With our increasingly aged and dysmetabolic population, the deleterious consequences of globally perturbed calcium metabolism become increasingly apparent. Net loss of bone mineral quantity and quality increases risk for osteoporotic fracture, whereas accumulating arterial calcium loads stiffen conduit arteries and impairs Windkessel physiology—the rubbery elasticity of conduit vessels that ensures smooth distal tissue perfusion throughout the cardiac cycle. Murine models were first used to identify that reciprocal change in skeletal versus vascular calcium accrual can occur in response to the dysmetabolic states of diabetes mellitus, uremia, and dyslipidemia. However, the Multiethnic Study of Atherosclerosis (MESA) firmly established the general connection between accrual of metabolic syndrome parameters—impaired fasting glucose, hypertension, obesity, low high-density lipoprotein, hypertriglyceridemia, or frank type 2 diabetes mellitus (T2D)—and arterial calcium load in humans. Recent studies implementing high-resolution peripheral quantitative computed tomography have shown that older men and women with T2D exhibit greater cortical bone porosity—a feature computed tomography have shown that older men and women with T2D exhibit greater cortical bone porosity—a feature that compromises bone strength and increases fracture risk. Patients with calcified peripheral arterial disease also exhibit deficiencies in trabecular bone structure on high-resolution peripheral quantitative computed tomography, further solidifying the relationship. Elegant human genetic studies by Mani et al highlighted that osteoporosis–atherosclerosis relationships are genetically determined in part by LRP6 signaling—with the cell-autonomous (osteoblast and vascular smooth muscle) contributions of LRP6 to bone and vascular dysfunction subsequently confirmed and mechanistically enlightened by murine genetic models.

However, the means and mechanisms whereby clinically relevant dysmetabolic states simultaneously perturb arterial and skeletal health are only beginning to be understood. Although parathyroid hormone, FGF23, and oxylipid signals have uncovered relationships between inflammatory signals arising in the dysmetabolic state, elegant human genetic studies by Mani et al highlighted that osteoporosis–atherosclerosis relationships are genetically determined in part by LRP6 signaling—with the cell-autonomous (osteoblast and vascular smooth muscle) contributions of LRP6 to bone and vascular dysfunction subsequently confirmed and mechanistically enlightened by murine genetic models. However, the means and mechanisms whereby clinically relevant dysmetabolic states simultaneously perturb arterial and skeletal health are only beginning to be understood. Although parathyroid hormone, FGF23, and oxylipid signals have uncovered relationships between inflammatory signals arising in the dysmetabolic state, elegant human genetic studies by Mani et al highlighted that osteoporosis–atherosclerosis relationships are genetically determined in part by LRP6 signaling—with the cell-autonomous (osteoblast and vascular smooth muscle) contributions of LRP6 to bone and vascular dysfunction subsequently confirmed and mechanistically enlightened by murine genetic models.

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AMPKα1
SUMO Wrestling Runx2 as a Strategy to Inhibit Arteriosclerotic Calcification
Dwight A. Towler

Why is this article so intriguing and important? First and foremost, these data provide compelling rationale for a
patient-oriented research study implementing metformin as a strategy to prevent arteriosclerotic calcification in those at greatest risk for progression; this encompasses patients with T2D and early-stage chronic kidney disease. At every level of renal dysfunction—even end-stage chronic kidney disease requiring dialysis—glycemic control interacts with the perturbed calcium phosphate homeostasis of chronic kidney disease to augment severity of cardiovascular calcification in T2D. Until recently, the concerns of metformin-induced lactic acidosis, a rare but well-described side effect of metformin administration, had limited its use in individuals with even mild renal insufficiency. In April of this year, the US Food and Drug Administration relaxed its recommendation to recognize that judicious use of metformin may be appropriate in T2D patients with chronic kidney disease stage 3 (an estimated glomerular filtration rate between 30 and 59 mL/min/1.73 m²) based on a recent meta-analysis. With careful oversight, a clinical dose-ranging trial assessing the impact of metformin-modulated AMPK signaling on coronary calcification and vascular stiffness holds potential to move the needle for patient management in this earlier-stage disease population at high risk for cardiovascular and renal disease progression—particularly so in the setting of increased thoracic aortic calcification and stiffness. Novel and selective activators of AMPKα1 may prove even more useful—and potentially minimize the risk of metabolic acidosis that infrequently arises with metformin. However, most intriguing to me are the implications of this study with respect to the fundamental metabolic relationships between osteoporosis and atherosclerosis as discussed above. Recently, Shimazu et al demonstrated that Smurf1, one of the key ubiquitin E3 ligases that controls Runx2 stability in the osteoblasts of bone, is also regulated by AMPK-dependent phosphorylation. However, the relative roles and regulation of AMPKα1 and AMPKα2 in osteoblasts have yet to be examined in detail. Nevertheless, these data converge with the truly exciting findings of Cai et al, who implicate cell type-specific control of Runx2 turnover—be it by AMPK-regulated SUMOylation or ubiquitination—as a molecular lynchpin in the global regulation of tissue mineralization in cardiometabolic disease. As such, this work does much to illuminate the metabolic origins of vascular calcification and offers new insights for treating our patients afflicted with or at high risk for arteriosclerosis.

Sources of Funding

D.A. Towler is supported by grants HL069229 and HL114806 from the National Institutes of Health, the J.D. and Maggie E. Wilson Distinguished Chair in Biomedical Research, and the University of Texas.

Disclosures

None.

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Key Words: Editorials ■ diabetes mellitus, type II ■ obesity ■ osteoporosis ■ renal insufficiency, chronic ■ uremia ■ vascular calcification
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Dwight A. Towler

*Circ Res.* 2016;119:398-400
doi: 10.1161/CIRCRESAHA.116.309237

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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