Determinants of normoglycemia and contribution to cardiovascular risk factors in a Chinese population: The Hong Kong Cardiovascular Risk Factor Study

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ABSTRACT. Background: Glucose intolerance is clearly associated with increasing risk of cardiovascular disease, but the association among increasing glycemia and cardiovascular risk factors, angina and coronary heart disease in normoglycemic subjects is less clear, particularly in Chinese. Methods: A total of 2763 subjects were recruited and the prevalence of glucose intolerance investigated, using fasting or 2-h 75-g oral glucose tolerance test (OGTT), glucose levels. Subjects normoglycemic by both criteria were selected and the relationship between glycemia and cardiovascular risk factors investigated using analysis of variance and stepwise multiple linear regression analyses. Results: 1931 (69.9%) subjects were normoglycemic by both tests. After adjustment for age and gender, quartiles of fasting and post-load glucose levels showed a clear positive relationship with cardiovascular risk factors, including obesity, blood pressure and lipid levels (p<0.001 for all). Additionally, other measures of glycemia and insulin resistance also dose-dependently increased with increasing fasting and post-load glucose levels (p<0.001 for all). Stepwise multiple regression showed that in females, age (standardised regression coefficient β (β)=0.23, p<0.001), insulin (β=0.17, p<0.001), waist circumference (β=0.11, p=0.007) were independently associated with fasting glucose levels; and body mass index (β=0.17, p<0.001), age (β=0.15, p<0.001) and triglycerides (β=0.15, p<0.001) were independently associated with post-load glucose levels. In males, age (β=0.19, p<0.001) and insulin (β=0.18, p<0.001) were independently associated with fasting glucose levels; and waist circumference (β=0.17, p<0.001), triglycerides (β=0.16, p<0.001) and insulin (β=0.12, p=0.001) were independently associated with post-load glucose levels.

INTRODUCTION

Type 2 diabetes is closely associated with micro- and macrovascular disease, the major causes of morbidity and mortality in these patients (1-3). Patients with Type 2 diabetes have a 2-3-fold increased risk from cardiovascular disease than those without diabetes (1, 3). Indeed, diabetic patients have a similar risk for a myocardial infarction as non-diabetic patients with myocardial infarction have for experiencing a secondary event (4). There is increasing evidence that patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), based on the 75-g oral glucose tolerance test (OGTT), also experience increased risk of cardiovascular disease complications (5, 6). In Japanese, patients with IGT were about twice as likely to die of coronary heart disease (CHD) compared to those with normal glucose tolerance (5). In Caucasians, subjects with IGT had 42% excess risk from all-cause mortality and 19% from cardiovascular mortality, compared to those with normal glucose tolerance (6). However, it is less clear at which level the risk from increasing glycemia begins. The Expert Committee on the Diagnosis and Classifica-
tion of Diabetes Mellitus of the American Diabetes Association recently reduced the lower limit for IFG from 6.1 to 5.6 mmol/l (7). Patients with normal fasting glucose levels, but glucose intolerance by the OGTT, have been reported to have increased risk of cardiovascular disease (8). However, there is limited data to suggest that the risk from glycaemia, which is a continuous variable, may begin below the current diagnostic levels for IFG or diabetes. In young Israeli males, high normal fasting glucose levels were associated with increased risk of developing diabetes (9). We have previously shown an independent contribution of increasing glycaemia within the normal range to worsening brachial arterial endothelial function and carotid intima-media thickening (10). However, that study group included Chinese subjects from several countries, and may thus have limited external validity (10). In the current study, after excluding subjects with IFG, IGT and diabetes, we examine the relationship between increasing levels of fasting and 2-h post-load glycaemia on cardiovascular disease and its risk factors in a population-based study of Hong Kong Chinese.

MATERIALS AND METHODS

In a cardiovascular risk factors prevalence study, 7730 Chinese, aged 25 to 74 yr, were randomly selected for telephone interviews, using random number dialling, in Hong Kong from 1994 to 1996, with a response rate of 78%. Subjects with serious diseases, such as cancer or who were hospitalised, were excluded. A standardised questionnaire modified from the questionnaire used in the 1992 Singapore National Health Survey was used, which included history of cardiovascular diseases and diabetes mellitus, and the addition of the World Health Organization (WHO) Rose-Angina Questionnaire (previously translated into Chinese and validated in a study of elderly Chinese). The method of telephone interview was validated in a morbidity survey in Hong Kong (11), and the study complied with the Declaration of Helsinki. The study was approved by the University of Hong Kong Ethics Committee and all subjects gave written, informed consent prior to participating in the study.

