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Early Recognition of Acute Kidney Injury: What's the Role of Biomarkers?

Dr. Koyner:
Acute kidney injury, or AKI, is a common problem that is faced by nephrologists, intensivists, general practitioners and surgeons. The incidence of AKI is increasing in hospitalized patients, and it is associated with increased risk for both short- and long-term morbidity and mortality. Being able to identify patients who are at increased risk for AKI is increasingly important in order to be able to impact their care and change their clinical course. Fortunately, recently there have been advances in several biomarkers of kidney injury that have allowed us to identify patients who are at increased risk.

This is CME on ReachMD. I'm Dr. Jay Koyner, a nephrologist at the University of Chicago, and I'm here today to talk to you about AKI, acute kidney injury, and biomarkers. I'm here with Dr. Sandra Kane-Gill, who is Professor of Pharmacy and Therapeutics at the University of Pittsburgh's School of Pharmacy, and I'm also here with Dr. John Kellum, who is a Professor of Critical Care Medicine and the Director of the Critical Care Nephrology Center at the University of Pittsburgh.

Welcome, Dr. Kane-Gill. Welcome, Dr. Kellum. Thanks for being here.

Dr. Kane-Gill:
Thank you very much, Dr. Koyner. It's a pleasure to be here.

Dr. Kellum:
Dr. Koyner, it's a distinct honor to be with you today.

Dr. Koyner:
Good to see you both. As I'm sure you're both aware, AKI is a common problem and can have dire consequences. Dr. Kellum, can you tell me a little bit about what exactly AKI is?

Dr. Kellum:
Sure. As you know, Jay, it's a big topic, but briefly, acute kidney injury is an abrupt decrease in kidney function. It can be caused by a host of different triggers from obstruction to toxic mediators, both endogenous and exogenous, including drugs, as well as disorders of other organs, like the liver or the heart. It has both important short-term and long-term complications, including fluid electrolyte abnormalities, bleeding complications, problems with metabolizing drugs that are cleared by the kidney and hence associated with adverse drug events. It also impacts cardiovascular risk significantly and can lead to immune dysfunction and, therefore, increase the risk of infection. Often acute kidney injury doesn't resolve and the kidney injury goes on to develop a chronic stage that we refer to as chronic kidney disease; and, of course, chronic kidney disease is associated with its own host of chronic problems.

Dr. Koyner:
Thank you. How do you diagnose acute kidney injury, Dr. Kellum?

Dr. Kellum:
It's a clinical diagnosis, and it involves looking at changes in kidney function with tests like serum creatinine or urine output, but these tests don't directly measure kidney damage, and so there has been an ongoing push, I think, to try to develop new diagnostic tests that

can measure damage in the kidney or, in the case of the markers we'll be talking about today, actually stress in the kidney, which happens before there is actual damage.

Dr. Koyner:
Dr. Kane-Gill, in follow-up to that, what do you think are the characteristics for an optimal biomarker of AKI?

Dr. Kane-Gill:
I think ideal characteristics would include that it's objective, that it's quantifiable, that it's specifically related to kidney injury, that it's reliable, and that it's very easy to measure. As Dr. Kellum already mentioned, those traditional biomarkers we think of are things like urine output and serum creatinine and proteinuria. Unfortunately, these biomarkers have some limitations, limitations such as urine output, very dependent on fluid status, and also can be very dependent on diuretic administration.

We also have serum creatinine, which is really not a realtime biomarker. In fact, after insult occurs, a rise in serum creatinine can lag behind by about 24–48 hours, and so that can be problematic because it doesn't allow us an opportunity to intervene or think about what our therapy should be for that patient because the function has already changed and the patient already has damage occurring.

In fact, we have these newer biomarkers that are available to us. We have biomarkers that are used for functional assessment. One is Cystatin C, so similar to serum creatinine in the sense that it may be able to help us with drug dosing in the future as we learn more about it, and maybe we use it instead of serum creatinine, or maybe we use it in addition to serum creatinine as a possibility. We have damage biomarkers that are available to us. One is KIM-1, something called NAG, also NGAL. These are damage biomarkers. We also have stress biomarkers, as Dr. Kellum had mentioned. Ones that are currently available are TIMP-2 and IGFBP7.

Dr. Koyner:
Great. It sounds like there are a lot of biomarkers out there for AKI. Which ones are you using in your clinical practice?

Dr. Kane-Gill:
For us at our institution, we actually use TIMP-2/IGFBP7, which is combined into a test called NephroCheck. We use it for various reasons, but one of them is the fact that it is the only biomarker for acute kidney injury that is FDA-approved in the United States to assess for risk of moderate to severe acute kidney injury in hospitalized, critically ill patients.

Dr. Koyner:
Great, thank you. For those of you just joining us, I'm Dr. Jay Koyner, a nephrologist at the University of Chicago, and you're listening to CME on ReachMD. I'm here with Dr. Sandra Kane-Gill and Dr. John Kellum, both of whom work at the University of Pittsburgh, and we're talking about AKI biomarkers.

