

# The Association Between a Family History of Type 2 Diabetes and Coronary Artery Disease in a Type 1 Diabetes Population

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**OBJECTIVE** — To examine whether a potential marker for type 2 diabetes (family history) is related to CAD in type 1 diabetic subjects. The two major types of primary diabetes, type 1 and type 2, are both associated with an increased risk of developing coronary artery disease (CAD). However, the etiology and associated risk factors may differ by type of diabetes. In type 2 diabetes, CAD is likely to be linked with the insulin resistance associated with the type 2 “process,” while CAD in type 1 diabetes has, so far, been more closely linked to renal disease. Because the etiologies of type 1 and type 2 diabetes are different, it is possible that some CAD in type 1 diabetes may be related to the coexistence of type 2 diabetes susceptibility (i.e., insulin resistance).

**RESEARCH DESIGN AND METHODS** — We evaluated the interrelationships between family history of type 2 diabetes (age at onset >30 years, no insulin for 1st year) and presence of CAD in a cohort of childhood-onset type 1 diabetic subjects using the Pittsburgh Epidemiology of Diabetes Complications study ( $n = 658$ ).

**RESULTS** — A first-degree family history of type 2 diabetes was reported in 112 subjects, and CAD was present in 119 subjects. Those subjects reporting a family history of type 2 diabetes were significantly older, had a longer duration of type 1 diabetes, had higher triglyceride and LDL cholesterol levels, and had a borderline significantly increased Beck depression inventory. Sex differences in CAD risk factors were also noted. Using logistic regression analysis, the odds ratio (95% CI) for the presence of CAD in association with a family history of NIDDM was 1.89 (1.27–2.84). The odds ratio (95% CI) after adjusting for disease duration, triglycerides, hypertension, Beck depression, and nephropathy status was 1.45 (0.87–2.28).

**CONCLUSIONS** — We conclude that a family history of type 2 diabetes is a risk factor for CAD in type 1 diabetic subjects. This supports the concept that insulin resistance may contribute to development of CAD in type 1 diabetes.

The two main forms of primary diabetes are associated with an increased risk of coronary artery disease (CAD) (1). Type 1 diabetes is an autoimmune disease leading to the destruction of the  $\beta$ -cells of the pancreas, resulting in an absolute insulin deficiency (2). Type 2 diabetes, while less well understood, is associated with insulin resistance and often

obesity, leading to hyperinsulinemia,  $\beta$ -cell dysfunction, hyperglycemia, and eventually insulin deficiency (3).

Type 1 and type 2 diabetes differ in their etiology and risk factors for cardiovascular disease. The cardiovascular disease seen in type 2 diabetes is linked mainly to insulin resistance (4), while the cardiovascular disease in type 1 diabetes

has been reported to be most closely linked to the presence of renal disease (5). Whether part of the cardiovascular risk in type 1 diabetes is also related to the inheritance of type 2 diabetes susceptibility (i.e., insulin resistance) is largely unexplored.

Since these two diseases differ in their etiologies, the possibility that both diseases could develop in a small group of individuals warrants consideration. The coexistence of an autoimmune insulin deficiency and an inherited or acquired insulin resistance would therefore be considered “double diabetes.” The implications of this coexistence would likely lead to a markedly increased risk for CAD.

To explore the possibility that those people with potential double diabetes have an increased risk for CAD, a positive family history of type 2 diabetes has been used as a marker for the presence of type 2 diabetes susceptibility in a type 1 (childhood-onset) diabetic population. A family history of type 2 diabetes has been shown to be associated with increased risk of type 2 diabetes, as well as an increased risk of CAD in normal and diabetic adults (6,7). Moreover, first-degree relatives of individuals with type 2 diabetes have been shown to be hyperinsulinemic and to have a more atherogenic pattern of cardiovascular risk factors (6). Therefore, we have examined the interrelationships between a positive family history of presumed type 2 diabetes and the macrovascular complications of type 1 diabetes.

