Familial History of Type 2 Diabetes in Patients from Southern Brazil and its Influence on the Clinical Characteristics of this Disease

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Daisy Crispim
Luís H. Canani
Jorge L. Gross
Balduíno Tschiedel
Kátia E.P. Souto
Israel Roisenberg

Departamento de Genética, Universidade Federal do Rio Grande do Sul, UFRGS (DC, IR); Divisão de Endocrinologia, Hospital de Clínicas de Porto Alegre, UFRGS (LHC, JLG); e Grupo Hospitalar Conceição (BT, KEPS), Porto Alegre, RS.

ABSTRACT

Objective: To investigate the presence of maternal and paternal history of type 2 diabetes mellitus (DM) in relatives of 644 type 2 diabetic patients from Southern Brazil, and also to evaluate its influence on the clinical characteristics of this disease. **Patients and Methods:** Familial history of type 2 DM was investigated by a questionnaire. The maternal and paternal history was investigated over two generations. Complete data sets on familial history were obtained from 396 patients. **Results:** In general, 76.6% of the patients reported at least one first-degree affected relative. Besides, 31.6% of the patients reported a maternal history of type 2 DM and 12.6% reported a paternal history. Patients with maternal and/or paternal history presented a lower age at type 2 DM diagnosis when compared to patients without familial history. In addition, patients with only paternal history presented a higher frequency of hypertension than patients with no familial history. **Conclusions:** This study suggests that there is a significant maternal effect in the transmission of type 2 DM in Southern Brazil, and that most of the clinical characteristics of this disease do not differ between patients with or without familial history of type 2 DM. **(Arq Bras Endocrinol Metab 2006;50/5:862-868)**

Keywords: African-Brazilians; Caucasian-Brazilians; Familial history of type 2 diabetes; Maternal transmission; Type 2 diabetes

RESUMO

História Familiar de Diabetes Tipo 2 em Pacientes do Sul do Brasil e sua Influência nas Características dessa Doença.
Objetivos: Investigar a presença de história materna e paterna de diabetes mellitus tipo 2 (DM) entre familiares de 644 pacientes diabéticos tipo 2 provenientes do sul do Brasil, bem como avaliar sua influência nas características clínicas dessa doença. **Materiais e Métodos:** A história familiar de DM tipo 2 foi investigada através de um questionário, sendo que a presença de história materna e paterna foi investigada em duas gerações. Dados completos sobre história familiar foram obtidos para 396 pacientes. **Resultados:** Em geral, 76,6% dos pacientes reportaram ao menos um familiar em primeiro grau afetado por DM tipo 2. Além disso, 31,6% dos pacientes relataram uma história materna de DM tipo 2 e 12,6% relataram uma história paterna. Pacientes com história materna e/ou paterna apresentaram uma idade de diagnóstico de DM tipo 2 mais baixa quando comparado a pacientes sem história familiar. Adicionalmente, pacientes que relataram apenas história paterna de DM tipo 2 apresentaram uma maior freqüência de hipertensão do que pacientes sem história familiar. **Conclusões:** Nosso estudo sugere que há um efeito materno significativo na transmissão do DM tipo 2 no Sul do Brasil, e que a maioria das características clínicas dessa doença não difere entre pacientes com e sem história familiar de DM tipo 2. **(Arq Bras Endocrinol Metab 2006;50/5:862-868)**

Descritores: Descendentes de africanos; Descendentes de europeus; História familiar de diabetes tipo 2; Transmissão materna; Diabetes tipo 2

IT IS ACCEPTED THAT FAMILIAL history is an important risk factor for the developing of type 2 diabetes mellitus (DM). In addition, type 2 diabetic patients are more likely to have diabetic mothers than diabetic fathers (1-9). However, this excess of maternal transmission of type 2 DM has not been consistently observed across races. Although this inheritance pattern has been observed in populations with lower prevalence of DM (North American [4,9], English [5], French [6], Chinese [3,8] and Japanese [1] populations), negative findings have been reported in some ethnic groups with high prevalence of this disease (Hispanics and South Asian Indians) (10-12).

Some studies have shown that the adult offspring of diabetic parents are more obese than those of non-diabetic parents and display higher fasting plasma levels of glucose, insulin, triglycerides, total cholesterol and LDL cholesterol (13). Similarly, in Pima Indians, maternal DM is associated with higher blood pressure (BP) in the offspring (14). Recently, a study reported that the offspring of diabetic mothers displayed higher body mass index (BMI) and triglycerides when compared to the offspring of diabetic fathers (15). However, there are still few studies regarding the influence of familial history on the clinical characteristics of type 2 DM, in particular concerning the role of the paternal history on these characteristics.