Dr. Kellum, we just heard a little bit from Dr. Kane-Gill about stress biomarkers. Can you tell me a little bit about how these stress biomarkers work and what they do to identify patients at risk for AKI?

Dr. Kellum:
Sure, Dr. Koyner. The test that combines them, as Dr. Kane-Gill just mentioned, is FDA-approved for risk assessment of acute kidney injury, and they were discovered by looking at really hundreds of candidate biomarkers in hundreds of patients to try to identify indicators of, predictors of acute kidney injury occurring over the next 12 hours. It was really only after their discovery and subsequent validation that it became clear that it isn't actually necessary for the cells in the kidney to be damaged or to die for these biomarkers to be released, and therefore, we think about them rather than as damage markers, we think about them as actually markers that go up before damage, and we think of them as stress markers, because just noxious stimuli can produce their release, their preformed proteins, and they are released very rapidly into the extracellular space or into the urine.

Levels of these markers, when they get to be above 0.3, represent an 8-fold increase in the risk of developing acute kidney injury over the next 12 hours, and when they get to be above 2.0, they represent a 16-fold increase in the risk. What this basically means is that the more stress in the kidney that you have the more likely there is going to be injury. The value, though, clinically is that there is a window of opportunity between the release of the stress markers and the development of injury or damage to the kidney that can be utilized as a way of triggering a response, and there have been a variety of studies—from the PrevAKI study in Germany, which was the first, to a recent study by Dan Engelman's group at Baystate, both in cardiac surgical patients—showing that you can interdict this process. You can identify patients that have kidney stress, and you can do things to alleviate that kidney stress, whether it's by better resuscitation of the patient, whether it's by improved function of the heart in the cardiac surgical patient population, for example, and you can reduce the risk of that patient going on to develop acute kidney injury. And that is why the most recent cardiac surgical guidelines actually recommend this kind of risk stratification and management of patients to avoid this complication of acute kidney injury, which happens quite often.

Now, in addition to cardiac surgery, there are a variety of other areas, such as drug-associated AKI and sepsis, where studies are currently underway and efforts are ongoing to reduce the risk of acute kidney injury in that setting as well.

Dr. Koyner:
Dr. Kane-Gill, given the wealth of data that exists around the outcomes of patients who have TIMP-2/IGFBP7 measured, how do you think this biomarker should be used?

Dr. Kane-Gill:
Sure. I think that, as we know, for acute kidney injury, about 1/4 to 1/3 of cases are associated with drugs, and drugs are that one modifiable risk factor that allow us to evaluate them, make sure we are providing them in an optimal manner so that maybe we can prevent the progression of acute kidney injury, or we can prevent AKI from occurring at all.

At our institution we actually have a protocol in place to help us with thinking about drug management. We have a clinical decision support alert that goes directly to the pharmacist when a patient is prescribed 3 or more nephrotoxins, so the moment that third nephrotoxin is ordered, the pharmacist gets an alert. It's an opportunity for them to do a risk assessment, and that would include evaluating TIMP-2/IGFBP7. And so, if that test comes back positive, greater than 0.3, in addition to the fact that they have some other risk factors, that is an opportunity to say, "Do you know what? We can not add this third nephrotoxin," or, "Maybe there is another nephrotoxic drug we can discontinue," or, "Maybe we need that diligent monitoring."

Dr. Koyner:
Great. At my hospital where we're also measuring TIMP-2/IGFBP7, we use it in a similar manner that you described, where we use it to adjust drugs like vancomycin or other drugs that require careful monitoring of drug doses and kidney function at the same time.

As we move to close, I guess I'd like to ask both of you to think about what you think the take-home message is around the use of biomarkers of acute kidney injury to identify patients who are at high risk. Dr. Kellum, why don't you start?

Dr. Kellum:
Yes, thank you, Dr. Koyner. For me, I think that one of the things that needs to be emphasized is that most clinicians think that they are already doing everything that needs to be done for patients at risk for acute kidney injury, and I think we need to explain to clinicians that, first of all, every patient doesn't need to have everything done. In fact, that is not good medicine. We need to provide the appropriate care for the appropriate patients. Some patients, for example, should have a nonsteroidal to avoid a narcotic, and other patients are at too high risk to receive that nonsteroidal, and sorting out that risk can be challenging, and we need to have better tools than simply waiting for the acute kidney injury to occur and then react to it. So I think my closing message would be that this is really an opportunity to be proactive and to be proactive in both directions, to do more for some patients and less for other patients, and to provide the right care for the right patients at the right time.

Dr. Koyner:
I think that is super interesting, Dr. Kellum, and couldn't agree more.

What about you, Dr. Kane-Gill? What do you think the take-home is?

Dr. Kane-Gill:
I think the take-home is consistent with what you both have described, which is an opportunity, right? It's an opportunity we didn't have previously with traditional biomarkers. It's an opportunity to identify risk early. It's an opportunity to intervene early.

Dr. Koyner:
I totally agree. Unfortunately, that's all the time we have today. I'd like to thank both Dr. Sandra Kane-Gill and Dr. John Kellum from the University of Pittsburgh for their time as we've talked today about acute kidney injury and new biomarkers.