## RESEARCH DESIGN AND METHODS

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study is a 10-year prospective study based on a well-defined cohort of childhood-onset (<17 years) type 1 diabetic subjects. There were 658 eligible subjects (325 women, 333 men) diagnosed between 1 January 1950 and 30 May 1980 who were first seen at baseline (1986–1988). They have been seen biennially thereafter.

For this analysis, a cross-sectional design was used in which the most recent

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**Abbreviations:** AER, albumin excretion rate; CAD, coronary artery disease; EDC, Pittsburgh Epidemiology of Diabetes Complications.

Table 1—Characteristics of subjects by family history of type 2 diabetes

|  | Present      | Absent       | P value |
|--|--------------|--------------|---------|
| n  | 112          | 546          |         |
| Age (years)  | 36.0 ± 0.72  | 32.9 ± 0.36  | <0.001  |
| Duration of diabetes (years)                             | 27.4 ± 0.76  | 24.7 ± 0.34  | <0.001  |
| LDL cholesterol (mg/dl)                                  | 129.7 ± 3.82 | 117.5 ± 1.66 | 0.003   |
| CAD (%)  | 30 (26.8)    | 89 (16.3)    | 0.009   |
| Ever smoker (%)  | 54 (48.2)    | 196 (36.4)   | 0.020   |
| Triglycerides (mg/dl)                                    | 102.2 ± 1.07 | 88.8 ± 1.03  | 0.025   |
| Beck depression index                                    | 8.6 ± 0.79   | 7.2 ± 0.33   | 0.066   |
| Hypertension (%)   | 35 (31.2)    | 134 (24.5)   | 0.139   |
| Overt nephropathy (%)                                    | 37 (35.9)    | 130 (25.5)   | 0.030   |
| Fibrinogen (mg/dl)                                       | 342.4 ± 10.4 | 332.3 ± 4.71 | 0.377   |
| HbA <sub>1c</sub> (%)                                    | 10.8 ± 0.18  | 10.7 ± 0.08  | 0.785   |
| Insulin dose (U · kg <sup>-1</sup> · day <sup>-1</sup> ) | 0.70 ± 0.02  | 0.71 ± 0.01  | 0.797   |
| Waist (cm)   | 81.1 ± 0.8   | 79.9 ± 0.4   | 0.207   |
| BMI (kg/m <sup>2</sup> )                                 | 17.5 ± 0.8   | 17.9 ± 0.3   | 0.652   |

Data are n (%) or means ± SE.

clinic visit data (up to the 8-year follow-up [1994–1996]) were used for each subject. This approach enables the subjects to be optimally characterized for CAD and family history of type 2 diabetes. In this particular analysis, the mean age was 33.4 years and the mean duration was 25.1 years.

Both a standardized medical history and clinical examination were performed by a trained internist to document cardiovascular disease. Coronary artery disease (CAD) comprised a diagnosis of angina by a clinic physician or a confirmed myocardial infarction (pathological Q waves or validated hospital records). A 12-lead electrocardiogram was obtained, along with blood pressures measured by a random-zero sphygmomanometer according to a standard protocol (8) after a 5-min rest period. Subjects were considered to be hypertensive if they were taking blood pressure medication and/or if they had a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Height was measured using the clinic stadiometer, and weight was measured on a Detecto physician scale. Waist circumference has been used as measure of visceral adiposity (9).

Family history information was ascertained on the general medical history questionnaire. A family history of presumed type 2 diabetes was initially identified as diabetes diagnosed after 30 years of age in the first-degree relatives of the participant. Those identified were further evaluated to validate the diagnosis and type of diabetes. A family history of type 2 diabetes was confirmed if insulin therapy was not initi-

ated within a year of diagnosis. Additional information, sought to further confirm the type of diabetes, included weight at diagnosis, history of ketoacidosis, and what the patient was told in terms of a diagnosis.

