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Original Article

Contribution of maternal diabetes to visceral fat accumulation in offspring

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ABSTRACT

Background/objectives: Genetic and epidemiological studies provide evidence supporting the contribution of a genetic background of diabetes to the development of obesity and further suggest differences in the metabolic and cardiovascular risks between offspring with a paternal versus maternal family history of diabetes (FHD). The goal of this study was to explore the contribution of a parental FHD to visceral fat area (VFA).

Subjects/methods: This study enrolled 1875 subjects with normal glucose tolerance (age range: 20–78 years). VFA was assessed with magnetic resonance imaging.

Results: The study population consisted of 1573 subjects without a FHD, 115 subjects with a paternal FHD, and 187 subjects with a maternal FHD. For both genders, VFA was greater in offspring with a maternal FHD compared with those without a FHD (both $P < 0.05$). For both genders, only VFA was an independent factor associated with a maternal FHD (both $P < 0.01$). Compared with those without a FHD, men and women with a maternal FHD, but not those with a paternal FHD, were more likely to develop abdominal obesity (both $P < 0.05$). After adjustment for independent factors related to VFA, VFA was increased by 9.60 cm^2 (standardized $\beta = 0.069$, $P = 0.012$) and 4.57 cm^2 (standardized $\beta = 0.056$, $P = 0.007$) in men and women with a maternal FHD, respectively.

Conclusion: A maternal FHD contributed to visceral fat accumulation independently in both genders. Maternal transmission had a pronounced effect on obesity and related cardiovascular risk factors.

Introduction

As one of the most important non-communicable diseases, diabetes threatens human health worldwide [1]. Both genetic and environmental factors contribute to the accelerated increase in the prevalence of diabetes [2]. As the number of patients with diabetes increases, the population of first-degree relatives of patients with diabetes is also increasing. Given that this population shares a common genetic background with diabetes patients, this population provides a simple method to explore genetic and environmental influences simultaneously. Therefore, studies in first-degree relatives of patients with diabetes are valuable for the prevention of diabetes and related metabolic diseases.

Diabetes and obesity share numerous overlapping risk factors and genetic architecture. Genome-wide association and sequencing studies established 88 loci for type 2 diabetes, and 10 of these loci provide further evidence of the overlap between obesity and lipid levels [3]. Additionally, dominant expression of rare susceptibility variants with large effects on adiposity was identified in greater than half of first-degree relatives of diabetes patients [4]. Epidemiological studies also provide evidence supporting the contribution of a genetic background of diabetes to the development of obesity [5,6]. Further investigations revealed that first-degree relatives of patients with diabetes suffer negative consequences primarily originating from increased visceral fat [7]. A prospective study found that a family history of diabetes (FHD) is a predictive factor for an altered distribution of abdominal fat [8].

Recent clinical findings suggest differences in metabolic and cardiovascular risks between offspring with paternal versus maternal FHD [6,9]. Visceral fat accumulation, a hallmark of adipose tissue dysfunction, is responsible for the negative metabolic and

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cardiovascular effects of obesity [10]. Therefore, investigating the relationship between parental FHD and visceral fat is important to explain the transmission of metabolic and cardiovascular risks based on the genetic background of diabetes. Magnetic resonance imaging (MRI) is able to distinguish between subcutaneous and visceral adipose tissue and is recommended as an accurate measurement of visceral fat by the International Diabetes Federation "platinum standard" definition [11]. However, no study to date has investigated the contribution of paternal versus maternal FHD to abdominal obesity in offspring as represented by a precise index. Using a precise index, namely, the visceral fat area (VFA) detected by MRI, the present study explored the contribution of parental FHD to visceral fat accumulation in a Chinese population with normal glucose tolerance. The data emphasize the importance of the mode of parental transmission when the influence of inheritance on visceral fat accumulation in participants with FHD and normal glucose tolerance is analysed.

Subjects and methods

Subjects

The study population was a subgroup of the Shanghai Obesity Study cohort [12]. Complete clinical data were available for all of the participants. Individuals with normal glucose tolerance were enrolled, and those with impaired glucose regulation or diabetes based on the 1999 World Health Organization criteria were excluded [13]. To minimize the influence of overall obesity on VFA, participants were restricted to those with a body mass index (BMI) < 30 kg/m^2 [14]. Participants with both a maternal and paternal FHD were excluded. Additionally, the final sample size was 1875 after exclusion of individuals with liver or renal dysfunction, hyperthyroidism or hypothyroidism, acute infection, psychiatric disorders, cancer, cardiovascular disease, current use of antihypertensive drugs or hypolipidemic agents, and current replacement therapy with systemic corticosteroids.

