主論文の要約

Association between parental history of diabetes and the incidence of type 2 diabetes mellitus differs according to the sex of the parent and offspring's body weight: A finding from a Japanese worksite-based cohort study

（両親の糖尿病既往歴と本人の 2 型糖尿病発症との関連は父母のどちらが糖尿病既往歴を持つか、及び本人の肥満の有無により有意に異なる：日本人を対象とした職域コホート研究）

名古屋大学大学院医学系研究科　総合医学専攻
社会生命科学講座　国際保健医療学・公衆衛生学分野
（指導：青山 温子　教授）
王 超辰

Introduction

Obesity is a well-known risk factor for type 2 diabetes (T2DM) development. However, some non-obese individuals develop T2DM, suggesting the existence of a familial influence. Indeed, family history was more strongly associated with diabetes prevalence in non-overweight individuals than in the overweight or obese in US blacks and Hispanics, but not in whites. Although the finding indicated existence of higher genetic influence in lean non-white populations, the issue has not been explored in other ethnicities, particularly in prospective studies. In addition, some previous studies have indicated a stronger maternal-offspring association with T2DM compared with the paternal-offspring association. Therefore, it would be relevant to examine the association of a parental history of diabetes with T2DM risk in the offspring according to the sex of the parent and the offspring's body weight.

Furthermore, it is known that one's weight could decrease or fluctuate due to worsened glycemic control. Alternatively, it is also possible for the weight to increase during the follow-up before the onset of diabetes.

Accordingly, in a worksite-based cohort of middle-aged Japanese men and women, we investigated the association of parental history of diabetes with T2DM risk in the offspring according to the sex of the parents and the offspring's body weight, which was longitudinally collected by mandatory annual health check-up at the worksite.

Methods

In 2002, 5,471 civil servants in a local government office in Japan participated in a self-administered questionnaire survey, which included their medical and family history of certain diseases, diet and lifestyle, and gave written informed consent to the use of their mandatory annual health check-up data in this study. Subjects with missing baseline information on BMI, smoking status, alcohol consumption, and physical activity (n = 374); with prevalent diabetes, diagnosed by self-reported medication use or baseline glucose levels ≥ 126 mg/dL (n = 651) were excluded. In total, 4,446 subjects (3,492 men and 954 women) were left for the present analysis. Subjects were followed until the end of March, 2011.

T2DM incidence was ascertained by two methods. First, participants' mandatory annual health check-up data from 2002 to 2011 were reviewed. Incidence was defined as the year when fasting glucose levels first reached ≥126 mg/dL. Second, subjects reported detailed medical histories of T2DM in approximately biennial self-administered questionnaire surveys carried out between 2004 and 2011. The year of diabetes diagnosis was also reported and we requested contact details for the physician (present or past) in charge of the disease management.

Parental history of diabetes was categorized as: "no parental history", "father only", "mother only", and "both". Age- and sex-adjusted means and proportions of potential

confounding factors across the categories were compared. T2DM incidence rates were calculated by Poisson regression adjusted for age and sex. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the T2DM risk among subjects in each category taking the "no parental history" as the reference. Model 1 adjusted for age, sex, smoking status, alcohol consumption, birth weight categories, physical activity (yes/no), and total energy intake. Model 2 included the covariates in Model 1 plus BMI. Model 3 included the covariates in Model 2 plus the number of metabolic syndrome components (0–5).

We carried out two sensitivity analyses restricted to (1) subjects continuously non-overweight from baseline to the end of follow-up, and to (2) subjects continuously non-overweight from young adulthood. Multiplicative interaction tests were performed using the likelihood ratio test, comparing the fit of models with a cross-product term between parental history categories and the BMI with that of models without this term.

Results

The mean (SD) age and BMI at baseline were 47.5 (7.1) years and 22.9 (2.8) kg/m^2, respectively. Of the 4,446 subjects, 614 (13.8%) reported a history of diabetes in at least one parent at baseline. **Table 1** shows that at baseline smoking status, physical activity, alcohol consumption, fasting glucose, systolic blood pressure, total energy intake and levels of total cholesterol, TG, and HDL-C, as well as the prevalence of metabolic syndrome did not differ significantly according to the parental history of diabetes.

During 8.9 years of follow-up, 277 newly developed T2DM cases were confirmed. The annual incidence rate was 7.9 per 1,000 person-years. Compared with a negative parental history, subjects in the "father only", "mother only", or "both parents" categories exhibited significantly higher risk of T2DM (**Table 2**). The corresponding multivariable-adjusted HRs and 95% CIs in Model 3 were 1.72 (1.19–2.47), 1.66 (1.07–2.58), and 3.46 (1.42–8.43) for the "father only", "mother only", or "both parents" categories, respectively. However, stratified analysis by subjects' classification as overweight at baseline revealed a statistically significant association of "mother only" history with T2DM incidence only in the non-overweight group (HR: 2.35, 95% CI: 1.41–3.91) and not in the overweight group (HR: 0.84, 95% CI: 0.34–2.08). In contrast, subjects in the "father only" category were associated with a higher risk of T2DM only in the overweight group (HRs: 1.52 (0.89–2.62) and 1.98 (1.19–3.28) in the non-overweight and overweight groups, respectively [**Table 3**]). In the "both parents" category, the HRs were 6.00 (1.89–19.08) and 2.49 (0.60–10.27) in the non-overweight and overweight groups, respectively. The multiplicative interaction by overweight status was significant for maternal history of diabetes (*P* for interaction = 0.014) but not for paternal history (*P* for interaction = 0.35). In sensitivity analyses, similar findings were observed.

Discussion

In this study, we identified a positive association between parental history of diabetes and T2DM incidence in general. However, stratified analysis by overweight status revealed that maternal history was more strongly associated with increased T2DM incidence in non-overweight subjects than paternal history.

The findings may suggest relevance of a hypothesis of personal fat threshold (PFT), in which exceeding pre-determined PFT can be metabolically detrimental even though the absolute weight is not considered as overweight or obese. It may be possible that low PFT is related to maternal history of diabetes. Maternal history of diabetes was reported to be associated with decline in disposition index or low first phase insulin response. As insulin action is essential to store excess fat in adipocyte, resulting accumulation of ectopic fat especially in muscle would be etiologically related to eventual development of T2DM. Mitochondrial dysfunction could also lead to the manifestation of this phenotype, and genetic factor characterized by maternal transmission could also be one of the postulated causes. Other potential mechanisms/hypotheses such as maternally determined environments (intrauterine and early postnatal nutritional or lifestyle influences) or genomic imprinting cannot be ruled out.

In our study, we also found that paternal history was associated with the incidence of T2DM in overweight offspring. We speculate that a paternal history may also represent a marker of a diabetogenic environment. Those with relatively high genetic susceptibility may develop T2DM in other circumstances that increase the likelihood of disease, such as obesity or poor lifestyle, which might be related to their fathers' history.

The current study has several limitations. First, parental history of diabetes was self-reported, with no distinction between type 1 and type 2 diabetes and might be under-reported. Second, we did not perform sex-stratified analysis due to the small number of cases in women. Third, we diagnosed diabetes based on a single measurement of fasting glucose, which is often employed in epidemiological studies, although HbA1c assessment and a glucose tolerance test would be ideal. Fourth, although this is a prospective analysis of non-diabetic participants, an aware of slightly higher blood glucose levels in previous health check-ups, could enhance the detail of the family history recalled.

Conclusion

Although parental history of diabetes was associated with higher T2DM risk in the offspring in the cohort as a whole, maternal history was significantly associated with T2DM risk only in non-overweight subjects.