Impact of glucose tolerance status on the relationship between vascular endothelial growth factor D and mortality in patients with suspected coronary artery disease: a subanalysis of the ANOX study

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Background: Vascular endothelial growth factor D (VEGF-D) is a secreted glycoprotein that can act as lymphangiogenic and angiogenic growth factors through binding to its specific receptors, VEGFR-3 and VEGFR-2. VEGF-D signaling via VEGFR-3 plays an important role in lipoprotein metabolisms which may contribute to coronary artery disease (CAD). We recently reported that serum levels of VEGF-D are independently associated with mortality in patients with suspected or known CAD. However, the impact of glucose tolerance status on the relationship between VEGF-D and mortality in patients with suspected CAD is unclear.

Methods: Serum VEGF-D levels were measured in 1,717 patients with suspected CAD undergoing elective coronary angiography, enrolled in the development of novel biomarkers related to angiogenesis or oxidative stress to predict CV events (ANOX) study, and followed up for 3 years. After excluding 67 patients with no HbA1c data, 1,650 patients were divided into 3 groups according to the glucose tolerance status: diabetes (DM, n=693), prediabetes (preDM, n=541) defined as an HbA1c of 5.7 to 6.4%, and normal glucose tolerance (NGT, n=416) defined as an HbA1c of 5.6% or less. The outcomes were total death, CV death, and major adverse CV events (MACE) defined as a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke.

Results: During the follow-up, 80 DM, 45 preDM, and 30 NGT patients died from any cause, 24 DM, 13 preDM, and 12 NGT died from CV disease, and 54 DM, 30 preDM, and 19 NGT developed MACE. After adjustment for established risk factors, VEGF-D levels were significantly associated with total death (hazard ratio [HR] for 1-SD increase, 1.28; 95% confidence interval [CI], 1.12–1.47), but not with CV death (HR, 1.20; 95% CI, 0.93–1.52) or MACE (HR, 1.23; 95% CI, 0.997–1.48) in DM; VEGF-D levels were not significantly associated with total death (HR, 0.97; 95% CI, 0.70–1.34), CV death (HR, 1.39; 95% CI, 0.92–2.11), or MACE (HR, 1.09; 95% CI, 0.74–1.50) in preDM; VEGF-D levels were not significantly associated with total death (HR, 1.34; 95% CI, 0.98–1.84), CV death (HR, 1.32; 95% CI, 0.78–2.13), or MACE (HR, 1.01; 95% CI, 0.66–1.46) in NGT. Even after incorporation of N-terminal pro-brain natriuretic peptide, contemporary sensitive cardiac troponin I, and high-sensitivity C-reactive protein into a model with established risk factors, the addition of VEGF-D levels further improved the prediction of total death (P=0.040 for continuous net reclassification improvement [NRI], P=0.007 for integrated discrimination improvement [IDI]), but not that of CV death or MACE in DM, while it did not significantly improved the prediction of total death, CV death, or MACE either in preDM or in NGT.

Conclusions: The VEGF-D level was independently associated with total death in DM, but not in preDM or in NGT. The relationship between VEGF-D and total mortality may depend on the presence of DM in patients with suspected CAD.