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Original Article

Etiopathological differentiation of diabetes mellitus in lean, young adults

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ABSTRACT

Objective: Classification of diabetes mellitus (DM) into type 1 or type 2 is difficult in lean, young individuals. We studied the β-cell function, insulin resistance (IR) and autoimmunity in young patients with recent onset DM.

Methods: In this cross-sectional study, we included patients (age below 35 years) with recent onset DM (<6 months) and normal body weight for evaluation. The detailed clinical examination was done to identify markers of IR. Autoimmune DM was diagnosed using glutamic acid decarboxylase 65 (GAD_{65}), insulin autoantibody (IAA) and islet cell antibody (ICA). Homeostasis model assessment (HOMA) models of HOMA-B and HOMA- IR were used for estimation of β-cell function and IR respectively. The patients were divided into four groups based on, the autoimmunity (A) and ketosis (K) as group 1 (A+K), group 2 (A−K+), group 3 (A+K−) and group 4 (A−K−). Appropriate statistical tests +)were used to analyze the results.

Results: The study population (n = 75, all males) had a mean age of 28.9 ± 4.3 years, body mass index 20.6 ± 1.9 kg/m^2, fasting plasma glucose 177.1 ± 31.4 mg/dl and HbA1c of 9.9 ± 2.1% at presentation. The number of patients in groups 1 to 4 are 8, 5, 10 and 52 respectively ($p < 0.0001$). HOMA-IR was higher in groups 2 and 4 (4.1 ± 1.3, 3.6 ± 1.1 respectively), whereas HOMA-B was higher in group 4 (3.6 ± 1.5) alone ($p = 0.0005$).

Conclusion: Type 2 DM is the most common etiology even in young, lean adults in India. Further studies with large numbers are required to confirm our findings.

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to either absolute or relative deficiency of insulin. The disease is classified by the American Diabetes Association (ADA) into type 1 (T1DM), type 2 (T2DM), secondary DM and gestational DM [1]. Autoimmunity and insulin resistance (IR) are the key determinants of T1DM and T2DM respectively. The distinction of various types is often not clear in patients at initial presentation. Regional specific variants like protein deficient DM in India and ketosis prone DM in Africa also blur the boundaries of this classification [2,3]. The rising prevalence of the childhood obesity increased the burden of T2DM in young individuals [4]. Another spectrum is the absence of autoimmunity despite a typical presentation with osmotic symptoms and ketosis. These individuals are classified as type 1 B DM and the simplicity of the ADA system ignores this heterogeneity of DM [5]. The β-cell dysfunction at onset of DM consists of a reversible and an irreversible component [6]. The long term outcomes of DM and lifelong insulin requirement are dependent on the β-cell function at the onset.

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune β-cell destruction characterized by onset around 30 years of age, circulating islet antibodies and initial lack of insulin requirement [7]. The profile of autoimmune markers differs between LADA and T1DM. Islet cell antibodies (ICA) and glutamate acid decarboxylase-65 (GAD_{65}) antibodies are typically seen in LADA, whereas tyrosine phosphatase–like insulinoma antigen 2 antibody (IA-2A) and insulin autoantibody (IAA) are uncommon [8]. Patients with LADA have preserved β-cell function at the onset, but experience rapid decline of β-cell function within 3 years of diagnosis. Few studies have reported about the β-cell dysfunction and IR at the onset of DM from our country [9,10]. However, they have studied a limited population,

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restricted to T2DM and lack proper assessment for the IR. Hence, we studied the β-cell function, IR and autoimmunity in lean, young patients with DM at onset to profile the underlying etiology.

2. Materials & methods

2.1. Study population

We conducted this cross-sectional, observational study in a tertiary care hospital of the armed forces. We included 75 male patients with recently diagnosed DM (age below 35 years, duration <6 months, normal weight) in this study. We excluded patients with secondary DM, known cardiac (ischemic heart disease, heart failure, angina, significant arrhythmias), renal (creatinine more than 1.5 mg/dL, acute kidney injury, an estimated glomerular filtration rate less than 60 ml/min) and gastrointestinal (acute or chronic liver disease, ascites, bariatric surgery) disorders from the study. We also excluded patients using drugs (glucocorticoids, androgens, cyclosporine and immunosuppressive drugs) that affect the IR and β-cell function. The local ethics committee approved the study protocol and all patients provided written informed consent. The patients were divided into four groups based on the presence of autoimmunity (A) and ketosis (K) into group 1 (A+K+), group 2 (A−K+), group 3 (A+K−) and group 4 (A−K−). All the patients were explained about healthy lifestyle measures and dietary advice to control the DM. The patients received appropriate management for the DM that includes the oral and injectable agents.

