# Studies on microcirculation on insulin resistance

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg.

Onsdagen den 16:e december 2015 kl. 13.00

av
Josefin Olausson

Fakultetsopponent: Professor John Pernow

Institutionen för medicin, Karolinska institutet, Stockholm

Avhandlingen baseras på följande delarbeten:

I. Bledar Daka*, Josefin Olausson*, Charlotte A Larsson, Margareta I Hellgren, Lennart Råstam, Per-Anders Jansson, Ulf Lindblad. Circulating concentrations of endothelin-1 predict coronary heart disease in women but not in men – a longitudinal observational study in the Vara-Skövde Cohort. *Accepted for publication in BMC Cardiovascular Disorders 2015.*

II. Josefin Olausson*, Bledar Daka*, Margareta I Hellgren, Charlotte A Larsson, Max Petzold, Ulf Lindblad, Per-Anders Jansson. Endothelin-1 as a predictor of impaired glucose tolerance and type 2 diabetes – A longitudinal study in the Vara-Skövde Cohort. *Submitted.*

III. Josefin Olausson, Reza Mobini, Per Fogelstrand, Karin Mossberg, Emanuel Fryk, Lena Strindberg, Lillemor Mattsson Hultén, Per-Anders Jansson. Delivery of insulin to subcutaneous adipose tissue and skeletal muscle in type 2 diabetes patients and healthy controls – A microdialysis study. *Manuscript*

IV. Lovisa Sjögren, Josefin Olausson, Lena Strindberg, Reza Mobini, Per Fogelstrand, Lillemor Mattsson Hultén, Per-Anders Jansson. Postprandial effects of the phosphodiesterase-5 inhibitor tadalafil in people with well-controlled type 2 diabetes mellitus: A randomised controlled trial. *Accepted for publication in Diabetic Medicine 2015.*

V. Josefin Olausson*, Lovisa Sjögren*, Reza Mobini, Emanuel Fryk, Per Fogelstrand, Lillemor Mattsson Hultén, Per-Anders Jansson. Tadalafil decreases expression of endothelin-1 in TNF-α-activated human endothelial cells – possible role of the c-Jun N-terminal Kinase pathway. *Manuscript.*

UNIVERSITY OF GOTHENBURG

Gothenburg 2015

# ABSTRACT

## Studies on microcirculation on insulin resistance

Josefin Olausson

Department of Molecular and Clinical Medicine, Institute of Medicine
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

The overall aim of this thesis was to investigate the microcirculation in insulin resistance, with focus on the expression of endothelin-1, through a translational approach.

**Specific aims:** 1) Investigate if circulating endothelin-1 levels predicts incident coronary heart disease events. 2) To assess if sex differences modify endothelin-1 as a predictor of type 2 diabetes. 3) To investigate if microvascular insulin resistance impairs insulin delivery to the subcutaneous adipose tissue and skeletal muscle. 4) To investigate if acute administration of the PDE-5 inhibitor tadalafil induces positive vascular, metabolic and anti-inflammatory effects in type 2 diabetes. 5) To further elucidate the molecular action of tadalafil in tumour necrosis factor-α (TNF-α) stimulated human endothelial cells.

**Principal findings:** The population-based cohort in Vara-Skövde was investigated for paper I-II. During baseline cardiovascular risk factors and endothelin-1 were assessed and incident coronary heart disease (CHD) was followed-up during a 10-year period *(paper I)*. Endothelin-1 levels had a predictive value for incident CHD in women, but not in men. A randomly selected subgroup was investigated in a follow-up after 10 years, and impaired glucose tolerance (IGT) and T2D was documented for *paper II*. Here, higher quartiles of endothelin-1 at baseline were associated with IGT/T2D at follow-up in women. *Paper III* investigates microvascular aspects of insulin resistance using microdialyis; participants with T2D and age-matched healthy controls were studied after an oral glucose load. Participants with T2D had decreased delivery of insulin to adipose tissue, and a blunted subcutaneous adipose tissue blood flow compared with controls. In *paper IV*, T2D participants received either placebo or tadalafil (20 mg) before a mixed meal in a randomized controlled trial. Tadalafil increased forearm blood flow, glucose uptake and capillary recruitment, and blunted a postprandial increase of endothelin-1. In *paper* V, the effects of tadalafil were studied in an experimental setting using TNF-α stimulated endothelial cells. Tadalafil treatment decreased expression of c-Jun N-terminal kinase (JNK) phosphorylation as well as reduced gene expression and secretion of endothelin-1.

**Conclusions:** This thesis shows that (i) endothelial dysfunction precedes IGT/T2D and CHD, and that endothelin-1 may pose as a risk factor for women, (ii) delivery of insulin from the circulation to subcutaneous adipose tissue is impaired in participants with T2D, and that participants with T2D exhibit a blunted postprandial blood flow response, (iii) acute administration of tadalafil induces positive vascular and metabolic effects in the postprandial state in T2D, and tadalafil decrease gene expression of endothelin-1 in cultured endothelial cells by decreasing activation of JNK.

**Keywords**: endothelinc 1, coronary heart disease, type 2 diabetes, phosphodiesterasec 5 inhibition, tadalafil, insulin resistance, endothelial dysfunction, c-Jun N-terminal kinase, nitric oxide, microdialysis.

**ISBN:** 978-91-628-9609-6 (Print), 978-91-628-9610-2 (PDF)