Type 2 Diabetes and Maternal Family History

An impact beyond slow glucose removal rate and fasting hyperglycemia in low-risk individuals? Results from 22.5 years of follow-up of healthy nondiabetic men

OBJECTIVE — Although an excess transmission of type 2 diabetes from mothers has been documented, whether this is an independent trait or whether the effect can be detected early through risk factors for type 2 diabetes remains to be elucidated. The objective of this study was to investigate the prevalence of and the possible prospective effect of family history on type 2 diabetes incidence adjusted for multiple diabetes risk factors in a 22.5-year follow-up study of healthy men.

RESEARCH DESIGN AND METHODS — A total of 1,947 apparently healthy nondiabetic men with fasting blood glucose (FBG) levels <110 mg/dl at baseline, in whom an intravenous glucose tolerance test (IVGTT) was administered and several conventional risk factors were measured, were followed for 22.5 years. Family history data were obtained at the baseline examination, and morbidity data were obtained from repeated investigations, hospital records, and death certificates.

RESULTS — A total of 131 men reported maternal diabetes family history only, 65 men reported paternal diabetes family history only, and 10 men reported both maternal and paternal diabetes family history. Among the 1,947 men, 143 cases of type 2 diabetes developed during 22.5 years of observation. Maternal family history and combined maternal and paternal family history predisposed to future type 2 diabetes both in univariate Cox analysis and in multivariate Cox regression analysis after adjusting for glucose disappearance rate (R_d) during an IVGTT, FBG level, BMI, physical fitness, triglyceride level, and age. Maternal family history showed a relative risk (RR) of 2.51 (95% CI 1.55–4.07), combined maternal and paternal family history showed an RR of 3.96 (1.22–12.9), and paternal family history showed an RR of 1.41 (0.657–3.05) in multivariate analysis.

CONCLUSIONS — Maternal family history appears to be an important risk factor for type 2 diabetes independent of prediabetic R_d, FBG, BMI, and physical fitness levels.

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Type 2 diabetes is known to have a strong genetic basis (1–3), and some single-gene mutations have been described (4). Contradictory findings have been published on the nature and strength of the genetic basis, which are conceivably related to population heterogeneity (5) and to the genetic basis for the disease itself (6). Although an excess transmission from mothers has been established (7,8), its quantitative role has been sparsely documented, and limited information exists on the association with others markers of increased type 2 diabetes risk.

Most studies are cross-sectional or case-control studies, which often focus on the association between family history and impaired glucose tolerance (9). To our knowledge, no prospective studies have been published in a low-risk population in which the independent role of parental family history for predicting type 2 diabetes is assessed after correcting for multiple established risk factors for future type 2 diabetes.

We dealt with these aspects in a 22.5-year prospective follow-up study of a low-risk population of healthy Caucasian men in whom the effect of family history was assessed after adjusting for several factors known to predict future type 2 diabetes, including fasting blood glucose (FBG) level and the glucose disappearance rate (R_d) derived from an intravenous glucose tolerance test (IVGTT).

RESEARCH DESIGN AND METHODS

Subjects
In 1972, all apparently healthy men 40–59 years of age working in 5 companies in Oslo, Norway, were invited to participate in a cardiovascular screening survey as described in detail elsewhere (10–12). In brief, all subjects were strictly healthy, and specifically men with a diagnosis of diabetes defined by glucosuria and/or an FBG level ≥140 mg/dl were primarily excluded.

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Abbreviations: FBG, fasting blood glucose; IVGTT, intravenous glucose tolerance test; R_d, glucose disappearance rate; RR, risk ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
Table 1—Baseline variables according to family history

<table>
<thead>
<tr>
<th></th>
<th>No family history</th>
<th>Maternal family history</th>
<th>Paternal family history</th>
<th>Maternal and paternal family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,741</td>
<td>131</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.6 (39.9–60.2)</td>
<td>49.5 (40.9–60.9)</td>
<td>50.3 (40.2–60.3)</td>
<td>49.6 (42.9–57.6)</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>79 (52–109)</td>
<td>79 (55–107)</td>
<td>81 (60–102)</td>
<td>82 (71–102)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>1.67 (0.184–3.71)</td>
<td>1.53 (0.404–3.21)</td>
<td>1.54 (0.916–2.68)</td>
<td>1.40 (0.771–2.00)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 (17.2–39.0)</td>
<td>24.5 (19.1–34.0)</td>
<td>24.8 (18.8–30.4)</td>
<td>25.0 (22.8–28.8)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>128 (88–214)</td>
<td>128 (90–192)</td>
<td>124 (94–172)</td>
<td>131 (112–148)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60 (36–113)</td>
<td>59 (43–101)</td>
<td>62 (47–91)</td>
<td>62 (49–74)</td>
</tr>
</tbody>
</table>

Data are n or medians (ranges). *P* = 0.049; **P** = 0.040; ***P*** = 0.0028 all for difference with no family history (Mann-Whitney U test).

