

# The prevalence of chronic diabetic complications and metabolic syndrome is not associated with maternal type 2 diabetes

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The maternal history of type 2 diabetes mellitus (DM) has been reported more frequently in patients with type 2 DM than paternal history. The aim of the present study was to determine if there was an association between maternal history of DM and the presence of chronic complications or metabolic syndrome (MetS) in patients with type 2 DM. A cross-sectional study was conducted with 1455 patients with type 2 DM. All outpatients with type 2 diabetes attending the endocrine clinics who fulfilled the eligibility criteria were included. Familial history of DM was determined with a questionnaire. Diabetic complications were assessed using standard procedures. The definition of MetS used was that of the World Health Organization and the National Cholesterol Education Program's Adult Treatment Panel III report criteria. Maternal history of DM was present in 469 (32.3%), absent in 713 (49.1%) and unknown in 273 patients (18.7%). Paternal history of DM was positive in 255 (17.6%), negative in 927 (63.8%) and unknown in 235 patients (16.1%). The frequency of microvascular chronic complications in patients with and without a positive maternal history of DM was similar: diabetic nephropathy (51.5 vs 52.5%), diabetic retinopathy (46.0 vs 41.7%), and diabetic sensory neuropathy (31.0 vs 37.1%). The prevalence of macrovascular chronic complications and MetS was also similar. Patients with type 2 DM were more likely to have a maternal than a paternal history of DM, although maternal history of DM was not associated with an increased prevalence of chronic complications or MetS.

Key words: Type 2 diabetes mellitus; Metabolic syndrome; Microvascular chronic complications; Diabetic retinopathy

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## Introduction

Parental history of diabetes mellitus (DM) is often reported by patients with type 2 DM. Maternal history of type 2 DM has been reported to be more frequent than paternal history by some investigators (1-7) and we have previously reported a maternal effect in DM transmission in a subset of 644 patients (8). However, other studies have not observed this association (9,10).

Recently, it was shown that insulin-resistant offspring of parents with type 2 DM have dysregulation of intramyocellular fatty acid metabolism, probably due to an inherited

defect in mitochondrial oxidative phosphorylation (11). This supports the hypothesis that decreased mitochondrial function is related to insulin resistance (12). Since mitochondrial DNA is transmitted exclusively by the mother, these data suggest the possible association between maternal DM and type 2 DM and/or insulin resistance in the offspring.

Furthermore, intrauterine environmental factors also seem to play a role in the post-natal development of insulin resistance (13-15). The presence of DM during pregnancy has been associated with insulin resistance, metabolic syndrome (MetS) or DM in offspring of several ethnic

groups (4,13-15). Even in the absence of DM during pregnancy, maternal history of DM could be associated with disturbances in carbohydrate metabolism compatible with the presence of insulin resistance in offspring (2,4,6,16). Since insulin resistance is also considered to be a risk factor for diabetic micro- and macrovascular complications (17,18), patients with type 2 DM and positive maternal history of DM could be at higher risk of presenting chronic complications of diabetes.

The aim of the present study was to determine if maternal history of DM is associated with MetS or the chronic complications of diabetes in patients with type 2 DM.

## Patients and Methods

### Patients

A total of 1455 patients with type 2 diabetes were identified in a multicentric study that began recruiting patients in Southern Brazil in 2002. The objective of that study was to determine risk factors for chronic complications of diabetes. Details of the recruitment procedure have been described (19). Briefly, the project included four centers located at general hospitals in the State of Rio Grande do Sul, namely Grupo Hospitalar Nossa Senhora da Conceição, Hospital São Vicente de Paula, Hospital Universitário de Rio Grande, and Hospital de Clínicas de Porto Alegre.

All outpatients with type 2 diabetes attending the endocrine clinics who fulfilled the eligibility criteria were included. The patients were eligible if they had type 2 DM diagnosed according to World Health Organization criteria (WHO) (20): absence of diabetic ketoacidosis, diagnosis after 35 years of age, and use of insulin beginning 2 years after diagnosis of DM or later. The study protocol was approved by all Hospitals Ethics Committees, and written informed consent was obtained from all patients.

