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Cardiovascular risk factors in pre-pubertal Malays: Effects of diabetic parentage

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Abstract

Diabetes prevalence is increasing rapidly in Asian populations but the influence of a family history of diabetes on cardiovascular risk is unknown. To assess this relationship, 120 urban-dwelling Malays were recruited to a cross-sectional case-control study. Sixty were pre-pubertal children, 30 of diabetic parentage (Group 1) and 30 with no diabetes family history (Group 2). Group 1 and 2 subjects were the offspring of adults with (Group 3) or without (Group 4) type 2 diabetes. Subjects were assessed for clinical and biochemical variables defining cardiovascular risk. Principal component analysis assessed clustering of variables in the children. Group 1 subjects had a higher mean waist:hip ratio, diastolic blood pressure and HbA_{1c} than those in Group 2, and a lower HDL:total cholesterol ratio ($P < 0.03$). Although there were no correlations between Group 1 and 3 subjects for cardiovascular risk variables, significant associations were found in Groups 2 and 4, especially HbA_{1c} and insulin sensitivity ($P \leq 0.004$). Of five separate clusters of variables (factors) identified amongst the children, the strongest comprised diabetic parentage, HbA_{1c}, insulin sensitivity and blood pressure. Features of the metabolic syndrome are becoming evident in the young non-obese children of diabetic Malays, suggesting that lifestyle factors merit particular attention in this group.

Keywords: Cardiovascular risk factors; Type 2 diabetes; Pre-pubertal; Familial clustering; Ethnicity

1. Introduction

There is a well-recognised increase in childhood obesity and the metabolic syndrome in the developed world [1]. However, there is also emerging evidence that, in developing countries undergoing nutritional transition, a lean body habitus in infancy increases the risk of impaired glucose tolerance (IGT) and type 2 diabetes in young adult life [2]. In the case of ethnic Malays, the prevalence of type 2 diabetes is already high [3]. In addition, recent evidence suggests that obesity may be a more common feature of type 2 diabetes in Malays than in other Asian groups [4]. Population-based data [5] and studies in high-risk groups [6] suggest that dyslipidaemia is also common in the Malay population, especially in young adult and paediatric age-groups [5,7] while the distribution of hypertension by age and gender resembles that in developed countries [8].

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Several studies have demonstrated familial clustering of components of the metabolic syndrome in Europids [9,10]. The influence of family history on cardiovascular risk factors in Asian populations is unknown but there is evidence that abnormal glucose tolerance is appearing at an earlier age than preceding generations in Asian countries [2,4]. This observation, and the preventive success of lifestyle measures in adults with IGT [11,12], suggests very early identification and intervention in young high-risk Asians, such as those with a family history of diabetes, may be justified. We have, therefore, examined vascular risk factors in pre-pubertal Malay children either with or without a parent with type 2 diabetes.

2. Materials and methods

2.1. Subjects

We recruited 120 residents of the city of Kuching, the capital of Sarawak State in Malaysian Borneo. All were born in Malaysia, self-identified as being of Malay ethnicity, were Muslim, had Malay names and spoke Bahasa Malaysia as their first language. In the case of the children, both parents were of Malay ethnicity. The subjects were divided into four groups:

(i) *Group 1*: 30 healthy pre-pubertal children with at least 1 diabetic parent.
(ii) *Group 2*: 30 healthy pre-pubertal children without a family history of diabetes.
(iii) *Group 3*: 30 adults with type 2 diabetes who were the parents of the Group 1 children and who attended at the Atas Road Polyclinic, the main private clinic in Kuching.
(iv) *Group 4*: 30 healthy staff who were the parents of Group 2 children. All were working at Sarawak General Hospital in Kuching or the Atas Road Polyclinic.

Adults in Groups 3 and 4 were of similar socioeconomic status and had no infections or inflammatory conditions. All 60 adults gave written informed consent for themselves and their children to participate and each child assented to study procedures. The study was approved by the Universiti Malaysia Sarawak (UNIMAS) Research Panel and the UNIMAS Faculty of Medicine and Health Sciences Research and Ethics Committee.

2.2. Methods

Each subject attended after a 10-h overnight fast. In the case of Group 3, morning medications were withheld until after blood/urine sampling (see below). A detailed history was taken and a physical examination was performed. Anthropometric measurements were taken by trained nurses using standard methods. Body mass index (BMI) was calculated as kg/m^2. Waist circumference was measured midway between the lower rib margin and iliac crest, hip circumference at the maximum circumference around the buttocks, and a waist:hip ratio (WHR) was calculated from these measurements. Blood pressure measurement was performed in triplicate with the cuff of sphygmomanometer covering at least two-thirds of the upper right arm. Each child's pubertal stage was determined from breast development and pubic hair growth in the girls and testicular volume (using Prader's orchidometer) and pubic hair growth in the boys [13].

A venous blood sample was drawn and first-morning midstream urine was taken for prompt quantitative determination of urinary microalbumin. The blood was centrifuged immediately and separated sera, plasma and erythrocytes either assayed for standard biochemical parameters (plasma glucose; serum urea, electrolyte and creatinine; liver function including serum alanine transaminase (ALT); serum uric acid; serum total, HDL- and LDL-cholesterol, and triglycerides; glycosylated haemoglobin (HbA_{1c}) or stored below $-40\ ^{\circ}C$ for later assay (serum insulin; C-reactive protein (CRP); LDL particle size). Serum LDL-cholesterol was calculated using the Friedewald equation [14] for specimens with serum triglycerides <4.5 mmol/L.

Biochemical tests including HbA_{1c} were performed on a Hitachi 912 Analyser (Roche Diagnostics GmbH, Mannheim, Germany) using commercially-available reagents and protocols recommended by the manufacturer. Serum insulin was measured by specific radioimmunoassay with <1% pro-insulin cross-reactivity and inter-assay coefficients of variation (CVs) of 8.7% at 6 mU/L and 3.5% at 30 mU/L. Serum CRP was measured by high-sensitivity nephelometry (Dade Behring BNII, Marburg, Germany) with intra- and inter-assay CVs of 3.7% and 6.5%. Serum LDL particle size was determined by gradient gel electrophoresis [15].

2.3. Data analysis

Beta cell function (%B) and insulin sensitivity (%S) were estimated from fasting serum glucose and insulin using Homeostasis Model Assessment (HOMA) [16]. This model estimates steady state %B and %S as percentages of those of a normal reference population, measures that correspond well with non-steady state estimates of beta cell function and insulin sensitivity derived from stimulatory models such as the hyperinsulinaemic clamp, the hyperglycaemic clamp, and the intravenous and oral glucose tolerance tests.

SPSS for Windows (v 11.5.0; SPSS Inc., Chicago, Illinois, USA) and SAS for Windows (v 8.02; SAS Institute Inc., Cary, NC, USA) were used for statistical analyses. Data were log-transformed (denoted as 'ln') as appropriate and are presented as proportions, means ± S.D. geometric mean (S.D. range), or, for variables not conforming to a normal or log-normal distribution, median [interquartile range, IQR]. Fisher's exact test was used to compare two independent proportions. Relationships between multiple variables were assessed using linear regression and Generalised Estimating Equations (GEE).

To further investigate relationships between correlated variables of interest in the paediatric subjects, we performed factor analysis using principal component analysis (PCA) and