Recent findings may help explain the calcium paradox—the relationship between osteoporosis and atherosclerosis—that plays a large role in aging and is a particular concern in those with chronic kidney disease (CKD).

Patients with CKD have a higher incidence of vascular calcification and a greatly increased risk of cardiovascular death. The mechanisms involved in the accelerated vascular calcification observed in CKD have recently become more clear, leading to the hypothesis that perhaps a lack of natural inhibitors of calcification may trigger calcium deposition.

Aging can be seen as a process of calcification, the literal ossification of the body’s tissues—including the arteries, heart, kidney, and brain—while at the same time calcium is lost from bone, resulting in thinning and fracturing of the bones, or osteoporosis.

Osteoporosis results when the body removes more bone than it replaces. Calcification outside the bone tissue is due to the body’s regulators of calcium metabolism becoming less efficient as aging progresses.

A recent study looked at the progression of aortic calcification in chronic dialysis patients with disorders of mineral metabolism (Nephrol Dial Transplant 2011; 5:1747–8).

“Aortic calcification progressed in almost a third of the patients during dialysis,” said Marlies Noordzil of the department of clinical epidemiology at the University of Amsterdam. “Hypercalcemia and hyperparathyroidism were associated with an increased risk of progression.”

It’s well known that Vitamin D3 and vitamin K-complex, as well as magnesium, help normalize the efficiency of calcium metabolism ensuring proper calcification of bone tissue while preventing pathological calcification of the vascular and organ systems. These vitamins work synergistically to keep calcium where it belongs.

Much has been written about vitamin D recently and the “monitoring and maintenance of vitamin levels throughout the stages of CKD” said Eleanor Lederer, professor of medicine at the University of Bonn in Bonn, Germany.

In the United States, about 25 percent of individuals infected with HIV are also infected with HCV. The rate among injection drug users is much higher. About 80 percent of users with HIV are also infected with HCV, according to the U.S. Centers for Disease Control and Prevention.

Hepatitis C Infection with HIV Raises Risk of Chronic Kidney Disease

Chronic hepatitis C virus (HCV) infection raises the risk for chronic kidney disease (CKD) in people infected with human immunodeficiency virus (HIV). Clearing the HCV infection appears to reverse this effect, researchers have found.

“In this whole era of treatability of HIV [and] the aging patient, it becomes of much bigger concern what other target organ damage are we going to see,” Jürgen Rockstroh, MD, told ASN Kidney News at the 13th European AIDS Conference in Belgrade, Serbia, late last year. Rockstroh is professor of medicine and head of the HIV clinic in the department of medicine at the University of Bonn in Bonn, Germany.

“In several observations we’ve seen there has been an independent association between hepatitis C co-infection and risk for development of chronic kidney disease,” Rockstroh said.

In the United States, about 25 percent of individuals infected with HIV are also infected with HCV. The rate among injection drug users is much higher. About 80 percent of users with HIV are also infected with HCV, according to the U.S. Centers for Disease Control and Prevention.

Using the prospective, observational study, Rockstroh found that HCV infection in people with HIV is associated with a higher risk of incident CKD.

The List

Nanotechnology, pediatric transplant disparities, gene therapy, measuring quality and comparing effectiveness all made our “top to watch in 2012” list.

Journal View

Can elevated levels of inflammation markers predict long-term risk of chronic kidney disease (CKD)?

Policy Update

CDC initiates electronic death certificate; ASN provides input

Up in Space

And down to earth again. ASN Past President Joseph V. Bonventre interviews space expert Jonathan B. Clark about the health effects of space and lessons for medicine on earth.

Detective Nephron

Hypomagnesemia and proton pump inhibitors
Calcium Paradox

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cine, Robley Rex VA Medical Center, and University of Louisville School of Medicine in Louisville, KY. "A fall in 1.25 hydroxyvitamin D is the first measurable change in mineral metabolism noted during the course of CKD, long before the onset of hyperparathyroidism, hyperphosphatemia, or hypercalcemia. The nearly universal prevalence of bone mineral disorders in this population suggests strongly the need for vitamin D replacement."

In December of 2010, the Institute of Medicine (IOM) raised the Recommended Daily Allowance (RDA) for vitamin D for young adults from 200 IU (International Units) to 600 IU while the RDA for people over 70 was raised to 800 IU.

