With our increasingly aged and dysmetabolic population, the deleterious consequences of globally perturbed calcium metabolism become increasingly apparent.¹ Net loss of bone mineral quantity and quality increases risk for osteoporotic fracture,² 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.³ 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 dyslipidemia⁴. 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.⁵ 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.⁶,⁷ Patients with calcified peripheral arterial disease also exhibit deficiencies in trabecular bone structure on high-resolution peripheral quantitative computed tomography, further solidifying the relationship.⁸ Elegant human genetic studies by Mani et al⁹ 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.¹⁰,¹¹ 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.¹² Thus, the authors conclude that the prosclerotic VSM Runx2 program¹³—held in check by AMPKalpha1-regulated mechanisms that control Runx2 stability in a cell-specific fashion and that pharmacological activation of AMPKalpha1 can mitigate atherosclerotic mineralization.

Why is this article so intriguing and important? First and foremost, these data provide compelling rationale for a healthy adaptation to states of altered fuel and lipid metabolism—have been largely overlooked.

AMPKα1
SUMO Wrestling Runx2 as a Strategy to Inhibit Arteriosclerotic Calcification

Dwight A. Towler

In this issue of Circulation Research, Cai et al¹⁴ begin to address this issue by examining the roles of AMPKalpha1 and AMPKalpha2 in atherosclerotic calcification, using the apolipoprotein E–null model of diet-induced dyslipidemia. The AMP kinases are master regulators that sense cellular energetics in part through the AMP/ATP ratio and mitochondrial reactive oxygen species production and coordinate cell-autonomous responses to metabolic stresses.¹⁵ Using conditional knockout strategies, they demonstrate that vascular smooth muscle (VSM) AMPKalpha1 plays a uniquely important role in the arterial defense to calcific responses arising from dyslipidemia. Loss of VSM AMPKalpha1 profoundly increased aortic calcium accrual in apolipoprotein E double-knockout mice, with concomitant upregulation of the osteochondrogenic differentiation program in VSM. Both processes were driven by the osteogenic transcription factor, Runx2. Importantly, deletion of AMPKalpha2 in the myeloid series had no impact on arterial calcification, nor did the removal of AMPKalpha2 in either cell lineage. Conversely, metformin, a first-line agent in the war on T2D that activates AMPK,¹⁶ significantly inhibited arterial calcification and downregulated arterial Runx2 expression, mediated via metformin-dependent enhancement of Runx2 turnover.¹⁷ In the osteoblasts of bone, Runx2 is prodigiously regulated at the level of ubiquitin E3 ligases Smurf1 and Smurf2, with ubiquitination directing Runx2 proteasomal degradation.¹⁸ This was not the case in VSM.¹⁹ Rather, the authors demonstrate that AMPK alpha1 enhances VSM Runx2 SUMOylation on lysine residue 181—a modification with a small ubiquitin-like modifier (SUMO)—that is dependent on the SUMO E3 ligase PIAS1. AMPKalpha1 was shown to activate PIAS1-dependent ligase function by phosphorylating PIAS1 on Ser-510. Moreover, a Ser-to-Ala mutation at this site completely abrogated metformin-dependent SUMOylation and destabilization of VSM Runx2, as did PIAS1 knockdown.¹⁴ This same signaling relay was required to inhibit induction of Runx2 by oxidized LDL, thereby linking modulation of fuel-sensing mechanisms to mitigation of inflammatory signals arising in the dysmetabolic state. Thus, the authors conclude that the prosclerotic VSM Runx2 program is held in check by AMPKalpha1-regulated mechanisms that control Runx2 stability in a cell-specific fashion and that pharmacological activation of AMPKalpha1 can mitigate atherosclerotic mineralization.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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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 to 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.

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