The aims of this study were to compare the prevalence of maternal and paternal history of type 2 DM in patients from Southern Brazil with type 2 DM, and to evaluate the roles of familial histories of DM on the clinical and laboratory characteristics of this disease.

PATIENTS AND METHODS

The study group consisted of 644 unrelated type 2 diabetic patients (514 Caucasian- and 130 African-Brazilians) participating in a multicenter study in the Brazilian State of Rio Grande do Sul. Diagnosis of type 2 DM was based on the World Health Organization criteria (16). Patients over 30 years old and who had been treated with oral glucose lowering agents for over two years with no history of ketoacidosis were included in the study. Ethnic definition was based on self-report. The Caucasian-Brazilians were descendents from Europeans, mainly from Portugal, Spain, Italy and Germany, whereas the African-Brazilians were descendents from people brought to Brazil, between the 17th and 18th centuries, mainly from the west coast of Africa, Angola and Mozambique. Written informed consent was obtained from all patients and the study was approved by the Hospitals' Ethical Committees.

All patients (242 men, 402 women; mean age at examination 58.3 ± 11.2 years; mean age at onset 47.0 ± 11.9 years) underwent standardized clinical and laboratory investigations. Weight and height were used to calculate BMI. Sitting BP was measured after a 5-min rest using a mercury sphygmomanometer. The mean value of the two measurements was used to calculate systolic and diastolic BP. Hypertension was defined as BP levels ≥ 140/90 mmHg or the use of anti-hypertensive drugs. Diabetic retinopathy was assessed by an ophthalmologist and classified as absent, non-proliferative, or proliferative. The renal status was based on the albumin excretion rate (AER) measured in at least two out of three consecutive 24-h timed urine collections. Patients were classified as normo- (AER< 20 mg/min), micro- (AER 20–199 mg/min), or macroalbuminurics (AER > 200 mg/min). Patients also answered a questionnaire about familial history of type 2 DM (parent, aunts and uncles, siblings and offspring). Responses to the questionnaire were requested as 'yes', 'no' or 'don't know'. A clear maternal or paternal history was defined as presence of relatives with type 2 DM in three consecutive generations or through two consecutive generations with at least three affected relatives.

Fasting blood glucose was determined using the glucose oxidase method; creatinine by the Jaffé reaction; glycated haemoglobin (HbA_{1c}) by an ion-exchange HPLC procedure (Merck-Hitachi L-9100 GhB Analyser, reference range: 4.7–6.0%); total plasma cholesterol and triglycerides by enzymatic methods; urinary albumin concentration by immunoturbidimetry (Sera-Pak immuno microalbuminuria, Bayer, Tarrytown, NY), and C-peptide levels by radioimmunoassay (Diagnostic System Laboratories Incorporation, Webster, USA).

Statistical analyses

Data are presented as means ± SD or percentage (n). The presence of familial history of type 2 DM was examined over two generations in three independent analyses, the results obtained in the first-generation analyses of mothers versus fathers and maternal aunts and uncles versus paternal aunts and uncles being confirmed by the second-generation analysis of men and women patients and their offspring. The percentage of patients with a positive history of diabetic mother or father was investigated according to the patients' age at type 2 DM diagnosis, divided into three age-range classes. Clinical and laboratory characteristics of the

patients grouped according to the presence of maternal, paternal, and both maternal and paternal history of type 2 DM were compared by ANOVA, Kruskal-Wallis or χ^2 tests (when differences were detectable, pairwise comparisons or analyses of the normalized residuals were done, as appropriate). All analyses were performed using the SPSS version 10.0 (SPSS, Chicago, IL, USA), and in all cases, a two-tailed probability value of $p < 0.05$ was considered significant.

RESULTS

The familial history of type 2 DM for the parents, including the proportion of patients who did not know the familial diabetic status were available for all 644 patients; while complete familial history data through two generations were available for only 396 patients. Table 1 shows the frequencies of patients who reported diabetic relatives. Caucasian- and African-Brazilians, as well as men and women, are presented together because they did not differ from any of the analyses made (data not shown).

