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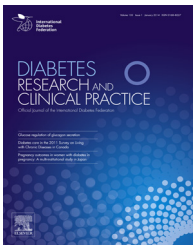

Insulin sensitivity and secretion in youth onset type 2 diabetes with and without visceral adiposity

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ABSTRACT

Aim: To investigate insulin sensitivity and insulin secretion patterns among Asian Indian youth without and with type 2 diabetes (T2DM-y defined as onset of diabetes at or below 25years) with normal and high visceral fat (VF) levels.

Methods: We recruited 74 T2DM-y individuals, within 18 months of diagnosis and compared them to 77 age-matched controls with normal glucose tolerance (NGT). Using L4/L5 abdominal CT images, VF levels were categorized as normal or high according to their median values. Oral glucose tolerance tests (glucose and insulin measures) were used to derive Matsuda index, insulin resistance (HOMA-IR) and oral disposition index (DIo). Relationships between measures of insulin sensitivity and secretion and T2DM-y by VF level were assessed using standardized multinomial regression models.

Results: Participants were categorized into four groups: NGT-normal VF; NGT-high VF; T2DM-normal VF, and T2DM-high VF. Among NGTs, those with high VF had significantly lower insulin sensitivity (0.013 vs.0.019 pM^{-1}) and Matsuda index (10.2 vs.13.8), than normal VF. When compared, T2DM-high VF had lowest insulin sensitivity (0.009 vs.0.019, 0.013, 0.012 pM-1; $p < 0.001$), Matsuda index (6.4 vs. 13.8, 10.2, 8.6; $p < 0.001$), $OGIS_{120}$ (305 vs. 396, 382, 316; $p < 0.001$) and DIo (0.48 vs. 3.75, 3.20, 0.55 mmol/L; $p < 0.001$). At every category of 2 h PG values, NGT-high VF had lower DIo than NGT-normal VF participants. In standardized multinomial models, that included DIo and Matsuda index adjusted for age, gender, BMI, and leptin, DIo (Odds ratio: 0.001; 95%Confidence interval: 0.000–0.020), matsuda index (0.26; 0.07–0.93), age (2.92; 1.18–7.19) and leptin (3.17; 1.12–8.99) were associated with high VF among T2DM.

Conclusion: Lower DIo and Matsuda index, younger age and higher leptin were independently associated with high visceral fat among T2DM participants. Also, lower DIo was seen with increasing 2 h PG values even among normal glucose tolerant individuals.

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Abbreviations: T2DM-y, type 2 diabetes in youth; VF, visceral fat; NGT, normal glucose tolerance; DIo, oral disposition index; HOMA-IR, homeostasis model assessment-Insulin resistance; Matsuda index, whole body insulin sensitivity index; $OGIS_{120}$, oral glucose insulin sensitivity.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is emerging as a serious health problem in children, adolescents and young adults [1,2]. The pathophysiology of T2DM has been explored extensively in adults, particularly with respect to the relative contributions of insulin resistance and β-cell dysfunction [3,4]. Some groups suggest that insulin resistance is the primary abnormality and that β-cell dysfunction is a late event that consequent to the prolonged, increased secretory demand placed on the β-cell by insulin resistance [5,6]. Others believe that reduced β-cell function, manifesting as decreased insulin release, is an early event and a prerequisite for the progression from NGT to hyperglycemia [3].

Adiposity appears to be an important factor predisposing to insulin resistance, which in the presence of β-cell dysfunction, results in glucose intolerance [7,8]. However there is little information about this important subject in non-obese populations like Asian Indians, particularly among youth. In this study, we compare insulin secretion and sensitivity in young Asian Indians with and without T2DM-y categorized by the level of visceral adiposity.

2. Methods

2.1. Study population

Newly diagnosed cases (within 18 months of first diagnosis) of T2DM-y with onset between ages 10 and 25 years were recruited from a tertiary diabetes centre in Chennai, India or from community screening efforts for diabetes in the young [9]. From the latter, age-matched participants with normal glucose tolerance (NGT) were also recruited.

Diabetes diagnosis was based on WHO consulting group criteria, i.e. fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) and/or 2 h plasma glucose ≥11.1 mmol/L (200 mg/dL) or if the participant was being treated for diabetes by a physician [10].

T2DM-y ($n = 74$) was defined based on absence of ketosis, good beta cell reserve as shown by C-peptide levels ≥0.6 pmol/mL, absence of pancreatic calculi on abdominal X-ray and adequate response to oral hypoglycaemic agents [11,12]. Age-matched participants ($n = 77$) who had a fasting plasma glucose <5.6 mmol/L (100 mg/dL) and 2-hour plasma glucose <7.8 mmol/L (140 mg/dL) [10] were defined as having NGT.

The study received approval from the Institutional Ethics Committee (IEC) prior to recruiting participants. Informed consent was obtained according to the local IEC guidelines from one of the parents in the case of children below 18 years of age along with the child's assent, while for those 18 years and above, the consent was obtained from the participants themselves.

2.2. Data collection—Measurements

Anthropometric measurements including height, weight, and waist circumference, were obtained using standardized techniques. Height was measured in centimetres using a stadiometer. Participants were requested to stand upright without shoes with their back against the wall, heels together, and eyes directed forward. Weight was measured with an electronic weighing balance that was kept on a firm horizontal surface. Participants were asked to wear light clothing and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated using the formula: weight (kg)/(height in m)^2.

Waist circumference was measured using a non-stretchable measuring tape. The participants were asked to stand erect in a relaxed position with both feet together on a flat surface; one layer of clothing was accepted. Waist girth was measured as the smallest horizontal girth between the costal margins and the iliac crests at minimal respiration. Blood pressure (BP) was recorded in the sitting position in the right arm with a mercury sphygmomanometer and rounded off to the nearest 2 mmHg. Two readings were taken 5 min apart and their mean was taken as the blood pressure. Physical examination included looking for presence of acanthosis nigricans and skin tags.

2.3. Data collection—Biochemical tests

All the participants recruited for the study underwent an oral glucose tolerance test (OGTT) using 1.75 g of glucose/kg body weight (maximum load of 75 g). Blood samples were drawn in the morning after a minimum of 8 to 10 h of overnight fasting and at 30, 60, 90, & 120 min after the glucose load.

Fasting plasma glucose (hexokinase method) was measured in a laboratory certified by the College of American Pathologists (CAP), USA and the National Accreditation Board for Testing and Calibration of Laboratories (NABL), India, on a Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany). Serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method), serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and HDL cholesterol (direct method-polyethylene glycol-pre-treated enzymes) were measured using a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula [13]. Glycated haemoglobin (HbA1c) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, CA., USA). The intra- and inter-assay co-efficient of variation for the biochemical assays ranged between 3.1% and 7.6%. Leptin was measured using the sandwich enzyme-linked immunosorbent assay (ELISA) by R&D systems (R&D systems, USA). The intra- and inter-assay co-efficient of variation of the ELISA were <5 and <10%, respectively.

2.4. Data collection—Imaging

Computerized tomography (CT) scan which is one of the gold standards for the quantitative assessment of intra-abdominal adipose tissue and direct method of assessing visceral fat deposition in both adult and paediatric populations [14]. CT was performed at a specialized centre for imaging and radiological studies. The observer and the radiologist who interpreted the scans were unaware of the clinical status of the study participants. Subcutaneous and visceral fat were