THE CLEVELAND CLINIC FOUNDATION

CLEVELAND CLINIC JOURNAL OF MEDICINE

CORONARY ARTERY CALCIFICATIONS

INTERPRETATION IN THE ABSENCE AND PRESENCE OF CHRONIC RENAL FAILURE

SUPPLEMENT EDITOR:
VINCENT W. DENNIS, MD
THE CLEVELAND CLINIC

SUPPLEMENT 3 TO VOLUME 69, 2002

SPECIAL ISSUE

THE CLEVELAND CLINIC FOUNDATION

CLEVELAND CLINIC JOURNAL OF MEDICINE

CORONARY ARTERY CALCIFICATIONS

INTERPRETATION IN THE ABSENCE AND PRESENCE OF CHRONIC RENAL FAILURE

SUPPLEMENT EDITOR:
VINCENT W. DENNIS, MD
THE CLEVELAND CLINIC

SUPPLEMENT 3 TO VOLUME 69, 2002

This publication is supported by an unrestricted educational grant from Braintree Laboratories.

Guidelines for sponsored supplements to the *Cleveland Clinic Journal of Medicine*

The *Cleveland Clinic Journal of Medicine* (CCJM) adheres to the International Committee of Medical Journal Editors' (ICMJE) 1994 guidelines, which include seven principles to ensure that supplements supported by outside funding sources do not reflect biases of funding sources in choice of topic, content, or point of view:

> Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as a second part of a regular issue, and are usually funded by sources other than the journal publisher. Supplements can serve useful purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities.[1]

ICMJE Guidelines

1. The journal editor must take full responsibility for policies, practices, and content of supplements. The journal editor must approve the appointment of any supplement editor and retain the authority to reject papers.

2. The sources of funding for research, meetings, and publications should be clearly stated and prominently located in the supplement.

3. Advertising in supplements should follow the same policies as the rest of the journal. [*The CCJM does not publish advertising in supplements*.]

4. Editors should enable readers to distinguish readily between ordinary editorial pages and supplement pages.

5. Editing by the funding organization should not be permitted.

6. Journal editors and supplement editors may not accept personal favors or excessive compensation from sponsors of supplements.

7. Secondary publication in supplements must be clearly identified by citing the original paper. Redundant publication must be avoided.

Additional CCJM Guidelines

"Industry-sponsored presentations by physician researchers can play an important part in informing and educating health care professionals...(provided they have)...independence, objectivity, balance, and scientific rigor."[2]

To ensure that these standards are met, the CCJM further requires the following:[2]

To ensure *independence*, sponsors may have neither express nor implied control over the scientific content, topics, or author selection.

To ensure *objectivity*, scientific content is peer-reviewed by the supplement editor.

To ensure *balance*, experts are expected to represent a diversity of legitimate medical opinion.

To ensure *scientific rigor*, the data presented must be reliable—ie, capable of forming an appropriate basis for medical decision-making.

References

1. **International Committee of Medical Journal Editors.** Advertising in medical journals. BMJ 1994; 308:1692.
2. **Kessler DA.** Drug promotion and scientific exchange: role of the clinical investigator. N Engl J Med 1991; 325:201-203.

Topics and editors for supplements to the *Cleveland Clinic Journal of Medicine* are determined by the *Journal's* editor-in-chief and staff. Supplement editors are chosen for their expertise in the topics discussed and are responsible for the scientific quality of supplements, including the review process. The *Journal* ensures that supplement editors and authors fully disclose any relationships with sponsors.

CLEVELAND CLINIC JOURNAL OF MEDICINE

The *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150) is published 12 times yearly by The Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal $95; institutional $120; single copy/back issue $16. Foreign: $120; single copy/back issue $16. Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Postmaster address changes: Cleveland Clinic Journal of Medicine, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): Phone (216) 444-2661; Fax (216) 444-9385; E-mail, ccjm@ccf.org World Wide Web address: http://www.ccjm.org

Printed in USA.

AMP

Medical logic and coronary calcifications

THE ABILITY TO PROCESS many bits of information scattered in time and origin and immersed in background noise is key to medical practice. Once information is gathered and verified, intelligent thought assembles it into a logical framework.

Formal courses in logic are absent from most medical school curricula, however, so we rely on training and experience. This is typified by the case study approach, in which medical logic is imparted to us as we observe the synthetic and analytic thought processes of our more experienced mentors and colleagues. This model can fail us, however, if we focus merely on the medical facts without appreciating the principles of the logical framework in which those facts are presented and analyzed.

Principles of logic are essential to the critical thought processes needed when we encounter new bodies of information, especially those prepackaged in the form of theories, diagnoses, conclusions, or advertising campaigns. At times we need Socrates more than Hippocrates.

A case study in medical logic

The current interest in coronary artery calcifications in patients on hemodialysis provides a case study in medical logic. There are facts and there is fancy. There are correlations disguised as causality. There are surrogate markers and surrogates of surrogate markers. There are legitimate concerns and illogical claims.

In this supplement, we seek to outline what is known and not known about coronary artery calcification in the normal population and in patients with chronic kidney disease.

Drs. Halliburton, Stillman, and White (page S-6) offer detailed insight into the technologies available for basic assessment of coronary artery calcification, with an emphasis on the strengths and weaknesses of various scoring options.

Drs. Schoenhagen and Tuzcu (page S-12) provide a critical analysis of current thought in cardiology on the biologic significance of coronary calcifications in terms of mechanisms of disease and clinical outcomes. It seems important for nephrologists to hear these views from experts in cardiology. Importantly, they conclude that the incremental value of coronary artery calcification scores in risk analysis is controversial in normal patients, and most assuredly in patients with chronic kidney disease.

Lastly, Dr. Fatica and I (page S-21) summarize the key observations in nephrology relevant to the question at hand.

Current state of the evidence

What do we know about coronary artery calcifications? Based on the literature and analyses outlined in this supplement, there should be at least tentative agreement on these points:

- Coronary artery calcification scores correlate with atherosclerotic burden, at least in individuals without chronic renal failure.
- The correlation of coronary calcification scores with acute coronary syndromes or "hard" coronary events is looser than that with atherosclerotic burden.
- Coronary artery calcification scores in patients with chronic renal failure and all its metabolic disarray cannot be interpreted in simple accord with values from patients without renal failure.

At times we need Socrates more than Hippocrates

This short list of tenable conclusions will undoubtedly grow in time. Studies are now under way to extend what little we know about the accumulation of calcium in coronary arteries of patients on dialysis. In the meantime, it is logical for nephrologists and other physicians who care for patients with chronic renal failure to focus on the established markers, risks, and treatments of cardiovascular disease.

VINCENT W. DENNIS, MD
Chairman, Department of Nephrology
and Hypertension
The Cleveland Clinic

SANDRA S. HALLIBURTON, PhD
Department of Diagnostic Radiology, The Cleveland Clinic

ARTHUR E. STILLMAN, MD, PhD
Department of Diagnostic Radiology, The Cleveland Clinic

RICHARD D. WHITE, MD
Chief, Section of Cardiovascular Imaging, Department of Diagnostic Radiology, The Cleveland Clinic

Noninvasive quantification of coronary artery calcification: Methods and prognostic value

KEY POINTS

Evaluation of coronary artery calcium can allow early identification of coronary artery disease in patients with chronic renal failure.

Computed tomography (CT) is a noninvasive method for detecting coronary calcium.

Several scoring methods can be used to quantify CT-defined calcium load.

The additive value of calcium scoring in cardiovascular risk assessment remains controversial.

Caution is needed when extrapolating data on the prognostic value of coronary calcium quantification to patients with altered calcium metabolism, such as those with chronic renal failure.

PATIENTS WITH CHRONIC RENAL FAILURE are at increased risk for developing coronary artery disease (CAD).[1] Early identification of CAD in asymptomatic patients can reduce morbidity and mortality. One marker for CAD is coronary artery calcification. Studies in patients without chronic renal failure have shown that calcifications are present in atherosclerotic arteries and absent in normal vessels. Patients with chronic renal failure, however, have markedly altered clearance and metabolism of calcium, including extraosseous calcifications. The significance of the presence of calcium in the arteries of these patients is not yet well understood.

In view of heightened interest in coronary artery calcium in patients with chronic renal failure and end-stage renal disease, this article reviews noninvasive techniques for detecting and quantifying coronary calcium and the clinical significance of measured values.

RADIOLOGIC DETECTION METHODS

X-ray techniques such as computed tomography (CT) provide a noninvasive method for detecting coronary calcification. Because of its relatively high atomic number, calcium strongly attenuates x-rays. As a result, calcium appears bright on the CT image and is easily distinguishable from surrounding soft tissue without the need to administer an iodinated contrast agent, which could compromise patients with renal failure.

Two distinct CT technologies are capable of detecting coronary artery calcium: electron-beam CT (EBCT) and mechanical CT.

Dr. White has indicated that he has received grant or research support from Siemens Medical Systems. Drs. Halliburton and Stillman have indicated that they have no affiliation with or financial interest in a commercial organization that poses a potential conflict of interest with their article.

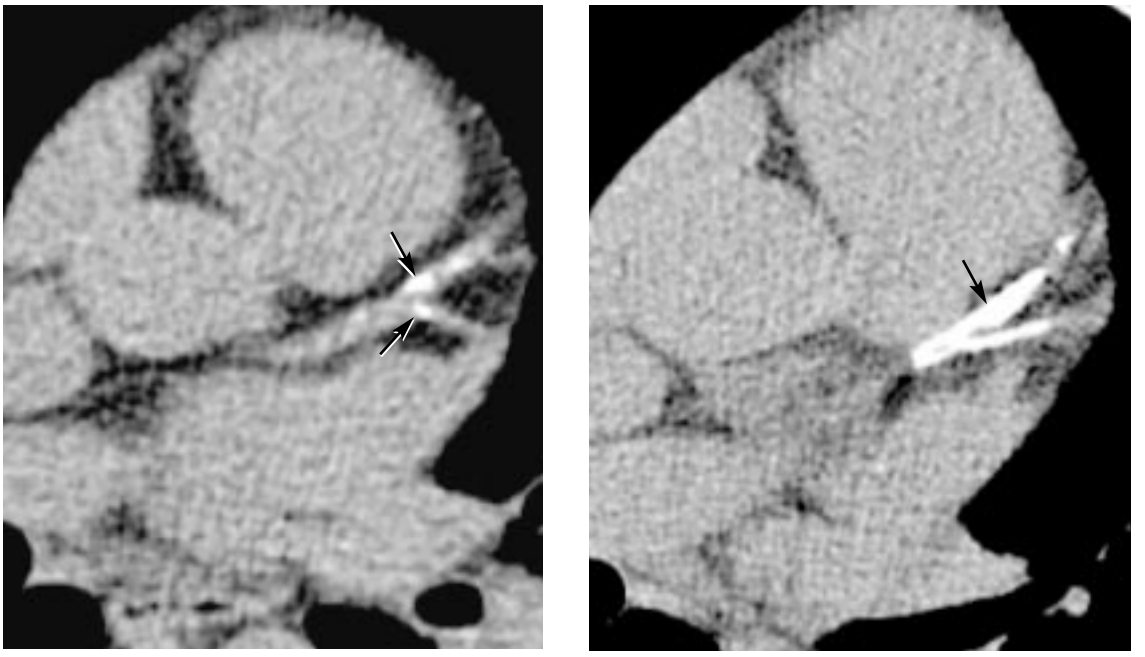

FIGURE 1. Mechanical multislice computed tomographic images of the left coronary system displaying mild (left) and severe (right) calcification (arrows).

