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Vascular calcification in cardiovascular pathologies: Role of O-glcnac modification

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Vascular complications from uncontrolled hyperglycemia are the leading cause of death in patients with diabetes mellitus. Previous reports have shown a strong correlation between hyperglycemia and vascular calcification, which increases mortality and morbidity in individuals with diabetes. However, the precise underlying molecular mechanisms of hyperglycemia-induced vascular calcification remain largely unknown. Transdifferentiation of vascular smooth muscle cells (VSMC) into osteoblast-like cells is a known culprit underlying the development of vascular calcification in the diabetic vasculature. Pathological conditions such as high glucose levels and oxidative stress are linked to enhanced osteogenic differentiation of VSMC both in vivo and in vitro. It has been demonstrated that increased expression of runt-related transcription factor 2 (Runx2), a bone-related transcription factor, in VSMC is necessary and sufficient for the induction of VSMC calcification. Addition of a single O-linked β-N-acetylglucosamine (O-GlcNAc) moiety to the serine/threonine residues of target proteins (O-GlcNAcylation) has been observed in the arteries of diabetic patients, as well as in animal models in association with the enhanced expression of Runx2 and aggravated vascular calcification. O-GlcNAcylation is a dynamic and tightly regulated process, that is mediated by 2 enzymes, O-GlcNAc transferase and O-GlcNAcase. Glucose is metabolized into UDP-β-D-N-acetylglucosamine, an active sugar donor of O-GlcNAcylation via the hexosamine biosynthetic pathway. Overall increases in the O-GlcNAcylation of cellular proteins have been closely associated with cardiovascular complications of diabetes. In this review, the authors provide molecular insights into cardiovascular complications, including diabetic vasculopathy, that feature increased O-GlcNAcylation in people with diabetes.