Of 2,341 eligible men, 2,014 (86%) accepted the invitation and gave their informed consent to participate. The examination took place from 28 August 1972 to 25 March 1975. Only the 1,947 men who had an Fasting Blood Glucose (FBG) level <110 mg/dl at baseline and who also had data from an IVGTT were included in the multivariate analysis on the possible impact of diabetes family history (25 men with an FBG level ≥110 mg/dl were excluded).

Examination Subjects were examined at the University Hospital in Oslo between 7:30 and 10:00 A.M., after at least 12 h of fasting and 8 h of abstaining from smoking. The survey examination program included a comprehensive health issue questionnaire, which was given to the participants 1 week before the baseline examination to provide ample time for filling in the questionnaire appropriately and for obtaining information from family members concerning family disease traits. On arrival at the examination, all questionnaires from all participants were scrutinized to ensure that all questions had been understood, that all items were complete, and that subjects had made no misinterpretations. Detailed data on diabetes family history represented 1 part of the questionnaire. The examination program further included a complete clinical examination, several blood tests, an IVGTT, a resting electrocardiogram, and an electrocardiogram-monitored exercise test as reported elsewhere (10).

Venous whole blood samples were analyzed immediately after being drawn, and blood glucose levels were determined by the glucose oxidase method. Approximately 30 min after the fasting sample was taken, an IVGTT designed to investigate the Rₜ was performed; an injection of 25 g glucose i.v. (50 ml 50% solution wt/vol) was administered for 2–3 min with the subject in a semisupine position. Time 0 was defined as the end of the injection. Blood glucose was determined before the injection at time 0 and subsequently every 10 min for 1 h in the 800 first individuals and every 15 min in the remaining subjects. The Rₜ was assessed by regression analysis of the logarithmic glucose values because of the exponential relationship.

Maternal family history was said to be present if only the biological mother was reported to have (or had, if deceased) a diagnosis of diabetes, paternal family history was said to be present if only the biological father was reported to have (or had, if deceased) a diagnosis of diabetes, and combined family history was said to be present if both biological parents had a diagnosis of diabetes.

Physical fitness was defined as working capacity (kilojoules) divided by body weight in kilograms. The former was defined as cumulative work performed during a symptom-limited bicycle exercise test. BMI was calculated as weight in kilograms divided by height in meters squared.

Follow-up Virtually identical examinations of subjects who were still alive were performed from 1980 to 1982 (survey 2), from 1989 to 1990 (survey 3), and from 1995 to 1996 (survey 4). A total of 91% of subjects met for survey 2, 86% met for survey 3, and 85% met for survey 4.

After having been granted legal permission from the Norwegian Data Inspectorate and the Norwegian Board of Health, we obtained diabetes morbidity data through the reexaminations, from hospital record review of all subjects who had been admitted or referred to any Norwegian hospital, and from death certificates coded according to the International Classification of Diseases, Ninth Revision, for all individuals who died on or before 31 December 1996. Nearly all (>90%) diagnoses of diabetes were confirmed by least 2 sources (physician confirmed). Because of the time span, all of the diagnoses of diabetes followed 1985 World Health Organization criteria (2-h blood glucose level after a glucose load ≥180 mg/dl [FBG ≥120 mg/dl]). The available clinical information and the age distribution for onset of diabetes indicated that at least 90% of the cases were type 2 diabetes. Diabetes was not diagnosed solely based on the results of the survey blood tests.

Statistical methods The associations between the time to diagnosis of type 2 diabetes and family history were investigated by Kaplan-Meier plots and log-rank tests. Multivariate analysis, including the variables of family history, Rₜ, FBG level, and numerous other selected variables, were carried out by means of Cox proportional hazard regression analysis.

