Impact of Positive Family History and Genetic Risk Variants on the Incidence of Diabetes

The Finnish Diabetes Prevention Study

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OBJECTIVE—We aimed to investigate the influence of positive family history (FH+) of diabetes and 19 known genetic risk loci on the effectiveness of lifestyle changes and their predictive value on the incidence of type 2 diabetes in the Finnish Diabetes Prevention Study (DPS).

RESEARCH DESIGN AND METHODS—A total of 522 subjects with impaired glucose tolerance (IGT) were randomized into the control (n = 257) and intervention (n = 265) groups. The mean follow-up was 6.2 years (median 7 years), and the lifestyle intervention, aimed at weight reduction, healthy diet, and increased physical activity, lasted for 4 years (range 1–6 years). An oral glucose tolerance test (OGTT) and assessment of basic clinical variables were performed annually.

RESULTS—The effect of intervention on the incidence of diabetes was almost similar in subjects with FH+ compared with subjects with a negative family history (FH−) of diabetes during the entire follow-up. In the Cox model, including FH, genetic risk SNPs, and randomization group, and adjusted for the effects of age, sex, BMI, and study center, only lifestyle intervention had a significant effect (hazard ratio 0.55, 95% CI 0.41–0.75, P < 0.001) on the incidence of diabetes. Further analyses showed that in addition to the baseline glucose and insulin values, 1-year changes in 2-h glucose and 2-h insulin achieved by lifestyle intervention had a significant effect on the incidence of diabetes.

CONCLUSIONS—These results emphasize the effectiveness of lifestyle intervention in reducing the risk of diabetes in high-risk individuals independently of genetic or familial risk of type 2 diabetes.

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The aim of the current study was to investigate whether an FH+ of diabetes or genetic variants of type 2 diabetes could modulate the effect of lifestyle changes achieved in the Finnish DPS (16,17) on the incidence of type 2 diabetes. Furthermore, we aimed to assess the ability of FH and genetic risk variants, in addition to lifestyle changes and basic clinical variables, to predict the incidence of type 2 diabetes in individuals at high risk of type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—The DPS is a clinical trial with five participating centers (Helsinki, Kuopio, Turku, Tampere, and Oulu) in Finland (NCT00518167). Details of the DPS study design, methods, and procedures have been published (16–19). Briefly, study participants were recruited mainly by screening of high-risk groups who voluntarily responded to local advertisements. The inclusion criteria were 1) age 40–64 years at screening, 2) BMI >25 kg/m² at screening, and 3) the mean value of two 75-g oral glucose tolerance tests (OGTTs) in the IGT range based on World Health Organization 1985 criteria. Exclusion criteria included recent (within 6 months) cardiovascular disease event. The randomization of participants started in 1993 and continued until 1998.

A total of 522 overweight men and women were randomly allocated to one of the two treatment modalities, the intensive diet-exercise counseling group (n = 265, 66% were women) or the control group (n = 257, 69% were women). The participants randomized to intensive lifestyle intervention were given individualized counseling by the study nutritionists to achieve the lifestyle goals. They were also advised to increase their level of physical activity, and voluntary physical activity sessions were offered. The lifestyle goals were 1) weight reduction of ≥5%, 2) <30% of the daily energy intake from fat, 3) <10% of the daily energy intake from saturated fat, 4) fiber intake ≥15 g per 1,000 kcal, and 5) moderately intense physical activity ≥30 min per day. The control participants were given general health behavior information at randomization. The median length of the active intervention period was 4 years (range 1–6 years).

All participants had an annual OGTT, a medical history, and a physical examination with measurements of height (without shoes), weight (in light indoor clothes), waist circumference (midway between the lowest rib and iliac crest), and systolic and diastolic blood pressure. Serum total cholesterol, HDL cholesterol, and triglycerides were determined from fasting samples using an enzymatic assay method.

The diagnosis of diabetes was based on the repeated OGTT (16,17). FH of diabetes was based on a questionnaire applied in the DPS. If one of the first-degree relatives (father, mother, sister, brother) had diabetes, FH was regarded as positive (FH+). These data are based on the follow-up of 4 years when active intervention was finished and on the 3 years of follow-up after active intervention with a total follow-up of an average of 6.2 years (median 7 years). Altogether, 75 persons (28%) in the intervention group and 110 persons (43%) in the control group developed diabetes during the entire follow-up. During the entire study period, the incidence of diabetes was substantially lower in the intervention group compared with the control group (HR 0.57, 95% CI 0.43–0.76, P < 0.001) (18). No significant difference was found in mortality rates between the groups (19).