A total of 2763 subjects had physical examinations, including anthropometry and blood tests (fasting and 2-h post 75-g anhydrous glucose load, OGTT). The biochemical parameters were measured in the Clinical Biochemistry Unit of Queen Mary Hospital, a teaching hospital of the Faculty of Medicine, the University of Hong Kong. The laboratory used standard methods and met international quality control standards. Blood pressure was measured in duplicate after 10 min rest, 2-3 min apart. If the readings differed by 4 or more mmHg, then a third reading was taken. Extreme blood pressures were confirmed on a subsequent visit. The attendees and non-attendees were generally shown to be similar and resemble the general population (12). The detailed methods of measurement had been reported elsewhere (12, 13). Subjects were considered hypertensive if their systolic and/or diastolic blood pressures were ≥140/90 mmHg or they were receiving blood pressure-lowering drugs (14). Subjects were classified as having a normal glyceremic profile if their fasting plasma glucose was <5.6 mmol/l and OGTT 2-h glucose concentration was <7.8 mmol/l. Diabetes was classified as a fasting glucose of ≥7.0 or post-load glucose of ≥11.1 mmol/l, or receiving hypoglycaemic medication, whereas glucose intolerance in the non-diabetics was classified as fasting glucose ≤5.6 and <7.0 mmol/l or post-load glucose of ≥7.8 and <11.1 mmol/l, respectively (7, 15). For the indices of insulin resistance we used the fasting insulin-glucose product, which if divided by 22.5 is numerically equivalent to the homeostasis model assessment (HOMA) (16), which has been shown to correlate well with both the results of the euglycemic hyperinsulinenic clamp in population-based studies (17) and the glucose as well as insulin results of the OGTT. Metabolic syndrome was classified using the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) guidelines (18), but with the WHO Asian criteria for central obesity, as described below (19). Dyslipidaemia was classified as either fasting plasma triglycerides ≥2.3 mmol/l and/or total cholesterol ≥6.2 mmol/l or between 5.2 and 6.2 mmol/l with a total to HDL-cholesterol ratio >5.0, or were receiving treatment to lower lipid concentrations (18, 20). General obesity was classified as a body mass index (BMI) ≥25.0 kg/m² and central obesity as a waist circumference ≥80 or ≥90 cm in females and males, respectively (19).

There were 1931 subjects without glucose intolerance or diabetes who were categorised by quartiles of their fasting glucose or 2-h OGTT post-load glucose concentrations. As glucose is recorded to only 1 decimal place and has a relatively narrow range, significant numbers of subjects were recorded as having the same glucose concentrations and were categorized within the same quartile, as such the numbers within the quartiles varied. Data from normally distributed parameters are presented as mean±SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals (CI). Analysis of covariance was used to determine the mean and standard error (SE) of the variables, following adjustment for age and gender. To obtain p-values for trend across the quartiles of increasing glycaemia following adjustment for age and gender, we used logistic regression for dichotomous dependent variables and multiple linear regression for continuous variables. The χ² test was used to determine differences in the prevalence rates of the categorical variables between the quartile groups.

The variables included in the analyses were linearly related to the dependent variables. For the stepwise multiple regression, age, gender, glucose, systolic and diastolic blood pressures, insulin, waist circumference, BMI, fibrinogen, LDL and HDL-cholesterol and triglycerides were included in the analyses to determine independent determinants of fasting and post-load glucose concentrations. The appropriateness of the regression model was judged from the Durbin-Watson statistic (testing for serial correlation of adjacent error terms) and partial plots of the residuals. The tolerance and variance inflation factors (VIF) were taken as measures of collinearity, with low tolerance and high VIF being signs of collinearity indicating that a variable should not be included in the model. The Statistical Package for the Social Sciences (SPSS for windows, version 11.0.1, 2001, SPSS Inc, Chicago, IL) was used for the following analyses.

RESULTS

Of the 2763 Chinese subjects recruited into the study, 69.9% of the population were determined to