

Kidney News

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New Blood Test Might Identify Calcification-Prone Patients

By Tracy Hampton

Although vascular and soft tissue calcification can be deadly, physicians currently have no reliable tools for determining an individual's calcification risk. This is particularly pertinent to nephrologists and others who care for patients with compromised kidney function because pathologic vascular calcification has been called "the killer of patients with chronic kidney disease" (Mizobuchi M, et al. *J Am Soc Nephrol* 2009; 20:1453–1464).

"We currently have quite a good idea about pathomechanisms triggering progressive calcification, and we think we know about a number of clinical factors predicting calcification progression including hyperphosphatemia, high calcium burden, and inflammation," said Markus Ketteler, MD, head of the division of nephrology at the University Hospital Würzburg, in Germany. "However, none of these factors shows a clear-cut linear relationship with the magnitude or progression of cardiovascular calcification or related events."

Now a newly developed nanoparticle-based test, which is described in a

recent issue of the *Journal of the American Medical Association*, could change practice and provide an effective way to measure an individual's overall propensity for calcification in serum (Pasch A, et al. *J Am Soc Nephrol* doi: 10.1681/ASN.2012030240 [published online ahead of print September 6, 2012]).

"This test may help to identify calcification-prone patients to guide and monitor their treatment. We regard this as an important step ahead in the field of calcification research and of potential importance for the treatment of patients with kidney disease worldwide," said first author Andreas Pasch, MD, of University Hospital and University of Bern, Inselspital, in Switzerland.

Calculating calcification

Calcifications in the body mainly consist of two components, calcium and phosphate, which combine to form calcium phosphate. Because calcium and phosphate concentrations in the blood are naturally near supersaturation, the balance of inhibitors and promoters of

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KIDNEY WEEK SCIENTIFIC SESSIONS

20 THURSDAY

Tolerance and Kidney Transplantation
State-of-the-Art Lecture: David H. Sachs

Sepsis AKI: Kidney as Amplifier and Target
Robert W. Schrier Endowed Lectureship: Robert A. Star

Mutations in the K⁺ Channel KCNJ5 Produce Primary Aldosteronism
Barry M. Brenner Endowed Lectureship: Richard P. Lifton

22 FRIDAY

Health Care Reform in America—Past, Present, and Future
State-of-the-Art Lecture: William L. Roper

Renal Glucose Transport from Man to Molecule
Homer W. Smith Address: Ernest M. Wright

Stone Formation in Dent's Disease

Jack W. Coburn Endowed Lectureship: Rajesh V. Thakker

Allocation of Health Care: Dialysis and Beyond

Christopher R. Blagg Endowed Lectureship: Bruce C. Vladeck

26 SATURDAY

Entering the Era of Genomic Medicine: Research Opportunities and Challenges

State-of-the-Art Lecture: Eric D. Green

28 SUNDAY

Where Kidney Disease Was and Where It Is Headed

State-of-the-Art Lecture: Robert W. Schrier

Podocyte Biology: The Key to Understanding Glomerular Disease
Young Investigator Award: Tobias B. Huber

Calcification-Prone Patients

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these minerals critically influences the development of calcification. Under physiologic conditions, calcium and phosphate mineralize only in bones and teeth, but pathologic states can lead to soft tissue and vascular calcifications.

Intensive treatment, especially self-medication with calcium-containing antacids and over-the-counter osteoporosis drugs, has led to a resurgence of the “milk alkali syndrome” associated with soft tissue calcifications and kidney damage. Also, patients with chronic kidney disease often have abnormally high blood calcium levels because of their compromised kidney function and metabolic insults of diabetes, dyslipidemia, oxidative stress, uremia, and hyperphosphatemia.

“Despite much progress in our molecular understanding of calcium homeostasis—particularly the role of the calcium-sensing receptor, renal phosphate handling, and epithelial calcium channels that are present in various tissues—the clinical determinants of pathologic calcifications are still incompletely understood,” said Pasch. “Individual calcification risk cannot be determined, and patients particularly [likely] to develop calcifications cannot be identified.”

Given the major clinical problem of accelerated calcification in many patients with chronic kidney disease, Pasch and his team set out to develop the first potentially widely available blood test that functionally integrates all the procalcification and anticalcification forces inherent in blood with one single measurement to obtain an estimate of the calcification propensity of individual serum samples.

The researchers found that when serum is artificially challenged with high amounts of calcium and phosphate, so-called primary calciprotein particles (CPPs) are formed. CPPs are protein-mineral aggregates that consist mainly of calcium, phosphate, and the two calcification-inhibiting serum proteins fetuin-A and albumin. Calcium and phosphate form an amorphous or colloidal state in primary CPPs, but with time, primary CPPs transform into secondary CPPs, which consist of a spectrum of proteins as well as crystalline (as opposed to colloidal) calcium phosphate. “The speed of transformation is a measure of calcification inhibition,” Pasch said. “The longer the delay of transformation, the stronger the calcification-inhibiting forces in a given serum.” In the presence of lower calcium and phosphate concentrations, CPP formation progresses only over weeks to months.

