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Research letter

Family history of diabetes and the risk of coronary heart disease in people with or without type 2 diabetes

1. Introduction

Numerous reports confirm the presence of significant correlation between a positive family history of type 2 diabetes (T2D) and its development later in life [1,2]. Moreover, people with a significant familial history of diabetes are more likely to have concurrent metabolic abnormalities characterized by a chronic state of heightened insulin resistance, abdominal obesity, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C), raised blood pressure and hyperglycaemia [3,4]. However, the question remains whether the presence of a positive family history of diabetes is predictive of the occurrence of cardiovascular diseases as common macrovascular complications associated with T2D.

Currently, there are insufficient data regarding the potential effect of a family history of T2D on the occurrence of coronary heart disease (CHD) or any other type of cardiovascular diseases. Therefore, we assessed the the association between family history of diabetes and the future risk of CHD in people with or without T2D.

2. Patients and methods

2.1. Protocol of the study

The present investigation is part of an ongoing biphasic (cross-sectional and prospective) observational study that has been continuously running in Tehran, the capital city of Iran, since 1995 onwards [phase I (cross-sectional) ran from 1995 to 2004 and phase II (prospective) from 2005 to the present]. The main goals have been to record the natural history and determinants of the metabolic syndrome through continuous monitoring of the status of glycemic control and progression to the microvascular and macrovascular complication of T2D in a representative sample of people residing in Tehran. The original cohort population comprised two subcohorts of people with or without T2D. Details of the sampling procedure, extrapolation of data to the general population and global characteristics of the cohort population over the years of follow-up have previously been described [5–8].

Briefly, a combination of demographic (gender, age and cigarette-smoking status), anthropometric and biochemical risk factors was assessed at baseline. The detailed protocol for assessing these risk factors has been reported elsewhere [5–8]. Height and weight were measured while wearing light clothing and no shoes. Waist circumference (WC) was measured in a standing position at normal end-expiration at a level midway between the iliac crest and lowermost rib, with values recorded rounded to the nearest 0.1 cm. After at least 10 min of rest in a supine position, systolic and diastolic blood pressure (SBP and DBP, respectively) were measured using a standard mercury sphygmomanometer. After 12 h of overnight fasting, venous blood samples were drawn for biochemical assessment. Fasting plasma glucose (FPG) was measured using the glucose-oxidase method. High-performance liquid chromatography (HPLC; DS5 Pink Kit; Drew Scientific Inc., Miami Lakes, FL, USA) was used to determine glycated haemoglobin (HbA_{1c}) levels. Radioimmunoassay using an antibody with no cross-reactivity with plasma C-peptide and proinsulin (Immunotech, A.s., Prague, Czech Republic) was used to determine fasting plasma insulin (FPI) levels. Serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C and triglycerides were assessed by direct enzymatic methods (Pars Azmun, Tehran, Iran). Serum creatinine was measured by the Jaffe method (Pars Azmun).

2.2. Outcome measures and definitions

The main outcome measure in our analysis was the first episode of physician-adjudicated CHD [identified according to the International Classification of Diseases, 10th revision (ICD-10), blocks 120–125], defined as angina pectoris, coronary insufficiency, fatal/nonfatal myocardial infection, coronary artery bypass graft (CABG) surgery, coronary angioplasty, percutaneous coronary intervention or other revascularization procedures attributed to CHD. Diagnosis of T2D was made according to the American Diabetes Association criteria [9]. Participants who reported smoking during the preceding year were considered as current smokers. Body mass index (BMI) was determined as weight divided by height squared (kg/m^2). Homoeostasis model assessment for insulin resistance (HOMA-IR) was calculated as FPG (mg/dL) multiplied by FPI (mU/L) and divided by 405 [10].

2.3. Statistical methods

SPSS software version 18.0 (IBM Corp., Armonk, NY, USA) was used for all analyses. Logistic regression analysis was

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employed to determine the association between family history of diabetes and incident CHD. For each model, the results of regression are presented as odds ratios (ORs) [95% confidence intervals (95% CI)]. The interaction term for the association between the concurrent presence of positive familial history of diabetes and diagnosis of T2D at baseline was entered in crude and multivariable models of logistic regression to determine the nature of the interaction as either multiplicative, synergistic or antagonistic, or as a nonmodifier. In all tests, a P value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the cohort population

For the present survey, data from 6472 subjects with no missing values were included in the analyses (3323 with T2D, the 'diabetic subcohort', and 3149 normal prediabetic subjects, the 'nondiabetic subcohort'). In total, 385 subjects experienced a first episode of CHD during the follow-up period. Data for the baseline characteristics of our study participants have been reported in comprehensive details elsewhere [5].

