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Original article

Coffee consumption, genetic susceptibility and risk of latent autoimmune diabetes in adults: A population-based case-control study

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ABSTRACT

Aim. – Coffee consumption is inversely related to risk of type 2 diabetes (T2D). In contrast, an increased risk of latent autoimmune diabetes in adults (LADA) has been reported in heavy coffee consumers, primarily in a subgroup with stronger autoimmune characteristics. Our study aimed to investigate whether coffee consumption interacts with HLA genotypes in relation to risk of LADA.
Methods. – This population-based study comprised incident cases of LADA (n = 484) and T2D (n = 1609), and also 885 healthy controls. Information on coffee consumption was collected by food frequency questionnaire. Odds ratios (ORs) with 95% CIs of diabetes were calculated and adjusted for age, gender, BMI, education level, smoking and alcohol intake. Potential interactions between coffee consumption and high-risk HLA genotypes were calculated by attributable proportion (AP) due to interaction.
Results. – Coffee intake was positively associated with LADA in carriers of high-risk HLA genotypes (OR: 1.14 per cup/day, 95% CI: 1.02–1.28), whereas no association was observed in non-carriers (OR: 1.04, 95% CI: 0.93–1.17). Subjects with both heavy coffee consumption ($\geq$ 4 cups/day) and high-risk HLA genotypes had an OR of 5.74 (95% CI: 3.34–9.88) with an estimated AP of 0.36 (95% CI: 0.01–0.71; P = 0.04370).
Conclusion. – Our findings suggest that coffee consumption interacts with HLA to promote LADA.

Introduction

Observational studies have consistently shown that coffee consumption is associated with a reduced risk of type 2 diabetes (T2D) [1]. The potentially protective effect has been attributed to improvement of insulin sensitivity and glucose metabolism [2–4], and reduced oxidative stress [5]. In contrast, an increased risk of latent autoimmune diabetes in adults (LADA) was recently observed in heavy consumers of coffee [6], although the excess risk was only apparent for LADA patients with high levels of glutamic acid decarboxylase antibodies (GADA). Indeed, a positive association between coffee intake and levels of GADA has been observed [6].

Such a finding suggests that coffee either triggers or promotes islet autoimmunity. This fits with findings in adolescents with type 1 diabetes (T1D), and is also consistent with data on per capita coffee consumption across different countries and incidence of T1D [7,8]. However, those studies were hampered by small numbers [8] and crude data [7]. Nevertheless, the impact of coffee intake on the immune system and autoimmune diseases has been receiving

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increasing attention [9], and high intakes have been linked to an increased risk of rheumatoid arthritis [10] as well as a reduced risk of multiple sclerosis [11].

Human leucocyte antigen (HLA) haplotypes are strongly linked to the development of autoimmune diabetes [12,13]. Autoimmune diabetes-related HLA haplotypes are found in about 90% of children with T1D [14], in 70% of patients with adult-onset autoimmune diabetes [15] and in 37–53% of the general Caucasian population [16,17]. However, as not all genetically susceptible individuals develop autoimmune diabetes, environmental factors are likely to be important in the initiation and/or progression of disease [18]. Yet, whether coffee intake interacts with HLA genotypes has not been previously explored. Thus, the aim of the present study was to investigate the risk of LADA in relation to coffee intake, using newly collected data from the same population as in our previous study [6], but with almost twice as many cases and including information on HLA genotypes associated with autoimmunity [12–15].

Subjects and methods

Study population and design

The study was based on the Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes (ESTRID), a Swedish population-based case-control study. Details of ESTRID have been described elsewhere [6]. In short, ESTRID is a substudy of the All New Diabetics in Scania (ANDIS) study (http://andis.ludc.med.lu.se/) [19], an extensive study aimed at characterizing all new cases of diabetes in southern Sweden. Since 2010, all newly diagnosed patients with LADA have been invited to enrol in ESTRID. In 2012, recruitment was expanded to All New Diabetics in Uppsala (ANDIU; www.andiu.se/), a sister study to ANDIS in the county of Uppsala (in the middle of Sweden). For each identified LADA patient, four incident cases of T2D were randomly selected from ANDIS/ANDIU and matched by date of participation.

Of the enrolled patients, 95% came from Scania and 5% from Uppsala, for whom questionnaire and clinical and genetic information was collected. Also, controls without diabetes ($\geq$ 35 years of age, n = 1909) were randomly selected from the national population register, which supplied questionnaire information, although no blood samples were taken. For purposes of the present study, data from population-based, randomly selected, controls recruited from a sister study of rheumatoid arthritis, the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) [20], were included. EIRA was carried out in the middle and southern parts of Sweden according to a similar methodology as in ESTRID, but with genetic information available.