The transformation from primary CPPs, which are spherical, to secondary CPPs, which are spindle-shaped, causes turbidity that can be optically moni-

tored with a commercial nephelometer, a photometer measuring scattered light. The test by Pasch and his team measures the kinetics of CPP transformation by detecting the changes in light scatter in a sample of serum. In its current format, the assay can measure approximately 200 serum samples per day.

Getting to the clinic

To prove the test’s utility, the researchers showed that in the presence of artificially elevated calcium and phosphate concentrations, their new nanoparticle-based assay detected the spontaneous transformation of primary CPPs to secondary CPPs. Also, the test found that both the sera of mice deficient in fetuin-A, a serum protein that inhibits calcification, and the sera of patients receiving hemodialysis had reduced intrinsic

properties to inhibit calcification. Blood from healthy volunteers did not.

“The test by Pasch et al. could show clear differences in calcification inhibitory capacity of calcification-prone fetuin-A knockout mice and dialysis patients versus wild-type mice and healthy volunteers, respectively,” said Georg Schlieper, MD, an assistant professor at the RWTH Aachen University Hospital, in Germany. “This discrimination appears as a very promising approach in identifying patients at high risk for calcification and has the later potential to guide through decalcification therapy.”

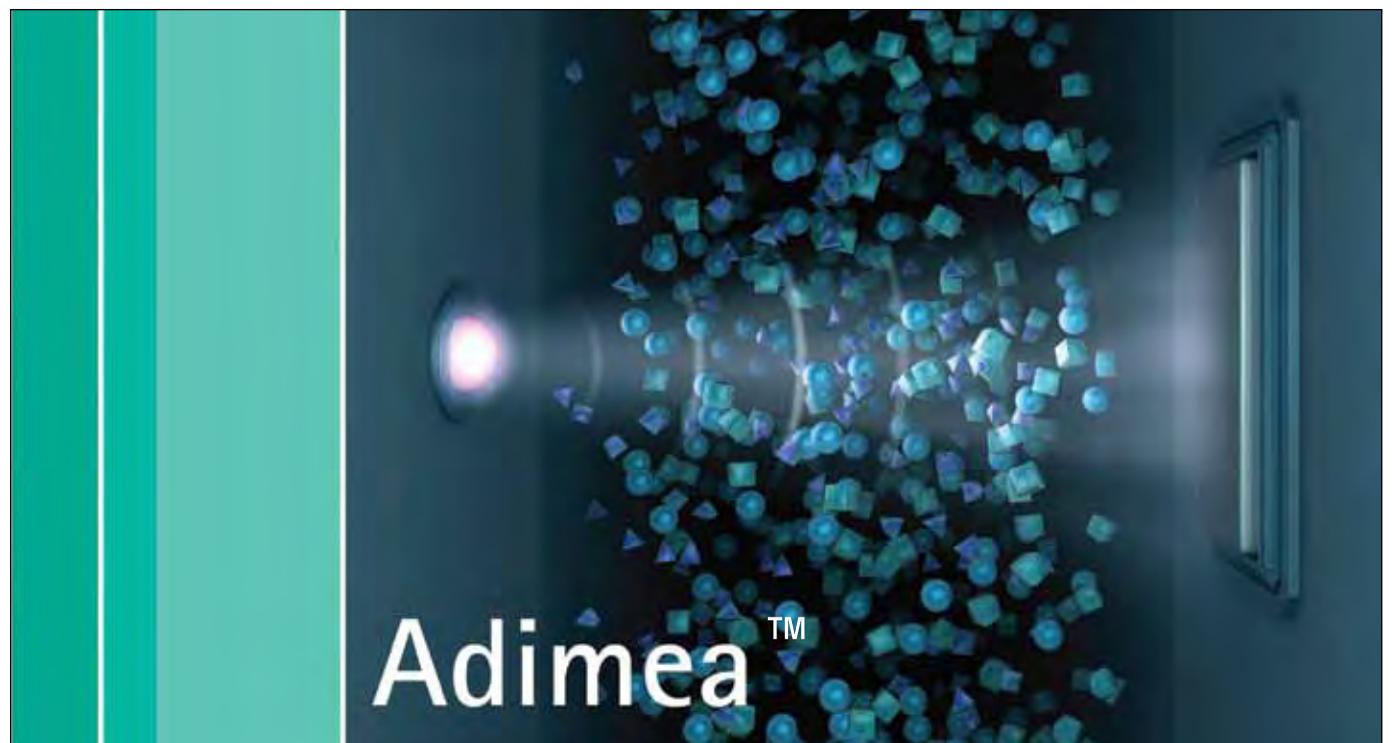
In other words, the test may also become an important tool for identifying and testing calcification inhibitors and may provide the basis for treatment monitoring in patients who receive such inhibitors.

Whereas the findings and their im-

plications are promising, “future experimental and clinical studies are essential in order to establish this calcification test for clinical use. These data need to be confirmed in patient cohorts in prospective studies, especially in conjunction with outcome parameters,” Schlieper said.

Ketteler added that “in addition to systemic or circulating calcification-modifying factors, there are some potent locally expressed and active calcification inhibitory systems at work—including matrix Gla protein, or MGP, and pyrophosphates—which may not be detected here.”

The test in its current form requires strict temperature control and liquid handling. Further automation and simplification could help make the test more useful for basic and clinical research, the investigators said. ●



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