Stents used to decrease cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) are prone to elevated restenosis. Mechanisms of restenosis in T2DM are incompletely elucidated; however, low wall shear stress (WSS) and altered intracellular signaling likely contribute. This work tests the hypothesis that neointimal hyperplasia (NH) after bare-metal stenting in T2DM is due to vascular remodeling (enhanced formation of advanced glycation end-products (AGEs), increased downstream vascular resistance (DVR), and decreased WSS) in T2DM; and that decreasing AGEs with ALT-711 (Alagebrum) mitigates this response.

Stents were implanted into the abdominal aorta of Zucker lean (ZL), obese (ZO), and diabetic (ZD) rats. After 21 days, blood flow and pressure data were recorded; and the stented region was sectioned for NH quantification, or casted and imaged for WSS distributions by computational fluid dynamics modeling. Arterial segments (thoracic and abdominal aorta, carotid, iliac, femoral and arterioles) were harvested to detect AGEs related collagen cross-linking, and protein expression including transforming growth factor beta (TGFβ) and receptor for AGE (RAGE).

DVR was elevated, whereas, WSS was significantly decreased in ZD compared to ZL and ZO rats, respectively (14.5 ± 1.9 vs 30.6 ± 1.6 and 25.4 ± 2.2 dyn/cm²; mean±SEM p<0.05). Intra-strut NH was increased in ZO but not ZD rats. ALT-711 reduced DVR in ZD rats (15.6 ± 2.5x10⁵ to 8.39 ± 0.6x10⁵ dyn·s/cm²), decreased NH (ZL: 7.7 ± 1.0 to 4.3 ± 0.9%; ZO: 12.0 ± 1.5 to 4.9 ± 0.8%; ZD: 9.4 ± 0.7 to 3.7 ± 0.4%) and restored WSS in ZD stented rats. Increases in AGEs related collagen cross-linking were present in the arterioles of ZD rats, but reduced by treatment with ALT-711. No differences in RAGE or TGFβ expression were observed in treated compared to untreated rats.

In conclusion, ALT-711 decreased AGEs related collagen cross-linking, DVR, and normalized intra-stent WSS in stented rats with T2DM. These findings suggest vascular remodeling may play an important role in modulating restenosis. Although TGFβ and RAGE expression did not appear to be modified by ALT-711, other intracellular signaling pathways remain to be explored.