Electron-beam CT

Most cardiac imaging with CT has been performed using EBCT, which is a well-established method for detecting coronary artery calcification.[2,3] With EBCT, x-rays are produced by decelerating electrons on a tungsten target ring encircling the patient.

Imaging is performed using either "step-volume" or "continuous-volume" scanning. Step-volume scanning refers to two-dimensional imaging in which a single transaxial slice is acquired and the patient table is moved to the next slice position. Continuous-volume scanning refers to three-dimensional imaging in which data are acquired during continuous rotation of the gantry and continuous movement of the patient table.

Step-volume scanning is the method most widely used for imaging of the coronary arteries because data acquisition can be referenced to the cardiac cycle using the patient's electrocardiographic (ECG) signal; data acquisition is triggered by the ECG signal during the diastolic phase of the cardiac cycle to minimize cardiac motion artifacts. Fast movement of the electron beam around the patient permits acquisition of a single axial image in 100 ms. For detection of coronary artery calcium, images are typically obtained with a thickness of 3 mm. The entire heart can be imaged during one or two breath-hold periods.

Mechanical CT

The establishment of mechanical CT for cardiac imaging has been more recent and followed the introduction of multislice CT (MSCT) scanners. State-of-the-art MSCT scanners capable of simultaneously acquiring four slices have facilitated the use of mechanical CT for detecting coronary artery calcification.

With mechanical CT, x-rays are produced in an x-ray tube rotating mechanically around the patient. Cardiac imaging is performed using either sequential scanning (analogous to step-volume scanning with EBCT) or spiral scanning (analogous to continuous-volume scanning). Both types of data acquisition can be referenced to the ECG signal. Slower movement of the mechanical system around the patient (compared with movement of the electron beam) requires at least 250 ms for acquisition of each image on currently available scanners.

For detection of coronary artery calcium, image thickness typically varies between 1.25 and 3 mm, depending on the method of MSCT data acquisition. With either the sequential or the spiral technique, the entire

Agatston scoring is the traditional method of quantifying coronary calcium

heart can be imaged during a single breathhold. **FIGURE 1** shows coronary artery images from patients with mild calcification and severe calcification obtained using sequential MSCT.

How the CT methods compare

Compared with EBCT, MSCT offers increased signal-to-noise ratios (because of the limited x-ray intensity of EBCT), shorter scan times, and higher spatial resolution. However, EBCT still has one major advantage—better temporal resolution and a resultant reduction of cardiac motion artifacts.

QUANTIFYING CORONARY CALCIUM

Calcium load in the coronary arteries can be quantified from either EBCT or MSCT images using different scoring algorithms. A recent study showed high correlation between EBCT and MSCT for calcium quantification.[4]

Agatston scoring

Any assessment of coronary calcification should also include a cardiovascular risk assessment

Agatston scoring, introduced in 1990, is the traditional method for quantifying coronary calcium with EBCT.[5] The method is based on the maximum x-ray attenuation coefficient, or CT number (measured in Hounsfield units [HU]), and the area of calcium deposits. First, calcified lesions are identified on CT images by applying a threshold of 130 HU to the entire image set; tissues with densities equal to or greater than the threshold are considered to correspond to calcium.

For each coronary artery, i, a region of interest (ROI) is drawn around each calcified lesion, j. The maximum CT number, CT_{ij}^{max}, of the ROI is determined and used to assign a weighting factor, w_{ij}. The area, A_{ij}, of the ROI is also determined. The Agatston score, S_{ij}, is computed as the product of the weighting factor and the area:

$$S_{ij} = w_{ij} \bullet A_{ij} \tag{1.1}$$

where

$$w_{ij} = \begin{cases} 1 \text{ if } 130 \text{ HU} \le CT_{ij}^{max} < 200 \text{ HU} \\ 2 \text{ if } 200 \text{ HU} \le CT_{ij}^{max} < 300 \text{ HU} \\ 3 \text{ if } 300 \text{ HU} \le CT_{ij}^{max} < 400 \text{ HU} \\ 4 \text{ if } 400 \text{ HU} \le CT_{ij}^{max} \end{cases} \tag{1.2}$$

The score for all lesions in all coronary arteries is summed to determine the total calcium burden:

$$S_{tot} = \sum_{i,j} S_{ij} \tag{1.3}$$

Although most existing data are based on Agatston scoring, this method has many limitations:

- It has a strong dependence on noise because it relies on the maximum CT number.
- Because weighting factors are used, the score increases nonlinearly with increases in the amount of calcium.
- Because the Agatston score was originally based on data from contiguous, nonoverlapping, 3-mm slices acquired with EBCT, the score as calculated using the above equations must be adjusted for non–3-mm slices and overlapping slices.
- The score does not correspond to a physical measure.

Volume scoring

Recent studies based on estimating the volume of calcium provide an alternative method of assigning a calcium score.[6–8] As with Agatston scoring, a threshold of 130 HU is applied and ROIs are drawn around each calcified lesion. For each ROI, the number of voxels exceeding the threshold is summed. The volume score is simply calculated as the product of the number of voxels containing calcium, N_{voxel}, and the volume of one voxel, V_{voxel}:

$$V_{ij} = V_{voxel} \bullet N_{voxel} \tag{1.4}$$

Again, the volume score of individual lesions is summed to obtain a total volume score:

$$V_{tot} = \sum_{i,j} V_{ij} \tag{1.5}$$

Volume scoring provides more reproducible results than Agatston scoring,[6,7] although it too has limitations. The volume score is vulnerable to overestimation of lesion size owing to partial volume effects; objects smaller than one voxel contribute to the score with the entire voxel volume. Also, the volume score does not necessarily represent the

true volume of calcium, which depends on the applied threshold. For this reason, the volume score is not a true physical measure.

Mass scoring

Quantification of calcium using absolute mass has also been proposed.[7,9] To obtain absolute values for calcium mass, a calibration measurement of a calcification with known hydroxyapatite density has to be performed and a calibration factor determined. The calibration factor, c_{HA}, is calculated as

$$c_{HA} = \frac{\rho_{HA}}{\overline{CT}_{HA} - \overline{CT}_{water}} \quad (1.6)$$

where ρ_{HA} is the density of the known calcification, $\overline{CT}_{HA}$ is the mean CT number of the known calcification, and $\overline{CT}_{water}$ is the mean CT number of water. Because the CT number of all materials except water depends on the x-ray spectrum, a specific calibration factor exists for each scanner and each scan protocol. The product of the calibration factor (c_{HA}), the volume (V_{ij}) as calculated in equation 1.4, and the mean CT number for each lesion ($\overline{CT}_{ij}$) gives the mass score (m_{ij}):

$$m_{ij} = c_{HA} \cdot V_{ij} \cdot \overline{CT}_{ij} \quad (1.7)$$

The total mass score is then the sum of the mass of all individual lesions:

$$m_{tot} = \sum_{i,j} m_{ij} \quad (1.8)$$

The mass score is given in milligrams and is a true physical measure. Initial results have shown mass scoring to be more reproducible than Agatston scoring,[7] but additional clinical studies must be performed.

HOW CALCIUM SCORING CONTRIBUTES TO RISK ASSESSMENT

The calcium–cardiac risk association

The prognostic value of quantifying coronary artery calcium has been reviewed extensively in several expert consensus documents.[2,3] Most information to date has been derived from Agatston scores obtained using EBCT. A significant association between coronary calcium scores and the risk for hard coronary events has been reported in studies in which the outcome evaluation was unadjusted for other cardiac risk factors.[10,11] A pooled analysis of the predictive value of EBCT Agatston scores from these studies showed an increase in positive predictive value and a corresponding decrease in negative predictive value with increasing calcium scores.[3]

Does calcium scoring have additive value?

On the other hand, additional studies that examined risk-adjusted outcomes that control for established cardiac risk factors failed to consistently show the incremental value of coronary calcium scores over traditional multivariate risk-assessment models such as the Framingham risk model.[12] The Framingham model is based on gender, age, blood pressure, cholesterol, high-density lipoprotein cholesterol, cigarette smoking, and plasma glucose. Detrano et al[13] reported that Agatston scores derived from EBCT added no significant incremental value to the risk determined from the Framingham and National Cholesterol Education Program risk factors. However, Taylor et al[14] concluded that the Framingham risk model and coronary calcium quantification were distinct methods of assessing risk for sudden cardiac death, and suggested a complementary role for these methods in identifying patients at high risk. Another study by Taylor et al[15] found that the Framingham risk model significantly underestimated the presence of premature, subclinical calcified coronary atherosclerosis in a cohort of low-risk subjects and recommended the use of calcium scoring as a screening test to identify persons needing to be promoted to a higher risk category.

The additive value of calcium scoring remains controversial, and any assessment of coronary calcification should also include a comprehensive cardiovascular risk-factor assessment.

Low or absent calcium scores have the greatest potential predictive value

Interpreting calcium scores

Guidelines have been proposed for interpreting Agatston scores for asymptomatic persons (**TABLE 1**).[16] They cover such issues as correlation to plaque burden, probability of significant CAD, implications for cardiovascular

TABLE 1

Recommended EBCT calcium score guidelines

EBCT CALCIUM SCORE	PLAQUE BURDEN	PROBABILITY OF SIGNIFICANT CAD	IMPLICATIONS FOR CV RISK	RECOMMENDATIONS
0	No identifiable plaque	Very low, generally < 5%	Very low	Reassure patient while discussing general public health guidelines for primary prevention of CV diseases
1–10	Minimal identifiable plaque burden	Very unlikely, < 10%	Low	Discuss general public health guidelines for primary prevention of CV diseases
11–100*	Definite, at least mild atherosclerotic plaque burden	Mild or minimal coronary stenoses likely	Moderate	Counsel about risk-factor modification, strict adherence with NCEP ATP II primary prevention cholesterol guidelines, daily ASA†
101–400*	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although obstructive disease possible	Moderately high	Institute risk-factor modification and secondary prevention NCEP ATP II guidelines. Consider exercise testing for further risk stratification
> 400*	Extensive atherosclerotic plaque burden	High likelihood (≥ 90%) of at least 1 "significant" coronary stenosis	High	Institute very aggressive risk-factor modification. Consider exercise or stress pharmacologic stress imaging to evaluate for inducible ischemia

*If score > 75th percentile for age/gender, advance to recommendations for next calcium score range.
†Oral administration of 80 to 325 mg.
ASA = acetylsalicylic acid; CAD = coronary artery disease; CV = cardiovascular; EBCT = electron-beam computed tomography; NCEP ATP II = National Cholesterol Education Program (Adult Treatment Panel II).

REPRINTED WITH PERMISSION FROM RUMBERGER JA, BRUNDAGE BH, RADER DJ, KONDOS G. ELECTRON BEAM COMPUTED TOMOGRAPHIC CORONARY CALCIUM SCANNING: A REVIEW AND GUIDELINES FOR USE IN ASYMPTOMATIC PERSONS. MAYO CLIN PROC 1999; 74:243–252.

risk, and recommendations for treatment. Guidelines for interpreting volume and mass scores have yet to be established.

Additional information for risk stratification can be gained from referencing a patient's calcium score to scores from asymptomatic individuals of the same gender and age to determine a percentile ranking. Reference databases exist for both Agatston scores and volume scores.[17] If a patient's Agatston score is greater than the 75th percentile for his or her age and gender, the patient is promoted to the next scoring range in TABLE 1.