Details regarding the clinical evaluation and metabolic evaluation have been previously reported (10,11). Fasting blood samples were taken from each EDC study participant for the measurement of lipids, lipoproteins, HbA<sub>1c</sub>, and fibrinogen (10,11). Stable HbA<sub>1c</sub> was originally measured in saline-incubated samples by microcolumn cation-exchange chromatography (Isolab, Akron, OH). On 26 October 1987, the method was changed to high-performance liquid chromatography (Diamat, Bio-Rad Laboratories, Hercules, CA). Readings of the two methods were shown to be almost identical ( $r = 0.95$ ; Diamat HbA<sub>1c</sub> =  $-0.18 + 1.00$  Isolab HbA<sub>1c</sub>). The difference between the means of the two methods was 0.158% (normal range, 4.9–7.3% HbA<sub>1c</sub>). The Beck depression inventory, a quantitative measure of depressive symptomatology, was also included among the medical history and lifestyle questionnaires (12).

Nephropathy status was determined based on consistent results from at least two of three (24-h, overnight, and random timed post-clinic urine) timed urine albumin excretion rates (AER). Overt nephropathy was defined as an AER >200 µg/min or end-stage renal disease (renal dialysis or transplant). In the absence of two complete urine collections, a urinary albumin-to-creatinine ratio (measured in milligrams) >0.31 was used to define overt

nephropathy as previously described. In the absence of any urine specimens, a serum creatinine >2 mg/dl was considered to be indicative of overt nephropathy. Urinary albumin was determined immunonephelometrically (13).

Cross-sectional analyses included Student's *t* test for continuous variables and  $\chi^2$  test for categorical variables. Logistic regression was used where odds ratios for continuous variables have been expressed per standard deviation of the variable. Odds ratios for categorical variables have been expressed per unit of variable. A forward stepwise multiple logistic regression was used to determine the model of best fit for predicting CAD using significant univariate predictors (Table 3). For those variables that were highly correlated with each other (i.e., age and duration, total and LDL cholesterol) only one was chosen (i.e., duration, LDL cholesterol). Family history of type 2 diabetes was then forced into the model, and the forward stepwise method was repeated to determine which variables accounted for the association between family history and CAD.

**RESULTS** — A positive first-degree family history of diabetes was initially reported by 145 subjects. Of these subjects, 26 had a first-degree relative with adult-onset type 1 diabetes. Of the remaining 119 subjects with a family history, 7 were not confirmed either because they had a history of gestational diabetes, secondary diabetes, or had improperly completed one of the questionnaires. Thus, 112 had a positive family history for type 2 diabetes, including 9 subjects with a family history of both type 1 and type 2 diabetes, and 12 subjects with 2 family members with a history of type 2 diabetes.

Table 1 shows that patients reporting a positive family history for type 2 diabetes were significantly older, had a longer type 1 diabetes duration, as well as increased triglycerides and LDL cholesterol. Those with a positive family history were also more likely to smoke and have overt nephropathy. These patients also had borderline significantly higher Beck depression index scores (a quantitative measure of depressive symptomatology) than those not reporting a family history.

Table 2 lists the characteristics of those with and without a reported family history of type 2 diabetes by sex. The men reporting a history of type 2 diabetes were significantly older and had a borderline increase