### Patient evaluation

Patients were evaluated for chronic complications of DM and for MetS features. A standard questionnaire was used to collect information about age, known duration of DM, drug treatment, smoking habits, and parental history of DM. All patients underwent a complete physical examination and laboratory tests. Patients were weighed in light outdoor clothes without shoes, and height was recorded. Body mass index was calculated as weight (kg) divided by height<sup>2</sup> (m<sup>2</sup>). Waist circumference was measured on a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Sitting blood pressure was measured twice on the right arm to the nearest 2 mmHg after a 10-min rest using a standard

mercury sphygmomanometer (phases I and V of Korotkoff sounds). A brief neurologic examination evaluated the presence of Achilles tendon reflexes, ability to recognize vibration from a 128-mHz tuning fork at the hallux, and the presence of sensory sensitivity (10 g Semmes-Weinstein monofilament at three places on each foot).

### Definition of variables

The presence of diabetic retinopathy was assessed by an ophthalmologist and graded as: 1) no signs of diabetic retinopathy; 2) non-proliferative diabetic retinopathy (microaneurysms, hemorrhage, hard exudates), or 3) proliferative diabetic retinopathy (newly formed blood vessels and/or fibrous tissue into the vitreous cavity).

Diabetic nephropathy was defined by increased urinary albumin excretion in the absence of urinary tract infection or other renal abnormalities. Based on a 24-h urine collection or casual spot urine samples, diabetic nephropathy was categorized as microalbuminuria (20-199 µg/min or 18-174 mg/L) and macroalbuminuria ( $\geq$ 200 µg/min or  $>$ 174 mg/L) (21).

The diagnosis of distal sensory neuropathy was based on abnormal Achilles tendon reflexes, vibration or sensory perception.

Peripheral vascular disease was diagnosed by the presence of intermittent claudication, assessed by the WHO questionnaire for cardiovascular disease (22) or the absence of posterior tibial pulse upon clinical examination.

The diagnosis of coronary heart disease was based on the presence of angina or possible infarct according to the WHO questionnaire for cardiovascular disease (23), and/or on the presence of resting ECG abnormalities (Minnesota Code) (23) and/or on the presence of perfusion abnormalities (fixed or variable) on myocardial scintigraphy at rest and after dipyridamole administration. The presence of stroke was established by history and/or the presence of compatible findings (sequelae).

Hypertension was considered to be present when blood pressure was  $\geq$ 140/90 mmHg, or if the patient was taking antihypertensive drugs. Obesity was defined as body mass index  $>$ 30 kg/m<sup>2</sup> and/or waist-hip ratio  $>$ 0.90 for men and  $>$ 0.85 for women. Dyslipidemia was defined by triglycerides  $\geq$ 150 mg/dL and/or high-density lipoprotein (HDL) cholesterol  $<$ 39 mg/dL for men and  $<$ 45 mg/dL for women.

Since all subjects had DM, MetS was diagnosed according to WHO recommendations (20) by the presence of two or more of the following: obesity, hypertension, dyslipidemia and microalbuminuria, and according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATP-III) (24) by the presence of two or more of the following: abdominal obesity (men  $>$ 102 cm

and women >88 cm), elevated triglycerides ( $\geq 150$  mg/dL), low HDL cholesterol (men <40 and women <50 mg/dL) and elevated blood pressure ( $130/\geq 85$  mmHg).

Insulin resistance was assessed using the homeostasis model assessment (HOMA-IR): fasting serum insulin (pmol/L) x fasting plasma glucose (mmol/L) / 22.5.

### Laboratory methods

Urinary albumin excretion rate was measured in 24-h sterile urine samples by immunoturbidimetry (Microalb, Ames-Bayer, USA; intra- and interassay coefficients of variation (CV): 4.5 and 11.0%, respectively) or in casual spot urine samples (25). The presence of microalbuminuria or macroalbuminuria was confirmed by at least two measurements performed 3 to 6 months apart.

Glucose levels were determined by a glucose oxidase method; creatinine by the Jaffé reaction; GHb by an ion-exchange HPLC procedure (Merck-Hitachi L-9100 Glycated Hemoglobin Analyser, Germany; reference range: 2.7-4.3%) (26) and triglycerides and cholesterol levels by enzymatic methods (Merck Diagnostica, Boehringer Mannheim, Germany) (27,28). Low-density lipoprotein cholesterol was calculated using the Friedewald equation (29). Serum insulin was measured by radioimmunoassay (ElecsysR Systems 1010/2010/modular analytics E170, Roche Diagnostics, USA; reference range: 2.6-24.9  $\mu$ U/mL; inter-assay CV = 3.45% and intra-assay CV = 2.0%).

