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Islet autoimmunity status in Asians with young-onset diabetes (12–40 years): Association with clinical characteristics, beta cell function and cardio-metabolic risk factors

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ABSTRACT

In this paper, the islet autoimmunity status and relation to clinical characteristics, beta cell function and cardio-metabolic risk factors in young-onset Asian diabetic patients are evaluated at baseline. The study population consisted of 912 patients (from China, India, Malaysia and Singapore) with age 12–40 years and diabetes duration <12 months. Autoantibodies to glutamic acid decarboxylase (GADA) and tyrosine phosphatase (IA-2A), beta cell function and cardio-metabolic risk parameters were assessed. Among our young patient cohort, 105 (11.5%) patients were GADA and/or IA-2A positives (Ab +ve). Ab +ve patients were younger, leaner, had more severe hyperglycaemia and lower beta cell function. The frequency of metabolic syndrome was significantly lower in Ab +ve patients (27%) compared to Ab −ve patients (54%). However, a substantial proportion of patients in both groups of patients had atherogenic dyslipidaemia, hypertension and albuminuria (micro or macro). In our study cohort, only one in 10 Asian youth with new-onset diabetes had evidence of islet autoimmunity. At least 60% of Ab +ve and 50% of Ab −ve patients demonstrated classical features of type 1 and type 2 diabetes respectively. Regardless of autoimmunity status, the cardio-metabolic risk factors, in particular atherogenic dyslipidaemia, hypertension and albuminuria were common in our patients with young-onset diabetes.

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[1] A list of other persons in ASDIAB Study Group and their affiliated institutions appears in the Appendix.

Abbreviations: Ab +ve, autoantibody-positive; Ab −ve, autoantibody-negative; GADA, autoantibodies against glutamic acid decarboxylase; IA-2A, autoantibodies against tyrosine phosphatase.

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1. Introduction

Type 1 diabetes in Asian populations is less common than in European populations [1,2]. In contrast, the prevalence of type 2 diabetes in developing countries in Asia is amongst the highest worldwide [3]. Another disturbing observation is the increasing trend of type 2 diabetes occurring in Asian children and adolescents, associated with increasing prevalence of obesity and a strong family history of type 2 diabetes [4–7]. Otani et al. [8] first reported the presence of young-onset type 2 diabetes patients among Japanese in 1990. Young-onset type 2 diabetes has since been reported to be present among other Asian youths in China, India, Korea, Malaysia and Singapore [7,9].

Categorizing patients with young-onset diabetes into different types of diabetes may often be more difficult than those with adult-onset diabetes [10,11]. Clinical phenotypes at onset frequently overlap [12–14] and age at diagnosis poorly differentiates between types. In addition, there are also differences in clinical, biochemical and immunological variables between Asian and Caucasian diabetic patients. For instance, in Europe and America, majority of children and adolescents with type 2 diabetes are obese while in the Indian subcontinent, children with type 2 diabetes patients are generally non-obese [7,12,15,16] Similarly, young-onset Japanese type 2 diabetes patients were on average not obese compared to the Western population [15–18]. In addition, the reported frequencies of islet-cell cytoplasm (ICA) or glutamic acid decarboxylase (GADA) positivity are higher in Caucasians compared to Asians [16,19–21].

There is a scarcity of data on young Asian patients with newly diagnosed diabetes from Chinese, Indian and Malay ethnic background. These are the three major ethnic groups within Asia, with documented high prevalence rates and are expected to contribute significantly to the predicted rise in the number of persons with diabetes in Asia [3]. Given the ethnic differences and heterogeneity in diabetes patients, data from previous studies may not be applied directly. Thus, the Asian Young Diabetes (ASDIAB) study was conducted to obtain detailed baseline as well as 5-year follow-up data on the clinical, immunological, metabolic characteristics and natural history of young patients with newly diagnosed diabetes from the three major ethnic groups within Asia. This paper aims to present the islet autoimmunity status and its relation to clinical characteristics, beta cell function and cardio-metabolic risk factors in our young-onset Asian diabetic patient cohort at baseline.

2. Materials and methods

Details of the ASDIAB study population, methodology and baseline characteristics have been previously published [22].

2.1. Patients

The study recruited 925 eligible young-onset diabetic patients of Chinese, Indian or Malay ethnicity aged 12–40 years within 12 months of the onset of disease. Autoantibodies data were available in 912 of these patients for analyses. Six centres from China (Beijing, Shanghai and Hong Kong), India (Chennai), Malaysia and Singapore were selected. These centres are involved mainly in hospital-based secondary care of diabetic patients in the respective cities. Patients were recruited from the pool of recently diagnosed patients with diabetes who either presented to these centres as hospital admissions or were referred from other clinics within their catchment area. All patients presented during the recruitment period, regardless of their mode of presentation and treatment, were recruited consecutively. Compliance of patients was monitored by a research nurse in the participating centre and patient retention was by means of education and maintenance of doctor–patient and nurse–patient relationships. Patients were recalled by phone, letter or home visit in one of the centres (Chennai) in case of defaulted follow-up. All patients gave written and signed informed consent and the protocol was approved by ethics committee in each centre. Those receiving oral hypoglycaemic agents prior to enrolment were given a wash-out period of 4 weeks in order to obtain baseline data. However, in cases where the fasting blood glucose exceeded 15 mmol/L after 1 week of stopping the oral agents, their oral treatment was reinstituted and they were then enrolled into the study at that point. This was not applicable to insulin-treated patients as they continued with their treatment. Exclusion criteria included: (1) participation in any interventional drug trial, (2) drug-induced diabetes, (3) gestational diabetes mellitus, (4) conditions which make it unlikely that the patients can be followed for the subsequent 5 years.

2.2. Laboratory and clinical examinations

Autoantibodies to GADA and tyrosine phosphatase (IA-2A) were assessed by a central laboratory (International Diabetes Institute, Caulfield, Victoria, Australia). The 65-kDa isoform of GADA was measured by a liquid-phase radioimmunoprecipitation assay developed by Chen et al. [23] and Law et al. [24], with interassay coefficient of variations (CVs) of 6.9% for low positive control serum and 6.1% for high positive control serum. IA-2A was determined by a commercial kit (RSR Ltd., Cardiff, UK) with sensitivity and specificity of 57% and 99% respectively [25].

Fasting and glucagon-stimulated plasma C-peptide (GSC-peptide) concentrations were measured by radioimmunoassay (human C-peptide Linco RIA kit, cat #HCP-20K) with an intra-assay CV ranging from 3.4–6.4% for five duplicate determinations of five different samples. In this study, a fasting C-peptide concentration of $\leq$0.3 nM or GSC-peptide taken 6 min after intravenous one mg glucagon of $\leq$0.6 nM, was considered low and inferred as indicating poor beta cell functional reserve. Blood samples were also taken for measurement of biochemical parameters including fasting plasma glucose (FPG), lipids, HbA_{1c} and insulin. Insulin concentrations were measured using Linco radioimmunoassay (RIA) kits (human insulin specific RIA kit, cat #HI-14K). Insulin resistance was calculated as a fasting plasma insulin (mU/L) and glucose (mmol/L) product divided by 22.5. This is numerically the same as that derived from the homeostasis model assessment (HOMA) equation: insulin resistance = fasting serum insulin/[22.5 $e^{-\ln(\text{fasting plasma glucose})}$] [26].