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 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...
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EuropeSIDA 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 persistent viremia does not persist 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 stages of clinical deterioration up to 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 a eGFR less than or equal to 60 mL/min/1.73 m² for individuals with baselines above this point, or 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 HCV RNA-positive. At baseline, the median age was 41 years, the median CD4 T cell count was 439 cells/µL (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 401 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 nephrotoxic 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 615 IU/mL).

Individuals with antibodies but who had undetectable viral loads (≥615 IU/mL) were at no greater risk for CKD compared to patients without HCV RNA. The incidence of CKD was not associated with the HCV viral genotypes.

Rockstroh 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 hepatoportal 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 subjects 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.

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 hypocalcemia. 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 in the digestive tract. 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 calcinulin, 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 inflammatory adhesion and disease 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 Glα proteins that prevent calcification. Thus, the vitamin is a key player in bone metabolism.

How does Vitamin K help prevent calcification outside of bone? It acts as a co-factor required to convert the amino acid glutamate into one of about 15 human proteins with Glα domains, including matrix Glα protein (MGP). MGP is a vitamin K-dependent protein secreted in cartilage, lung, heart, kidney, and arteries. While the precise mechanism of action is not completely understood, it is generally accepted that MGP is a strong inhibitor of soft tissue calcification.

In the April 2010 issue of the Clinical Journal of the American Society of Nephrology, Leon Schurgers noted that “Vitamin K-dependent MGP acts as a calcification inhibitor,” and that, “levels of the inactive, dephosphorylated, uncleavable MGP (dp-muc MGP) increased progressively in a CKD setting, and thus could be a target for vascular calcification in CKD.”

Noting that “the majority of dialysis patients exhibit pronounced vitamin K deficiency,” the authors of a February 2011 Journal of the American Society of Nephrology article said that more study needs to be done to see whether vitamin K supplementation alters outcomes in hemodialysis patients. The article, “Circulating nonphosphorylated carboxylated Glα protein predicts survival in ESRD,” was jointly authored under G.Schlieper of the Department of Nephrology and Clinical Immunology, Rheinische Westfälische Technische, in Aachen, Germany.

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

By Leon Schurgers

Vitamin K has long been regarded solely as a coagulant, co-factor, thus the name “the coagulation vitamin.” This concept is now outdated. Vitamin K-dependent proteins have a role outside coagulation.

Vitamin K, as its namesake suggests, is a family name for a series of compounds that have in common a 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 menaquinone 4 (MK-4) or menaquinone 7 (MK-7). The reason for this is that both synthetic vitamins are available on the market for many years. Awareness of the beneficial properties of long-chain menaquinones (MK-7, only, in the last decade. Studies by our group and others showed that long chain menaquinones benefit from the great intestinal absorption, a long plasma half-life, and a high bioactivity compared with both K1 and MK-4.

An 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.

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 PIVKAII (protein induced by vitamin K absence II; ucC1) is very rare unless uncarboxylated osteocalcin and uncarboxylated matrix Glα-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 K intake was 50 percent lower than in the lowest tertile for vitamin K intake. Such association was not found for pylophoione. These findings are consistent with 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 not a reduction of vascular disease of 9 percent for every 10 µg of dietary K2.

Longitudinal studies in healthy volunteers and patients suffering from vitamin K deficiency will address whether vitamin K supplementation can inhibit vascular calcification and outcome. A recent pilot study demonstrated that the dose-dependent supplementation of MK-7 in hemodialysis patients resulted in a significant reduction of the circulating inactive form of matrix Glα-protein.

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

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