### Data analysis

Data are reported as means  $\pm$  standard deviation (SD) or absolute numbers and percentages. Variables with normal distribution were analyzed by the Student *t*-test. Variables with non-Gaussian distribution were analyzed by the Mann-Whitney test. The chi-square test was used for categorical data. A (two-sided) *P* value <0.05 was considered to be significant.

### Results

The mean age of the patients was 57.8  $\pm$  10.2 years, 47.5% were males and the average duration of DM was 12.8  $\pm$  9.2 years (see Table 1).

Maternal history of DM was present in 469 (32.3%), absent in 713 (49.1%), and unknown in 273 patients (18.7%). Paternal history of DM was positive in 256 (17.6%), negative in 927 (63.8%) and unknown in 272 patients

(18.6%). Among the patients with known parental history (N = 1182), maternal history was almost twice as frequent as paternal history (39.6 vs 21.5%, *P* < 0.05). Isolated maternal history represented 369 (31.2%) answers and isolated paternal history represented only 155 (13.1%, *P* < 0.05). One hundred patients (8.4%) reported both maternal and paternal history and 558 (47.2%) patients had no parental history of DM.

The clinical and laboratory characteristics of the patients grouped according to the presence or absence of maternal history of DM are also reported in Table 1. Patients with a maternal history of DM were younger. On the other hand, positive maternal history of DM was not associated with characteristics of MetS such as hypertension, obesity, dyslipidemia, increased abdominal circumference, HOMA-IR, and glucose metabolic control.

The frequency of micro- or macrovascular complications of DM is reported in Table 2. Patients with and without maternal history of DM had the same prevalence of microvascular complications: diabetic nephropathy (51.5 vs 52.5%), diabetic retinopathy (46 vs 41.7%) and distal sensory neuropathy (31.0 vs 37.1%). Similarly, patients with and without maternal history had the same proportion of microalbuminuria (25.8 vs 20.6%) and macroalbuminuria or dialysis (26.8 vs 32.2%). The proportion of macro-

**Table 1.** Clinical and laboratory characteristics of patients with or without maternal diabetes mellitus (DM).

	Maternal history of diabetes	
	Positive (N = 469)	Negative (N = 713)
Age (years)	56.5 $\pm$ 9.87	59.4 $\pm$ 10.5*
Male gender (%)	49.5%	46.1%
Duration of DM (years)	13.3 $\pm$ 9.5	12.4 $\pm$ 9.2
White (%)	73.0%	70.5%
Systolic blood pressure (mmHg)	140.4 $\pm$ 22.3	142.7 $\pm$ 22.1
Diastolic blood pressure (mmHg)	85.3 $\pm$ 13.5	86.5 $\pm$ 12.8
Hypertension (%)	78.1%	80.1%
Body mass index (kg/m <sup>2</sup> )	28.7 $\pm$ 5.2	28.6 $\pm$ 5.2
Abdominal circumference (cm)	98 $\pm$ 11.5	97.9 $\pm$ 12.09
Fasting glucose (mg/dL)	178.3 $\pm$ 77.1	172.5 $\pm$ 81.2
A1C (%)	7.28 $\pm$ 2.12%	7.25 $\pm$ 2.21%
Total cholesterol (mg/dL)	204.0 $\pm$ 51.9	208.4 $\pm$ 55.8
HDL cholesterol (mg/dL)	44.5 $\pm$ 14.1	44.7 $\pm$ 13.8
Triglycerides (mg/dL)	138 (36-1236)	149 (26-1669)
HOMA-IR	5.25 (0.27-64.65)	5.49 (0.30-61.98)

Data are reported as means  $\pm$  SD or percent except for triglycerides and HOMA-IR, which are reported as median (range). A1C = glycated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment for insulin resistance. There were no statistically significant differences between patients with or without maternal diabetes except for age. \**P* < 0.001 (Student *t*-test).

vascular complications was also similar between patients with and without a maternal history of DM: coronary heart disease (52.7 vs 52.3%), peripheral vascular disease (18.9 vs 23.5%) and stroke (7.7 vs 8.1%). The prevalence of MetS in both groups was also similar (70.3 vs 73.5%; Table 2). The same pattern for the presence of micro- and macrovascular complications according to the maternal history of DM, as well the frequency of MetS, were observed when the data were stratified by sex (data not shown).

