GLP-2 predicts cardiovascular outcomes in patients with myocardial infarction and increases atherosclerosis in mice

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Funding Acknowledgements: Type of funding sources: Foundation. Main funding source(s): EFSD, ERA-CVD

Background: GLP-1 and GLP-2 (glucagon-like peptide-1/2) are incretin hormones that are co-secreted from intestinal L-cells in response to food intake and inflammatory stimuli. While GLP-1 is known to induce postprandial insulin secretion and to improve cardiovascular outcomes in patients with diabetes, GLP-2 enhances intestinal nutrient absorption. GLP-2 agonists are clinically used for the treatment of patients with short bowel syndrome. The relevance of GLP-2 beyond the gut is not well understood. The aim of this study was to investigate the role of GLP-2 for cardiovascular disease (CVD).

Methods: Total GLP-2 levels were assessed at time of admission in 918 patients with myocardial infarction presenting with acute chest pain, among them 597 patients with NSTEMI and 321 with STEMI. The primary composite outcome of the study was the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke (3-P-MACE) with a median follow-up of 311 days. To induce atherosclerosis, Glp2r−/− or WT mice were injected with PCSK9 virus and fed a diet high in cholesterol (HCD) for 12 weeks.

Results: Kaplan-Meier survival plots (separated by the median of GLP-2 with a cut-off value of 4.4 pM) and univariable cox regression analyses found GLP-2 levels to be associated with adverse outcome (3-P-MACE and all-cause mortality; logarithmized GLP-2 values HR: 2.87; p<.0001). Further adjustment for age, sex, smoking, hypertension, hypercholesterinemia, previous CVD and diabetes mellitus did not affect this association (logarithmized GLP-2 values HR: 2.66; p=0.0055). Receiver operating characteristic curve (ROC) analyses illustrated that GLP-2 is a strong indicator for early events (area under the curve of the combined endpoint at 7 days: 0.74; 14 days: 0.76; 30 days: 0.76; 6 months: 0.72), which proved to be superior to Troponin T and hs-CRP. To assess the functional role of GLP-2 in CVD in an experimental approach we injected Glp2r−/− or WT mice PCSK9 virus (to induce functional Ldlr-deficiency and hypercholesterolemia) and fed these mice a HCD. After 12 weeks Glp2r−/− mice compared to WT littermates presented with a significant reduction in plaque volume and lesion size. While body weight and circulating leukocyte numbers (FACS analysis) were unaffected, Glp2r−/− mice had lower cholesterol levels.

Conclusion: Circulating GLP-2 levels are associated with cardiovascular events in patients with acute myocardial infarction while inactivation of the GLP-2 system reduces atherosclerosis in mice. Future studies are needed to investigate whether the GLP-2 receptor might provide a novel therapeutic target for cardiovascular disease.