



# Karolinska Institutet

From the Department of Clinical Science and Education, Karolinska Institutet,  
Södersjukhuset, Stockholm, Sweden

## STUDIES ON INCRETINS AND CARDIOVASCULAR FUNCTION

### AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid  
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# Abstract

## BACKGROUND

Type 2 diabetes (T2DM) is a strong risk factor for coronary heart disease (CHD). A great many diabetic subjects suffer from congestive heart failure (CHF), a condition with a high concomitant mortality. So far, attempts aimed at reducing macrovascular complications in T2DM have been essentially futile. Hence, there is a need for finding glucose-lowering agents that exert direct positive effects on vasculature and the heart. Glucagon-like peptide-1 (GLP-1) is a peptide secreted from the L-cells in the small intestine. GLP-1 decreases plasma glucose by increasing insulin secretion without an increased risk for hypoglycemia.

## AIMS

The aim of this work was to evaluate the putative role and potential effects of GLP-1 and related peptides on the vasculature and heart and to elucidate the mechanisms behind these effects.

## STUDY I AND II

These papers are based on studies performed within the ULSAM (Uppsala longitudinal study of adult men) cohort, a community-based prospective cohort study of elderly men started in 1970. The participants were examined at age 50 and 70 and the data was completed with annual updates on mortality and morbidity. The examination at age 70 forms the baseline of the present studies. A subsample from this cohort consisting of 509 men performed an oral glucose tolerance test (OGTT), plasma samples were stored frozen and GLP-1 concentrations were analyzed in 2007. At baseline, echocardiographic measurements of left ventricular function were done. Information concerning incident disease was collected from official Swedish registries. The studies did not reveal any longitudinal associations between plasma GLP-1 levels and the incidence of CHD or CHF. Cross-sectionally, however, we found correlative associations between plasma GLP-1 levels and impaired glucose tolerance and diastolic cardiac dysfunction.

## STUDY III

This was a double-blinded randomized cross-over study. Twenty patients with T2DM hospitalized for decompensated congestive heart failure (CHF) were enrolled in the study. Primary outcome was the proportion of subjects achieving a 20% increase of cardiac index (CI) and a 20% decrease of pulmonary capillary wedge pressure (PCWP), i.v. infusions with exenatide or placebo, 18 hours apart. Hemodynamic variables were monitored by heart catheterization. Exenatide evoked a 21% increase in CI, a 29% increase of heart rate, a 15% decrease of PCWP and a 17% decrease of right atrial pressure.

## STUDY IV

The aim of this study was to investigate whether exenatide could protect against endothelial dysfunction induced by lipotoxicity and if there were any differences in vasorelaxant capacity between GLP-1 (7-36), the degradation metabolite GLP-1 (9-36) and exenatide in femoral arterial rings from non-diabetic rats *ex vivo*. Exenatide did not protect against lipotoxicity, whereas GLP-1 (7-36) and GLP-1 (9-36) exerted vasorelaxation with 23% and 38%, respectively, vs. only 3% with exenatide.

## STUDY V

We studied the effects of exenatide, GLP-1 (7-36) and GLP-1 (9-36) on human coronary artery endothelial cell (HCAEC) proliferation and potential underlying mechanisms. Exenatide, GLP-1 (7-36) and GLP-1(9-36) elicited dose-dependent increases in DNA synthesis and increased cell numbers. This was associated with enhanced eNOS and Akt activity, which – along with the augmented cell proliferation - were inhibited by PKA-, PI3K-, Akt- and eNOS-inhibitors and by a GLP-1 receptor antagonist.

## CONCLUSIONS

Altered plasma GLP-1 levels were not found to predict incident CHD or CHF, while significant cross-sectional correlations were found between GLP-1 impaired glucose tolerance (IGT) and diastolic cardiac function in elderly men. GLP-1 and related peptides stimulate proliferation of HCAEC cells, exert vasorelaxant effects on rat arterial rings *ex vivo* and evoke potent hemodynamic effects in T2DM patients with CHF. These effects seem to occur independent of changes in glucose concentrations. These findings prompt further efforts and mechanistic studies aimed at characterizing potential beneficial cardiovascular effects of incretin hormones in the clinical management of T2DM patients.