## Discussion

The present study shows a higher prevalence of maternal history of DM compared to paternal history of DM in patients with type 2 DM.

The increased maternal history of DM was not associated with a higher prevalence of chronic complications of DM or MetS, despite the large number of patients included. This indicates that the presence of maternal history of DM cannot be used in clinical practice to identify individuals at higher risk of developing MetS or the complications of chronic diabetes.

Two other studies explored this issue in patients with type 2 DM (30,31). In the first (30), patients with MetS had a higher prevalence of parental history of DM and hypertension, with a slightly higher prevalence of maternal than paternal history of type 2 DM. Other diabetic complications were not evaluated in this study. The second study of type 2 DM (31) reported findings similar to ours: no association was found in the prevalence of chronic complications and

familiar history of DM. Other reports have also shown a higher prevalence of microvascular complications (especially diabetic nephropathy) in patients with type 1 DM who had a family history of type 2 DM (32,33) and in one report specifically a maternal history of type 2 DM (34). A recent study (35) showed that family history of type 2 DM, especially maternal history, was associated with an increased prevalence of type 2 DM and other obesity-related traits (including increased body mass index, waist-hip ratio, fasting triglycerides, HOMA-IR, plasma glucose, and lower HDL).

As in other studies, the present data regarding family history were self-reported. This type of data is susceptible to bias, because patients may remember more facts about their mothers than about their fathers. Thorand et al. (36) stated that this could explain the higher prevalence of maternal history of DM. However, Kahn et al. (37) concluded that patients with DM were able to report an accurate family history when carefully questioned. Another possible source of bias is the fact that the life expectancy of men is shorter than that of women, and thus the likelihood of DM diagnosis is higher in women. Our data suggest that these two sources of bias did not occur in this study, because the prevalence of unknown history was similar for fathers and mothers (15 vs 17%). Another possible limitation of the present study is the definition used for the presence of coronary heart disease. This was based on clinical history, resting ECG abnormalities or on myocardial scintigraphy. No systematic coronary catheterism was performed. Therefore, some false-positive or false-negative results might be present.

In the present study, maternal history of DM was defined as the presence of any type of DM at any moment during the life of the mother. We assumed that mothers with a history of DM had at some point presented some degree of insulin resistance during pregnancy, since the pre-diabetic status can precede the clinical onset of DM by several years (38). Our data did not include information such as age at onset of DM in the mothers or birth weight of the patients, which could indicate which patients were really exposed to a diabetic environment in the uterus. However, despite the lack of evidence of intra-uterine exposure to diabetes, maternal history of DM seems to be a risk factor for the development of metabolic syndrome, DM and/or impaired carbohydrate metabolism when offspring reach adulthood (16,25).

**Table 2.** Frequency of chronic diabetic complications and metabolic syndrome in patients with or without maternal diabetes mellitus.

	Maternal history of diabetes	
	Positive (N = 469)	Negative (N = 713)
Diabetic nephropathy	239 (51.5%)	370 (52.5%)
Diabetic retinopathy	216 (46%)	292 (41.7%)
Distal sensory neuropathy	146 (31%)	264 (37.1%)
Coronary heart disease	244 (52.7%)	370 (52.3%)
Peripheral vascular disease	85 (18.9%)	164 (23.5%)
Stroke	33 (7.7%)	57 (8.1%)
Metabolic syndrome (WHO)	328 (70.3%)	520 (73.5%)
Metabolic syndrome (ATP-III)	372 (79.3%)	575 (80.6%)

Data are reported as number of patients with percent within parentheses. WHO = World Health Organization; ATP-III = National Cholesterol Education Program's Adult Treatment Panel III report. There were no statistically significant differences in complications and metabolic syndrome in patients with or without maternal diabetes (chi-square test).

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