

Insulin resistance and cardiovascular function

- observational, translational and interventional studies

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska Akademin, Göteborgs Universitet
kommer att offentligen försvaras i Hjärtats Aula, Vita Stråket 12,
Sahlgrenska Universitetssjukhuset, Göteborg
Fredag den 17 juni kl. 09.00

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Avhandlingen baseras på följande delarbeten

- I. Westergren HU, Svedlund S, Momo RA, Blomster JI, Wählander K, Rehnström E, Greasley PJ, Fritsche-Danielson R, Oscarsson J, Gan LM.
Insulin resistance, endothelial function, angiogenic factors and clinical outcome in non-diabetic patients with chest pain without myocardial perfusion defects. Cardiovascular Diabetology 2016;15: 36.
- II. Westergren HU, Michaëlsson E, Blomster JI, Miliotis T, Svedlund S, Gan LM.
Determinants of coronary flow reserve in non-diabetic patients with chest pain without myocardial perfusion defects. Resubmitted to PLoS One 2016.
- III. Westergren HU, Grönros J, Heinonen SE, Miliotis T, Jennbacken K, Sabirsh A, Ericsson A, Jönsson-Rylander AC, Svedlund S, Gan LM.
Impaired Coronary and Renal Vascular Function in Spontaneously Type 2 Diabetic Leptin-Deficient Mice. PLoS One 2015;10(6): e0130648.
- IV. Westergren HU, Gan LM, Månsson M and Svedlund S.
Effects of a Personalized Supervised Lifestyle Intervention Program on Cardiovascular Status in Sedentary Healthy Volunteers. Submitted 2016.

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Abstract

Background: Microvascular disease is now recognized as an important driver for cardiovascular mortality and morbidity. Diabetic patients are known to suffer from this condition, leading to e.g. coronary ischemia as well as kidney dysfunction. Accumulating evidences indicate that the vascular pathological alterations may be a direct consequence of impaired glucose homeostasis and may occur long before diabetes is diagnosed. Early risk identification and a better understanding of associated mechanisms could be of great importance in disease management. Thus, the overall hypothesis of this thesis was that impaired glucose homeostasis already in the non-diabetic stage is associated with coronary and peripheral microvascular dysfunction and an unfavorable systemic risk profile, possibly facilitating progression of cardiovascular disease. For translational understanding, we hypothesized that obese insulin resistant leptin-deficient (ob/ob) mice could be a potential model for microvascular dysfunction and associated mechanisms. Finally, we hypothesized that short-term personalized lifestyle intervention may improve coronary microcirculation in healthy subjects.

Summary of results: My thesis shows that high insulin resistance assessed by the Homeostatic model assessment for insulin resistance (HOMA-IR) added independent prognostic value in patients with chest pain without myocardial perfusion defects. HOMA-IR was inversely associated with decreased peripheral vascular function, increased systemic pro-inflammatory state and decreased levels of pro-angiogenic vascular growth factors (Paper I). Also, impaired coronary flow reserve (CFR) predicted cardiovascular outcome in these patients and HOMA-IR was the strongest biochemical marker associated with decreased CFR. Interestingly, upon gender specific analysis, HOMA-IR seemed to be the strongest predictor of decreased CFR in men while systolic blood pressure was the strongest predictor in women (Paper II). Furthermore, impaired CFR and increased renal vascular resistance were observed in the ob/ob mice compared to lean controls. Possible mechanisms behind these observations were an impaired nitric oxide pathway as well as decreased renal vascular density (Paper III). Finally, CFR was improved with a personalized and supervised exercise and diet program in healthy volunteers (Paper IV).

Conclusions: This thesis suggests that insulin resistance measured by HOMA-IR confers independent prognostic information in non-diabetic patients with chest pain without myocardial perfusion defects. Furthermore, increased HOMA-IR is associated with poor cardiovascular status and there seems to be gender specific mechanisms associated with coronary microvascular dysfunction. In addition, the ob/ob mice may be a useful translational model for interventional studies to improve understanding of microvascular complications in impaired glucose homeostasis. Finally, three months of personalized life style intervention can enhance cardiovascular function in healthy subjects.

Keywords: Insulin resistance, microvascular function, peripheral vascular function, coronary flow reserve, prognosis, myocardial perfusion scintigram, animal model