Calcium scores have their greatest potential predictive value when they are absent or low (< 10 for Agatston scoring), which almost certainly indicates low risk for development of coronary heart disease.[2,3] Also, a positive calcium score may indicate that a patient considered to be at intermediate risk for coronary heart disease is actually at high risk—a finding that could particularly benefit asymptomatic patients in whom other risk factors could be modified.[2,3] Published evidence to date has not defined which asymptomatic patients would benefit from calcium scoring.

Calcium scoring in end-stage renal disease

It is not clear how much these observations apply to patients with chronic renal failure. Although the incidence of CAD is increased in patients with renal insufficiency, such patients also have altered calcium metabo-

lism.[1] Therefore, caution is needed when extrapolating available data to this special patient group. Further studies are needed to determine the additive predictive value of coronary calcium scoring for risk stratification in patients with renal failure.

REFERENCES

1. **Goldsmith DJA, Covic A.** Coronary artery disease in patients with renal failure. Int J Clin Pract 2001; 55:196–210.
2. **Wexler L, Brundage B, Crouse J, et al.** Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association Writing Group. Circulation 1996; 94:1175–1192.
3. **O'Rourke R, Brundage B, Froelicher V, et al.** American College of Cardiology/American Heart Association expert consensus document on electron beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol 2000; 36:326–340.
4. **Becker CR, Kleffel T, Crispin A, et al.** Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. AJR Am J Roentgenol 2001; 176:1295–1298.
5. **Agatston AS, Janowitz WR, Hildner FJ, et al.** Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15:827–832.
6. **Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P.** Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998; 208:807–814.
7. **Yoon H, Greaser L, Mather R, et al.** Coronary artery calcium: alternate methods for accurate and reproducible quantitation. Acad Radiol 1997; 4:666–673.
8. **Ohnesorge B, Kopp AF, Fischbach R, et al.** Reproducibility of coronary calcium quantification in repeat examinations with retrospectively ECG-gated multi-slice spiral CT. Eur Radiol (in press).
9. **Hong C, Becker CR, Schoepf UJ, Ohnesorge B, Bruening R, Reiser M.** Coronary artery calcium: absolute quantification in nonenhanced and contrast-enhanced multi-detector row CT studies. Radiology 2002; 223:474–480.
10. **Arad Y, Spadaro M, Goodman KG, et al.** Prediction of coronary events with electron beam computed tomography: 19-month follow-up of 1173 asymptomatic subjects. Circulation. 1996; 93:1951–1953.
11. **Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R.** Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. Circulation. 1997; 96:1122–1129.
12. **Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB.** Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97:1837–1847.
13. **Detrano RC, Wong ND, Doherty TM, et al.** Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. Circulation 1999; 99:2633–2638.
14. **Taylor AJ, Burke AP, O'Malley PG, et al.** A comparison of the Framingham risk index, coronary artery calcification, and culprit plaque morphology in sudden cardiac death. Circulation 2000; 101:1243–1248.
15. **Taylor AJ, Feuerstein I, Wong H, Barko W, Brazaitis M, O'Malley PG.** Do conventional risk factors predict subclinical coronary artery disease? Results from the Prospective Army Coronary Calcium Project. Am Heart J 2001; 141:463–468.
16. **Rumberger JA, Brundage BH, Rader DJ, Kondos G.** Electron beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. Mayo Clin Proc 1999; 74:243–252.
17. **Raggi P, Callister TQ, Cooil B, et al.** Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000; 101:850–855.

ADDRESS: *Sandra S. Halliburton, PhD, Section of Cardiovascular Imaging, Division of Radiology, Hb6, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail hallibs@ccf.org*

PAUL SCHOENHAGEN, MD
Fellow, Cardiovascular Medicine,
Department of Cardiovascular Medicine,
The Cleveland Clinic

E. MURAT TUZCU, MD
Department of Cardiovascular Medicine,
The Cleveland Clinic

Coronary artery calcification and end-stage renal disease: Vascular biology and clinical implications

KEY POINTS

Coronary artery calcifications appear to be an indicator of total atherosclerotic disease burden, but their relation to the stability of individual atherosclerotic plaques is not well understood.

Plaque rupture and acute coronary syndromes can occur without plaque calcification and may be more often associated with noncalcified, soft plaque.

Pharmacologic control of calcium and phosphate metabolism should be guided by the nephrologic and endocrinologic needs of the renal failure patient and not withheld out of concern about coronary calcifications.

Efforts to slow coronary artery disease progression in patients with end-stage renal disease should emphasize aggressive control of recognized cardiovascular risk factors.

Both authors have indicated that they have no affiliation with or financial interest in a commercial organization that poses a potential conflict of interest with their article.

THE METABOLIC CHANGES associated with end-stage renal disease (ESRD) and its treatment may accelerate development of cardiovascular disease. In fact, cardiovascular disease, particularly coronary artery disease and chronic heart failure, is the leading cause of death in patients with ESRD.[1,2] Yet the pathophysiology of this association is complex and only partially understood.[3]

Increased coronary artery calcification is one of the metabolic changes related to ESRD. This review summarizes current knowledge on the clinical significance of coronary calcification in patients with ESRD, the role of pharmacologic therapies to prevent skeletal bone loss, and their impact on calcium deposition in the vascular wall.

CALCIFICATION AND ESRD: A CONNECTION TO CARDIOVASCULAR DISEASE?

The strong association between coronary artery disease and ESRD may be partly explained by the many risk factors shared by the two conditions, such as advanced age, hypertension, diabetes mellitus, hyperhomocysteinemia, and hyperlipidemia.[3,4] As reviewed separately in this supplement,[5] recent attention has focused on disorders of calcium and phosphate metabolism and their treatments as potential accelerants of cardiovascular disease in ESRD. Briefly, decreased phosphate excretion and hypovitaminosis D cause hyperphosphatemia and subsequent hyperparathyroidism.[6–8] These changes cause altered bone metabolism with skeletal bone resorption (renal osteodystrophy) and extraosseal calcifications (**FIGURE 1**). Extraosseal cal-

cifications apparently result from passive precipitation of calcium if the level of the calcium/phosphate product in blood increases above local conditions of saturation.[6] Calcifications are prominent in the kidney but have also been described in various cardiovascular tissues, such as heart valves, myocardium, and coronary arteries.[9–12] Clear and compelling data have shown an increased prevalence of cardiac calcifications in ESRD, especially after long-term dialysis, but the pathogenesis and clinical significance of these calcifications are incompletely understood.

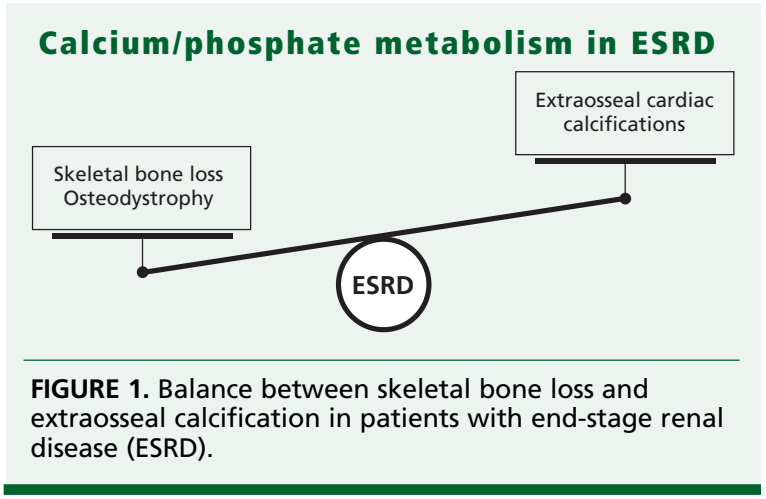

FIGURE 1. Balance between skeletal bone loss and extraosseal calcification in patients with end-stage renal disease (ESRD).

CORONARY CALCIFICATIONS AND ATHEROSCLEROTIC PLAQUE

Two seemingly discordant principles must be understood about the role of calcification in the development of atherosclerotic coronary plaques and their relation to coronary risk:

- The prevalence of coronary atherosclerosis and calcifications is high in persons who do not have clinically evident coronary artery disease.
- Plaque rupture and acute coronary syndrome can occur without calcification and, in fact, may be more frequently associated with noncalcified, soft plaque.

Biology of coronary calcifications

Coronary artery calcifications occur almost exclusively at sites of atherosclerotic lesions.[13] Calcification in the development of these plaques is a complicated, actively regulated process of mineralization that is similar to bone formation and remodeling.[14–17] Coronary artery calcification is found in small amounts in early lesions and more extensively in advanced lesions (**FIGURE 2**).[18]

Calcium phosphate (hydroxyapatite) is formed in vesicles that pinch off from arterial wall cells, analogous to the way that matrix vesicles pinch off from chondrocytes in developing bone. A close spatial association exists between cholesterol deposits and hydroxyapatite. Atherosclerotic lesions in younger adults reveal small aggregates of crystalline calcium among the lipid particles of the necrotic plaque core. It has been postulated that membrane vesicles derived from apoptotic foam cells within extracellular, lipid-rich necrotic plaque cores may serve as the sites of calcium deposits. Macrophages in atherosclerotic lesions express 1-alpha-hydroxylase activity, producing 1,25-vitamin D,[19] and also have osteoclastic capacity for phagocytic removal of calcium mineral from the artery wall.

Epidemiology of coronary calcifications

There are many risk factors for coronary artery calcifications besides ESRD,[20–23] including advanced age,[22] male gender,[24] elevated plasma cholesterol,[25,26] diminished high-density lipoprotein cholesterol,[26] cigarette smoking,[20,21] elevated blood pressure,[21] obesity,[26] diabetes,[20] and elevated triglycerides.[26]

Coronary calcifications and atherosclerotic plaque are much more common than clinically symptomatic coronary artery disease, positive stress tests, or angiographic stenosis. Coronary calcification is present in 50% of persons 40 to 49 years old and 80% of those 60 to 69 years old.[21,23,24,27–30] Similarly, histologic studies and intravascular ultrasonography show that the prevalence of atherosclerotic plaque rises from 40% to 50% among persons 20 to 29 years old to 60% to 80% among those 30 to 39 years old.[31,32] However, results from the Framingham study[33] indicate that the expected 8-year incidence of coronary events ranges from less than 1% for persons younger than 40 to 15% for those older than 80, and significant angiographic stenoses are present in 30% of persons 60 to 69 years old.[34] Thus, the prevalence of coronary calcifications correlates better with the prevalence of atherosclerotic plaque than with coronary events[35,36]

The prevalence of cardiac calcifications is increased with ESRD, especially after long-term dialysis

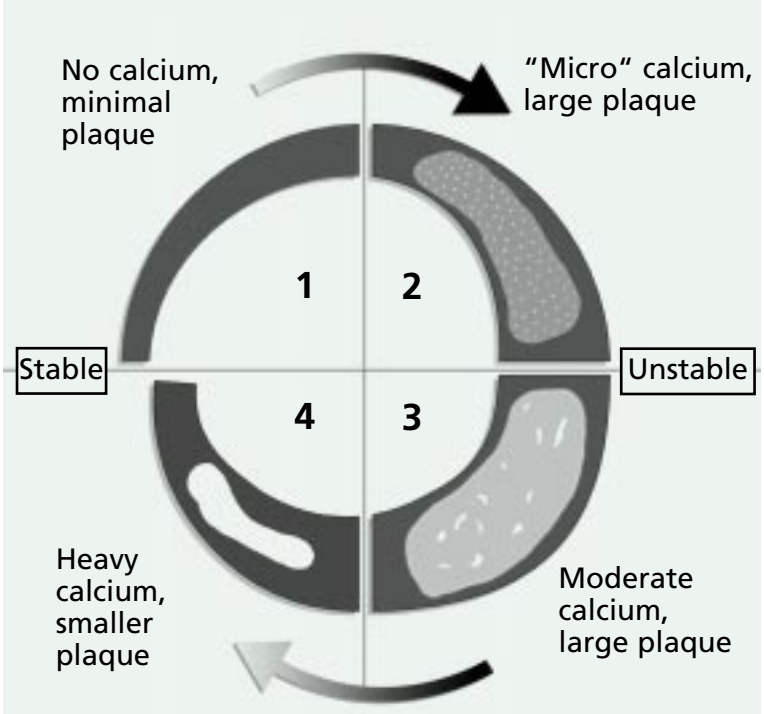

FIGURE 2. Atherosclerotic lesion development and the role of calcification. Different phases of plaque development are shown in the four quadrants, indicating temporal development. Calcium's role in lesion instability is complex and incompletely understood.

or angiographically severe stenosis.

