Prognosis of LADA-latent autoimmune diabetes in adults and type 2 diabetes; influence of genes, lifestyle and treatment

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Background
LADA (Latent autoimmune diabetes in adults) is the most common form of autoimmune diabetes with adult onset\(^1\) and may account for 5\% of all diabetes\(^2\). Described as a hybrid form of diabetes, it is characterized by anti-bodies against the pancreatic B-cells, adult onset, slower B-cell destruction than type 1 diabetes (T1D), and type 2 diabetes (T2D)-associated features like insulin resistance\(^3\). Cross-sectional studies indicate that LADA patients have lower prevalence of the metabolic syndrome than patients with T2D but worse glycemic control\(^4\). A contributing factor may be lack of exogenous insulin production resulting in more variation in glucose levels. Also, there is no established treatment strategy for LADA, possibly contributing to high HbA1c levels\(^5-6\). Matters of uncertainty include beneficial effects of early insulin initiation, and whether it is optimal to combine insulin treatment with insulin sensitizers like metformin. Prospective studies on complications in LADA are few. Our findings based on the Norwegian HUNT study confirm that patients with LADA have a more favorable metabolic risk profile than subjects with T2D. In spite of this, mortality in LADA was as high as in T2D\(^7\), as was the risk of myocardial infarction, and associations were strongest in women, similar to T2D\(^8\). No clear differences were seen for insulin treatment, but there was a strong link to high HbA1c levels\(^7-8\). Despite being the largest prospective study on macrovascular complications to date, HUNT only includes ~200 LADA cases and the largest study on microvascular complications included 173 cases\(^9\). High risk HLA genotypes has been linked to complications in T1D\(^10\), and these genotypes are frequent in LADA\(^11\) but has never been explored in relation to complications. Clearly, additional studies with larger numbers are warranted to clarify the long term consequences of LADA and factors contribution to poor prognosis.

Objective
The overall aim is to study mortality and morbidity in LADA and to assess the prognostic role of glycemic control, treatment, b-cell function, metabolic risk factors and lifestyle. We will use data from ESTRID (Epidemiological Study of Risk factors for LADA and T2D), the world’s largest study of LADA including detailed clinical, lifestyle and genetic information. In this cohort we will follow patients with LADA or T2D and controls from diagnosis/index date and study:

1. How HbA1c and metabolic risk profile develops after diagnosis in LADA/T2D.
2. The risk of CVD (stroke, MI and heart failure) and mortality (all-cause and CVD).
3. The risk of microvascular disease (renal impairment, retinopathy).
4. The influence of sex, metabolic syndrome, glucose control, HLA genotype, beta-cell function, treatment, sociodemographic and lifestyle factors on these associations.
Methodology

**Study population:** ESTRID is an ongoing case-control study\textsuperscript{12} that enrolls patients in Skåne and Uppsala (ki.se/imm/estrid), through the ANDIS (andis.ludc.med.lu.se) and ANDiU (www.andiu.se) studies. Since 2010 we have recruited 510 incident LADA cases, 1712 T2D cases (4 per LADA cases) and 2083 randomly selected controls, matched by time and region (incidence density sampling). **Prognostic factors:** *Lifestyle factors:* At baseline, all subjects answer an extensive questionnaire on health, psychosocial, sociodemographic and lifestyle factors including tobacco, alcohol, physical activity, family history and diet. **Clinical and genetic data:** At inclusion, information on Hba1C, blood lipids, treatment, height and weight is obtained together with blood samples analysed for >150 genetic variants. Patients are classified according to diabetes type based on age, GADA (glutamic acid decarboxylase antibodies) and C-peptide. Insulin resistance and β-cell function are assessed by HOMA\textsuperscript{13}. During follow-up, information on treatment and Hba1C is available by linkage to the national prescription and diabetes registries.

**Follow-up:** Patients with LADA or T2D and controls will be linked to the national health registries (inpatient, outpatient, cause-of death, prescription), and followed from diabetes onset/inclusion date. We will analyze incidence of hospitalizations, CVD (myocardial infarction, stroke), mortality and microvascular disease (renal impairment and/or severe retinopathy). Between 2010 and 2017 we can expect 370 cases of myocardial infarction (50 in LADA), 200 cases of stroke (30 in LADA) and 500 deaths (60 in LADA), based on national incidence figures, the number of individuals included to date and baseline age (mean 59 yrs). Preliminary data indicate that already at baseline, Hba1C is higher in LADA than in T2D patients (74.8 vs. 60.7 mmol/mol), insulin treatment (42 vs. 6%) and HLA DR4-DQ8 (54 vs. 26%) is more frequent and BMI is lower (28.0 vs. 31.1 kg/m\textsuperscript{2}). Ethical approval has been obtained for ESTRID and for part of the linkage to hospital and prescription registries, additional approval will be sought.

**Work plan**

This multidisciplinary project is built on expertise in epidemiology, biostatistics, cardiology (Bruna Gigante) and registry-based research at IMM, combined with expertise in endocrinology and molecular biology found through collaboration within the EXODIAB (Excellence of Diabetes Research in Sweden) network at Lund (Leif Groop) and Uppsala University (Per-Ola Carlsson) and the University of Helsinki (Tiinamaija Tuomi). The work will be carried out at the Unit of Epidemiology at IMM, which was ranked “excellent” in the latest KI evaluation. The post doc will work closely together with the supervisor (S Carlsson), and five other colleagues in the diabetes epidemiology group, including a senior biostatistician. The work involves applying for ethical approval, handling registry linkages, analyzing data, writing papers and presenting the findings at international conferences including the annual meetings of ADA and EASD.

**References**

2. All New Diabetics In Scania - ANDIS. http://andis.ludc.med.lu.se/.


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