**NOVEL REGULATION OF VASCULAR CALCIFICATION**

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Vascular calcification is prevalent in patients with atherosclerosis, diabetes mellitus and end stage renal disease, which increases risk of cardiovascular events and mortality. We and others have shown increased vascular calcification in diabetic patients and animal models of diabetes. We have furthered demonstrated that increased vascular calcification was associated with elevated protein O-linked GlcNAc modification (O-GlcNAcylation) in human diabetic arteries, and in low-dose streptozotocin (STZ)-induced and Akita mutant diabetic mice. As protein O-GlcNAcylation is dynamically regulated by two enzymes, O-GlcNAc transferase (OGT) that adds O-GlcNAc onto proteins and O-GlcNAcase (OGA) that removes O-GlcNAc, we determined the effects of inhibition of OGA and OGT on vascular calcification in vascular smooth muscle cells (VSMC) in vitro and diabetic mice in vivo. Inhibition of OGA, either by a pharmacological inhibitor, Thiamet-G, or shRNA increased O-GlcNAcylation and promoted VSMC calcification. Consistently, administration of Thiamet-G to STZ-induced diabetic mice increased aortic O-GlcNAcylation and accelerated vascular calcification. In contrast, knockdown of OGT by shRNA inhibited VSMC calcification. Using a novel SMC-specific OGT deletion mice, we demonstrated that SMC-specific OGT deletion did not affect blood glucose, but significantly inhibited protein O-GlcNAcylation exclusively in SMC and inhibited vascular calcification in STZ-induced diabetic mice. At the molecular level, we found increased O-GlcNAcylation induced activation of AKT, an important upstream signal that upregulates the key osteogenic factor Runx2; which was significantly inhibited by OGT deletion. Mechanistic studies identified two new O-GlcNAcylation sites on AKT, at T430 and T479, were critical for AKT activation, Runx2 upregulation and VSMC calcification. In summary, we have demonstrated a crucial role for vascular O-GlcNAcylation in regulating diabetic vascular calcification, and identified a new mechanism of AKT O-GlcNAcylation in promoting Runx2 upregulation and VSMC calcification. Our studies have uncovered novel mechanisms linking glucose metabolism to vascular dysfunction and revealed therapeutic targets for diabetic vascular calcification.