The analytical sample for the present study comprised all patients [LADA: n = 484 (465 from ANDIS, 19 from ANDIU); T2D: n = 1609 (1519 from ANDIS, 90 from ANDIU)] included in ESTRID from 2010 up to July 2017, with complete information on coffee consumption and potential confounders, together with all controls from EIRA, recruited from 2005 to 2009, with complete information on coffee consumption, confounders and HLA genotypes (n = 885). Of the cases, 48% were from our previous paper, which was based on cases collected during 2010–2013 [6]. Ethics approvals for both ESTRID and EIRA were obtained from the relevant ethics committees in Stockholm, and all participants gave their informed consent.

Coffee consumption and covariates

At the time of recruitment, patients (ESTRID) and controls (ESTRID and EIRA) answered an extensive questionnaire that was identical as regards many items, including physical activity, education and smoking, as well as a validated [21] food frequency questionnaire (FFQ). Participants were asked to report their average daily or weekly intake of coffee (brewed coffee, boiled coffee and espresso, each type separately) over the past year. Diabetes patients received the questionnaire soon after their diagnosis and were specifically instructed to report their average intakes for the year prior to diagnosis. While there was no question regarding decaffeinated coffee, in Sweden, brewed coffee is the most common type [22], accounting for 91% of the total coffee intake in our study population, and consumption of decaffeinated coffee is highly unusual [22].

Total daily coffee intake was calculated as the sum of coffee consumption in number of cups (150 mL) per day. Also, the nutrient intake of each food item in the FFQ was estimated by multiplying frequency of consumption by nutrient content as per the Swedish National Food Agency Database [23], taking into account age-specific portion sizes [24]. Total energy intakes (kcal/day) were also calculated. Body mass index (BMI) was self-reported, and calculated as weight (in kg) divided by the square of height (in m). Average alcohol intakes were categorized as none, 0.1–4.9, 5–14.9 or $\geq$ 15 g/day. Subjects were categorized into current, former and never smokers. Highest achieved level of education was categorized into three levels: low (primary school); medium (upper secondary school); and high (university). Physical activity was assessed by validated questions [25] about average leisure-time physical activity during the preceding year with four response options, ranging from sedentary to very active.

Definition of diabetes subtypes

At the time of diagnosis, blood samples were drawn from all patients, and analyzed for GADA by enzyme-linked immunosorbent assay (Elisa) [26] and for C-peptide by the IMMULITE 2000 immunoassay system (Siemens Healthcare GmbH, Erlangen, Germany) or by cobas 6000 e601 immunology analyzer (Roche Diagnostics, Basel, Switzerland) [27]. In ANDIS and ANDIU, patients aged $\geq$ 35 years at diabetes onset were classified as either LADA if they were GADA-positive ($\geq$ 10 IU/mL) with C-peptide $\geq$ 0.2 nmol/L (IMMULITE)/or $\geq$ 0.3 nmol/L (cobas), or as T2D if they were GADA-negative ($<$ 10 IU/mL) with C-peptide $>$ 0.6 nmol/L (IMMULITE)/or $>$ 0.72 nmol/L (cobas). C-peptide criteria in the definition of T2D excludes those with relative insulin deficiency according to the definitions used in ANDIS/ANDIU [28]. At a GADA cut-off of 10.7 IU/mL, sensitivity was 84% and specificity was 98% [26]. LADA patients were also stratified according to median GADA levels ($<$ 233 and $\geq$ 233 IU/mL) into $LADA_{low}$ and $LADA_{high}$, respectively. Homoeostasis model assessment to approximate insulin resistance (HOMA-IR) and to estimate β-cell function (HOMA-β) were calculated based on fasting plasma glucose and C-peptide [29].

Genetic analysis

At the Lund University Diabetes Centre, DNA was extracted from blood samples taken of all study patients and analyzed for $>$ 300 different gene variants, using iPLEX Gold genotyping technology (Sequenom, San Diego, CA, USA). Controls from EIRA were genotyped for single-nucleotide polymorphisms (SNPs) using the Infinium Illumina 300K immunochip custom array (Illumina, San Diego, CA, USA) [30]. The focus was on carriers of high-risk HLA class-II *DR/DQ* genotypes, known to be associated with autoimmune diabetes [12]. Three SNPs in the major histocompatibility complex (MHC) region (rs3104413, rs2854275, rs9273363), shown to predict high-risk HLA *DR/DQ* genotypes relevant to autoimmune diabetes with an overall accuracy of 99.3% [31], were available in both ESTRID and EIRA. Combinations of these three SNPs were used

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