Göteborg, 2018

Addison's Disease and Type 1 Diabetes Mellitus

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula,
Sahlgrenska Universitetssjukhuset/Sahlgrenska,
fredag den 8:e juni 2018 kl 09.00

av **Dimitrios Chantzichristos**

Fakultetsopponent:
Professor Simon HS Pearce
Newcastle University, United Kingdom

Avhandlingen baseras på följande delarbeten

I. Chantzichristos D, Persson A, Eliasson B, Miftaraj M, Franzén S, Svensson A-M & Johannsson G
"Incidence, prevalence, and seasonal onset variation of Addison's disease among persons with type 1 diabetes mellitus: nationwide, matched, cohort studies"
Eur J Endocrinol 2018; 178: 115-122

II. Chantzichristos D, Persson A, Miftaraj M, Eliasson B, Svensson A-M & Johannsson G
"Early clinical indicators of Addison's disease in patients with type 1 diabetes mellitus: a nationwide, matched, observational, cohort study"
Manuscript

III. Chantzichristos D, Persson A, Eliasson B, Miftaraj M, Franzén S, Bergthorsdottir R, Gudbjörnsdottir S, Svensson A-M & Johannsson G
"Mortality in patients with diabetes mellitus and Addison's disease: a nationwide, matched, observational cohort study"
Eur J Endocrinol 2017; 176: 31-39

IV. Chantzichristos D*, Stevens A*, Svensson P-A, Glad C, Walker B, Bergthorsdottir R, Ragnarsson O, Trimpou P, Jansson P-A, Skrtic S, Johannsson G (* joint first authors).
"Identification of down-stream biomarkers of glucocorticoid action in man using subjects with adrenal insufficiency as experimental model"
Manuscript

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Addison's Disease and Type 1 Diabetes Mellitus

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Abstract

Background: Patients with type 1 diabetes (T1DM) and patients with Addison's disease (AD) need life-long replacement therapy with insulin and glucocorticoids (GCs), respectively. Both groups have reduced life-expectancy. Autoimmune polyendocrine syndrome combining T1DM and AD is rare and with very limited outcome data available. Patients with concurrent T1DM and AD comprise a treatment challenge due to the counter-balancing effects of insulin and GCs on glucose metabolism. In patients with diabetes, glycated haemoglobin is an excellent diagnostic and therapeutic biomarker. No such biomarker of GC action is available for patients with AD.
Aims: To study the epidemiology of patients with concurrent T1DM and AD. More specifically, to investigate the incidence and mortality in patients with T1DM and AD, and elucidate early indicators for AD development in this population. To discover putative biomarkers of GC action.

Methods: Population-based, real-world data were derived from six linked Swedish National Registries, including the National Diabetes Register. Depending on the research question, cases were matched to five control subjects: we determined AD incidence (T1DM *vs* general population), and early indicators and mortality (T1DM+AD *vs* T1DM). The main statistical methods used were: Cox regression analysis, analysis of covariance, estimated group proportions, and Kaplan-Meier survival curves. The biomarker study was a randomised, crossover study in patients with AD, where patients were studied during states of near-physiological GC exposure and GC withdrawal. Gene expression from peripheral blood mononuclear cells and circulating microRNAs and metabolites were integrated into a network analysis.

Results: The incidence of AD among patients with T1DM was 193 (95% CI: 152–245) per million patient-years. The risk of developing AD among patients with T1DM was 10.8 (95% CI: 7.1–16.5) times higher than in the general population. Prodromal signs for the development of AD in patients with T1DM were treatment for thyroid disease, infections requiring hospital admission, multiple diabetic complications (retinopathy in particular), and rescue therapy for hypoglycaemia. Patients with concurrent T1DM and AD had 4.3 (95% CI: 2.6–7.0) times increased risk for death than patients with T1DM alone and died most frequently from diabetic complications. The biomarker study succeeded in generating two completely different states of GC exposure. Integration of gene expression data, miRNA and metabolomic data delivered a network model with modules of putative biomarkers of GC action.

Conclusions: The higher risk of AD among patients with T1DM and the higher mortality in patients with concurrent T1DM and AD indicate the need of an improved strategy for patient management. Finally, the experimental study identified novel, potential biomarkers of GC action for further validation.

Keywords: Addison's disease, type 1 diabetes mellitus, glucocorticoids, incidence, early indicators, drug prescription, mortality, biomarkers.

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