2.2. Study measures

Clinical data were collected from the participants, including demographic details like age, presenting complaints (osmotic features, amount of weight loss), family history of DM, dietary (special reference to the daily calorie intake) and drug history. Weight was recorded on a digital weighing scale using OMRON HN 286 (Omron Corporation, Kyoto, Japan with a sensitivity of 100 g), height by using a SWWS05 stadiometer (Multicare Company, Delhi, India with a sensitivity of 0.1 cm) and body mass index (BMI) was calculated as weight in kilograms divided height in meters squared. A comprehensive evaluation was done for all the microvascular and macrovascular complications of the diabetes at the baseline visit as per the ADA guidelines [1]. Waist and hip circumferences (to the nearest 0.5 cm) were measured to calculate the waist-to hip ratio (WHR).

2.3. Study interventions

Fasting venous blood samples were collected after an overnight fast for more than 12 h and analyzed for hematological and biochemical parameters. They include glucose, glycosylated hemoglobin (HbA1c), lipid profile (TC – Total Cholesterol, TG – Triglycerides, HDL – High Density Lipoprotein Cholesterol, LDL – Low Density Lipoprotein Cholesterol), hormonal profile (Insulin, C-peptide) and autoimmune markers (GAD_{65}, ICA, IAA). The morning urine sample was collected for the microalbuminuria estimation. Blood samples for insulin and C- peptide estimation were taken in insulin naive patients or after converting patients to short acting insulin regime for 24 h. Plasma glucose was estimated by a glucose-oxidase method, HbA1c by high-performance liquid chromatography and lipids by enzymatic spectrophotometric techniques. Plasma LDL cholesterol was calculated using the Friedewald equation except when the triglycerides exceed 400 mg/dL. Plasma insulin and C-peptide were measured by radioimmunoassay with an intra and inter-assay variation of less than 9% respectively. A quantitative assay for urine micoalbumin was done using the automatic DCA 2000 analyzer. Autoantibody assays (GAD_{65}, IAA, ICA) were performed using the Enzyme immunoassay method.

2.4. Study definitions

Homeostasis model assessment (HOMA) models were used for the estimation of β-cell function (HOMA-B) and IR (HOMA-IR) as per the standard formula [11]. The autoimmune diabetes was diagnosed with the positive values for any of the three antibodies (GAD_{65}, ICA, IAA) evaluated. We checked for the ICA and IAA in 50 patients only and GAD_{65} antibody was checked in all the 75 patients.

2.5. Statistical analysis

Data are presented as mean, standard deviation (SD) and descriptive statistics were used for the data analysis. ANOVA test was used to compare the data between the groups. A two-tailed p value of less than 0.05 was considered significant for all the tests and the statistical analysis was done using the Graph Pad Prism Software, Version 6 (Graph Pad Software, San Deigo, CA, USA).

3. Results

The study population (n = 75, all males) had a mean age of 28.9 ± 4.3 years, BMI 20.6 ± 1.9 kg/m^2, fasting plasma glucose 177.1 ± 31.4 mg/dl and HbA1c of 9.9 ± 2.1% at presentation. The number of patients in groups 1 to 4 includes 8, 5, 10 and 52 respectively as shown in Fig. 1 ($p < 0.0001$). A total of 20 (26.7%) patients presented with diabetic ketoacidosis and 42 (56%) patients had osmotic symptoms at onset. Other findings at presentation include the seizures (due to cortical venous thrombosis) and non-healing ulcer. Microvascular complications were detected in 5 patients that include background retinopathy [2], microalbuminuria [1] and sensory neuropathy [2]. The mean WHR was 0.85 ± 0.06 (range: 0.83–0.93), LDL 92.4 ± 18.2 (46–218) mg/dl, HDL 42.2 ± 7.3 mg/dl [13–22] and triglycerides were 119.4 ± 41.1 (range: 42–204) mg/dl.

GAD_{65} antibodies were tested positive in 18 patients, IAA in 11 (out of 50) patients and ICA in 8 (out of 50) patients. Eleven patients tested positive for all three antibodies, five for the two and the remaining two patients had a single antibody positive result. Autoimmune diabetes was diagnosed in 18 (24%) patients based on the presence of ketosis and antibodies. The remaining 57 (76%) could be having other forms of diabetes. The comparison between the clinical and biochemical parameters between the groups is shown in Table 1. HOMA-IR was higher in groups 2 and 4 (4.1 ± 1.3, 3.6 ± 1.1 respectively), whereas HOMA-B was higher in group 4

n=75		Autoimmunity	
		Present	Absent
Ketosis	Present	Group 1 N=8	Group 2 N=5
	Absent	Group 3 N=10	Group 4 N=52

Fig. 1. Patient profile and their groups.

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