Reviewer's report

Title: Association of Cystatin C and Creatinine with Inflammatory and Procoagulant Markers in a Diverse Cohort: A Cross-Sectional Analysis from the Multi-Ethnic Study of Atherosclerosis (MESA)

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Reviewer: Richard J MacIsaac

Reviewer's report:

Comments to Authors

Major points

The authors need to clearly reflect on what they are trying to show in this study. In the abstract, it is stated that the study investigates the association of kidney function with multiple biomarkers in a diverse cohort. However, in the background to the paper, the authors state ‘Inflammation in a potential mediator of the association between cystatin C and cardiovascular disease’. The authors need to make it clear to readers of this paper as to what they think serum cystatin C levels reflect. Do they think that cystatin C levels simply reflect GFR levels but represent a far more accurate way of estimating try GFR when compared to creatinine based methodology? Or do the authors feel that cystatin C levels measure something more than GFR alone. i.e. that subclinical inflammation also influences cystatin C levels. It is appreciated that this type of question can only truly be answered in studies that include a reference GFR measurement and that in a large population study such as the ‘MESA’ study this approach is not practical. Nevertheless, I do not believe that the paper as presented in its current format helps to sort out this issue or is indeed even designed to answer this question.

Why have the authors investigated the relationship between cystatin C and biomarkers with the relationship between creatinine and biomarkers with eGFR > 60 given the obvious insensitivities of creatinine to detect GFR levels above 60 ml/min? If the authors really want to look at the relationship between kidney function (GFR) and the biomarkers measured in this study a comparison between eGFR measurements, instead of creatinine, versus the relationship between cystatin C and the biomarkers should have at least been made. I would suggest that a useful approach to looking at the data that the authors have collected would be to ask the question as to whether an early decline in renal function is associated with markers of inflammation and a procoagulant state. In the introduction, the authors state that in subjects with kidney disease but not on haemodialysis, kidney function has been associated with markers of inflammation for GFR levels < 60 ml/min whereas above this threshold other studies have not been able to demonstrate an association using creatine-based estimates of GFR. This may be because creatinine-based estimates of GFR lack
the accuracy to pick up early decline in true GFR. GFR estimates based solely on cystatin C levels have clearly been shown to out-perform creatinine based estimates of GFR and to be an excellent predictor of true GFR levels in the high to normal GFR range (Perkins et al JASN 2005, 16, 1404). Why not compare the relationship between biomarkers and a GFR based on cystatin C levels with an eGFR based on the MDRD equation? As mentioned above, I can see little point in comparing biomarkers with creatinine levels alone.

Minor points

Abstract
Background: the authors have not given us a background to the study but have simply stated the aim of the study.

Main body
Results: In the results section, the authors state the main cystatin C and creatinine levels but don’t mention what the mean eGFR level was. Could they please add the mean eGFR level to the results section?