Atherosclerotic plaque and coronary calcifications are frequently present in asymptomatic persons. While the overall plaque burden may predict cardiovascular risk, only a small proportion of persons with atherosclerosis and detectable coronary calcium will eventually experience clinical coronary events.

Plaque vulnerability and acute coronary syndromes

Traditional models of coronary artery disease described slow, progressive plaque growth with increasing passive calcification, eventually leading to vessel occlusion and acute coronary syndromes. According to these models, the amount of calcification in individual lesions should be directly related to the risk of these lesions causing ischemic events. These advanced, calcified plaques were often compared to "rusty pipes."

More recent vascular biology studies show that this analogy is incomplete and even misleading.[37,38] Several angiographic studies show that the progression of coronary artery disease in humans is neither linear nor predictable.[39–42] It has become apparent that sudden, episodic changes of mildly stenotic coronary plaques residing in the vessel wall are most important in disease progression.[43] Most acute coronary events result from rupture of these "vulnerable" plaques, which often accompany more advanced atherosclerotic lesions, and subsequent thrombosis.[37] These vulnerable lesions may account for as many as two thirds of cases of unstable angina or other acute coronary syndromes.

"Plaque vulnerability" describes the tendency of atherosclerotic lesions to cause acute coronary syndromes. Vulnerable lesions are characterized by an accumulation of inflammatory cells and the formation of a lipid-rich, necrotic core separated from the lumen by a fibrous cap.[43–45] The relatively large size of these atheromas is not well reflected by luminal stenosis because adaptive arterial enlargement maintains lumen size in spite of increasing plaque burden. This compensatory vessel enlargement in response to plaque growth is termed positive arterial remodeling[46–48] and appears to be associated with development of acute coronary syndromes.[49–52]

The junction between the necrotic core of the plaque and the normal vessel wall (plaque shoulder) is a location of high stress that is predisposed to rupture.[53,54] Local secretion of proteolytic enzymes (such as matrix metalloproteinases and myeloperoxidase) by smooth muscle cells and macrophages contributes to degradation of the intercellular matrix of the fibrous cap, initiating plaque rupture.[55,56]

As described above, coronary artery wall calcification is part of the development of atherosclerosis. The relation of coronary calcifications to the probability of plaque rupture is unknown, and plaques vulnerable to rupture or erosion are frequently not calcified.[17,57] In fact, intravascular ultrasonography indicates that vulnerable plaques are most often not calcified[49,50,58,59] and that calcification is associated with plaques causing stable rather than unstable coronary syndromes.

It has been hypothesized that early micro-

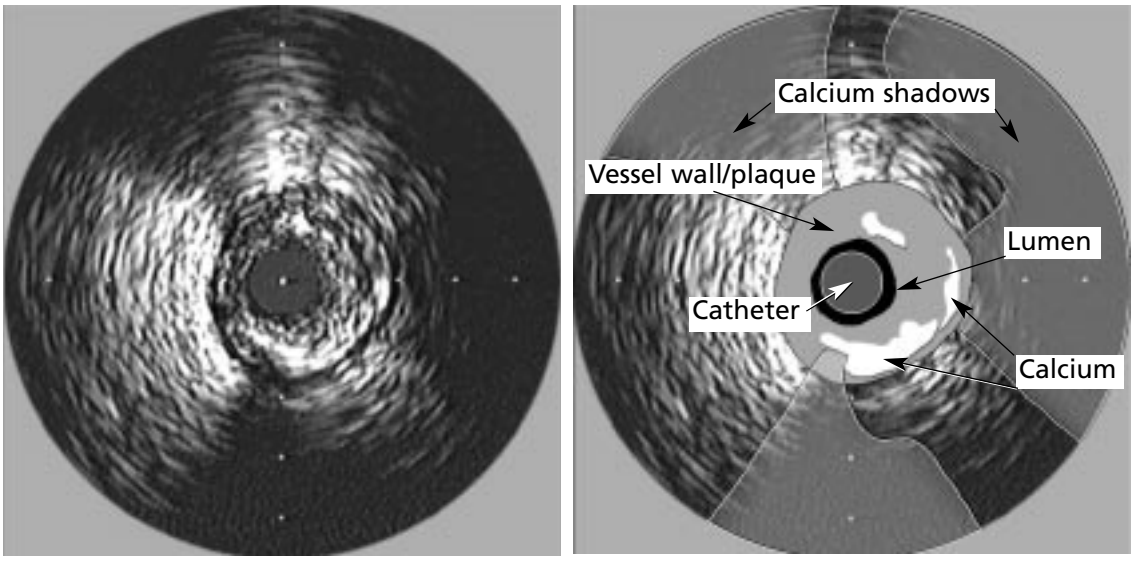

FIGURE 3. Intravascular ultrasound image of a highly stenotic, calcified coronary lesion.

calcifications near the junction of the plaque and the adjacent normal intima may lead to increased stress at the interface between calcified and noncalcified atherosclerotic sections, which could facilitate plaque rupture. However, more extensive calcification and fibrosis of the vessel could eventually eliminate these weak points and reduce the risk of rupture. Biomechanical data support the concept that calcified lesions are much stiffer than cellular lesions and are unlikely to be associated with sites of plaque rupture.[60] According to these concepts, calcifications could in fact represent an attempt to stabilize weakened atherosclerotic plaque prone to rupture.

METHODS FOR IDENTIFYING LESION CALCIFICATIONS

Intravascular ultrasonography

Intravascular ultrasonography, performed during cardiac catheterization, provides tomographic images of the vessel wall that demonstrate vessel size, plaque size, and plaque morphology.[61,62] A miniature ultrasound catheter is placed beyond the target lesion site and is then withdrawn during continuous imaging, resulting in a series of cross-sections. The vessel wall of each cross-section can be described by its signal characteristics on a continuum from echodense (bright echo signal) to echolucent (faint echo signal).

Several studies demonstrate the reliability of ultrasound imaging in predicting the composition of atherosclerotic plaque relative to histology.[58,59] Calcified tissues are recognized as bright echoes with a characteristic signal shadow (**FIGURES 3 AND 4**).

Ultrasound imaging shows significant superiority over fluoroscopy or angiography in detecting coronary calcification.[63] The severity of calcification has been quantified according to the angle subtended by the calcified arc of the vessel wall.[64,65] When calcium was detected angiographically, the calcification detected by ultrasound was likely greater than 90 degrees.[64] The image characteristics of microcalcifications, as described above, are incompletely understood.[57]

Only a small share of patients with atherosclerosis and coronary calcium will experience coronary events

Computed tomography

Computed tomography (CT) is very sensitive in detecting and quantifying coronary artery calcifications and can survey the entire coronary tree noninvasively. Computed tomography techniques are described more fully in an accompanying article in this supplement.[66] Briefly, different calcium scoring algorithms, including the traditional Agatston score,[67] the total calcium volume score,[68,69] and calcium mass,[70,71] can be applied to either electron-beam CT or mechanical CT images and provide a measure of total coronary plaque burden.[72,73] The prognostic value of this informa-

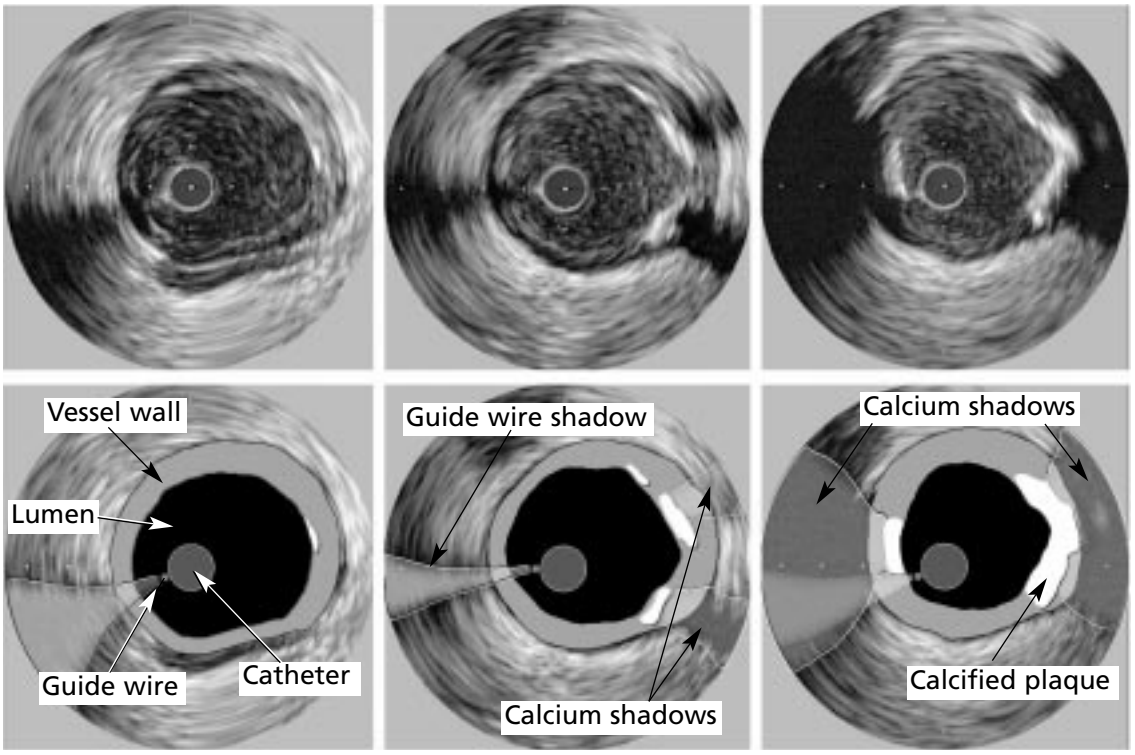

FIGURE 4. Intravascular ultrasound images of a mildly stenotic plaque with calcification. Three adjacent images of the same lesion are shown.