**Genotyping**

Nineteen type 2 diabetes-susceptibility SNPs (PPARG rs1801282, KCNJ11 rs5219, TCF7L2 rs7903146, SLC30A8 rs13266634, HHEX rs1111875, CDKN2B rs10811661, IGF2BP2 rs4402960, CDKAL1 rs7754840, FTO rs9939609, HNF1B rs757210, WFS1 rs10010131, JAZF1 rs864745, CDC123 rs12779790, TSPAN8 rs7961581, THADA rs7585979, ADAMTS9 rs4607103, NOTCH2 rs10923931, KCNQ1 rs2283228, MTRNR1B rs10830963) were genotyped using the TaqMan Allelic Discrimination Assay (Applied Biosystems, Foster City, CA). The genotyping call rate was 99.2–100%. Genotype distributions of all SNPs were in Hardy–Weinberg equilibrium (P > 0.05).

**Calculations**

Genetic risk score (GRS) for type 2 diabetes was calculated as a sum of type 2 diabetes-risk alleles in 19 confirmed type 2 diabetes-susceptibility SNPs. Furthermore, GRSSEC from the insulin secretion (at loci KCNJ11, TCF7L2, SLC30A8, HHEX, CDKN2B, IGF2BP2, CDKAL1, MTRNR1B) (20) was calculated.

**Statistical analysis**

Baseline differences in characteristics of the FH+ group and the group with a negative family history (FH−) of diabetes were tested with the t test for continuous variables and the Fisher exact or χ² test for dichotomous variables. Changes during follow-up (∆ values between the value at 1 year of follow-up and the baseline value) in body weight, glucose, and other variables were analyzed with the general linear model, adjusting for age, sex, study center, BMI, and fasting glucose at baseline. Interaction between FH and the randomization group was tested for each model, modeled as fixed factor. Variables with non-normal distribution were log-transformed before analyses. Kaplan–Meier method was used to estimate the incidence of diabetes in the two groups. The difference in incidence between the groups was tested with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio for the development of diabetes between the groups. Hazard ratios for continuous traits are expressed as unit change per 1 SD. If not stated otherwise, the models were adjusted for age, sex, BMI at baseline, fasting glucose at baseline, and study center. No multicollinearity problems were found for any model. Interaction between FH (or GRS) and randomization group was modeled as a covariate in Cox regression. All comparisons of the end points were based on the intention-to-treat principle. The results for continuous variables are given as means ± SD. P < 0.05 was considered statistically significant. Analyses were done with the statistics package Stata version 10.1 (StataCorp., College Station, TX) and SPSS 14.0 (SPSS Inc., Chicago, IL).

**RESULTS**

**Baseline characteristics and 1-year changes in clinical variables by family history**

No significant difference in the prevalence of FH of diabetes was observed between the intervention and control groups (66% vs. 61%). Table 1 shows baseline characteristics of the DPS participants according to the FH of diabetes. With the exception of the 1-year difference in age (P = 0.012), the two groups (FH+ vs. FH−) did not differ significantly from each other. Furthermore, persons with FH+ and FH− were similar regarding their diet at baseline, but the total leisure time physical activity was greater in persons with FH−.

The 1-year changes in the main clinical and metabolic characteristics according to FH and randomization group (intervention vs. control group) are
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Table 1—Baseline characteristics, diet, and physical activity of the DPS participants by family history of type 2 diabetes