In general, 76.6% of the patients reported at least one first-degree affected familial member. History of type 2 DM among mothers was reported by a higher percent of the diabetic patients compared to the history of type 2 DM among fathers (48.4% versus 21.3%; $\chi^2 = 103.516$; $p < 0.001$). The same pattern was observed for history of type 2 DM among maternal aunts or uncles compared to the paternal relatives (14.9% versus 6.1%; $\chi^2 = 15.558$; $p < 0.001$); thus suggesting an excess of maternal transmission in this generation. In addition, 35.2% of the patients reported only a diabetic mother when compared to 9.9% who reported only a diabetic father ($\chi^2 = 116.509$; $p < 0.001$); while 10.0% presented both the parents with type 2 DM. The excess of maternal history was reinforced by results found in the second generation: 17.2% of the diabetic mothers had diabetic children when compared to 6.3% of the diabetic fathers ($\chi^2 = 7.241$; $p = 0.007$).

When we grouped the patients according to their age at type 2 DM diagnosis, divided into three-range classes (figure 1), we observed that in the 30–42 years-old class (n= 167), 62.3% of the subjects reported a diabetic mother and only 26.3% reported a diabetic father ($\chi^2 = 42.235$; $p < 0.001$), while in the 42.1–52 years-old class (n= 145), 48.9% had evidence of an affected mother and 17.2% of an affected father ($\chi^2 = 31.276$; $p < 0.001$), and in the 52.1–86 years-old class (n= 157), 44.6% had an affected mother and 12.7% had an affected father ($\chi^2 = 35.837$; $p < 0.001$). The percentage of patients who reported diabetic mothers decreased from 62.3% to 44.6% ($\chi^2 = 9.486$; $p = 0.002$) as age at diagnosis increased, and the percentage of patients who reported a diabetic father decreased from 26.3% to 12.7% ($\chi^2 = 4.759$; $p = 0.029$); but the maternal effect was homogeneous over the three classes ($\chi^2 = 1.639$; $p = 0.441$).

Table 1. Percentages of type 2 diabetic patients with familial history of type 2 DM.

Family Relationship	Percentage (number)
At least one first-degree relative	76.6 (493)
Mother[a]	48.4 (312)
Father[a]	21.3 (137)
Siblings	51.7 (333)
Maternal aunt or uncle[b]	14.9 (59)
Paternal aunt or uncle[b]	6.1 (24)
Offspring	12.9 (51)
When the patient is a man[c]	31.6 (125)
When the patient is a woman[c]	12.6 (50)
Clear maternal history[d]	6.3 (10)
Clear paternal history[d]	17.2 (41)

Details about the frequencies of diabetic mothers, fathers and siblings, and first-degree relatives were available for 644 patients, while details about the frequencies of diabetic offspring, maternal and paternal aunts and uncles, and clear maternal and paternal history were available for 396 patients. [a]$\chi^2 = 103.516$ and $p < 0.001$ for comparison of frequencies of affected mother versus affected father; [b]$\chi^2 = 15.558$ and $p < 0.001$ for comparison of frequencies of affected maternal aunt or uncle versus paternal aunt or uncle; [c]$\chi^2 = 7.241$ and $p = 0.007$ for comparison of presence of diabetic offspring between males and females; [d]$\chi^2 = 40.167$ and $p < 0.001$ for comparison of frequencies of clear maternal history versus clear paternal history.
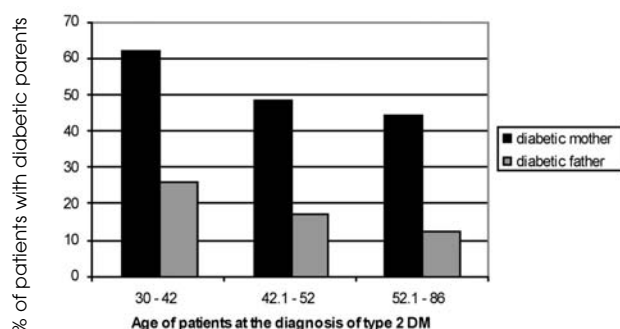
Figure 1. Percentages of type 2 diabetic patients with diabetic mothers or fathers, according to their age at type 2 DM diagnosis. The maternal effect was homogeneous over the three classes (p= 0.441).

