

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Serum creatinine has been used routinely by the clinical laboratory as a biomarker for the diagnosis and monitoring of kidney disease for more than 60 years. The importance of serum creatinine measurements has been enhanced by the introduction of formulae and reporting guidelines for EGFR, or estimated glomerular filtration rate, in chronic kidney disease staging.

Despite this the professional perception of serum creatinine as a poor biomarker of glomerular function and more specifically as an insensitive for early detection of kidney disease continues to grow. The May issue of *Clinical Chemistry* included a report on the use of serum creatinine to diagnose and monitor kidney disease.

Dr. Neil Dalton is the Professor of Pediatric Biochemistry at Kings College London, and Director of The WellChild Laboratory at the Evelina Children's Hospital in London and the Author of an editorial on this subject in the same issue. He is also our guest in this Podcast.

So tell us, Dr. Dalton, what is creatinine?

Dr. Neil Dalton: Creatinine is an end product of creatine metabolism. Creatine is synthesized in the liver, and in its phosphorylated form it's a major energy source in both muscle and brain. Creatinine which is what we talking about today is produced at a relatively constant rate by non-enzymatic dehydration of creatine.

Bob Barrett: Why is a serum creatinine a measure of kidney function?

Dr. Neil Dalton: Well the creatinine that's formed is not metabolized anywhere else in the body and is only excreted by the kidney. As glomerular filtration rate, this is the primary function of the kidney declines, the serum concentration of creatinine increases as a receptor function. That means that for each 50% decline in the glomerular filtration rate or GFR then there is a doubling of the serum creatinine.

Bob Barrett: Now how important it is to diagnose kidney disease early?

Dr. Neil Dalton: Kidney function is absolutely essential for normal physiological homeostasis. But despite this the clinical manifestations of kidney disease are largely silent until the patient ends up in end stage renal disease requiring a dialysis and/or transplantation. So it's important to know that a routine blood test, that measuring creatinine can pick this disease early before you can reach that stage.

What's probably as important is that as kidney function declines, even within the early stages, then cardiovascular risk and overall mortality increased dramatically. This was published by Weiner et al in JASN in 2004, showing really a remarkable increase in your cardiovascular risk as kidney function declines.

In addition, there have been studies over the last 10 years, particularly the study by Corish and others that appeared in the American Journal of Kidney Disease in 2003, showing that the prevalence of kidney disease in America is rising really quite significantly, even at that time the prevalence was about 11% in the USA and in patients who were older than 65 years of age, 11% had stage three or worst that is already in quite significant decline in renal function.

I think it's important to point out at this point that chronic kidney disease is a progressive condition and continues even when the original cause is often being resolved.

Bob Barrett: Is it possible to slow the progression of end stage renal disease?

Dr. Neil Dalton: Early detection and intervention with particularly blood pressure control, to some extent diet and statins if appropriate can really very significantly reduce morbidity and mortality and slow the rate of progression. The aim is really to pick up kidney disease early and try and maintain function so that the personal and financial burdens of end stage renal disease services are delayed and hopefully not required.

Bob Barrett: If serum creatinine is so universally used to measure glomerular filtration rate, then why has the poor perception of it developed?

Dr. Neil Dalton: Well there are several reasons that have really conspired to create this poor perception of creatinine. I think the first thing is to go back a long time now, probably 70 or 80 years when creatinine was first being looked at in man and the recognition that 20% of it is actually actively secreted by the proximal tubule of the kidney.

As the consequence of that, drugs that interfere with that tubular secretion like trimethoprim and cimetidine will cause an increase in plasma creatinine, even though you haven't affected the glomerular filtration rate. On the corollary of that, you can have changes in production rate, so that drugs like growth hormone therapy for short stature or Fenofibrate, which is a cholesterol-lowering drug. They can increase plasma creatinine because they increase its production rate. In liver disease, particularly chronic liver disease, the synthesis of creatinine is reduced and therefore

creatinine production falls, and you get inappropriately low creatinine for your actual glomerular filtration rate.

On top of that and probably better known is because we have known creatinine for so long, there is a long analytical history and a lot of interferences in the assays have been recognized and reported, and as a consequence manufacturers have tried to develop their analytical systems to reduce the amount of interferences. As a consequence, there is no standard methodology, and it's only recently that it has become a requirement that assays that are sold have to be traceable to isotope dilution mass spectrometry.

All those things have been around for a long time but the vital piece of information comes from the publication in 1985 by Shemesh working with Bryan Myers where they shared a lovely diagram demonstrating that serum creatinine was within the normal range in a significant proportion of patients with renal disease. That is that the diagnostic sensitivity of creatinine was low, and this view has been consolidated by subsequent publication suggesting that due to compensating tubular secretion of creatinine, the levels do not rise until the glomerular filtration rate is fallen by about 50%, giving the so-called creatinine blind range.

Bob Barrett: Well that's really crucial. Surely, it severely limits the use of serum creatinine in clinical practice.

Dr. Neil Dalton: I agree. If it were true, you would be right. However, and I use the word advisedly, the concept of a creatinine blind range is false. Unfortunately but understandably, the statement even appears in kitchen inserts for alternative GFR markers, and as a consequence, there is pressure not only to define the biomarkers but to change to other markers such as the Cystatin-C or beta trace protein.

Bob Barrett: Your editorial was prompted by the paper by Dr. Spanaus and colleagues. Why should this paper change our perception?