Table 2—Characteristics of subjects by family history of type 2 diabetes and sex

|  | Men          |             |         | Women        |             |         |
|--|--------------|-------------|---------|--------------|-------------|---------|
|  | Present      | Absent      | P value | Present      | Absent      | P value |
| n  | 48           | 285         |         | 64           | 261         |         |
| Age (years)  | 35.5 ± 1.0   | 33.0 ± 0.5  | 0.047   | 36.3 ± 1.0   | 32.7 ± 0.5  | 0.003   |
| Duration of diabetes (years)                             | 26.8 ± 1.1   | 25.2 ± 0.4  | 0.187   | 27.9 ± 1.0   | 24.1 ± 0.5  | 0.001   |
| LDL cholesterol (mg/dl)                                  | 131.6 ± 5.2  | 122.3 ± 2.2 | 0.114   | 128.1 ± 5.5  | 112.3 ± 2.4 | 0.005   |
| Ever smoker (%)  | 28 (58.3)    | 106 (37.9)  | 0.008   | 26 (40.6)    | 90 (34.9)   | 0.393   |
| Triglycerides (mg/dl)                                    | 113.6 ± 1.1  | 95.9 ± 1.0  | 0.070   | 94.1 ± 1.1   | 81.7 ± 1.0  | 0.092   |
| Beck depression index                                    | 7.2 ± 1.2    | 6.0 ± 0.4   | 0.258   | 9.8 ± 1.0    | 8.5 ± 0.5   | 0.248   |
| Hypertension (%)   | 15 (31.2)    | 83 (29.1)   | 0.766   | 20 (31.2)    | 51 (19.5)   | 0.042   |
| Overt nephropathy  | 17 (38.6)    | 77 (29.0)   | 0.196   | 20 (33.9)    | 53 (21.7)   | 0.050   |
| Fibrinogen (mg/dl)                                       | 326.1 ± 16.1 | 333.6 ± 6.8 | 0.676   | 354.4 ± 13.6 | 330.8 ± 6.4 | 0.107   |
| Insulin dose (U · kg <sup>-1</sup> · day <sup>-1</sup> ) | 0.75 ± 0.04  | 0.74 ± 0.01 | 0.752   | 0.67 ± 0.03  | 0.68 ± 0.01 | 0.778   |
| HbA <sub>1c</sub> (%)                                    | 10.9 ± 0.3   | 10.8 ± 0.1  | 0.764   | 10.6 ± 0.2   | 10.7 ± 0.1  | 0.846   |
| Waist (cm)   | 85.2 ± 1.0   | 83.4 ± 0.5  | 0.190   | 78.0 ± 1.1   | 76.0 ± 0.5  | 0.090   |
| BMI (kg/m <sup>2</sup> )                                 | 17.6 ± 1.2   | 18.2 ± 0.5  | 0.629   | 17.4 ± 1.1   | 17.5 ± 0.5  | 0.914   |
| CAD (%)  | 11 (22.9)    | 50 (17.5)   | 0.375   | 19 (29.7)    | 39 (14.9)   | 0.006   |

Data are n (%) or means ± SE.

in triglycerides compared with those not reporting a family history. The women with a family history of type 2 diabetes were found to have significant increases in age, duration, LDL cholesterol, and hypertension. The women also were found to have borderline increases in waist circumferences and triglycerides.

Table 3 shows the major risk factors for CAD status. By 1996, there were 119 cases of CAD. As shown in Table 3, the individuals with CAD were more likely to have a family history than those without CAD. The odds ratio (95% CI) for the presence of CAD in association with family history of type 2 diabetes was 1.89 (1.27–2.84). Taking into account the number of family members with a case of type 2 diabetes, the  $\chi^2$  test for trend in association with the presence of CAD is 9.96 (P = 0.001), where the odds ratio for one family member is 1.62 and increases to 5.13 for two family members. A family history of type 2 diabetes was significantly associated with the presence of CAD even after separate adjustments for duration, triglycerides, hypertension, Beck depression index, and nephropathy status.

Multiple logistic regression analysis is presented in Table 4. Allowing the variables that were significant in univariate analysis to enter the model using a forward stepwise method, the family history of type 2 diabetes does not enter the model (model 6). To examine which variables primarily account for the prediction of CAD by family history, modeling was repeated having forced family history into the model. Family history

remains significant after inclusion of both duration and nephropathy status (model 3). However, on inclusion of Beck depression index, family history is no longer significant (model 4). Interestingly, the model fit is better (i.e., -2 log likelihood ratio is smaller) for model 5 (including family history) than for model 6 (without family history), although not significantly.