Reliable identification of vulnerable plaques is currently not possible

tion has been examined in several studies[74] in individuals without chronic renal failure, as discussed in detail elsewhere in this supplement.[66] Because compensatory vessel enlargement (positive remodeling) allows plaque accumulation without stenosis, the correlation of calcium area with luminal dimension is only moderate.[75,76]

Coronary angiography

Coronary angiography is not a sensitive method for evaluating calcification compared with intravascular ultrasound and CT.[63,64,77–79] The coronary angiogram shows a silhouette of the vessel lumen but not the vessel wall and plaque.[38,80] Information on calcifications of the vessel wall is limited, although the extent of fluoroscopic calcifications is a marker of the overall atherosclerotic disease burden and does have prognostic value.[81–83]

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a noninvasive technique that differentiates tissue structures on the basis of their proton magnetic properties. A wide range of image contrast can be obtained with different pulse sequences, which is more helpful for differentiation of soft-tissue structures than for calcifications.[84–86] Shinnar et al[86] described the diagnostic accuracy of MRI for plaque characterization and emphasized the significant technical improvements in resolution and gating that are needed before this technique can be used to examine coronary arteries in clinical settings.

CLINICAL IMPLICATIONS OF CORONARY CALCIFICATION IN ESRD

Uncertain value for risk assessment

Noninvasive quantification of coronary calcium with electron-beam CT calcium scores has been shown to reflect the total atherosclerotic plaque burden,[17,35,36] at least in individuals without chronic renal failure. For this reason, CT can help to predict future risk and offers the potential, through serial imaging, to follow disease progression, stabilization, and possible regression.[87,88] This information can

help guide the aggressiveness of risk-factor modification.

However, according to a current consensus statement of the American Heart Association and American College of Cardiology,[89] the incremental value of calcium scores over "traditional" multivariate risk-assessment models has not yet been established. This consensus statement does not recommend CT screening of coronary calcification for asymptomatic individuals, but it concludes that such screening may be justified in select patient groups with intermediate risk (ie, those in whom CT results could change the aggressiveness of risk-factor modification).

Applying these consensus recommendations to patients with chronic renal failure or ESRD is particularly difficult. As discussed above, these patients are already in a high-risk group and aggressive risk-factor modification may be justified independent of the CT result. It is conceivable that asymptomatic young patients with moderate renal failure could fall into an intermediate-risk group. This needs to be examined in further studies, especially since current guidelines for lipid management do not provide specific recommendations for patients with ESRD.

Vulnerable plaques hard to pinpoint

It is important to understand that calcium scoring has prognostic value but does not localize areas of vulnerable plaque. Studies in individuals without chronic renal failure show that coronary calcium scores correlate with atherosclerotic plaque burden. However, while more calcifications (ie, a higher calcium score) may be associated with a greater number of vulnerable plaques overall, coronary calcifications of individual lesions are not markers of lesion vulnerability and are often found in stable patients.[90] Currently, reliable identification of vulnerable plaques is not possible,[91] but preliminary results with intravascular ultrasound[92] and contrast-enhanced multislice CT[93,94] demonstrate the potential role of these tomographic imaging techniques.

Role of medications

The derangements of calcium, phosphate, vitamin D, and parathyroid hormone in patients with chronic renal failure or ESRD are characterized by extraosseal calcifications (**FIGURE 1**), including cardiac calcifications. The high prevalence of coronary calcification in ESRD occurs in a clinical context far removed from the extensive studies done on coronary calcifications and cardiac risks in persons without chronic renal failure. This context includes the common use of calcium, calcium-containing phosphate binders, and pharmacologic doses of vitamin D in a setting where renal clearance of calcium and phosphate is markedly reduced or absent.

As a result, questions arise about the effect of these medications on coronary calcifications and how to interpret calcifications in this markedly different patient population. For example, excessive intake of vitamin D or its metabolites and analogues may lead to arterial calcifications,[95,96] but appropriate doses of vitamin D metabolites given to control secondary hyperparathyroidism might actually reduce the propensity for vascular calcification.[97]

A direct interaction between these medications and coronary calcifications has not been consistently shown. In addition, there is no evidence of an increased risk of coronary calcifications independent of atherosclerotic atheroma burden. Therefore, the pharmacologic control of calcium and phosphate metabolism should be directed by the patient's nephrologic and endocrinologic needs and not be withheld for concern about coronary calcifications. The cardiologist should emphasize aggressive cardiovascular risk-factor modification to slow progression of coronary artery disease in patients with ESRD. This includes tight control of hypertension, diabetes mellitus, and lipid abnormalities. Unfortunately, current lipid management guidelines do not specify a particular strategy for patients with ESRD.

Guidelines for lipid management do not specify a strategy for patients with ESRD

CONCLUSION

Studies in subjects without chronic renal failure indicate that coronary calcifications are a manifestation of coronary atherosclerosis and develop in an actively controlled mineralization process. Their quantity correlates with the overall extent of atherosclerotic disease burden. The role of coronary calcifications in

the development of acute coronary syndromes is complex and incompletely understood. Calcification of individual lesions may not be a marker of lesion instability. However, the presence of calcified lesions implies the likely association of lipid-rich and possibly unstable plaque.

Although calcified coronary lesions are more common in patients with ESRD, no independent increase in cardiovascular risk has been associated with these calcifications. Current evidence does not support the concept that specific attempts to reduce coronary calcium may benefit patients with renal failure. On the other hand, these patients have a high risk of developing coronary artery disease and are candidates for aggressive risk-factor modification, including control of hypertension, diabetes mellitus, and hypercholesterolemia.

CT helps to predict future risk and enables monitoring of disease progression

REFERENCES

1. **Foley RN, Parfrey PS, Sarnak MJ.** Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32:S112–S119.
2. **U.S. Renal Data System.** USRDS 200 Annual Report. Bethesda, Md: National Institute of Diabetes and Digestive and Kidney Diseases; June 2000.
3. **Rostand SG.** Coronary heart disease in chronic renal insufficiency: some management considerations. J Am Soc Nephrol 2000; 11:1948–1956.
4. **Moustapha A, Gupta A, Robinson K, et al.** Prevalence and determinants of hyperhomocysteinemia in hemodialysis and peritoneal dialysis. Kidney Int 1999; 55:1470–1475.
5. **Fatica RA, Dennis VW.** Cardiovascular mortality in chronic renal failure: hyperphosphatemia, coronary calcification, and the role of phosphate binders. Cleve Clin J Med 2002; 69(suppl 3):S-21–S-27.
6. **Block GA, Hulbert-Shearon TE, Levin NW, Port FK.** Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31:607–617.
7. **Rostand SG, Drueke TB.** Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int 1999; 56:383–392.
8. **Watson KE, Abrolat ML, Malone LL, et al.** Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997; 96:1755–1760.
9. **Schwarz U, Buzello M, Ritz E, et al.** Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000; 15:218–223.
10. **Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR.** Aortic and mitral valve calcification in patients with end-stage renal disease. Lancet 1987; 2:875–877.
11. **Maher ER, Pazianas M, Curtis JR.** Calcific aortic stenosis: a complication of chronic uremia. Nephron 1987; 47:119–122.
12. **Rostand SG, Sanders C, Kirk KA, Rutsky EA, Fraser RG.** Myocardial calcification and cardiac dysfunction in chronic renal failure. Am J Med 1988; 85:651–657.
13. **Blankenhorn DH.** Coronary arterial calcification: a review. Am J Med Sci 1961; 242:41–49.
14. **Demer LL.** A skeleton in the atherosclerosis closet. Circulation 1995; 92:2029–2032.
15. **Fitzpatrick LA, Severson A, Edwards WD, et al.** Diffuse calcification in human coronary arteries. Association of osteopontin with atherosclerosis. J Clin Invest 1994; 94:1597–1604.
16. **Doherty TM, Detrano RC.** Coronary arterial calcification as an active process: a new perspective on an old problem. Calcif Tissue Int 1994; 54:224–230.
17. **Wexler L, Brundage B, Crouse J, et al.** Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. Circulation 1996; 94:1175–1192.
18. **Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ.** Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. Circulation 1991; 83:1764–1770.
19. **Cadranel J, Garabedian M, Milleron B, Guillozo H, Akoun G, Hance AJ.** 1,25(OH)2D2 production by T lymphocytes and alveolar macrophages recovered by lavage from normocalcemic patients with tuberculosis. J Clin Invest 1990; 85:1588–1593.
20. **Detrano RC, Wong ND, French WJ, et al.** Prevalence of fluoroscopic coronary calcific deposits in high-risk asymptomatic persons. Am Heart J 1994; 127:1526–1532.
21. **Goel M, Wong ND, Eisenberg H, Hagar J, Kelly K, Tobis JM.** Risk factor correlates of coronary calcium as evaluated by ultrafast computed tomography. Am J Cardiol 1992; 70:977–980.
22. **Lie JT, Hammond PI.** Pathology of the senescent heart: anatomic observations on 237 autopsy studies of patients 90 to 105 years old. Mayo Clin Proc 1988; 63:552–564.
23. **Beadenkopf WG, Daoud AS, Love BM.** Calcification in the coronary arteries and its relationship to arteriosclerosis and myocardial infarction. Am J Roentgenol 1964; 92:865–871.
24. **Wong ND, Kouwabunpat D, Vo AN, et al.** Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. Am Heart J 1994; 127:422–430.
25. **Hoeg JM, Feuerstein IM, Tucker EE.** Detection and quantitation of calcific atherosclerosis by ultrafast computed tomography in children and young adults with homozygous familial hypercholesterolemia. Arterioscler Thromb 1994; 14:1066–1074.
26. **Mahoney LT, Burns TL, Stanford W, et al.** Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. J Am Coll Cardiol 1996; 27:277–284.
27. **Blankenhorn DH, Stern D.** Calcification of the coronary arteries. Am J Roentgenol 1959; 81:772–777.
28. **Eggen DA, Strong JP, McGill HC Jr.** Coronary calcification: relationship to clinically significant coronary lesions and race, sex, and topographic distribution. Circulation 1965; 32:948–955.
29. **Frink RJ, Achor RW, Brown AL Jr, Kincaid OW, Brandenburg RO.** Significance of calcifications of the coronary arteries. Am J Cardiol 1970; 26:241–247.
30. **Janowitz WR, Agatston AS, Kaplan G, Viamonte M Jr.** Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. Am J Cardiol 1993; 72:247–254.
31. **Strong JP, Malcom GT, McMahan CA, et al.** Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from pathobiological determinants of atherosclerosis in youth study. JAMA