The results for all variables included relative risks (RRs) after adjustment for all other variables in the model. For continuous variables, the RR of type 2 diabetes associated with an increase of 2 SD is reported. For discrete variables, the relative risks of type 2 diabetes between groups are presented. The proportional hazards assumption was checked with a graphical plot of log S versus log, for the variables included in the model (S denoted the survival function, and t denoted time) and was found to be acceptably fulfilled. All P values are 2-tailed. Mann-Whitney U tests were used to assess any difference between continuous variables. Physical fitness and triglyceride levels were
log-transformed because of skewed distributions. All models were computed with StatView Version 5.0 for the Macintosh (Abacus Concepts, Berkeley, CA).

**RESULTS** — A diabetes family history was reported by 206 men. A total of 131 men reported a maternal family history, 65 men reported a paternal family history, and 10 men reported a combined family history. Among the 1,947 men, 143 cases of type 2 diabetes developed during a median of 22.5 years (range 21–24) of follow-up. Median time to development of diabetes was 14 years (1–22 years). Baseline characteristics according to diabetes family history are presented in Table 1, which demonstrates small but significant differences between family history groups for FBG, R, BMI, and triglyceride levels.

The 22-year type 2 diabetes rate was markedly higher in the group with a maternal family history of diabetes (P < 0.0001) than in men reporting no family history (Table 2), whereas the rates in the other 2 groups with family history are not significantly different from the diabetes rate among men with no family history. We did not observe a significant difference in the 22.5-year incidence rates between maternal and paternal family history of diabetes. Kaplan-Meier analysis confirmed these results (Fig. 1).

In a Cox proportional hazards model including family history data alone (Table 3), maternal family history showed an RR of 2.65 (95% CI 1.64–4.25) for developing type 2 diabetes compared with no family history. A paternal family history was associated with an RR of 1.79 (0.78–3.61), and combined family history was associated with an RR of 6.89 (2.18–21.7). FBG, R, BMI, physical fitness, and triglyceride levels were all important predictors of future type 2 diabetes (Table 4), and, apart from triglycerides (which lost its independent predictive ability), the model was only minimally affected by the intro-

<table>
<thead>
<tr>
<th>Family History</th>
<th>Type 2 Diabetes (no)</th>
<th>Type 2 Diabetes per 1,000 Person-Years of Observation</th>
<th>Type 2 Diabetes Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No family history</td>
<td>1,741</td>
<td>3.24 (2.64–3.84)</td>
<td>6.49 (5.33–7.65)</td>
</tr>
<tr>
<td>Maternal family history</td>
<td>131</td>
<td>8.31 (4.69–11.9)</td>
<td>15.3 (9.11–21.4)</td>
</tr>
<tr>
<td>Paternal family history</td>
<td>65</td>
<td>5.41 (1.41–9.41)</td>
<td>10.8 (3.23–18.3)</td>
</tr>
<tr>
<td>Maternal and paternal family history</td>
<td>10</td>
<td>19.0 (0–40.3)</td>
<td>30.0 (1.60–58.4)</td>
</tr>
</tbody>
</table>

Data are n or rates (95% CIs). *P < 0.0001 for difference with no family history.

Figure 1 — Kaplan-Meier curves according to family history of type 2 diabetes. Log-rank tests for difference with no family history. Combined family history, P = 0.0001; maternal family history, P < 0.0001; paternal family history, P = 0.174.
Maternal family history and type 2 diabetes

Table 3—Results from a Cox proportional hazards model presenting the effect of family history compared with no family history on the risk of developing type 2 diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal family history</td>
<td>2.65 (1.64–4.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Paternal family history</td>
<td>1.79 (0.785–3.61)</td>
<td>0.181</td>
</tr>
<tr>
<td>Maternal and paternal family history</td>
<td>6.89 (2.18–21.7)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Production of family history (detailed data not shown).

CONCLUSIONS — This prospective report on the possible effect of diabetes family history among working middle-aged healthy Caucasian men indicates that maternal family history is a strong risk factor for type 2 diabetes even after correcting for several factors known to predispose to type 2 diabetes. The same applies to combined family history. These findings differ from recent large cross-sectional studies in a low-risk population (13) but agree with several other cross-sectional studies (7–9,14).

