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Performance of Cystatin C– and Creatinine-Based Estimated Glomerular Filtration Rate Equations Depends on Patient Characteristics

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Guest:
Dr. John Lieske is Professor of Medicine and Director of the Renal Function Laboratory in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Calculating an Estimated Glomerular Filtration Rate or EGFR on the basis of plasma creatinine has become a standard practice to assess kidney function, but which equation should be used to make that calculation, and are there better markers than creatinine to use?

The October 2015 issue of *Clinical Chemistry* published a study of the performance of both creatinine and cystatin C based EGFR equations and how well they perform with different patient populations. The senior author of that paper is Dr. John Lieske; he is Professor of Medicine and Director of the Renal Function Laboratory in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota. And he is our guest in this podcast.

Doctor, your study looked at both cystatin C and creatinine for estimating glomerular filtration rates. What were the main findings of your study?

Dr. John Lieske: Here at the Mayo Clinic we have the advantage that we have a relatively large clinical population of patients that I have measured GFR using iothalamate clearance, and in general these fall into three major groups; there are potential kidney donors, people that are potentially going to donate a kidney to somebody. And these are people that are relatively healthy and we think do not have any kidney disease.

And then we have patients that have had a transplant so they are the recipients that are being followed at their yearly follow-up visits, and then patients that might be in nephrology clinic that have chronic kidney disease that's known that their doctors want to measure their GFR.

So what we found in our study was, if we take these three groups and look at these various equations with cystatin C and creatinine that the performance of the equations varies by patient group, that in particular I think the major things to highlight would be that using an estimated GFR by creatinine, there was a relatively large negative bias in these healthy kidney donors, meaning it's giving you a lower number than they probably truly have, and then with the cystatin C, the estimated GFR was also a negative bias, but in this case it was in the transplant patients.

So again, it's giving you a lower number than actually they would have if you measure the GFR. And then if we just sort of look across all of the patients, if you use the combined equation it sort of averages all this out so that if you didn't know what kind of patients you have that probably the safest as far as bias at least would be to use the combined creatinine-cystatin C equation.

Bob Barrett: Why do nephrologists need to follow EGFR, aren't the creatinine measurement sufficient?

Dr. John Lieske: Well, certainly GFR is the key overall measure of kidney function, so that below a certain level your kidney is not compatible with life. But at levels that are above this, where it's low but not that low, there are certain things we need to do such as adjust medications, avoid certain toxins that might make kidney function worse. There are things we do to try to delay progression of kidney failure and people like this and there are certain things we need to start watching for like high potassium in patients so we now have low GFR.

So for lots of reasons, it's important to know when it's low and to try to treat and prevent it from getting worse.

Bob Barrett: Are there other ways to estimate GFR, other than tests based on serum measurements?

Dr. John Lieske: Well certainly creatinine and cystatin C, they both work to measure GFR because they are freely filtered and then they also have a relatively constant rate of production so that at a given steady state the blood level will reflect what your kidney function is.

The issue is that, with the creatinine in particular, it comes from your muscles and since muscle mass varies a lot between people the level of creatinine in a given person at the same GFR might vary a lot if you're somebody with a lot of muscle or very little. The ways to get around this are to do a 24-hour urine collection so you can actually measure the creatinine and then just calculate a creatinine clearance.

The other ways to get around this are, much as we do here clinically in certain patients, where you can inject something like iothalamate or iohexol and then measure how the kidney clears that exogenous substance.

I think the issue with all of these is it's not very practical to do this on a large number of patients, that collecting 24-hour urine is not very easy, and scheduling one of these other kind of tests takes a number of hours and so it's not practical to do this on large numbers of people.

Bob Barrett: Doctor, which of the commonly used equations to estimate glomerular filtration rate seem to perform best in your study?

Dr. John Lieske: So I think to get back to sort of what our main method would be, is that certainly the EGFR creatinine works well in the vast majority of people, and then the cystatin C works very well in the vast majority of people, but there are certain patient populations where there might be a bias and we can predict this.

So I think if we take this in account, we might choose one or the other in certain kinds of individuals, and if you don't know, the average one I'd say works the best, so if you use the combined equation that uses both creatinine and cystatin C that will probably get you the closest to the truth in the vast majority of patients.

Bob Barrett: Your study found differences in EGFR results based on patient characteristics. Talk a little more about that, and why do you think cystatin C did not work as well in the transplant group?

Dr. John Lieske: Well, I think it's been well recognized that inflammation probably increases cystatin C production by cell such as endothelial cell and indeed that might be why estimated GFR where the cystatin C seems to be a better prognostic indicator that having a lower EGFR cystatin C seems to have correlate with worse outcomes with cardiovascular events and things like that.

And that's probably somewhat true in the transplant patients, they probably have some amount of inflammation related to, perhaps their medications that they get to prevent rejection or just the fact that they have a transplant, but that's probably slightly increasing their cystatin C production and then that makes it slightly less of a better indicator of GFR in that particular patient group.

Bob Barrett: Doctor, the authors of the editorial accompanying your paper suggests that your group may have somewhat

overstated the clinical importance of your study. Now, how would you respond to that?

Dr. John Lieske: Well, I think that we are just pointing out some of the issues with the various equations. I think these are things that certainly a trained nephrologist would like to know, and to be able to use these equations to their best. So I don't think we are understating or overstating, I think we are just showing the data and then people can interpret that as they will.

Bob Barrett: Well, finally doctor, given the results of your study, what is the best way to measure or estimate GFR in the clinic and do you see better equations and markers in the near future?

Dr. John Lieske: Well certainly, I think creatinine is still probably going to be the gold standard for the foreseeable future. It's very cheap; with the estimated GFR equations, it gets you very close to the truth as far as what the GFR is in the vast majority of people. But I think it's also important for people to recognize that the estimated GFR is sort of an average number that that's really what it's trying to do that for a given person that's of the age, and sex and race that you are seeing and you have that creatinine number, that's what the average GFR would be.

So really the question to ask yourself when you see a patient, is this an average sort of pace and especially in relation to their muscle mass? So if there are reasons to think that they may have either more or less muscle mass than an average person of that age then I think you might want to do one of these other secondary measurements like cystatin C.

Certainly, if you have an unexpected result with your creatinine I think that's a good time to measure a cystatin C and see if it correlates with that or not. I think it seems unlikely that there is ever going to be a perfect marker, I mean certainly we thought cystatin C was going to get around these issues with muscle mass and it does, but then there are these other potential confounders with that, with increased production with inflammation.

There may indeed someday be a marker that you can just measure blood level and not have to worry about estimated GFR but at least in my mind I don't think that's real likely and I think we actually have enough tools with the current measurements that we can probably, for the vast majority of patients, really have a good idea of what their GFR is.

Bob Barrett: Dr. John Lieske is Professor of Medicine and Director of the Renal Function Laboratory in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester,

Minnesota. He has been our guest in this podcast from *Clinical Chemistry* on creatinine and cystatin C based EGFR equations.

I am Bob Barrett. Thanks for listening!