analysis of under 1 year and thus do not answer the durability issue. The third trial did follow subjects for 24 months, but was only able to identify improvement in patients with severe prolapse. Further studies into the longevity of effect must be conducted before we can reliably recommend pelvic floor muscle training as a viable treatment. Ultimately, it comes down to patient choice as conditions of pelvic floor dysfunction are quality of life issues and each patient has a unique set of goals as opposed to the physician’s goal of anatomical correction.

REFERENCES

The effect of reclassification of subjects into the CKD stages by determination of eGFR based on serum cystatin C and by equations using both cystatin C and creatinine was studied in this meta-analysis. The analysis comprised 11 studies of general population-based subjects and five studies of cohorts of subjects with established CKD (creatinine-based eGFR <60 ml/minute).

The total number of subjects in this meta-analysis was 90 750 from the general population and 2960 patients with CKD. The outcomes of interest were all-cause mortality, cardiovascular mortality and end-stage renal disease (ESRD). The follow-up duration of the subjects was between 7 and 9 years in various cohorts. The baseline variable was eGFR based on either serum creatinine or serum cystatin C alone, or a combination of creatinine and cystatin C using the latest equations from the CKD Epidemiology Collaboration (CKD-EPI). These equations incorporate kidney-filtration markers (serum creatinine or cystatin C) as well as age, sex and race (black vs. non-black), except for the cystatin C-based eGFR, for which the data on race were not required (Box 1).

The outcomes were analysed after appropriate adjustments for known standard risk factors. The results of the analysis showed no significant difference in the mean eGFR for both the study populations, i.e. general population and CKD cohorts. As expected, the analysis showed the well-established correlation of reduced eGFR with all-cause mortality. The threshold level at which this effect became significant was an eGFR of 88 ml/minute/1.73 m² for cystatin C-based values whereas the corresponding thresholds were 59 and 83 ml/minute/1.73 m² for the creatinine-based and combination-based equations.

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Classification of chronic kidney disease:
Cystatin C or serum creatinine?

Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT; CKD Prognosis Consortium. (Division of General Internal Medicine, San Francisco Veterans Affairs Medical Center, USA; Departments of Medicine, Epidemiology and Bio-statistics, University of California San Francisco, San Francisco, USA; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; Department of Public Health and Caring Sciences/Geriatrics Uppsala University, Uppsala, Sweden; School of Health and Social Studies, Dalarna University, Falun, Sweden; Division of Nephrology, Tufts Medical Center, Boston, USA; University of Washington, Seattle, USA; Department of Nephrology, Monash Medical Centre, Department of Medicine, Monash University, Melbourne, Australia; Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg; Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, USA; Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.) Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369:932–43.

SUMMARY
The impact of serum cystatin C-based estimated glomerular filtration rate (eGFR) on the staging of chronic kidney disease (CKD) and its association with outcomes was examined in this meta-analysis. Earlier studies have shown that serum cystatin C improves the prediction of eGFR as compared to serum creatinine-based eGFR. The effect of reclassification of subjects into the CKD stages by determination of eGFR based on serum cystatin C and by equations using both cystatin C and creatinine was studied in this meta-analysis. The analysis comprised 11 studies of general population-based subjects and five studies of cohorts of subjects with established CKD (creatinine-based eGFR <60 ml/minute).

The total number of subjects in this meta-analysis was 90 750 from the general population and 2960 patients with CKD. The outcomes of interest were all-cause mortality, cardiovascular mortality and end-stage renal disease (ESRD). The follow-up duration of the subjects was between 7 and 9 years in various cohorts. The baseline variable was eGFR based on either serum creatinine or serum cystatin C alone, or a combination of creatinine and cystatin C using the latest equations from the CKD Epidemiology Collaboration (CKD-EPI). These equations incorporate kidney-filtration markers (serum creatinine or cystatin C) as well as age, sex and race (black v. non-black), except for the cystatin C-based eGFR, for which the data on race were not required (Box 1).