The importance particularly of maternal family history was apparent from all of the analyses performed in this population. Because of a lower prevalence of paternal family history of diabetes, its effect could have been underestimated, although the Cox model suggests an RR in the range of 1.4, which is still lower than the RR for maternal family history. The RR for a possible excess paternal transmission was not significantly different from unity, and establishing a definite role of paternal transmission in larger studies is necessary.

The predictive power of maternal family history appears only to be moderately affected by information on prediabetic $R_d$ and FBG levels in this low-risk population, which expands the recent findings of Kekäläinen et al. (15). The effect of the other variables remained virtually unchanged when corrected for family history patterns, in particular $R_d$ and FBG (detailed data not shown). Only triglyceride level lost its predictive ability when family history was introduced in the model, and the higher triglyceride level observed at baseline in the group with maternal family history may suggest a possible biochemical link. The findings also suggest that the maternal diabetes family history does not show its penetrance via $R_d$ and FBG levels at this very early prediabetic stage.

Our multivariate Cox regression analysis dealt with several acknowledged risk factors for future type 2 diabetes (16–21), including elements of lifestyle such as BMI and physical fitness. Lack of insulin data may in part be compensated for by other variables: physical fitness (which is associated with insulin resistance) (22), $R_d$, and FBG levels. The $R_d$ derived from our IVGTT probably to a great degree reflects the muscle glucose uptake, and although the strength of the association between $R_d$ and insulin sensitivity has been poorly described (23), low values probably reflect muscle insulin resistance. Until we have more data on the possible mechanisms, men with a maternal history of diabetes should receive close follow-up and preventive measures.

The results from this prospective study should only be accepted if they are free of significant bias. Recall bias is probably small in this study because all participants had filled in the questionnaire on arriving for the survey examination and confirmed their written answers when asked the same questions by the physician in charge. Moreover, the selection mode and the prospective nature of the study ought to ensure the presence of little recall bias.

Bias may be suspected considering the skewed distribution of reported maternal diabetes compared with paternal diabetes. Because women in the relevant time period had a life expectancy of 4–5 years longer than men, older age may explain part of this. Moreover, according to Westlund (24), the same female preponderance as reported in our study was present regarding the prevalence of diabetes from 1925 to 1954 and diabetes as a cause of death from 1900 to 1950 (which is nearly twice as high in women than in men) in Oslo. This time interval covers the relevant parental period for developing diabetes, and the finding was also confirmed by Ustvedt and Olsen (25) when investigating the diabetes incidence in Oslo from 1956 to 1965. We therefore believe that the skewed distribution of maternal versus paternal family history of diabetes reflects true sex differences in diabetes prevalence in this region of Norway at that time and not bias.

Because participants at baseline were 40–59 years of age and healthy and because most cases of diabetes probably represented type 2 diabetes, the present data can only be considered relevant for type 2 diabetes.

The mechanism behind the strong effect of maternal family history is obscure. Some metabolic derangements with an association with triglyceride metabolism may be present. Moreover, that the mitochondria are inherited from the mother (4,26) and that the important intrauterine environment (27) of course only can reflect factors regarding the mother are well known. We do not have data on the relevant pregnancies or birth weights or on gestational diabetes in the mothers.

In this study, a maternal family history of diabetes appears to be a strong risk factor for type 2 diabetes in a low-risk Caucasian male population. The predictive power of maternal family history was apparent an average of 15 years before type

Table 4—Results from a Cox proportional hazards model presenting the effect of change of 2 SD or comparing groups (family history, FBG quartile IV vs. quartiles I–III) of the variables studied on the risk of developing type 2 diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal family history</td>
<td>2.51 (1.55–4.07)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Paternal family history</td>
<td>1.41 (0.657–3.05)</td>
<td>0.376</td>
</tr>
<tr>
<td>Maternal and paternal family history</td>
<td>3.96 (1.22–12.9)</td>
<td>0.022</td>
</tr>
<tr>
<td>FBG</td>
<td>3.19 (2.37–4.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$R_d$</td>
<td>0.331 (0.216–0.504)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>2.65 (1.92–3.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fitness*</td>
<td>0.466 (0.317–0.686)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Triglycerides*</td>
<td>1.32 (0.943–1.83)</td>
<td>0.106</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.712–1.49)</td>
<td>0.876</td>
</tr>
</tbody>
</table>

*Log-transformed.
2 diabetes was diagnosed and was at that time independent of important predictors of type 2 diabetes such as FBG and $R_d$.

References