1999; 281:727–735.
32. **Tuzcu EM, Kapadia SR, Tutar E, et al.** High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults. Circulation 2001; 103:2705–2710.
33. **Grundy SM, Pasternak R, Greenland P, Smith S, Fuster V.** Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. J Am Coll Cardiol 1999; 34:1348–1359.
34. **Tejada C, Strong JP, Montenegro MR, Restrepo C, Solberg LA.** Distribution of coronary and aortic atherosclerosis by geographic location, race, and sex. Lab Invest 1968; 18:509–526.
35. **Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA.** Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: a quantitative pathologic comparison study. J Am Coll Cardiol 1992; 20:1118–1126.
36. **Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS.** Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. Circulation 1995; 92:2157–2162.
37. **Libby P.** Molecular bases of the acute coronary syndromes. Circulation 1995; 91:2844–2850.
38. **Libby P.** Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001; 104:365–372.
39. **Giroud D, Li JM, Urban P, Meier B, Rutishauser W.** Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis prior to angiography. Am J Cardiol 1992; 69:729–732.
40. **Ambrose JA, Tannenbaum MA, Alexopoulos D, et al.** Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12:56–62.
41. **Little WC, Constantinescu M, Applegate RJ, et al.** Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988; 78:1157–1166.
42. **Ambrose JA, Winters SL, Arora RR, et al.** Angiographic evolution of coronary artery morphology in unstable angina. J Am Coll Cardiol 1986; 7:472–478.
43. **Ross R.** The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362:801–809.
44. **Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT.** Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. Circulation 1994; 90: 775–778.
45. **Shah PK, Falk E, Badimon JJ, et al.** Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Circulation 1995; 92:1565–1569.
46. **Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ.** Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987; 316:1371–1375.
47. **Gibbons GH, Dzau VJ.** The emerging concept of vascular remodeling. N Engl J Med 1994; 330:1431–1438.
48. **Clarkson TB, Prichard RW, Morgan TM, Petrick GS, Klein KP.** Remodeling of coronary arteries in human and non-human primates. JAMA 1994; 271:289–294.
49. **Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM.** Extent and direction of arterial remodeling in stable and unstable coronary syndromes. Circulation 2000; 101:598–603.
50. **Smits PC, Pasterkamp G, de Jaegere PPT, de Feyter PJ, Borst C.** Angioscopic complex lesions are predominantly compensatory enlarged: an angioscopic and intracoronary ultrasound study. Cardiovasc Res 1999; 41:458–464.
51. **Nakamura M, Nishikawa H, Mukai S, et al.** Impact of coronary artery remodeling on clinical presentation of coronary artery disease: an intravascular ultrasound study. J Am Coll Cardiol 2001; 37:63–69.
52. **Wexberg P, Gyongyosi M, Sperker W, et al.** Pre-existing arterial remodeling is associated with in-hospital and late adverse cardiac events after coronary interventions in patients with stable angina pectoris. J Am Coll Cardiol 2000; 36:1860–1869.
53. **Richardson PD, Davies MJ, Born GV.** Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 1989; 2:941–944.
54. **Loree HM, Kamm RD, Stringfellow RG, Lee RT.** Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. Circ Res 1992; 71:850–858.
55. **Schoenhagen P, Vince DG, Ziada K, et al.** Increased presence of matrix-metalloproteinase 3 in human coronary lesions with positive arterial remodeling [abstract]. J Am Coll Cardiol 2000; 35(2supplA):58A.
56. **Pasterkamp G, Schoneveld AH, Hijnen DJ, et al.** Atherosclerotic arterial remodeling and the localization of macrophages and matrix metalloproteases 1, 2 and 9 in the human coronary artery. Atherosclerosis 2000; 150:245–253.
57. **Schmermund A, Erbel R.** Unstable coronary plaque and its relation to coronary calcium. Circulation 2001; 104:1682–1687.
58. **Gussenhoven EJ, Essed CE, Lancee CT, et al.** Arterial wall characteristics determined by intravascular ultrasound imaging: an in vitro study. J Am Coll Cardiol 1989; 14: 947–952.
59. **Hodgson JMcB, Reddy KG, Suneja R, Nair RN, Lesnefsky EJ, Sheehan HM.** Intracoronary ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome, and procedural results in patients undergoing coronary angioplasty. J Am Coll Cardiol 1993; 21:35–44.
60. **Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT**. The impact of calcification on the biomechanical stability of atherosclerotic plaques. Circulation 2001; 103:1051–1056.
61. **Nissen SE, Gurley JC, Grines CL, et al.** Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. Circulation 1991; 84:1087–1099.
62. **Nissen SE, Yock P.** Intravascular ultrasound: novel pathophysiological insights and current clinical applications. Circulation 2001; 103:604–616.
63. **Mintz GS, Douek P, Pichard AD, et al.** Target lesion calcification in coronary artery disease: an intravascular ultrasound study. J Am Coll Cardiol 1992; 20:1149–1155.
64. **Tuzcu EM, Berkalp B, De Franco AC, et al.** The dilemma of diagnosing coronary calcification: angiographic versus intravascular ultrasound. J Am Coll Cardiol 1996; 27: 832–838.
65. **Honye J, Mahon DJ, Jain A, et al.** Morphological effects of coronary balloon angioplasty in vivo assessed by intravascular ultrasound imaging. Circulation 1992; 85:1012–1025.
66. **Halliburton SS, Stillman AE, White RD.** Noninvasive quantification of coronary artery calcification: methods and prognostic value. Cleve Clin J Med 2002; 69(suppl 3): S-6–S-11.
67. **Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R.** Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15:827–832.
68. **Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P.** Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. Radiology 1998; 208:807–814.
69. **Callister T, Janowitz W, Raggi P.** Sensitivity of two electron beam tomography protocols for the detection and quantification of coronary artery calcium. AJR Am J

Roentgenol 2000; 175:1743–1746.
70. **Yoon HC, Greaser LE, Mather R, Sinha S, McNitt-Gray MF, Goldin JG.** Coronary artery calcium: alternate methods for accurate and reproducible quantitation. Acad Radiol 1997; 10:666–673.
71. **Detrano R, Tang W, Kang X, et al.** Accurate coronary calcium phosphate mass measurements from electron beam computed tomograms. Am J Card Imaging 1995; 3:167–173.
72. **Becker CR, Knez A, Leber A, et al.** Initial experience with multi-slice detector spiral CT in diagnosis of arteriosclerosis of coronary vessels. Radiologe 2000; 40:118–122.
73. **Becker CR, Kleffel T, Crispin A, et al.** Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. Am J Roentgenol 2001; 176:1295–1298.
74. **Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R.** Electron beam computed tomographic coronary calcium as a predictor of coronary events. Circulation 1997; 96:1122–1129.
75. **Tanenbaum SR, Kondos GT, Veselik KE, Prendergast MR, Brundage BH, Chomka EV.** Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography. Am J Cardiology 1989; 63:870–872.
76. **Sangiorgi G, Rumberger JA, Severson A, et al.** Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 1998; 31:126–133.
77. **Baumgart D, Schmermund A, Goerge G, et al.** Comparison of electron beam computed tomography with intracoronary ultrasound and coronary angiography for detection of coronary atherosclerosis. J Am Coll Cardiol 1997; 30:57–64.
78. **Kajinami K, Seki H, Takekoshi N, Mabuchi H.** Coronary calcification and coronary atherosclerosis: site-by-site comparative morphologic study of electron beam computed tomography and coronary angiography. J Am Coll Cardiol 1997; 29:1549–1556.
79. **Becker CR, Jakobs TF, Aydemir S, et al.** Helical and single-slice conventional CT versus electron beam CT for the quantification of coronary artery calcification. AJR Am J Roentgenol 2000; 174:543–547.
80. **Topol EJ, Nissen SE.** Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995; 92:2333–2342.
81. **Detrano RC, Wong ND, Tang W, et al.** Prognostic significance of cardiac cinefluoroscopy for coronary calcific deposits in asymptomatic high-risk subjects. J Am Coll Cardiol 1994; 24:354–358.
82. **Detrano R, Hsiai T, Wang S, et al.** Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996; 27:285–290.
83. **Margolis JR, Chen JTT, Kong Y, Peter RH, Behar VS, Kisslo JA.** The diagnostic and prognostic significance of coronary artery calcification. Radiology 1980; 137:609–616.
84. **Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL.** Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. Circulation 1996; 94:932–938.
85. **Worthley SG, Helft G, Fuster V, et al.** Serial in vivo MRI documents arterial remodeling in experimental atherosclerosis. Circulation 2000; 101:586–589.
86. **Shinnar M, Fallon JT, Wehrli S, et al.** The diagnostic accuracy of ex vivo MRI for human atherosclerotic plaque characterization. Arterioscler Thromb Vasc Biol 1999; 19:2756–2761.
87. **Janowitz WR, Agatston AS, Viamonte M.** Comparison of serial quantitative evaluation of calcified coronary artery plaque by ultrafast computed tomography in persons with and without coronary artery disease. Am J Cardiol 1991; 68:1–6.
88. **Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ.** Effect of HMG-CoA reductase inhibitors on coronary artery disease by electron-beam computed tomography. N Engl J Med 1998; 339:1972–1978.
89. **O'Rourke RA, Brundage BH, Froelicher VF, et al.** American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. Circulation 2000; 102:126–140.
90. **Mintz GS, Pichard AD, Popma JJ, et al.** Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic and intravascular ultrasound study. J Am Coll Cardiol 1997; 29:268–274.
91. **Schoenhagen P, McErlean ES, Nissen SE.** The vulnerable coronary plaque. J Cardiovasc Nurs 2000; 15:1–12.
92. **Yamagishi M, Terashima M, Awano K, et al.** Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. J Am Coll Cardiol 2000; 35:106–111.
93. **Schroeder S, Kopp AF, Baumbach A, et al.** Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. J Am Coll Cardiol 2001; 37:1430–1435.
94. **Becker CR, Knez A, Ohnesorge B, Schoepf UJ, Reiser MF.** Imaging of noncalcified coronary plaques using helical CT with retrospective ECG gating. AJR Am J Roentgenol 2000; 175:423–424.
95. **Milliner DS, Zinsmeister AR, Liebermann E, Landing B.** Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int 1990; 38:931–936.
96. **Hsu CH.** Are we mismanaging calcium and phosphate metabolism in renal failure? Am J Kidney Dis 1997; 29:641–649.
97. **Watson KE, Abrolat ML, Malone LL, et al.** Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997; 96:1755–1760.

ADDRESS: *E.M. Tuzcu, MD, The Cleveland Clinic Foundation, F25, 9500 Euclid Avenue, Cleveland OH 44195; e-mail tuzcue@ccf.org.*

RICHARD A. FATICA, MD
Department of Nephrology and Hypertension, The Cleveland Clinic

VINCENT W. DENNIS, MD
Chairman, Department of Nephrology and Hypertension, The Cleveland Clinic

Cardiovascular mortality in chronic renal failure: Hyperphosphatemia, coronary calcification, and the role of phosphate binders

KEY POINTS

Hyperphosphatemia is a strong and unique risk factor for cardiovascular mortality in patients on dialysis for chronic renal failure.

Overall treatment of hyperphosphatemia should focus on achieving and maintaining a serum phosphate level less than 5.5 mg/dL.

Calcium-containing phosphate binders remain standard therapy, although selected patients may benefit from the addition or substitution of calcium-free phosphate binders.

Reducing cardiovascular risk in patients with chronic renal failure should focus on addressing traditional cardiovascular risk factors.

The incremental risk-assessment value of coronary artery calcium scoring is limited.

Both authors have indicated that they have no affiliation with or financial interest in a commercial organization that poses a potential conflict of interest with their article.

THE CARDIOVASCULAR MORTALITY RATE is 20 to 40 times higher for adults on dialysis than for the general population.[1] In treating patients on dialysis, nephrologists contend with the cumulative effects of the processes that cause renal failure, the generic consequences of globally disordered renal function, and the potential adverse effects of treatment or lack of treatment.

Recent observations implicate hyperphosphatemia and increased calcium-phosphate product (Ca × P) as contributing factors to increased mortality in dialysis patients.[2–4] A major proposed mechanism is accelerated coronary calcification, perhaps related to inadequate or inappropriate treatment of hyperphosphatemia. While this is an attractive hypothesis, it remains unproven.

The interrelationships among chronic renal failure, phosphate, calcium, vascular disease, and the treatment of divalent ion disorders are complex, and the significance of coronary artery calcifications is controversial, especially in patients with chronic renal failure. Moreover, clinical concerns about hyperphosphatemia, calcium, calcium-phosphate product, and vascular calcifications are further clouded by issues raised in the marketing of phosphate binders.[5]

This review summarizes the major reports that relate disordered calcium and phosphate metabolism to mortality in dialysis patients. It then places these findings in the context of what is and is not known about coronary artery calcifications in patients with and without chronic renal failure.