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eGFR. Further, across all categories of creatinine-based eGFR, the reclassification based on cystatin C-based eGFR was associated with a corresponding increased or decreased risk of mortality depending on reclassification being in the lower or higher eGFR category, respectively.

Similar trends were observed for cardiovascular mortality data in relation to creatinine-based eGFR reclassification with cystatin C-based eGFR. The cystatin C-based eGFR threshold at which significant elevation in risk was noted was 69 ml/minute/1.73 m² for the creatinine-based equation, and 86 and 83 ml/minute/1.73 m², respectively for the cystatin C-based and combination equation.

With regard to the development of ESRD, the results again showed increased risk of ESRD with reclassification to lower eGFR categories with the cystatin C-based equation. The effect was more prominent for general population cohorts than for CKD cohorts. Overall, the net reclassification improvement was not significant with regard to ESRD unlike the mortality statistics. The authors concluded that cystatin C-based eGFR and combined (cystatin C- and creatinine-based) eGFR equations showed better association with risk of mortality and ESRD in the general population and CKD patients than conventional creatinine-based eGFR. Further, the threshold for prediction of increased risk of death was better with cystatin C-based eGFR as it became significant at values as high as 88 ml/minute/1.73 m².

COMMENT
CKD is a recognized public health problem worldwide affecting more than 10% of adults, and its prevalence is increasing steadily. The functional parameter of the kidney is the GFR and its value has been made the backbone of classification of CKD. Until recently, GFR measurement was left to research laboratories or it was done infrequently by the more cumbersome methods, viz. 24-hour urinary clearance studies or radionuclide scans. Serum creatinine is the most commonly used parameter of kidney function. However, it is far too insensitive for early CKD and not very reliable in advanced CKD. Various equations have been developed for estimating GFR based on surrogate markers such as age, gender, body weight, serum creatinine, etc. The Cockcroft Gault and Modification of Diet in Renal Disease (MDRD) equations were till recently the most commonly used ones. Even these equations are based on serum creatinine as one of the variables and thus are subject to limitations inherent in serum creatinine measurement as a function of GFR. The most important limitations of serum creatinine are its variation with diet, secretion from renal tubules after filtration at glomerulus, and to some extent gut and its correlation with muscle mass. The loss of muscle mass, which is common in patients who are very sick, reduces serum creatinine and thus leads to overestimation of GFR. In such situations, the serum creatinine level may be low, yet the true GFR is impaired. In contrast, in other patients, the serum creatinine level may be high, but the true GFR is normal (e.g. in patients with African ancestry, a muscular body habitus or a high protein diet). Additionally, most of these equations have not been found useful or validated for advanced age, GFR >60 ml/minute/1.73 m² and across all races. Despite all these limitations, the past decade has seen CKD being classified more systematically based on eGFR measurements and this has unearthed the ‘epidemic of CKD’ leading to its recognition as a major public health problem.

The search for a better kidney filtration marker led to studies on serum cystatin C. This is a 13-kDa, 120 amino acid non-glycosylated protein that is synthesized and secreted at a nearly constant rate by virtually all nucleated cells. It is freely filtered by the glomeruli and is subsequently completely metabolized by the proximal tubule. The development of eGFR equations that incorporated cystatin C by the CKD-EPI coupled with the development of international laboratory reference standards for cystatin C have permitted its use as a clinical tool. The 2012 CKD-EPI equations for eGFR based on cystatin C are an improvement over the 2009 CKD-EPI creatinine equations, which itself is more precise than the MDRD equation.

This sets the stage for finding out if cystatin C-based eGFR would be a better clinical tool than creatinine-based eGFR. The utility of any eGFR calculation should translate into its association with and/or prediction of outcomes in the form of mortality (all-cause and cardiovascular mortality) and progression to ESRD. It is important to emphasize that cardiovascular disease is the major cause of mortality in CKD and that reduced GFR is a strong risk factor for cardiovascular disease.