**CONCLUSIONS** — These results suggest that a positive family history for type 2 diabetes is a risk factor for CAD in individuals with type 1 diabetes. It also appears

that the number of family members with type 2 diabetes is also significantly associated with increasing risk. This supports the concept that insulin resistance may contribute to the development of CAD in type 1 diabetes, as those with more than one relative with type 2 diabetes would have an increased probability of inheriting the susceptibility than those with only one relative.

Previous studies have shown that a family history of type 2 diabetes is associated with increased CAD risk factors both in those with (7) and in those without (6,7) type 2 diabetes. Of current interest is

Table 3—Characteristics of subjects by CAD status

|  | Present      | Absent      | P value |
|--|--------------|-------------|---------|
| n  | 119          | 539         |         |
| Age (years)  | 39.2 ± 0.7   | 32.1 ± 0.3  | <0.001  |
| Duration of diabetes (years)                             | 30.7 ± 0.7   | 23.9 ± 0.3  | <0.001  |
| Cholesterol (mg/dl)                                      | 213.9 ± 5.1  | 190.1 ± 1.8 | <0.001  |
| LDL cholesterol (mg/dl)                                  | 130.8 ± 3.9  | 117.0 ± 1.6 | <0.001  |
| Ever smoker (%)  | 57 (48.3)    | 193 (36.2)  | <0.001  |
| Triglycerides (mg/dl)                                    | 125.2 ± 1.1  | 84.6 ± 1.0  | <0.001  |
| Beck depression index                                    | 11.6 ± 0.8   | 6.5 ± 0.3   | <0.001  |
| Hypertension (%)   | 60 (50.4)    | 109 (20.2)  | <0.001  |
| Overt nephropathy (%)                                    | 61 (58.1)    | 106 (20.9)  | <0.001  |
| Fibrinogen (mg/dl)                                       | 368.8 ± 10.4 | 326.3 ± 4.6 | <0.001  |
| HbA <sub>1c</sub> (%)                                    | 11.1 ± 0.2   | 10.7 ± 0.1  | 0.017   |
| Insulin dose (U · kg <sup>-1</sup> · day <sup>-1</sup> ) | 0.65 ± 0.02  | 0.72 ± 0.01 | 0.007   |
| Family history of type 2 diabetes                        | 30 (25.2)    | 82 (15.2)   | 0.009   |
| Waist (cm)   | 82.5 ± 0.9   | 79.6 ± 0.4  | 0.002   |
| BMI (kg/m <sup>2</sup> )                                 | 17.5 ± 0.8   | 17.9 ± 0.3  | 0.678   |

Data are n (%) or means ± SE.

Table 4—Multiple logistic regression analyses with CAD as a dependent variable

| Independent variable         | Model 1           | Model 2           | Model 3           | Model 4           | Model 5           | Model 6           |
|------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| History of type 2            | 1.89 (1.27–2.84)† | 1.62 (1.04–2.51)† | 1.64 (1.04–2.61)† | 1.53 (0.95–2.46)* | 1.45 (0.87–2.28)  | —                 |
| Duration of diabetes (years) | 8¶                | 2.61 (2.04–3.34)§ | 2.56 (1.97–3.33)§ | 2.59 (1.99–3.37)§ | 2.49 (1.88–3.30)§ | 2.51 (1.90–3.33)§ |
| Nephropathy status           | —                 | —                 | 3.16 (2.13–4.69)§ | 2.97 (1.97–4.47)§ | 1.93 (1.23–3.05)† | 1.93 (1.22–3.05)† |
| Beck depression index        | 7.5¶              | —                 | —                 | 1.73 (1.39–2.14)§ | 1.73 (1.39–2.15)§ | 1.74 (1.40–2.16)§ |
| Triglycerides (mg/dl)        | 110¶              | —                 | —                 | —                 | 2.30 (1.51–3.50)§ | 2.36 (1.55–3.60)§ |
| Hypertension                 | —                 | —                 | —                 | —                 | 1.98 (1.18–3.31)† | 1.94 (1.16–3.26)† |
| –2 log likelihood            | 568.5             | 499.3             | 463.0             | 438.0             | 413.7             | 415.9             |