Vitamin D3 is a vital cofactor in both bone mineralization and calcium absorption and plays a role in the renin-angiotensin system. When synthesized in the kidneys, the vitamin is released into the circulation and acts as a hormone, regulating (among other things) the concentration of calcium and phosphate in the bloodstream, promoting the healthy mineralization, growth, and remodeling of bone tissue. It does this by binding to vitamin D-binding protein (VDR). The binding of vitamin D3 to the VDR acts as a transcription factor that modulates gene expression of transport proteins such as TRPV6 and calbindin, which are involved in calcium absorption in the intestine.

Vitamin D also acts to inhibit vascular calcification by blocking the release of fat-derived inflammatory cytokines that contribute to both inflammation and adhesion in the arteries and elsewhere. These cytokines play a role in atherosclerosis and osteoporosis. Several inflammatory cytokines are induced by oxidative stress, and are a factor in chronic inflammation.

Also taking center stage for its role in maintaining calcium regulation is vitamin K. Research shows that without adequate vitamin K to mediate this process, calcium saturates the arterial walls and other soft tissues. It appears that vitamin K deficiency helps to explain the "calcium paradox"—the apparent relationship between osteoporosis and atherosclerosis.

The discovery that blood vessel cells can transform into bone-forming cells confirmed this link. While low vitamin D is linked with arterial disease and osteoporosis, vitamin K’s role is to stimulate bone formation and modify specific Glu proteins that prevent calcification. The presence of bone could be divided into vitamin K1 and the menaquinones (vitamin K2). Vitamin K is a family name for a series of compounds that have in common 2-methyl-1,4-naphthoquinone ring structure but differ in their alphatic side chain at the 3-position.

Most studies on vitamin K use either MK-4 or menaquinone-4 (MK-4). The reason for this is that both synthetic vitamins have been available on the market for many years. Awareness of the beneficial properties of long-chain menaquinones like MK-7 only arose in the last decade. Studies by our group and others showed that long chain menaquinones benefit from great intestinal absorption, a long plasma half-life, and a high bioavailability compared with both K1 and MK-4.

"Vitamin K deficiency is therefore very uncommon in the normal population," Schurgers said. A redistribution of K vitamins for extrahepatic tissues occurs in the liver. The hypothesis is that only at hepatic vitamin K sufficiency is vitamin K (notably the longchain menaquinones) incorporated into LDL and available for extrahepatic tissues. Thus, the first signs of vitamin K insufficiency are seen in bone and vasculature. Indeed, the occurrence of PIVKA-II (protein induced by vitamin K absence leaflet II) is very rare whereas uncarboxylated osteocalcin and uncarboxylated matrix Gla-proteins are very common in the general population.

In cross-sectional analysis among ~5000 elderly apparently healthy individuals in the Netherlands, we have demonstrated that dietary vitamin K intake was inversely associated with vascular calcification and mortality. After adjustment for potential confounders, the cardiovascular mortality in the highest tertile for vitamin K2 intake was 50 percent lower than in the lowest tertile for vitamin K2 intake. Such association was not found for phylloquinone. These findings are supported by a recent analysis of over 16,000 postmenopausal women. It was found that the forms of vitamin K2 with the highest cardioprotective activity were the long-chain menaquinones MK-7, MK-8, and MK-9. These are the forms found in cheese and curd cheese. In this study, the effect of vitamin K2 was confirmed, and the independent supplementation of MK-7 in hemodialysis patients resulted in a significant reduction of the circulating inactive form of matrix Gla-protein. Whether the supplementation of vitamin K2 could inhibit vascular calcification and subsequent cardiovascular mortality is the subject of current research.

Leon Schurgers, MD, is with the Department of biochemistry, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands.

Hepatitis CKD Risk

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EuroSIDA international cohort of more than 16,500 HIV-infected patients, investigators found that when compared to HIV-infected people who were negative for HCV antibodies, individuals who were positive for HCV antibodies had a 98 percent increased incidence of CKD.

HCV antibodies indicate exposure to the virus, but do not mean that the virus is present, even if the virus is cleared from the body naturally or by treatment. Viremia, or circulating HCV RNA, indicates an active infection.

Patients eligible for the study had at least three strong criteria for determination after January 1, 2004. Their HCV antibody status was known. The baseline estimated glomerular filtration rate (eGFR) was the first one recorded, and CKD was defined either as an eGFR less than or equal to 60 mL/min/1.73 m² for individuals with baselines above this point, or as a 25 percent decline in eGFR for individuals whose baseline was at or below 60 mL/min/1.73 m².