|                          | FH+          | FH−          | P value |
|--------------------------|--------------|--------------|---------|
| N, men/women             | 327, 95/231  | 195, 76/119  | 0.012   |
| Age, years               | 55 (7)       | 56 (7)       |         |
| Men, BMI kg/m²           | 30.1 (3.8)   | 29.6 (3.3)   | 0.365   |
| Women, BMI kg/m²         | 32.1 (5.0)   | 31.4 (4.3)   | 0.185   |
| Fasting glucose, mmol/L  | 6.1 (0.7)    | 6.2 (0.8)    | 0.737   |
| 2-h glucose, mmol/L      | 8.9 (1.4)    | 8.9 (1.6)    | 0.897   |
| Fasting insulin, mU/L    | 15 (7)       | 14 (8)       | 0.381   |
| 2-h insulin, mU/L        | 96 (60)      | 94 (73)      | 0.282   |
| HOMA-IR                  | 4.2 (2.3)    | 4.0 (2.3)    | 0.250   |
| HOMA-B                   | 120 (67)     | 115 (67)     | 0.217   |
| Drug treatment for hypertension, % | 28.8 | 30.4 | 0.692 |
| CVD at baseline          | 7.9          | 8.6          | 0.866   |
| Energy intake, kcal/day  | 1,788 (529)  | 1,705 (511)  | 0.079   |
| Fat, E%                  | 36.6 (6.6)   | 36.4 (6.6)   | 0.724   |
| Saturated fats, E%       | 16.6 (4.2)   | 16.5 (4.2)   | 0.784   |
| Carbohydrates, E%        | 43.5 (6.9)   | 43.2 (7.4)   | 0.644   |
| Protein, E%              | 17.5 (3.5)   | 17.8 (3.3)   | 0.364   |
| Dietary fiber, g/1,000 kcal | 11.6 (3.7) | 11.9 (4.4) | 0.305   |
| Total LTPA, h/week       | 6.6 (5.6)    | 8.1 (6.5)    | 0.007   |
| Moderate-vigorous LTPA, h/week | 2.6 (3.0) | 2.9 (3.2) | 0.279   |

Means (SD) are shown for continuous variables. Boldface data indicate the significance of P value (P < 0.05 or less). CVD, cardiovascular disease; LTPA, leisure time physical activity.

shown in Supplementary Table 1. As shown previously, weight reduction was greater and glycemic control improved more in the intervention group than in the control group (17,18). In the intervention group, persons with FH+ achieved significantly greater reduction in 2-h plasma glucose than did persons with FH−. However, no significant interactions between FH and control/ intervention groups were found in the changes in body weight, fasting plasma glucose, 2-h plasma glucose, homeostasis model assessment (HOMA) of insulin resistance, HOMA of insulin sensitivity, or energy intake. In addition, no major differences were found in the distribution of macronutrients or physical activity between FH+ and FH− groups after 1 year of intervention (data not shown).

Incidence of type 2 diabetes by family history

Incidence of type 2 diabetes in the intervention and control group by FH of diabetes is shown in Fig. 1 (data in Supplementary Table 2). During the original randomized trial period of 4 years on average, the incidence of diabetes seemed to be lower in the intervention group than in the control group in persons with FH+ (P = 0.61). After adjustment for age, sex, baseline BMI, fasting glucose, and study center, the HR for diabetes in the intervention group compared with the control group was 0.42 (95% CI 0.26–0.70, P = 0.0008) in persons with FH+, whereas it was 0.61 (95% CI 0.33–1.12, P = 0.11) in persons with FH−. During the entire follow-up, in the adjusted model, the effect of intervention was, however, significa-

Effect of gene variants and genetic risk score on the incidence of type 2 diabetes

We did not find any significant effects of the 19 risk variants on the incidence of type 2 diabetes (data not shown). Similarly, combined type 2 diabetes risk alleles of 19 SNPs (presented as GRS) did not have a significant effect on the incidence of diabetes during the entire follow-up period (P = 0.784 in the adjusted model). GRS based on eight SNPs influencing insulin secretion (20) (GRSSEC) also did not have a significant effect (P = 0.459). The persons with FH+ and FH− did not differ in the GRS (17.5 ± 2.7 vs. 17.6 ± 2.8, P = 0.726). No statistical evidence for an interaction between GRS (or GRSEC) and randomization group on the incidence of type 2 diabetes was found (P = 0.656 or 0.340 for the interaction).

Predictors of the incidence of type 2 diabetes

In the Cox regression analysis, including GRS (19 SNPs), FH, and randomization group, adjusted for age, BMI, sex, and center, only the intervention group had a significant effect on the incidence of diabetes (Table 2). A further Cox regression analysis including age, sex, BMI, fasting and 2-h glucose and fasting and 2-h in-

CONCLUSIONS—The current study aimed to investigate whether the FH+ per se, or the genetic risk variants and GRS based on 19 known type 2 diabetes-risk SNPs, modulated the effects of lifestyle intervention in the DPS participants. FH did not affect the result of lifestyle intervention during the entire follow-up. We did not observe any aggregation of known genetic risk variants in persons with FH+, nor did genetic risk variants modify the incidence of diabetes. On the basis of different analyses, in addition to the intervention, fasting and 2-h plasma glucose and fasting insulin at baseline, and the 1-year changes of 2-h plasma glucose and 2-h insulin were the main determinants of the development of diabetes.
during the follow-up, independently of the effects of genetic risk variants and FH.

