not so much to the lowering of BP. This suggests the optimal renoprotective dosage of an antihypertensive drug such as losartan should be established not

See related article, “Screening for Albuminuria Identifies Individuals at Increased Renal Risk,” on pages 852–862.

Drug Dosing for Renoprotection: Maybe It’s Time for a Drug Efficacy-Safety Score?

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