Among 8001 patients, 1964 (24.5 percent) were positive for HCV antibodies. Of these, 972 (49.5 percent) were HCV RNA-positive. At baseline, the median age was 41 years, the median CD4+ T cell count was 439 cells/mm³ (range 294–627), and the median eGFR was 97.6 mL/min/1.73 m² (range 83.8–113.0). Progression to CKD occurred in 410 patients (5.1 percent)—an incidence of 13.6 per 1000 person-years of follow up. For those who progressed to CKD these variables were accounted for: cumulative use of nephrotic drugs and antiretroviral drugs, CD4 counts and nadirs, age, gender, and diabetes.

Patients with HCV antibodies who had HCV viremia or had unknown HCV RNA status in their blood were at significantly higher risk for CKD. The higher the viral load, the higher the incidence of CKD (p< 0.04 for all viral loads greater than or equal to 60 mL/min/1.73 m²). Individuals with antibodies but who had undetectable viral loads (>615 IU/mL) were at no greater risk for CKD compared to patients without HCV antibodies. The incidence of CKD was not associated with the HCV viral genotype.

Rocstroh said it is not known why patients with HCV are at higher risk for the development of CKD. "One point could be that patients who have chronic hepatitis C obviously will have different stages of liver disease, and in very end stage liver disease you can often have what we call hepatoesophageal syndrome, so there are perfusion issues with the kidney, and then you can get kidney failure," he speculated. Another contributing factor could be altered drug metabolism by the liver, leading to levels of antiretroviral drugs that may cause renal tubular damage.

A remaining question is whether successful treatment and clearance of HCV can reverse kidney disease. The EuroSIDA database probably has too few successfully treated patients to answer the question since many come from Eastern Europe, where treatment is often not available.

At this point, Rockstroh recommends careful selection of any renal toxic antiretroviral drugs. Beyond that, "we just have to monitor renal function and renal disease parameters more closely in [HIV] patients with hepatitis C in the future," he said.

Know your Vitamin K: Some Forms Protect Heart and Kidneys More than Others

By Leon Schurgers

Vitamin K has long been regarded somewhat as a coagulant vitamin, thus the name “the coagulation vitamin.” This concept is now outdated. Vitamin K-dependent proteins have a role outside coagulation. Studies have shown that vitamin K can be subdivided into vitamin K1 and the menaquinones (vitamin K2). Vitamin K is a family name for a series of compounds that have in common 2-methyl-1,4-naphthoquinone ring structure but differ in their alphatic side chain at the 3-position.

Most studies on vitamin K use either MK-4 or menaquinone-4 (MK-4). The reason for this is that both synthetic vitamins have been available on the market for many years. Awareness of the beneficial properties of long-chain menaquinones like MK-7 only arose in the last decade. Studies by our group and others showed that long chain menaquinones benefit from great intestinal absorption, a long plasma half-life, and a high bioavailability compared with both K1 and MK-4.

"Absorption, all K vitamins are incorporated into chylomicrons and enter the bloodstream, and are then rapidly cleared by the liver. A vitamin K deficiency is therefore very uncommon in the normal population," Schurgers said. A redistribution of K vitamins for extrahepatic tissues occurs in the liver. The hypothesis is that only at hepatic vitamin K sufficiency is vitamin K (notably the longchain menaquinones) incorporated into LDL and available for extrahepatic tissues. Thus, the first signs of vitamin K insufficiency are seen in bone and vasculature. Indeed, the occurrence of PIVKA-II (protein induced by vitamin K absence leaflet II) is very rare whereas uncarboxylated osteocalcin and uncarboxylated matrix Gla-proteins are very common in the general population.

In cross-sectional analysis among ~5000 elderly apparently healthy individuals in the Netherlands, we have demonstrated that dietary vitamin K intake was inversely associated with vascular calcification and mortality. After adjustment for potential confounders, the cardiovascular mortality in the highest tertile for vitamin K2 intake was 50 percent lower than in the lowest tertile for vitamin K2 intake. Such association was not found for phylloquinone. These findings are supported by a recent analysis of over 16,000 postmenopausal women. It was found that the forms of vitamin K2 with the highest cardioprotective activity were the long-chain menaquinones MK-7, MK-8, and MK-9. These are the forms found in cheese and curd cheese. In this study, the effect of vitamin K2 was confirmed, and the independent supplementation of MK-7 in hemodialysis patients resulted in a significant reduction of the circulating inactive form of matrix Gla-protein.

Whether the supplementation of vitamin K2 could inhibit vascular calcification and subsequent cardiovascular mortality is the subject of current research.