The present study was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Every subject provided written informed consent prior to participation.

Anthropometric and biochemical assessments

Anthropometric variables, including body weight, height, waist circumference (W), and resting blood pressure (BP) were measured as previously described [12]. BMI was calculated as weight (kg)/height^2 (m^2). Laboratory measurements of levels of fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), glycated haemoglobin A1c (HbA1c), fasting serum insulin (FINS), total cholesterol(TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and C-reactive protein (CRP) were performed according to standard methods [12]. The insulin resistance index (homeostasis model assessment-insulin resistance [HOMA-IR]) [15] was calculated as FINS (mU/L) × FPG (mmol/L)/22.5.

Measurements of body fat content and distribution

Total body fat mass (FM) and free fat mass (FFM) were assessed using an automatic bioelectrical impedance analyser (TBF-420B; Tanita Corp., Tokyo, Japan). Abdominal fat distribution (VFA and subcutaneous fat area [SFA]) was detected with a clinical MRI scanner (Archiva 3.0T; Philips Medical Systems, Amsterdam, The Netherlands). Average VFA and SFA values were calculated using image analysis software (slice-O-matic, version 4.2; Tomovision Inc., Montreal, Quebec, Canada) based on a protocol previously described [12]. Abdominal obesity was defined as VFA ≥ 80 cm^2 [16].

Statistical analysis

Statistical analyses were performed using SPSS 16.0 statistical software package (SPSS Inc., Chicago, IL, USA) in a total of 1875 participants with normal glucose tolerance and no obesity selected from the Shanghai Obesity Study cohort. The one-sample Kolmogorov–Smirnov test was used to determine the normality of the data distributions. Data were expressed as the mean ± standard deviation or median with interquartile range for data with normal or skewed distributions, respectively. Inter-group comparisons were conducted with an unpaired Student's t-test or the Mann–Whitney U-test for continuous data with normal or skewed distribution, respectively, and Chi-squared test for categorical data. Logistic regression analysis defined paternal or maternal FHD as a dependent variable to identify indexes of obesity independently associated with paternal or maternal FHD and abdominal obesity as a dependent variable to determine its association with the presence of parental FHD. Multiple stepwise regression analysis was performed to identify independent factors affecting VFA and the contribution of parental FHD to VFA. The threshold of statistical significance was set at 0.05 for two-tailed *P*-values.

Results

Clinical characteristics of the study participants

The study population of 1875 participants (age range: 20–78 years, median 51.9 [45.3–57.1] years) consisted of 1573 subjects without a FHD, 115 subjects with a paternal FHD, and 187 subjects with a maternal FHD. In comparisons of body fat content and distribution with those of subjects without a FHD, subjects with a maternal FHD exhibited increases in FM, VFA, and SFA and a decrease in FFM, whereas subjects with a paternal FHD only exhibited an increase in FM (all $P < 0.05$). With respect to other clinical characteristics, FPG, HbA1c, FINS, HOMA-IR, TC, TG, LDL-c, and CRP levels were considerably increased in subjects with a maternal FHD, whereas only the HbA1c level was increased in subjects with a paternal FHD (all $P < 0.05$). Other variables did not differ between subjects with a maternal FHD and no FHD or those with a paternal FHD and no FHD (all $P > 0.05$). Comparisons between subjects with a paternal versus maternal FHD revealed that those with a maternal FHD were older and had less FFM (both $P < 0.05$). No differences in other variables were noted between these groups (all $P > 0.05$; Table 1).

Contribution of parental FHD to obesity

In both men and women, VFA was greater in offspring with a maternal FHD compared with those without a FHD (both $P < 0.05$; Fig. 1). However, only women with a maternal FHD exhibited an increase in SFA compared with those without a FHD (193.68 [146.10–238.40] versus 177.70 [142.40–215.67], $P = 0.017$), and those with a paternal FHD exhibited an increase in FM (17.65 [14.63–21.35] versus 16.30 [13.40–20.05], $P = 0.043$). Logistic regression analysis was performed separately for men and women. Paternal and maternal FHD were defined as dependent variables, and BMI, W, FM, FFM, VFA, and SFA were defined as independent variables. In both genders, only VFA stood out as an independent factor associated with a maternal FHD (men: odds ratio [OR] = 1.012, 95% confidence interval [CI] = 1.004–1.021, $P = 0.005$; women: OR = 1.012, 95% CI = 1.006–1.019, $P < 0.001$). However, none of these indexes of obesity was associated with a paternal FHD in either men or women (all $P > 0.05$).

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