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Original Article

Effect of parental history of diabetes on markers of inflammation, insulin resistance and atherosclerosis in first degree relatives of patients with type 2 diabetes mellitus

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ABSTRACT

Aim and objective: To study the effect of parental history of diabetes on markers of inflammation, insulin resistance, adiposity indices and carotid intima media thickness (cIMT) in first degree relatives of patients with type 2 diabetes mellitus (T2DM).
Materials and methods: Normal glucose tolerant (NGT) first degree relatives of T2DM patients of age group 20–40 years designated as $FH^{positive}$ were enrolled in the cross sectional study. Depending on the parental history of diabetes they were divided into three groups: family history positive in father (FH^{father}), family history positive in mother (FH^{mother}) and family history positive in both (FH^{both}). Age, sex and BMI matched controls without any history of diabetes in their parents designated as $FH^{negative}$ were taken for comparison. All subjects underwent detailed clinical evaluation and biochemical investigations. cIMT and adiposity indices like visceral adipose tissue thickness (VAT) and subcutaneous adipose tissue thickness (SAT) were assessed using ultrasonography.
Results: No difference existed with regards to BMI, hsCRP, degree of insulin resistance, adiposity markers and cIMT between FH^{mother} and FH^{father} group. Subjects in FH^{both} group had significantly higher degree of insulin resistance, subclinical inflammation, increased atherosclerosis and adiposity indices in contrast to those who have a single parent T2DM family history.
Conclusions: hsCRP and cIMT are significantly higher in the first degree relatives of type2 diabetes mellitus patients than controls. Individuals with history of T2DM in both parents have significantly worse glycemic status, increased cIMT and adverse cardiovascular risk profile than those with T2DM history in only single parent.

1. Introduction

Type 2 diabetes mellitus (T2DM) has a strong genetic component. According to Joslin Study the cumulative risks of T2DM in siblings with no diabetic parent, one diabetic parent and two diabetic parents were 14.0%, 29.2%, and 41.9% respectively [1]. Insulin resistance is fundamental to the pathogenesis of the metabolic syndrome and T2DM and is a heritable trait [2]. Consequently; first-degree relatives of subjects with T2DM demonstrate the metabolic accompaniments of insulin resistance before they develop overt diabetes. Non-diabetic first degree relatives of T2DM have increased obesity, insulin resistance (IR) and increased prevalence of cardiovascular risk associated with metabolic syndrome [3].

Inflammation and inflammatory cytokines have been postulated to be important additional pathogenetic factors in the development of insulin resistance and T2DM.Whether inflammation causes insulin resistance, or an epiphenomenon of obesity itself, remains unresolved [4]. C-reactive protein (CRP), a nonspecific marker of the inflammatory response, is most consistently associated with the development of T2DM [5]; however a causal association remains unproven. In addition to genetic factors, excess body fat, particularly visceral fat, has been linked to the pathogenesis of insulin resistance and T2DM [6]. Excess lipid supply, via skeletal muscle triglyceride (or other lipid moieties such as diacylglycerols), is responsible for insulin

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resistance. Ultrasound is a non-invasive, inexpensive and validated method for measuring abdominal fat compartments and has a good correlation with that of CT scan [7,8].

Family history of diabetes appears to increase the risk of coronary heart disease (CHD), even in nondiabetic subjects [9]. Differences in anthropometric, metabolic, cardiovascular, and hemostatic parameters may explain this phenomenon. Intima-media thickness is a well-known marker of subclinical atherosclerosis and it also can indicate future cardiovascular diseases like stroke and myocardial infarction [10]. It is a noninvasive, feasible, reliable and inexpensive method for detecting development of subclinical atherosclerosis. It has been reported that children of T2DM parents have comparatively higher insulin resistance, inflammatory markers, visceral obesity and intima media thickness than the children of nondiabetic parents [3,[9],11]. However there are few studies comparing the effect of either paternal, maternal or both paternal & maternal history of diabetes on these parameters in their first degree relatives. To the best of our knowledge only one previous study has been published which specifically addressed the above question in Indian population [12]. However they did not look at impact of positive family history in both parents versus positive family history in only single parent on various parameters. Hence this study was planned to see the effect of parental history of T2DM in their first degree relatives on various anthropometric and metabolic parameters.

2. Material and methods

Normal glucose tolerant (NGT) young adults, aged 20–40 years hence designated as $FH^{positive}$ were included. Depending on the parental history of diabetes they were divided into three groups: family history positive in father (FH^{father}), family history positive in mother (FH^{mother}) and family history positive in both parents (FH^{both}). Age, sex and BMI matched subjects having neither parents nor relatives up to third generation (i.e., grandparents, sons, daughters, uncles, aunts and cousins) with T2DM were taken as controls (designated as $FH^{negative}$). The exclusion criteria was smoking, having history of known cardiovascular, cerebrovascular or peripheral vascular disease, history of known hyperlipidemia, hypertension or thyroid disorder, chronic hepatic, renal, or any other serious chronic medical illness, history of intake of any kind of medications known to affect carbohydrate or lipid metabolism, presence of any acute infection, history of connective tissue disorders, women with PCOS, pregnant and lactating women.