Although the participants with FH+ seemed to have a lower incidence of diabetes than those with FH− during the first 4 years of follow-up when the active intervention was carried out, this early difference disappeared during the entire follow-up. The seemingly better early response could be explained by the fact that individuals with FH+ may be more aware of the risk of diabetes than others (21) and thus more motivated, as suggested by their greater decrease in total caloric intake during the first year of intervention ($P = 0.012$). In addition, the mean 1-year change in the 2-h plasma glucose values was greater among the participants with FH+ in the lifestyle intervention group. It should be noticed that at baseline no differences were found in any clinical or biochemical measurements, which could explain the present findings of the differences during the intervention phase in the incidence of diabetes between individuals with FH+ and FH−.

The known genetic risk variants were not associated with the FH of diabetes. However, this may not be an unexpected finding because it is known that risk loci confer only 10% of the risk of type 2 diabetes (2,22). Furthermore, all participants in the DPS had screened IGT based on two OGTTs and 60% had an FH+, which also might indicate an aggregation of genetic risk variants. In the general population, FH+ varies from 25% to 40% depending on selection of populations in different studies (4,12–14). It could be argued that a small sample size could explain why no significant association between genetic risk variants and FH or the type 2 diabetes risk was found. However, this may not be the case, because in regression analyses not even a trend to an association with the diabetes risk was found. It is of note that the total number of diabetes cases was 185 during the entire follow-up. This figure is almost comparable to 255 cases in the Framingham Offspring Study (5), including 2,377 participants with 28 years of follow-up. In that study, the adjusted C-statistic was 0.595 without the genotype score and 0.615 with the score ($P = 0.11$). In a larger study on Swedish and Finnish cohorts, including 18,831 individuals (4), of whom 2,201 developed diabetes during a median follow-up of 23.5 years, the addition of specific genetic information to clinical factors slightly improved the prediction of

Figure 1—Incidence of type 2 diabetes during the intervention period of 4 years (A) (end indicated by a vertical line) and during the entire follow-up period (B) by FH and randomization group (intervention vs. control) in the DPS. Solid line is for the control group. During the intervention follow-up of 4 years on average, intervention had significant effect on the incidence of type 2 diabetes in the FH+ group ($P = 0.0002, *P = 0.0008$) but not in the FH− group ($P = 0.61, *P = 0.11$). During the entire follow-up, intervention had an effect in both FH+ ($P = 0.0004, *P = 0.002$) and FH− ($P = 0.13, *P = 0.006$) groups. $P$ is from Kaplan–Meier analysis, *$P$ after adjustment for age, sex, baseline BMI, baseline fasting glucose, and study center in Cox regression model.
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Table 2—Effect of family history of diabetes, genetic risk score, intervention, and clinical variables on the incidence of type 2 diabetes

|                          | HR     | 95% CI      | P value |
|--------------------------|--------|-------------|---------|
| A                        |        |             |         |
| Family history of T2DM   | 0.78   | (0.57–1.06) | 0.118   |
| GRS (19 SNPs)            | 1.04   | (0.90–1.20) | 0.617   |
| Intervention vs. control group | 0.55   | (0.41–0.75) | 1.2 × 10⁻⁴ |
| B                        |        |             |         |
| Family history of T2DM   | 0.80   | (0.57–1.11) | 0.180   |
| GRS (19 SNPs)            | 1.02   | (0.87–1.18) | 0.940   |
| Intervention vs. control group | 0.52   | (0.38–0.72) | 5.9 × 10⁻⁵ |
| Fasting glucose (baseline) | 1.69   | (1.44–1.99) | 2.2 × 10⁻⁹ |
| 2-h glucose (baseline)   | 1.35   | (1.14–1.60) | 0.0005  |
| Fasting insulin (baseline) | 1.25   | (1.03–1.53) | 0.025   |
| 2-h insulin (baseline)   | 0.81   | (0.63–1.02) | 0.076   |
| BMI (baseline)           | 1.17   | (0.98–1.39) | 0.077   |
| C                        |        |             |         |
| Family history of T2DM   | 0.92   | (0.65–1.29) | 0.609   |
| GRS (19 SNPs)            | 1.02   | (0.88–1.18) | 0.797   |
| Intervention vs. control group | 0.74   | (0.52–1.06) | 0.106   |
| Fasting glucose (baseline) | 1.93   | (1.57–2.38) | 3.5 × 10⁻¹⁰ |
| Δ Fasting glucose (1-year change) | 1.15   | (0.96–1.38) | 0.129   |
| 2-h glucose (baseline)   | 1.69   | (1.39–2.05) | 9.1 × 10⁻⁸ |
| Δ 2-h glucose (1-year change) | 1.62   | (1.32–1.98) | 3.4 × 10⁻⁶ |
| Fasting insulin (baseline) | 1.35   | (1.06–1.73) | 0.015   |
| Δ Fasting insulin (1-year change) | 1.18   | (0.97–1.44) | 0.103   |
| 2-h insulin (baseline)   | 1.05   | (0.79–1.39) | 0.755   |
| Δ 2-h insulin (1-year change) | 1.36   | (1.05–1.75) | 0.018   |
| BMI (baseline)           | 1.18   | (0.99–1.40) | 0.061   |
| Δ BMI (1-year change)    | 1.19   | (0.98–1.44) | 0.084   |