Dr. Neil Dalton: Well at first rating this paper by Spanaus et al. looks just like another comparison of a series of biomarkers in relation to glomerular filtration rate. This highly expected group has been monitoring kidney function using formal glomerular filtration rate measurements by iohexol clearance in a fairly large cohort of 227 patients with mild to moderate kidney disease for many years now and has taken the opportunity to compare the diagnostic performance in terms of both disease staging and prediction of progression of serum creatinine and two plasma protein markers of glomerular filtration rate, Cystatin-C and beta trace protein.

The data are all compelling and the conclusion is very simple. All three biomarkers are equivalent. I think the paper provides unequivocal evidence of the concept of the creatinine blind range is false. As glomerular filtration rate declines, the mean values of the three biomarkers increase proportionately. This should not be unexpected but because of our perception it will come as a surprise to many and hopefully it will promote some discussion and reassessment of serum creatinine.

Bob Barrett: But the increase in serum creatinine is still relatively small in the early stages of kidney disease.

Dr. Neil Dalton: Yes, it is but that's true for any GFR marker, in the early stages all GFR biomarkers appear insensitive. The dropping GFR from 100 to milliliters per minute will only lead to a doubling in the serum concentration. In another sense the hunt for a more sensitive glomerular filtration marker is flawed. If the concentration increases by a greater amount, then it can not be a GFR marker. So in terms of value in clinical practice of the criteria that we will come onto become more important.

Bob Barrett: Clearly serum creatinine is no worse than Cystatin-C or beta trace protein, but surely the corollary is that creatinine is no better than other GFR biomarkers.

Dr. Neil Dalton: This is where we get to the really interesting and important discussions regarding laboratory interpretation of test results and the evaluation of new biomarkers. Laboratory results are consistently interpreted by reference to a normal range. There are obviously good reasons for this, but this approach is not universally valid. When we try and validate new biomarkers, the most commonly used comparison is the receiver operator curve or ROC curve, a test of both diagnostic specificity and sensitivity, but in clinical diagnostics, we are not only interested in diagnosis but also in the monitoring of progression or response to treatment.

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The Spanaus data suggest that the markers are equivalent, and this is entirely true for the population studies and new tests are usually assessed on populations. But I think it's important to ask about the individual. The example that I like to use is where we monitor kidney function after kidney transplantation. There is a real risk of rejection or immunosuppressive toxicity. Both of these lead to a reduction in glomerular filtration rate and early detection is crucial to patient management.

Creatinine is exclusively used in this context, but not by using a normal range but by looking at the changes within

the individual, so that adjustments can be made to their immunosuppressive therapy. This is an example of truly personalized medicine.

Bob Barrett: Well, how do we make this leap to personalized medicine?

Dr. Neil Dalton: It really comes from our understanding of biological variation of the analytes that we're measuring. In the seminal report by Gowans and Fraser in 1988, they showed that the biological variation of serum creatinine was very low around about 4%, but the papers suggested it maybe as high as 7% but still the concentration is very tight within an individual. What that means is that with a very precise assay less than 2% variation which is easily obtainable on routine analyzers these days, very small changes in GFR can be identified. Their implicit conclusion is that a reference interval or a normal range shouldn't really be used for serum creatinine.

Of course if we look at the Shemesh paper and the diagram they produced, the problem in interpretation is really the misuse of that normal range. This is really not generally appreciated, and it's not normally applied in current laboratory practice.

In the case of Cystatin C, the intraindividual variation has been reported as high as 75%, meaning the small changes in glomerular filtration rate within an individual cannot really be determined. It works well on a population base but not for the individual.

Low biological variation of serum creatinine means it's overall in terms of clinical application. Serum creatinine is far superior to Cystatin C.

Bob Barrett: So given the importance of early diagnosis of kidney disease, are you implying that this could be achieved by longitudinal monitoring of serum creatinine in any individual?

Dr. Neil Dalton: Yes. I mean it's unrealistic to suggest that this might be applied as a primary healthcare strategy for early diagnosis of kidney disease in the general population. But, it is extremely valuable in patients at high risk of developing kidney failure, for example patients with Type 1 or Type 2 diabetes.

The fact is that serum creatinine is an exquisitely sensitive marker of changes in glomerular filtration rate and explains why it has become and remains the cornerstone of laboratory and clinical renal transplant monitoring, which is equally sensitive in other clinical situations, for instance where nephrotoxic drugs are being administered.

It is worth pointing out that it is particularly valuable in safety monitoring in pharmaceutical trials specifically at phase one stage. In the future as we move to personalized medicine our experience with serum creatinine represents the ideal for the characteristics of any new biomarker, i.e., low biological variation coupled with accurate and precise measurement. Creatinine also provides a model for the critical evaluation of any biomarker with regard to the individual as well as population based studies.

- Bob Barrett: But this is not new.
- Dr. Neil Dalton: No, I agree, but it appears that it needs to be emphasized.
- Bob Barrett: So despite the perception, the reality is that serum creatinine is an excellent biomarker for glomerular filtration rate.
- Dr. Neil Dalton: Serum creatinine demonstrates the chasm that often separates perception and reality. However, it is not the perfect biomarker of glomerular filtration rate, tubular secretion, an altered production rate, and analytical specificity, all mean it is not applicable in all situations, interpretation often remains in odd.

Consequently the search for the perfect endogenous glomerular filtration marker will continue but the take-home messages from Spanaus paper are clear. The professional perception that serum creatinine is an insensitive biomarker of early changes in GFR is totally incorrect. The reality is that the serum creatinine is still a very good measure of glomerular filtration rate and is by far the most sensitive biomarker for detecting small changes in glomerular filtration rate in an individual.

- Bob Barrett: Dr. Neil Dalton is the Professor of Pediatric Biochemistry at Kings College London, Director of The WellChild Laboratory of the Evelina Children's Hospital in London and has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.

Total Duration: 15 Minutes.