Healthy offspring, aged 20–40 years, of patients with T2DM attending the outpatient department of Endocrinology, S.C.B Medical College, Cuttack were recruited between January 2016 to June 2016. All subjects were asked about frequency of doing exercise vigorously enough to work up a sweat. We considered participants reporting vigorous exercise at least once weekly to be active [13]. Only normoglycemic healthy adults were included in the study.

Height and weight were measured with subjects in light clothes and without shoes, using a standard apparatus. Waist circumference was measured midway between the lower rib margin and the iliac crest at the end of a gentle expiration. Hip circumference was measured around the widest portion of the buttocks. Each measurement was repeated twice; if the measurements were within 1 cm of one another, the average was calculated. Body mass index (BMI) was calculated as the weight in kg divided by the height in m^2 .Blood pressure was measured after resting for at least 5 min in supine position using a mercury sphygmomanometer with an appropriate cuff size.

After an overnight fast and a 24 h period of abstinence from alcohol and vigorous physical exercise, a standard 75 g oral glucose tolerance test (OGTT) with fasting plasma glucose (FPG), 2 h post glucose plama glucose (PGPG) and HbA1C testing were performed in each subject. NGT was defined according to the recommendation of the ADA Guideline, 2015 [14]. Baseline complete blood count, serum creatinine and liver function tests were performed to rule out any chronic medical illness. Overnight fasting blood samples were drawn for estimation of lipid parameters like serum total cholesterol (T-Chol), triglyceride (TG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), fasting insulin and high sensitive C-reactive protein (hsCRP). Plasma glucose was measured by glucose oxidase-peroxidase method. Serum total cholesterol (T-Chol) was measured by cholesterol esterase oxidase peroxidase method and triglyceride (TG) by colormetric enzymatic method. High density lipoprotein (HDL) was estimated by direct enzymatic method. Low density lipoprotein (LDL) was calculated by using Friedewald formula [15]. HbA1C was measured by high pressure liquid chromatography (HPLC) method. Serum insulin was measured by chemiluminescent microparticle immunoassay (CMIA) method (Abbott Architect Plus i 2000 SR) with inter-assay and intra-assay coefficient of variability of 5.38% and 2.46% respectively. Serum hsCRP was measured by nephelometry method (Siemens nephlometer BN II) with inter-assay and intra-assay coefficient of variability of 1.15% and 1.36% respectively. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated as [FPG (mg/dl) X fasting insulin (mU/L)]/405 [16].

cIMT was measured by high resolution–B mode ultrasound having electrical linear transducer (5–9 MHz). Measurement was done from the far wall of the distal common carotid arteries (immediately proximal to the carotid bulb) in supine position with head turned slightly to contra- lateral side and was reported as the mean value for the bilateral measurements. On the same sitting subcutaneous tissue thickness (SAT) was measured as the vertical distance from the skin to the linea alba with a 9L transducer (2.5–8.0 MHz) in the transverse position and visceral adipose tissue thickness (VAT) as the vertical distance from the peritoneum to the front edge of the vertebra with a 5C transducer (1.5–4.5 MHz) placed longitudinally [17]. Both SAT and VAT was assessed twice and was calculated as the average of the two measurements. The images were recorded and scanned by a single person who was blinded for the group.

2.1. Statistical analysis

The results were presented in number, mean and standard deviation. Normality distribution was checked using Shapiro-Wilk test. Comparison between two groups was done by Student's t or Mann Whitney *U* test for parametric and non parametric data respectively. For more than two groups comparison, Kruskal Wallis test with multiple comparison was used. For categorical comparisons, Chi-square test was used. Pearson's and Spearman's correlation coefficient were used for correlation analysis for parametric and non parametric data respectively. A $p < 0.05$ was considered statistically significant. The data were analysed using the SPSS 21 statistical software (IBM Corp., Armonk, NY, USA).

3. Results

A total of 64 cases were included in $FH^{positive}$ group. Among them 21 subjects belonged to FH^{father} group, 29 subjects to FH^{mother} group and 14 subjects to FH^{both} group respectively. A total of 42 age and sex matched individuals were recruited as control group ($FH^{negative}$).The mean age of $FH^{positive}$ group was 28.31 ± 4.91 years versus 28 ± 4.23 years in $FH^{negative}$ group ($p = 0.538$). We observed that subjects in $FH^{positive}$ group had significantly elevated mean total cholesterol and LDL in comparison to $FH^{negative}$ group ($p < 0.01$ for both). No significant difference was observed with

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