HYPERPHOSPHATEMIA IN CHRONIC RENAL FAILURE

The kidney is the major organ for maintaining phosphate homeostasis. Intestinal absorption of dietary phosphate is largely unregulated, so phosphate homeostasis is maintained primarily by renal excretion.[6] The kidney also plays an important role in calcium homeostasis by generating calcitriol and clearing calcium. Accordingly, some of the earliest disturbances in homeostasis that occur as chronic renal failure progresses result from the abnormal retention of phosphate and changes in overall calcium metabolism.[7]

Phosphate retention occurs early and inevitably as the glomerular filtration rate declines. This is offset initially by increased secretion of parathyroid hormone (PTH) triggered by decreased ionized calcium. Parathyroid hormone levels tend to maintain serum calcium and phosphate concentrations in the normal range,[8] but without treatment hyperphosphatemia typically ensues as the glomerular filtration rate falls below about 20 to 30 mL/min. Hyperphosphatemia may further affect calcium metabolism by augmenting PTH secretion, reducing calcitriol production, and inducing skeletal resistance to PTH, thereby limiting calcium resorption from bone.[9]

Phosphate retention occurs early and inevitably as glomerular filtration rate declines

In animal models, early reduction in phosphate intake can prevent or delay many of these changes,[8] but dietary restriction of phosphate in humans has limited clinical effectiveness because phosphates are ubiquitous in normal diets, especially with the high protein intake recommended for patients on dialysis. Weekly phosphate intake in patients on hemodialysis exceeds weekly removal by approximately 1,030 mg.[7] Moreover, calcitriol or vitamin D analogues are often given to suppress PTH secretion and prevent or reverse secondary hyperparathyroidism.[10,11] These may increase the intestinal absorption of calcium and phosphate.

HYPERPHOSPHATEMIA AND MORTALITY

Although the concern about disordered phosphate and calcium metabolism in chronic renal failure focuses mainly on bone disease, recent observational studies connect hyperphosphatemia to cardiovascular mortality in patients on dialysis.

USRDS mortality analysis

Using two large random cross-sectional samples of patients on hemodialysis from the United States Renal Data System (N = 6,407), Block et al[2] found that 39% of patients had serum phosphate concentrations above 6.5 mg/dL. These hyperphosphatemic patients had a relative risk (RR) of mortality of 1.27 compared with patients with serum phosphate levels between 2.4 and 6.5 mg/dL. All patients had been on dialysis for at least 1 year (average 4.5 years). About 20% of patients had a calcium-phosphate product greater than 72 mg^2/dL^2, and these patients had a significantly higher risk of death compared with a reference group with calcium-phosphate products between 42 and 52 mg^2/dL^2 (RR = 1.34; $P < .01$). Serum calcium concentration was not an independent risk factor at any level, however, so the association between calcium-phosphate product and mortality was attributed to hyperphosphatemia. Parathyroid hormone levels were weakly associated with mortality risk, and this association was heavily influenced by a small group of patients with very high PTH values (> 1,000 pg/mL). The authors concluded that hyperphosphatemia represents a risk for increased mortality in patients on dialysis for at least 1 year and that serum phosphate levels should be maintained below 6.5 mg/dL.

Analysis of cardiovascular mortality

Ganesh et al[4] extended these findings by assessing cardiovascular-specific deaths as a function of serum phosphate concentrations in a similar cohort of 12,833 patients on hemodialysis. A total of 4,120 deaths occurred over 2 years, of which 27% were sudden deaths and 18% were attributed to coronary artery disease or other cardiac causes. Patients with serum phosphate concentrations greater than 6.5 mg/dL had a relative risk of 1.41 for cardiac death and of 1.20 for sudden death compared with patients whose concentrations were between 2.4 and 6.5 mg/dL. When adjusted for age, duration of end-stage renal disease, race, gender, diabetes, smoking, AIDS, and neoplasm, the relative risk of mortality was a continuous function of serum

phosphate concentration and calcium-phosphate product. A weak association was found between increased mortality risk and PTH levels between 496 and 9,476 pg/mL.

Correlation, not causality

These two studies draw heightened attention to the potential adverse effects of hyperphosphatemia in the context of hemodialysis. As observational studies, however, they demonstrate correlations rather than causality and cannot provide a mechanism. Notably, each study indicates that the consistent risk factor is hyperphosphatemia, not hypercalcemia or hyperparathyroidism.

PREVENTION OF HYPERPHOSPHATEMIA WITH PHOSPHATE-BINDING AGENTS

Because restriction of dietary phosphate is largely ineffective, the primary way to prevent hyperphosphatemia in patients with chronic renal failure is by inhibiting intestinal phosphate absorption through the use of phosphate binders. There are primarily two types of agents currently used as intestinal phosphate binders:

- **Calcium salts of acetate** (PhosLo, Braintree Laboratories, Braintree, Mass) or **calcium salts of carbonate** (eg, Tums, GlaxoSmithKline, London, UK, and other generic products)
- **Sevelamer hydrochloride** (Renagel, Genzyme, Cambridge, Mass), a calcium-free allylamine polymer.

Both calcium salts are commonly prescribed as phosphate-binding agents, although calcium acetate is more efficient than calcium carbonate and provides less absorbable calcium.[6] Calcium acetate and sevelamer are marketed specifically for use as phosphate binders in chronic renal failure and have been compared in a clinical trial.

Calcium acetate vs sevelamer

Only one randomized comparative trial of calcium acetate and sevelamer has been published to date. It was a crossover study of 80 patients on hemodialysis that found sevelamer and calcium acetate to have similar efficacy in controlling hyperphosphatemia.[12] At the end of the 8-week treatment periods, serum phosphate concentrations were comparable with the two agents, averaging 6.4 $\pm$ 1.7 mg/dL with sevelamer and 5.9 $\pm$ 1.7 mg/dL with calcium acetate. The calcium-phosphate products also were similar between the treatments (60.0 $\pm$ 16.1 mg^2/dL^2 vs 57.1 $\pm$ 16.2 mg^2/dL^2, respectively). There was a trend toward higher serum calcium concentrations and lower PTH concentrations during treatment with calcium acetate. Sixty-six percent of all patients received vitamin D analogues during the study, with stable calcium intakes of about 550 mg/d and phosphate intakes of 780 to 800 mg/d. Hypercalcemia, defined as at least one instance of serum calcium levels of 11 mg/dL or greater during the 8-week study periods, occurred in 22% of patients while on calcium acetate versus 5% while on sevelamer.

Thus, the two agents had comparable efficacy in reducing hyperphosphatemia and calcium-phosphate products in patients with chronic renal failure, although hypercalcemia was more common with calcium acetate.

Comparative costs

Both treatments required a high daily intake of medication.[12] The mean dosage of calcium acetate started at 3.4 g/d and rose to 5.0 g/d; the mean dosage of sevelamer started at 3.4 g/d and rose to 4.9 g/d. This translates to a cost of about $22 to $32 per month for calcium acetate and $142 to $205 per month for sevelamer.* Typically, when one product has such a high cost premium and little if any discernible therapeutic advantage, it tends to have little attraction. Sevelamer emerged, however, at a time when a series of independent studies raised questions about a correlation between calcium intake and vascular calcifications in patients on dialysis. A subsequent aggressive marketing program linked these observations to "cardiac calcification."[5]

Coronary atherosclerosis occurs at an earlier age in patients with end-stage renal disease

CORONARY CALCIFICATIONS IN PATIENTS ON DIALYSIS

It has long been held that patients on dialysis have accelerated atherosclerosis.[13] Athero-

*Based on costs from www.drugstore.com (PhosLo 667 mg: $14.35 per 100 tablets; Renagel 800 mg: $111.81 per 100 tablets).

sclerotic plaques tend to calcify. Electron-beam computed tomography (EBCT) is a recent imaging technology that provides a noninvasive, highly sensitive measurement of coronary artery calcification.[14–16] Calcification scores derived from EBCT correlate with atherosclerotic burden, at least in patients without chronic renal failure.

Clinical findings

Goodman et al[17] examined coronary calcification by EBCT in 39 young adults on peritoneal dialysis or hemodialysis and compared the findings to those in 60 age-matched normal subjects. The patients on dialysis were divided into those under age 20 (n = 23) and those between ages 20 and 30 (n = 16). Fourteen of the 16 older patients demonstrated coronary calcifications, and they had a strikingly high average Agatston score of 1,157 (range 2 to 7,047; median 297). None of the 23 patients under age 20 and only 3 of the 60 normal subjects had coronary calcifications. The mean patient age was 26 ± 3 years in the calcification group compared with 15 ± 5 years in the group without calcifications.

Factors other than atherosclerotic burden are involved in calcification

Although both groups were young, their cumulative medical experiences were profoundly different. For the group with coronary calcifications, the median age at the start of dialysis was 13 years, which means that they had lived half their lives on dialysis or with a transplanted kidney. The prevalence of calcifications was much higher (13/27) in patients who had had kidney transplants than in those who had not (1/12). The mean duration of dialysis was longer for the group with coronary calcifications (14 ± 5 years) than for those without calcifications (4 ± 4 years). There was no difference in distribution between patients undergoing peritoneal dialysis as opposed to hemodialysis.

Given the youth of these patients and their strikingly high calcification scores, the authors hypothesized that abnormal divalent ion metabolism and its treatments may contribute to development of coronary calcifications in patients with end-stage renal disease. In this regard, the average serum phosphate concentration was marginally higher in those with coronary calcifications than in those without (6.9 vs 6.3 mg/dL; $P = .06$), and the calcium-phosphate product was significantly higher in those with coronary calcifications than in those without (65.0 vs 56.4 mg^2/dL^2; $P < .04$). Serum calcium concentrations and PTH levels were not different. Hyperphosphatemia, which has been correlated with increased mortality risk among patients on dialysis in other studies,[2,4] was not associated with higher coronary calcium scores.[17]

On the basis of these observations, Goodman et al[17] attributed the prevalence of coronary calcifications (ie, coronary atherosclerosis) to the duration of dialysis and attributed the high calcification scores to higher calcium intake, including intake of calcium-containing phosphate binders. This is distinct from concluding (1) that disordered mineral metabolism caused the atherosclerosis that became calcified, (2) that there is concordance between calcium scores in patients with end-stage renal disease and otherwise normal subjects with similar degrees of coronary disease, or (3) that calcification scores in patients on dialysis correlate linearly with cardiovascular events.

Along these lines, Braun et al[18] correlated calcification scores and coronary angiographic findings in 49 patients on chronic dialysis and compared them with findings in 102 patients with coronary artery disease who were not on dialysis. Calcification scores were 2.5 to 5 times higher in patients on dialysis and correlated with age and hypertension but not with serum phosphate, calcium, or PTH concentrations. A similar study by Utsunomiya[19] in 30 patients with and 22 patients without renal failure also found that calcification of coronary atherosclerosis is higher in the presence of renal failure. These two studies were further supported by morphologic and x-ray diffraction analysis of coronary arteries from 27 patients with end-stage renal disease that showed increased medial thickness and increased plaque calcification relative to coronary arteries from matched patients without renal failure.[20]

Calcium scores: the interpretation challenge

The interpretation of coronary artery calcifications as a surrogate for coronary atherosclerosis and cardiovascular events is central to concerns about calcium and phosphate bal-

ance in patients with chronic renal failure. Other articles in this supplement[14,15] and a consensus statement from the American College of Cardiology and American Heart Association[16] review the technical aspects of assessing coronary artery calcifications and the challenges of interpreting their clinical significance and utility. At least in patients without chronic renal failure, coronary artery calcifications correlate with atherosclerotic burden, although not necessarily with acute coronary events. In asymptomatic patients, EBCT-derived calcification scores have a strong negative predictive value (> 99%) for major coronary events over 3 to 4 years but a much weaker positive predictive value (11% to 18%).[16] Although there is a quantitative relationship between atherosclerosis and calcium scores, this relationship is nonlinear. Interscan reliability is fair to poor, as variability ranges from 14% to 51%. Overall, it is not clear that calcification scores as determined by EBCT provide incremental information to that available from risk analysis by Framingham Heart Study or National Cholesterol Education Program methods.