Data are odds ratios (95% CI). Model 6 is the forward stepwise logistic regression, which included family history, LDL cholesterol, waist circumference, fibrinogen, HbA<sub>1c</sub>, smoking, and insulin dose in addition to the variables that entered the model. Models 1–5 are the forward stepwise regression after forcing family history into the model with the same variables available to the model. \* $P < 0.1$ ; † $P < 0.05$ ; ‡ $P < 0.01$ ; § $P < 0.001$ ; ¶odds ratio expressed per standard deviation of the variable.

whether individuals with type 1 diabetes are at increased risk, independent of the typical type 1 risk factors, for cardiovascular disease in the presence of a family history of type 2 diabetes. In this study, a family history of type 2 diabetes in this type 1 cohort was associated with an increased prevalence of CAD.

The multivariate analyses indicate that this association appears to be linked with age and duration. This is not surprising as the older subjects would likely have older relatives and therefore be more likely to develop type 2 diabetes. In addition to duration, the relationship of family history to CAD appears to be associated with depression. While the current analysis is a cross-sectional design, we have reported previously that depressive symptomatology predicts incidence of CAD (15). We therefore do not feel that the cross-sectional association within this analysis is entirely the result of the CAD causing depressive symptomatology. While family history of type 2 diabetes does not enter the model in the forward stepwise method, inclusion of family history before the forward stepwise regression yields a slightly lower log likelihood, suggesting an equivalent model. At the completion of the 10-year follow-up of the EDC study, we should have sufficient numbers of incident cases of CAD to examine this relationship prospectively.

The relationship between a family history of type 2 diabetes and CAD risk factors in the type 1 diabetic subjects is less clear. While many CAD risk factors were increased in those with a family history, only triglycerides and hypertension were significant independent predictors of CAD in multivariate models. LDL cholesterol is strongly associated with CAD in our population but does not enter any of the multivariate models. These findings may reflect

the complexity of the overlapping disease etiologies. Renal impairment, which confers risk for CAD in type 1 diabetes, is associated with increased LDL cholesterol levels, which may explain why LDL cholesterol is not independent of renal disease.

Our observations are limited by both the proxy measure of insulin resistance and the cross-sectional design. The proxy measure of insulin resistance, family history of type 2 diabetes, does not account for the interrelationships between the genetic and environmental determinants of insulin resistance. Furthermore, it is clearly an imprecise marker of type 2 diabetes that not all subjects with a family history of type 2 diabetes will develop type 2 diabetes. The association is therefore likely to be much stronger. This imprecise classification may explain the lack of a relationship between family history and either HbA<sub>1c</sub> or insulin dose. However, these cross-sectional analyses can only suggest an association between a family history and presence of CAD. Further investigation including prospective analyses (in progress) are needed to clarify the relationship between insulin resistance and both the risk factors and CAD in type 1 diabetes.

To our knowledge only one other study has investigated the associations between insulin resistance and macrovascular complications in subjects with type 1 diabetes (14). Martin et al. (14) found prospectively that a decreased glucose assimilation index was associated with death from vascular disease. While the study did use a prospective design, some methodological issues warrant consideration. First, the initial assessment of glycemic control was made before the introduction of HbA<sub>1c</sub>. Second, the study had a limited sample size ( $n = 51$ ) and select criteria. Individuals were selected with the criteria that they were nonobese

and have a duration of diabetes  $>15$  years at commencement of the study. Interestingly, in this nonobese population a significant association between insulin resistance and atherosclerotic disease was noted, although no measure of body composition was mentioned.

In summary, a family history of type 2 diabetes is a significant univariate risk factor for the presence of CAD in our type 1 diabetes cohort. Apart from its correlation with time-dependent variables (age, duration), this association appears to be particularly linked to depressive symptomatology. We conclude that this supports the concept of double diabetes with an accompanying increased risk of CAD, and suggests that a family history of type 2 diabetes may be a useful marker to identify a subgroup of type 1 diabetic subjects with increased CAD risk.

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