Approximately 31.6% of the patients reported a clear maternal history of type 2 DM and 12.6% reported a clear paternal history (χ^2= 40.167; p< 0.001). Of these patients, 18.4% presented only maternal history, 5.3% presented only paternal history (χ^2= 30.458; p< 0.001), and 6.1% presented maternal and paternal history. The percentage of diabetic patients who did not know the familial history was also analyzed: 24.7% of the patients did not know the diabetic status of the maternal line and 28.7% did not know the diabetic status of the paternal line (χ^2= 2.479; p= 0.115).

The clinical and laboratory characteristics of the patients grouped according to the presence of maternal, paternal, and both paternal and maternal history are depicted in table 2. Patients with clear maternal and/or paternal history of type 2 DM were younger at type 2 DM diagnosis when compared to patients with no familial history. In addition, patients with only paternal history presented a higher frequency of hypertension than individuals without familial history. Moreover, those patients who did not know the diabetic status of the maternal and/or paternal lines of the family were older (p= 0.017) and had the type 2 DM diagnosed later (p= 0.023) than patients who were able to reported all the affected relatives in at least the two generations analyzed.

DISCUSSION

Seventy-six percent of the type 2 diabetic patients investigated in this study reported at least one first-degree affected familial member, reinforcing the strong familial aggregation of type 2 DM (1-9,17,18). We found a significant excess of maternal history of type 2 DM (presence of a diabetic mother was approximately twice more frequent than presence of a diabetic father), suggesting a maternal transmission of this type of DM, which is in line with several previous studies (1-9,18). Alcolado and Alcolado (5), investigating parental type 2 DM in Britain, found that 36.0% of the mothers of diabetic patients were themselves diabetic when compared to only 15.0% of the fathers. These values were nearly identical to those of a French study conducted by Thomas et al. (6): 33.0% of the mothers and 17.0% of the fathers of type 2 diabetic patients being affected. Furthermore, our results are in agreement with another Brazilian study, which reported 71.5% of patients with at least one diabetic among first degree relatives and found that 25.0% of the 116 analyzed type 2 diabetic patients reported a diabetic mother when compared to 15.5% who reported a diabetic father (18). In the same way that our study, these latter two studies also confirmed the maternal effect with data obtained from the offspring of diabetic parents.

Ethnic differences in the transmission of type 2 DM have been suggested as one reason for some differing results existing in literature (10-12). In the present study, the frequency of maternal DM did not differ between Caucasian- and African-Brazilians, suggesting that there are not ethnic differences in our population.

We observed that the frequency of patients who reported an affected mother and/or father decreased as the age at type 2 DM diagnosis was later. This result is in agreement with some studies (6,17), which had indicated that the severity of DM and the age at type 2 DM onset are genetically determined, and that environmental factors are more important when onset of DM occurs later in life.

Both genetic and environmental factors can contribute to the excess of maternal transmission of type 2 DM. It has been postulated that women with type 2 DM during their pregnancy have an increased risk of transmitting this disease to their offspring compared with non-diabetic women (19,20). Some authors hypothesized that excessive nutrition may be teratogenic, and argued that the factors associated with the diabetic environment *in utero* may have a direct effect on the fetus, increasing insulin secretion and perhaps leading to the development of insulin resistance in the child (21,22).

Mitochondrial DNA mutations can also be invoked to explain the excess of maternal inheritance of type 2 DM, since they are transmitted exclusively from women to offspring. Indeed, an A to G substitution at nucleotide 3243 of the tRNALeu(UUR) mitochondrial gene have been described in several families

Table 2. Clinical characteristics of patients according to maternal and/or paternal history of type 2 DM.

	Maternal history	Paternal history	Maternal and paternal history	Without familial history	P
Age (years)	56.8 ± 10.8	56.5 ± 10.2	57.3 ± 11.1	57.9 ± 10.8	0.121
Age at diagnosis (years)*	44.9 ± 11.6ª	41.7 ± 11.2ª	42.5 ± 10.9ª	49.3 ± 11.0ᵇ	0.045
Hypertension (%)*	61.9ª	90.5ᵇ	70.8ª	54.0ᶜ	0.004
BMI (kg/m²)	28.9 ± 5.1	28.7 ± 5.6	28.7 ± 5.3	30.0 ± 4.7	0.684
Fasting glucose (mmol/l)	10.6 ± 3.6	10.9 ± 3.9	11.1 ± 4.1	9.0 ± 3.1	0.189
HbA1c (%)	6.7 ± 1.8	5.9 ± 2.1	7.3 ± 1.7	6.0 ± 1.6	0.851
Total cholesterol (mmol/l)	5.6 ± 1.1	5.6 ± 1.3	6.0 ± 1.4	5.6 ± 1.3	0.417
Creatinine (mmol/l)	75.2 (35.3–300.5)	77.8 (53.8–265.2)	79.6 (44.2–356.6)	76.2 (35.3–265.2)	0.251
Triglycerides (mmol/l)	1.7 (0.5–4.4)	2.3 (0.7–16.3)	1.7 (0.6–6.8)	1.6 (0.4–16.6)	0.487
C-peptide (nmol/l)	0.8 ± 0.5	0.9 ± 0.6	0.8 ± 0.6	1.1 ± 0.6	0.086
Retinopathy (%)	40.0	46.7	50.0	52.2	0.428
Nephropathy (%)	36.8	39.3	27.7	40.3	0.837