Only limited additional information is available on the significance of coronary artery calcifications in patients with chronic renal failure and its associated disorders. In a study of 24 dialysis patients with an average age of 53 ± 14 years and average dialysis duration of 64 ± 69 months, 1-year progression of coronary calcification as detected by EBCT was associated with a higher baseline calcium score, preexisting dyslipidemia, a high triglyceride level, and a low high-density lipoprotein cholesterol level.[21] Progression was not associated with serum phosphate concentration.

PHOSPHATE AND VASCULAR CALCIFICATION

Vascular calcification is an active process similar to bone mineralization.[22–24] In cultures of human aortic smooth muscle cells, increasing the concentration of inorganic phosphate in the culture media increased cell mineralization, predominantly bioapatite. This mineralization effect of high ambient phosphate concentrations also occurs in human fetal, adult, and atherosclerotic plaque-derived smooth muscle cells.[22] When cultured in high-phosphate media, human smooth muscle cells upregulate the transcription of osteocalcin, a promoter of vascular calcium deposition. These cells undergo a dramatic phenotypic change to osteogenic cells under in vitro conditions that promote culture or vascular calcification.[23] In addition to osteocalcin, several other bone-related proteins listed in TABLE 1 are involved in either a protective or a promoting effect on vascular calcification in human and cell culture models.[23]

TABLE 1

Bone-associated proteins associated with vascular calcification

INDUCERS	INHIBITORS
Osteocalcin	Osteopontin
Osteonectin	Matrix Gla protein
Bone morphogenic protein type 2a (BMP-2a)	Osteoprotegerin
Alkaline phosphatase	Type 1 collagen
Bone sialoprotein	PTHr-peptide

This background provides a strong foundation for concern about hyperphosphatemia as a key factor that can promote vascular calcification. The clinical significance of this calcification as either a cause or a consequence of atherosclerotic or other vascular pathology may not be entirely clear in patients with chronic renal failure, but it is presumably unfavorable.

Systematic replacement of calcium-containing phosphate binders is not warranted

CALCIUM INTAKE AND DURATION OF DIALYSIS

Because phosphate binders are inherently associated with dialysis therapy, the duration of dialysis and the prescribed intake of phosphate binders are likely to be linearly related. Since aluminum-containing agents were abandoned (because of aluminum-related bone and neurologic diseases[6]), the prevalent phosphate binders have contained calcium. Accordingly, the length of time on dialysis

therapy, the cumulative prescribed dose of phosphate binders, and the cumulative calcium intake are potentially confounded variables, in that an event related to one is highly likely to be correlated with another. A related point concerns the uncertain relationships among prescribed versus ingested doses of calcium-containing phosphate binders, as well as the net absorption of calcium. Chronic renal failure typically results in decreased intestinal absorption of calcium and negative calcium balance because of reduced intake[25] and reduced calcitriol production.[26] Calcium balance studies show that patients with chronic renal failure have a slightly negative calcium balance but can achieve a positive balance with a normal or high-calcium diet.[7]

Because the kidneys serve as the major alternative route of calcium clearance other than deposition in bone and soft tissue, patients with chronic renal failure who are on dialysis have limited means of accommodating any excess calcium intake from diet or hemodialysis. Hsu[7] outlined the approximate intake of calcium in patients on dialysis three times per week, using a 2.5 or 3.5 mEq/L dialysate calcium concentration. For a 2.5 mEq/L concentration, the net calcium balance per day is estimated to be 216 mg, assuming daily intake of 800 mg. This exceeds the estimated threshold balance of 114 mg/d for 18- to 30-year-olds. The fate of any calcium accumulation is uncertain, but it presumably rests in bone and soft tissue.

Coronary artery disease screening should be as intense for dialysis evaluation as for pretransplant evaluation

RECOMMENDATIONS AND CONCLUSIONS

Hyperphosphatemia is emerging as a strong and unique risk factor for cardiovascular morbidity and mortality in patients on dialysis for chronic renal failure. Control of hyperphosphatemia now assumes added and dominant importance beyond concerns about metabolic bone disease and secondary hyperparathyroidism, conditions that may be overtreated by our current regimens of high-dose vitamin D.

Treatment goals

Overall treatment should focus on achieving and maintaining a normal serum phosphate concentration of less than 5.5 mg/dL (and thereby usually a normal calcium-phosphate product). This can usually be achieved through dietary restrictions, adequate or intensified dialysis, rational use of phosphate binders, and conservative use of oral or intravenous vitamin D or its analogues.

Use of phosphate binders

Calcium-containing phosphate binders remain standard therapy because they are effective, affordable, and safe, and they have an added advantage of providing supplemental calcium. Adjustments in their use are needed if hyperphosphatemia is uncontrolled or hypercalcemia emerges. These adjustments should include attention to correct use, review of vitamin D exposure and dialysate calcium concentration, and assessment of parathyroid function and bone mineralization. Selected patients may benefit from the addition or substitution of calcium-free phosphate binders, but the systematic replacement of calcium-containing phosphate binders is not warranted.

Cardiovascular risk reduction

Reducing cardiovascular risk in patients with chronic renal failure should focus on addressing the traditional risk factors of hypertension, dyslipidemias, diabetes, cigarette smoking, obesity, and homocysteinemia. Screening and evaluation of coronary artery disease should be no less intense for dialysis evaluation than it is for pretransplant evaluation, and it should rely on traditional cardiovascular risk-factor analysis and appropriate stress tests.

Value of calcium scoring

For patients with or without chronic renal failure, the incremental value of coronary artery calcium scoring by EBCT is limited. Because of the very high negative predictive value of EBCT evaluation, its greatest usefulness may be in screening for the *absence* of significant atherosclerotic burden or luminal obstructive coronary disease in patients with one or more risk factors. Alternately, if EBCT evaluation is positive, it may be useful in identifying patients who should be upgraded to a higher risk category.

The limited data on coronary artery calcium scoring in the setting of chronic renal failure and dialysis indicate that factors other than atherosclerotic burden are involved in

calcification and that scores tend to be higher in patients with rather than without renal failure. Caution is therefore warranted before ascribing the degree of calcification to the extent of atherosclerosis or to the risk of an acute coronary event. In particular, changes in calcification scores cannot now be attributed to changes in either atherosclerotic burden or risk of a coronary event. The data tend to confirm that coronary atherosclerosis occurs at an earlier age in patients with end-stage renal disease, but the limited observations to date do not allow fully adjusted risk comparisons with normal subjects. Within these limitations, coronary artery calcium scores in chronic renal failure show some correlation with age, dyslipidemias, hypertension, duration of dialysis, and exposure to phosphate binders that until most recently were almost exclusively calcium-containing agents.

REFERENCES

1. **Collins AJ, Li S, Ma JZ, Herzog C.** Cardiovascular disease in end-stage renal disease patients. Am J Kidney Dis 2001; 38(suppl 1):S26–S29.
2. **Block GA, Hulbert-Shearon TE, Levin NW, Port FK.** Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31:607–617.
3. **Block GA, Port FK.** Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. Am J Kidney Dis 2000; 35:1226–1237.
4. **Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon TE, Port FK.** Association of elevated serum PO4, Ca x PO4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131–2138.
5. **Johannes L, Armstrong D.** Why some dialysis patients take $12-a-day drug instead of Tums. Wall Street Journal. June 26, 2001:B1.
6. **Dennis VW.** Phosphate disorders. In: Kokko JP, Tannen RL, eds. Fluids and Electrolytes. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1996:359–419.
7. **Hsu CH.** Are we mismanaging calcium and phosphate in renal failure? Am J Kidney Dis 1997; 29:641–649.
8. **Slatopolsky E, Bricker NS.** The role of phosphate restriction in prevention of secondary hyperparathyroidism in chronic renal disease. Kidney Int 1973; 4:141–145.
9. **Slatopolsky E, Brown A, Dusso A.** Role of phosphorus in the pathogenesis of secondary hyperparathyroidism. Am J Kidney Dis 2001; 37(suppl 2):S54–S57.
10. **Drueke TB.** Control of secondary hyperparathyroidism by vitamin D derivatives. Am J Kidney Dis 2001; 37(suppl 2): S58–S61.
11. **Pitts TO, Piraino BH, Mitro R, et al.** Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. J Clin Endocrinol Metab 1988; 67:876–881.
12. **Bleyer AJ, Burke SK, Dillon M, et al.** A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. Am J Kidney Dis 1999; 33:694–701.
13. **Lindner A, Charra B, Sherrard DJ, Scribner BH.** Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974; 290:697–701.
14. **Halliburton SS, Stillman AE, White RD.** Noninvasive quantification of coronary artery calcification: methods and prognostic value. Cleve Clinic J Med 2002; 69(suppl 3): S-6–S-11.
15. **Schoenhagen P, Tuzcu EM.** Coronary artery calcification and end-stage renal disease: vascular biology and clinical implications. Cleve Clinic J Med 2002; 69(suppl 3): S-12–S-20.
16. **O'Rourke RA, Brundage BH, Froelich VF, et al.** American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. Circulation 2000; 102:126–140.
17. **Goodman WG, Goldin J, Kuizon BD, et al.** Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. New Engl J Med 2000; 342:1478–1483.
18. **Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC.** Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 1996; 27:394–401.
19. **Utsunomiya M.** Angiographic study of calcification of coronary vessels in long term dialysis patients: examination of risk factors for coronary calcification. Nippon Jinzo Gakkai Shi 1996; 38:155–163.
20. **Schwarz U, Buzello M, Ritz E, et al.** Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. Nephrol Dial Transplant 2000; 15:218–223.
21. **Tamashiro M, Iseki K, Sunagawa O, et al.** Significant association between the progression of coronary artery calcification and dyslipidemia in patients on chronic hemodialysis. Am J Kidney Dis 2001; 38:64–69.
22. **Giachelli CM, Jono S, Shioi A, Nishizawa Y, Mori K, Morii H.** Vascular calcification and inorganic phosphate. Am J Kidney Dis 2001; 38(suppl 1):S34–S37.
23. **Cozzolino M, Dusso AS, Slatopolsky E.** Role of calcium-phosphate product and bone-associated proteins on vascular calcifications in renal failure. J Am Soc Nephrol 2001; 12:2511–2516.
24. **Moe SM, O'Neill KD, Duan D, et al.** Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. Kidney Int 2002; 61:638–647.
25. **Clarkson EM, Eastwood JB, Koutsaimainis KG, de Wardener HE.** Net intestinal absorption of calcium in patients with chronic renal failure. Kidney Int 1973; 3:258–263.
26. **Koenig KG, Lindberg JS, Zerwekh JE, Padalino PK, Cushner HM, Copley JB.** Free and total 1,25-dihydroxyvitamim D levels in subjects with renal disease. Kidney Int 1992; 41:161–165.

ADDRESS: *Richard A. Fatica, MD, Department of Nephrology and Hypertension, Desk A51, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail faticar@ccf.org*