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Dipeptidyl peptidase-4 inhibitor gemigliptin protects against vascular calcification in an experimental chronic kidney disease and vascular smooth muscle cells

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Objectives : Although dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of antidiabetic drugs, have various pleiotropic effects, it remains undetermined whether gemigliptin has a beneficial effect on vascular calcification (VC). Therefore, this study was performed to evaluate the effect of gemigliptin on VC in a rat model of adenine-induced chronic kidney disease (CKD) and in cultured vascular smooth muscle cells (VSMCs).

Methods : Calcification was induced by feeding with adenine for 4 weeks in Sprague-Dawley rats. The effect of gemigliptin was evaluated by von Kossa staining in the abdominal aorta. In cultured VSMCs, calcification by phosphate (3 mM) treatment was assessed by calcium content and alizarin red staining. The markers of cell phenotype and WNT pathway-associated molecules were assessed by qRT-PCR. ROS generation was evaluated by DCF-DA fluorescence and NADPH oxidase (p22 and NOX4 mRNA) expression. PI3K/AKT expression was assessed by western blot.

Results : Gemigliptin attenuated calcification of abdominal aorta and increased the expression of RUNX2 in adenine-induced CKD rats. In cultured VSMCs, phosphate-induced increase in calcium content was reduced by gemigliptin. Gemigliptin reduced phosphate-induced PIT-1 mRNA expression, reactive oxygen species (ROS) generation, and NADPH oxidase mRNA expression (p22 and NOX4). The reduction of oxidative stress by gemigliptin was associated with downregulation of phospho-PI3K/AKT expression. High phosphate increased the expression of FDZ3 and decreased the expression of DKK-1 in the Wnt pathway. These were attenuated by gemigliptin treatment. Gemigliptin restored the decreased expression of VSMCs markers (α -SMA and SM22 α) and increased expression of osteogenic makers (CBFA1, OSX, E11, and SOST) induced by phosphate.

Conclusions : Gemigliptin attenuated VC and osteogenic trans-differentiation in

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VSMCs via multiple steps with downregulation of PIT-1 expression, and suppression of ROS generation, phospho-PI3K/AKT, and the Wnt signaling pathway.

Keywords : chronic kidney disease, vascular calcification, vascular smooth muscle cells, dipeptidyl peptidase-4 inhibitors