Data are shown as means ± SD,% or geometric mean (range).
* Analyses with significant differences: means or % indicated by the same letter do not differ significantly at α< 0.05 and means or % indicated by different letters differed from the others.

with DM and deafness (23). Our group reported that the m.3243A>G mutation occurs in a frequency of only 0.4% in the same type 2 diabetic group analyzed in the present study and in none of the healthy controls subjects (24). Thus, it seems unlikely that this mutation plays an important role in the maternal transmission of type 2 DM in our population. However, we cannot exclude the possibility that other mitochondrial mutation could contribute to the excess of maternal transmission of type 2 DM. Recently, we observed the m.1888G>A variant in the mitochondrial 16S rRNA gene in 12.3% of the Caucasian-Brazilian type 2 diabetic sample also studied in the present work and in 0.8% of the control group (25). The relatively high frequency of this variant in Caucasian-Brazilian type 2 diabetic patients from Southern Brazil could explain a fraction of the excess of maternal transmission reported by us.

As in other studies (1-6), the present data were self-reported. This type of data is susceptible to bias because patients can provide more facts about maternal relatives than about paternal relatives (6). Thorand et al. (26), investigating the association between DM and parental history among the participants of the MONICA Augsburg Study, reported that "unknown" maternal status was more common than "unknown" paternal status (17.3% versus 8.8%), concluding that the higher prevalence of maternal history could be explained by this bias. However, Kahn et al. (27) concluded that patients with DM were able to report an accurate family history when carefully questioned. The present data suggests that this bias had not occurred because the patients answered that did not know the

familial history of type 2 DM in a similar frequency to the maternal and paternal line of the family.

There are other potential censoring and reporting biases that also could explain the excess of maternal history on segregation of the type 2 DM. Longer average life span in women could increase the likelihood that mothers develop type 2 DM (6), and as a corollary, men with insulin resistance-associated cardiovascular disease could die before the clinic diagnostic of DM (28). However, the fact that three times as many women as men probands, whose mean ages were similar (approximately 57.3 ± 11.0 years for both), reported offspring with type 2 DM in our study, would argue against such bias. Furthermore, women may be more likely to be diagnosed because of their greater exposure to the healthcare system. In addition, mothers may develop DM at an earlier age than fathers. However, earlier onset of type 2 DM in women was not noted in our study because age at diagnosis did not differ between the sexes (about 46.8 ± 10.1 years for both). The homogeneity of the maternal excess across probands' age at diagnosis provides additional evidence against potential biases associated with a delay in the age of diagnosis in fathers relative to mothers.

Regarding to the influence of familial history in the clinical and laboratory characteristics of type 2 DM; age at type 2 DM diagnosis was associated with maternal and/or paternal history, whereas hypertension was associated with only paternal history. These data are in agreement with the study of Bo et al. (29) and suggest that environmental factors may be more relevant in determining the other clinical and labora-

tory characteristics (as metabolic control and diabetic complications) studied in our population.

In summary, a significant excess of maternal history of type 2 DM was observed in the present study. Besides, considering that the frequency of parental type 2 DM was higher in patients who presented an earlier age at type 2 DM diagnosis, and that patients with parental history of type 2 DM did not differ in respect to the clinical and laboratory characteristics, this study indicates that in type 2 DM, the genetic component is more important to its development when the disease is diagnosed at an earlier age, while is possible that environmental factors become more relevant in later-onset patients.

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Endereço para correspondência:

Israel Roisenberg
Av. Bento Gonçalves 9500
Caixa Postal 15053
91501-970 Porto Alegre, RS
Fax: (51) 3316-7311
E-mail: israberg@ufrgs.br