For dichotomous variables, HRs are shown for the intervention group. FH+ of T2DM, and male subjects. For continuous variables, HRs are expressed as unit change per 1 SD. A, B, C represent alternative models: A = effects of FH, GRS, and intervention without clinical variables. B = including clinical variables at baseline. C = including 1-year changes in these variables (Cox regression, all models are adjusted for age, sex, baseline BMI, and study center). Boldface data indicate the significance of P value (P < 0.005 or less). T2DM, type 2 diabetes mellitus.

The main predictors of the incidence of type 2 diabetes in our study were the lifestyle intervention, fasting and 2-h glucose, fasting insulin at baseline, and 1-year change in 2-h glucose and 2-h insulin. The finding that the 1-year changes in the 2-h glucose and insulin levels were powerful predictors of diabetes, whereas the 1-year change in fasting glucose level, which primarily reflects insulin secretion, did not contribute to the success rate of prevention, suggests a significant role of an improvement of insulin sensitivity along with weight reduction. Indeed, in a substudy of DPS, there was a marked improvement of insulin sensitivity based on intravenous glucose tolerance test along with weight loss, but only small changes were found in insulin secretion (23). Overall, these results show that an elevation of fasting glucose with poor insulin secretion capacity and the degree of insulin resistance and obesity remain the main predictive factors among known risk factors for type 2 diabetes. We cannot exclude the possibility that the known genetic risk variants could have been operative in an earlier phase of development of diabetes, but along with this line, the changes in lifestyle also might be more effective in earlier phases of this disease.

Because insulin secretion and insulin sensitivity are not independent of each other, both mechanisms could be operative when searching biological explanations for the markedly decreased risk of diabetes in prevention trials such as the DPS. It has been hypothesized that lifestyle intervention may have beneficial effects on insulin secretion avoiding the exhaustion of β-cells and thus delaying the progression of disturbed insulin secretion capacity. Because the decrease in the 2-h glucose and insulin had a marked impact on the risk reduction of diabetes, we believe that an improvement in insulin sensitivity and perhaps concomitant recovery of β-cell sensitivity to glucose (24) could mainly explain the observed beneficial effects of changing lifestyles on the diabetes risk.

To conclude, conventional risk factors and lifestyle changes known to decrease the risk of diabetes are the most important predictors of type 2 diabetes in persons with IGT, and lifestyle changes overcome the impact of the known genetic and familial risk. This information is important both for health professionals and for persons at increased risk for type 2 diabetes. Our results in conjunction with some former population-based studies and the DPP genetic studies indicate that genetic risk testing at this point may not offer much additional information applicable to prevention strategies of type 2 diabetes to that obtained from patients’ FH and the well-known clinical risk markers.

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M.I.U. and J.T. are the principal investigators of the DPS. M.I.U. and A.S. wrote the article. A.S. and M.P. analyzed the data. J.T., J.L., M.I.U., S.K.-K., S.A., P.I.-P., and J.G.E. participated in the data collection and interpretation of the results. M.L. was responsible for genetic analyses and contributed to the interpretation of the results. All authors have seen the final version of the article and have commented on it before the acceptance of the article.

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