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# Metabolic alterations and adipose tissue dysfunction in individuals with a family history of type 2 diabetes

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, 413 90 Göteborg, den 11 mars 2022, kl 09.00.

av Josefin Henninger

Fakultetsopponent:

Magnus Löndahl, docent

Lunds universitet, Lund, Sverige

**Avhandlingen baseras på följande delarbeten**

I Henninger AM, Eliasson B, Jenndahl LE, Hammarstedt A. Adipocyte hypertrophy, inflammation and fibrosis characterize subcutaneous adipose tissue of healthy, non-obese subjects predisposed to type 2 diabetes. *PLoS One. 2014 Aug 22;9(8):e105262*

II Henninger J, Hammarstedt A, Rawshani A, Eliasson B. Metabolic predictors of impaired glucose tolerance and type 2 diabetes in a predisposed population - A prospective cohort study. *BMC Endocr Disord. 2015 Sep 25;15:51*

III Henninger J, Rawshani A, Hammarstedt A, Eliasson B. Metabolic characteristics of individuals at a high risk of type 2 diabetes - a comparative cross-sectional study. *BMC Endocr Disord. 2017 Jul 14;17(1):40*

IV Rawshani A, Eliasson B, Rawshani A, Henninger J, Mardinoglu A, Carlsson Å, Sohlin M, Ljungberg M, Hammarstedt A, Rosengren A, Smith U. Adipose tissue morphology, imaging and metabolomics predicting cardiometabolic risk and family history of type 2 diabetes in non-obese men. *Scientific Reports 2020 Jun 19;10(1):9973*

V Henninger J, Eliasson B, Smith U, Rawshani A. Identification of markers that distinguish adipose tissue and glucose and insulin metabolism using a multi-modal machine learning approach. *Scientific Reports. 2021 Aug 23;11(1):17050*

**SAHLGRENSKA AKADEMIN**
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# Metabolic alterations and adipose tissue dysfunction in individuals with a family history of type 2 diabetes

**Josefin Henninger**

Avdelningen för molekylär och klinisk medicin, institutionen för medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige.

## Abstract

The overall aim was to further characterize anthropometric and metabolic data and adipose tissue distribution and dysfunction in individuals with known predisposition to type 2 diabetes (T2D), referred to as first degree relatives (FDR), and to bring further understanding of the underlying mechanisms behind this groups' increased risk of T2D.

We recruited 200 individuals with heredity for T2D, and 73 controls without heredity. The cohort of FDR was examined both longitudinally in paper II and cross-sectionally, compared to controls, in paper III. Subgroups of these cohorts were examined in paper I, IV and V. We collected anthropometric data, OGTT glucose and insulin concentrations, and subcutaneous adipose tissue biopsy data. The subjects also underwent an IVGTT to assess β-cell function, as well as a euglycemic clamp to assess insulin resistance. In study IV and IV we included radiological data of subcutaneous and ectopic adipose tissue distribution, as well as explored targeted and non-targeted serum metabolites. To account for the large amount of data in these last two studies we used machine learning methods to assess differences between groups.

In summary, we found that FDR displayed subcutaneous adipocyte dysfunction and inflammation compared to controls. When examined longitudinally, the FDR that later developed IGT and T2D displayed both markers of impaired insulin sensitivity and impaired insulin secretion, as well as adipose tissue dysfunction at baseline, preceding dysglycemia. Cross-sectionally examined, we found differences in several OGTT measurements between groups, indicating that OGTT can be an easy yet effective measure to assess glucose tolerance in high risk individuals. Finally, in study IV, we found that visceral fat accumulation and age predicted ectopic fat storage in heart and liver, and found metabolites associated with a family history of T2D. In study V, we presented metabolites predicting markers of glucose and insulin metabolism, as well as markers of adipose tissue morphology and distribution.

In this doctoral thesis we further characterized the development of T2D in individuals predisposed to the condition, with a focus on adipose tissue dysfunction and the usefulness of the OGTT. We finally explored novel metabolomic markers of T2D.

**Key words: Type 2 diabetes mellitus – OGTT – insulin resistance – β-cell function - ectopic fat – dysfunctional adipose tissue – metabolomics**

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