This study by Shlipak et al. attempts to answer these questions by determining the association of eGFR based on serum creatinine, cystatin C and their combination with all-cause deaths, cardiovascular deaths and development of ESRD over a follow-up of 7-9 years in the general population and CKD cohorts. The analysis included a sizeable number of subjects from both populations. The results once again established the graded association of eGFR reduction with all three outcomes. The value of using cystatin C-based eGFR lies in its more linear association with mortality than creatinine-based eGFR. This association becomes significant at a GFR level of 88 ml/minute/1.73 m² unlike for creatinine-based eGFR value of 59 ml/minute/1.73 m². Hitherto, eGFR values based on creatinine were not good enough to predict outcomes at GFR >60 ml/minute/1.73 m². Cystatin C-based eGFR allows for early detection of CKD to modify risk factors for mortality.

Cystatin C-based eGFR reclassified subjects to higher or lower categories with a corresponding change in risk for outcomes. This reclassification was most significant for a sizeable 42% of subjects with eGFR between 45 and 59 ml/minute/1.73 m² who got reclassified to eGFR >60 ml/minute/1.73 m². This relieved these subjects of the unnecessary burden of CKD class and its associated risk (a 34% decreased risk). An accurate classification would also allow for more judicious use of resources and intensity of intervention in the subjects who have actual eGFR <60 ml/minute/1.73 m².

A few limitations of the study need to be pointed out. The participants in the studies included in the meta-analysis were mainly white or black. This limits the generalization of the results to other races. Further, the commonest cause of CKD is diabetes but only two of the five studies of CKD cohorts in the analysis had subjects with diabetes.

The last word on eGFR calculation has not been written. The equations based on cystatin C alone or the combination of cystatin C and creatinine are a definite improvement but more studies are needed especially in subjects with GFR in the higher ranges, i.e. for eGFR >60 ml/minute/1.73 m². Cystatin C-based eGFR came into picture due to the limitations of creatinine-based equations. Therefore, the utility of cystatin C-based eGFR lies in resolving the areas of uncertainty. For instance, an isolated decreased creatinine-based eGFR in otherwise healthy individuals could be proven by cystatin-based eGFR as a false-positive value particularly if there are no risk factors for kidney disease or markers of kidney damage. Similarly, cystatin C-based eGFR could be useful when a more accurate value is needed than creatinine-based eGFR, e.g. determining eligibility for kidney donation or adjusting dosage of toxic drugs that are excreted by the kidneys.
As per the current KDIGO (Kidney Disease-Improving Global Outcomes) guidelines, it has been suggested (and not forcefully recommended) that cystatin C could be measured in adults with creatinine-based eGFR 45–59 ml/minute/1.73 m² who do not have markers of kidney damage if confirmation of CKD is required. And, if the cystatin C-based eGFR is <60 ml/minute/1.73 m² then the diagnosis of CKD is confirmed or else it stands refuted.\(^3\)

There is substantial evidence in favour of cystatin C- or cystatin C–creatinine-based eGFR determination for the diagnosis and classification of CKD. The improvement in accuracy and utility over creatinine-based eGFR argues strongly in favour of cystatin C-based eGFR as a routine clinical marker. However, for most countries including India, even serum creatinine estimation is still far from perfect and lacks quality control. The cost of cystatin C is at least 10-fold the cost of serum creatinine and even this will need quality control to be useful and reliable. The current therapeutics of CKD and cardiovascular disease in these subjects are really not much different for the range of eGFR to make a case for routine use of cystatin C. Nevertheless, clinicians now have a very good marker for research studies and for resolving uncertainties in CKD classification.

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Erratum

The selected summary titled ‘The impact of deworming on child mortality in programmatic conditions’, published in Vol. 27, No. 1 of the *Journal*, was authored by Priyamadhaba Behera and Kiran Goswami. Dr Behera’s name on page 20 was misspelt. We regret the error.

—Editor