3.2. Family history of diabetes and risk of incident CHD

Pooled analysis of the data revealed a significant correlation between family history of diabetes and incident CHD (OR [95% CI]: 1.720 [1.461–2.025]; $P < 0.001$). Primary adjustment for a personal diagnosis of T2D resulted in this association becoming nonsignificant (OR [95% CI]: 1.004 [0.844–1.194]; $P = 0.0965$). Because of this confounding role of a T2D diagnosis on the association between family history of diabetes and future CHD, subgroup analyses were carried out in those with or without T2D. Crude and multivariable subgroup associations of a positive family history of diabetes and incident CHD are summarized in Table 1 (I). In general, the serial inclusions of different cardiometabolic risk factors into stepwise models of logistic regression analysis resulted in nonsignificant predictions of CHD based on family history of diabetes in patients with T2D and in prediabetic subjects [$P > 0.05$ for both groups in fully adjusted models; Table 1 (I)]. Moreover, correlation of the interaction term (personal diagnosis of T2D at baseline × family history of diabetes) with the occurrence of CHD was not significant [Table 1 (II), (III)], thus demonstrating that a familial history of diabetes is not associated with incident CHD in patients with T2D diagnosed at baseline.

4. Conclusion

The core finding of the present report is that a positive family history of diabetes does not contribute to an increased risk of CHD in patients with T2D or prediabetic subjects. Although the correlation of family history of diabetes, different cardiometabolic risk markers and subclinical atherosclerosis has been studied in several previous reports [11,12], our present investigation is the first to address the contribution of a familial history of diabetes for predicting future coronary events in a sample population with or without T2D. In our study, the subgroup associations of a family history of diabetes and CHD as stratified by the occurrence of hard or soft events were not considered. Nevertheless, the majority of recorded CHD episodes belonged to the category of hard events (including fatal/non-fatal myocardial infection, CABG surgery, coronary angioplasty, percutaneous coronary intervention or other revascularization procedures). Notably, those with a baseline diagnosis of T2D, but no concomitant familial history of diabetes, had risk-adjusted increased odds of around 3.3 for the occurrence of incident CHD, which was approximately the same as the odds calculated for the presence of both a baseline diagnosis of T2D and positive family history of diabetes (~ 3.4).

Contrary to our present findings, a recent cohort of 6434 asymptomatic people from the general population reported significant associations between the presence of a positive family history of diabetes and signs of subclinical atherosclerosis [noncalcified plaques detected by coronary computed tomography angiography (CCTA)] [11]. Nevertheless and consistent with our present results, a family history of diabetes had no significant association with the occurrence of major atherosclerotic signs (CCTA-proven significant coronary artery stenosis or calcified plaques) [11].

Subjects with a positive family history of diabetes are at substantially increased risk for development of T2D. More important, the link between family history of diabetes and risk of T2D is not mediated through anthropometric, lifestyle or genetic risk factors, suggesting that having a family history of diabetes remains a strong, independent and easily accessible risk factor of T2D [1]. Such a family history has also been highlighted as an independent risk factor for the development of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis and other forms of advanced liver fibrosis in those with or without T2D [13]. In addition, exercise-induced insulin sensitivity has been demonstrated to be greater in the presence of a family history of diabetes [14]. Another report found subjects with either low or high birth weights and a recorded family history of diabetes to have increased risks of the metabolic syndrome. In contrast, those without a family history of diabetes had greater risk of progression to the metabolic syndrome only in cases of high birth weights [15].

These data categorically support the suggestion that a family history of diabetes may be related to an increased susceptibility to the main components of cardiometabolic dysfunction—namely, impaired insulin signalling and increased insulin resistance, dyslipidaemia, elevated blood pressure, central obesity and chronic hyperglycaemia—and the subsequent heightened risk of atherosclerotic plaque formation [3,4]. At present, the reasons for the observed nonsignificant associations between family history of diabetes and incident CHD among both prediabetic subjects or patients with T2D are unclear. However, it is imperative to note that the correlation involving a familial history of diabetes and cardiovascular events is more complicated than simply the subclinical atherosclerotic alterations. Other major, non-diabetes-related and modifiable cardiovascular risk factors (such as smoking habits and sedentary lifestyles) could be actively contributing to or determining