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Relationship of betatrophin with youth onset type 2 diabetes among Asian Indians

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ABSTRACT

Background and Aims: Betatrophin is emerging as a marker for compensatory beta cell proliferation. While betatrophin has been mainly investigated in adults, there is a lack of data on betatrophin levels in youth-onset type 2 diabetes mellitus (T2DM-Y). The aim of this study was to determine levels of betatrophin and its association with T2DM-Y in Asian Indian participants.

Methods: We recruited 100 individuals with normal glucose tolerance (NGT; $n = 50$) and newly-diagnosed cases (within 18 months of first diagnosis) of T2DM-Y ($n = 50$) with onset between 12 and 24 years of age from a large tertiary diabetes center in Chennai in southern India. Insulin resistance was measured by homeostatic model (HOMA-IR) and insulin secretion by oral disposition index (DIO). Betatrophin levels were measured by enzyme-linked immunosorbent assay.

Results: Betatrophin levels were significantly lower in the T2DM-Y group compared with the NGT group (803 vs 1104 pg/ml, $p < 0.001$). Betatrophin showed a significant inverse correlation with waist circumference ($p = 0.035$), HOMA-IR ($p < 0.001$), fasting and 2 h postprandial glucose ($p < 0.01$), glycated hemoglobin ($p = 0.019$) and a positive correlation with fasting C-peptide ($p < 0.001$) and DIO ($p = 0.012$). In regression analysis, betatrophin was independently associated with T2DM-Y even after adjustment for age, gender, and waist circumference (OR per standard deviation: 0.562, 95% CI: 0.342–0.899, $p = 0.019$). However, the association was lost when HOMA-IR was included in the model (OR: 1.141, 95% CI: 0.574–2.249; $p = 0.646$).

Conclusion: Betatrophin levels are lower in T2DM-Y and this association is likely mediated through insulin resistance.

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Abbreviations: T2DM-Y, youth-onset type 2 diabetes mellitus; NGT, normal glucose tolerance; DIO, oral disposition index; GAD, glutamic acid decarboxylase; WHO, World Health Organization.

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1. Introduction

Type 2 diabetes (T2DM) is a complex metabolic disorder characterized by insulin resistance and progressive pancreatic beta cell failure [1]. T2DM often remains undiagnosed for many years, and exposure to hyperglycemia over time could lead to the development of chronic micro- and macro-vascular complications [2]. There is evidence to show that insulin resistance causes compensatory expansion of pancreatic beta cell mass due to circulating growth factors [3–5]. Studies have also demonstrated that systemic hepatocyte-derived growth factors promote beta cell proliferation in mouse and human islets, supporting a liver-to-pancreas axis in the adaptive beta cell growth response to insulin resistance [6,7].

Yi et al. [5] recently identified a novel hormone, betatrophin, primarily expressed in the liver and adipose tissue that induces a 17-fold increase in the rate of pancreatic beta cell proliferation. Hepatic over-expression of betatrophin, in pharmacological and genetic mouse models of insulin resistance, causes an increase in the rate of beta cell proliferation, islet size, and insulin content with benefits on glucose homeostasis [5]. Betatrophin has emerged as a signaling molecule favoring a compensatory beta cell growth in response to insulin resistance [5,8]. Studies have reported that betatrophin levels are correlated significantly with an atherogenic lipid profile in high-risk cohorts with morbid obesity or T2DM [9,10]. It is also believed to play a role in dysfunctional lipid metabolism involving the regulation of hepatic very low-density lipoprotein secretion as well as in altered lipoprotein lipase activity [11,12].

Betatrophin has been mainly investigated in older adults [5], and there are no studies on youth-onset T2DM (T2DM-Y). Studies on patients with T2DM-Y may be especially informative, as they may be less affected by various comorbid factors. Moreover, decline in beta cell function may be more rapid compared with individuals with later-onset T2DM [13,14]. Asian Indians, in particular, are known to be more insulin resistant [15] and have high rates of type 2 diabetes at younger ages [16] but there is a lack of data on betatrophin levels in Asian Indians. The aim of this study was to determine betatrophin levels and its association with T2DM-Y among Asian Indians.

1.1. Research design and methods

Recruitment of study participants: Fifty individuals with newly-diagnosed T2DM with onset between 12 and 24 years of age (within 18 months of first diagnosis) and individuals with normal glucose tolerance (NGT; $n = 50$) were recruited from a large tertiary diabetes center at Chennai in southern India.

Institutional Ethics Committee approval was obtained prior to the start of the study. Written informed consent was obtained from the individuals aged 18 years and above, and ''assent'' from the study participants along with written informed parental consent was obtained for those under 18 years of age. Participants completed interviewer-administered questionnaires, were examined for anthropometric and clinical measurements, and provided bio-specimens.

1.2. Anthropometric measurements

Anthropometric measurements including weight, height, and waist circumference were obtained by trained data collectors using standardized methods [17]. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressure was recorded from the right arm in a sitting position to the nearest 2 mmHg using a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 min apart and the mean of the two was taken as the blood pressure.

1.3. Biochemical tests

Fasting plasma glucose (hexokinase method), serum cholesterol (cholesterol oxidase–peroxidase-aminopyrine method), serum triglycerides (glycerol phosphate oxidase–peroxidase-aminopyrine method) and high density lipoprotein (HDL) cholesterol (direct method-polyethylene glycol-pretreated enzymes), were measured using Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany). Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Glycated hemoglobin (HbA1c) was measured by high pressure liquid chromatography using a Variant machine (BioRad, Hercules, California, USA). Serum insulin concentration was estimated using the electrochemiluminescence method (COBAS E 411; Roche Diagnostics). The intra- and inter-assay coefficients of variation for the biochemical assays ranged between 3.1 and 7.6%. All measurements were performed in a laboratory certified by the College of American Pathologists (Northfield, IL) and the National Accreditation Board for Testing and Calibration of Laboratories (New Delhi, India).

1.4. Betatrophin measurements

Betatrophin was measured by competitive inhibition enzyme linked immunosorbent assay (Wuhan Eiaab Science, Wuhan, China) according to the manufacturer's protocol. The values were expressed in pg/ml units. The intra- and inter-assay coefficients of variation were $<5\%$ and $<10\%$, respectively.

1.5. Definitions

Diabetes was defined as fasting plasma glucose $\geq$126 mg/dl (7.0 mmol/l) and/or 2 h postprandial glucose level $\geq$200 mg/dl (11.1 mmol/l), or a past medical history (self-reported diabetes under treatment by a physician), or drug treatment for diabetes (insulin or oral hypoglycemic agents) [18]. T2DM-Y was classified based on the following criteria: onset before 25 years of age, recruitment within 18 months of diagnosis, adequate response to oral hypoglycemic agents and negative for glutamic acid decarboxylase (GAD), IA-2 and zinc transporter antibodies, absence of ketosis, good beta cell reserve as shown by C-peptide assay (fasting: $\geq$0.6 pmol/ml and stimulated: $\geq$1.6 pmol/ml), and absence of pancreatic calculi on abdominal X-ray [18,19]. NGT was defined as fasting plasma glucose $<$5.6 mmol/L ($<$100 mg/dl) and 2 h postprandial glucose value $<$7.8 mmol/L ($<$140 mg/dL) [18].

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