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Women relatives of hispanic patients with Type 2 diabetes are more prone to exhibit metabolic disturbances.

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Key words: Type 2 diabetes relatives, metabolic syndrome, gender, body fat, hispanics.

Abstract. Hyperinsulinemia and impaired insulin action are familial and predictive of Type 2 diabetes onset. Since high levels of insulin are characteristic of our general (venezuelan)hispanic population, the purpose of this investigation was to identify early metabolic defects in a group of healthy first degree relatives of Type 2 diabetic patients.We studied 46 (29 women and 17 men; ages ranging 18-66 y) first degree relatives of Type 2 diabetic patients comparing them with 22 (12 women and 10 men; ages ranging 22-60 y) subjects who had no family history of diabetes. All subjects underwent resting blood pressure and anthropometric measurements; a 75 g oral glucose tolerance test with determination of glucose and insulin and a fasting lipid profile. The relatives of Type 2 diabetic patients had higher tricipital (TC) and subscapular (SC) skinfolds, and elevated DBP in relation to the control group. The skinfolds elevation was more evident in women, while in men the elevation in DBP predominates. None of the relatives had glucose intolerance, however the glucose-stimulated insulin response was elevated at all points in men as well as in women. No difference was observed in the HOMA values for IR and beta cell function, or in the $\Delta I_{30}/\Delta G_{30}$ ratio. The lipid profile showed a marked elevation in TG levels in men as well as in women, with low HDL-C values in men. No other lipid abnormalities were observed. Correlation analysis revealed strong association between BMI and WHR with skinfolds and several parameters of the carbohydrate metabolism in women, but not in men. IR in women was possitively associated with skinfolds, SBP and lipid parameters and beta cell function with VLDL-C.Adult relatives of Type 2 diabetic venezuelan patients from

hispanic origin had, early in their lives, several parameters of the metabolic syndrome as hyperinsulinemia, obesity, dyslipidemia and high blood pressure. These alterations were more prominent in women, group in which the association among BMI, WHR and IR were statistically significant respect to SBP, DBP, basal insulin, insulin/glucose ratio, TG and HDL-C.

Las mujeres, familiares de pacientes hispanos con diabetes Tipo 2, son más propensas a exhibir alteraciones metabólicas.
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Palabras clave: Familiares de diabéticos, síndrome metabólico, género, grasa corporal, hispanos.

Resumen. La hiperinsulinemia, en conjunto con una alteración de la acción de la insulina, pueden predecir la aparición de diabetes Tipo 2. Dado que la población venezolana (de origen hispánico) se caracteriza por presentar niveles elevados de insulina, el propósito de esta investigación fue identificar defectos metabólicos tempranos en un grupo de individuos sanos con antecedentes familiares, en primer grado, de diabetes Tipo 2. Se estudiaron 46 sujetos (29 mujeres y 17 hombres, con rango de edad entre 18 y 66 años) con antecedentes familiares, en primer grado de diabetes Tipo 2. Este grupo se comparó con 22 individuos (12 mujeres y 10 hombres, con rango de edad entre 22 y 60 años) sin antecedentes familiares de diabetes. A cada uno de los sujetos en estudio se le determinó presión arterial en reposo, medidas antropométricas, respuesta de glucosa e insulina a una carga oral de 75 g de glucosa y perfil lipídico en ayunas. Los familiares de los diabéticos Tipo 2 presentaron presión arterial diastólica (PAD) mas elevada que el grupo sin antecedentes familiares de diabetes, predominando esta elevación en los hombres. Los pliegues tricipital (TC) y subescapular (SE) fueron mas altos en los familiares de diabéticos Tipo 2 comparados con el grupo control y esta elevación fue mas evidente en las mujeres. Ninguno de los familiares presentaron intolerancia a la glucosa, sin embargo, tanto los hombres como las mujeres de este grupo mostraron una respuesta insulínica estimulada por glucosa, superior en todos los puntos de la prueba, a la del grupo control. Los valores del HOMA para IR (HOMA-IR) y para la función de las células beta (HOMA-FCB), así como la relación $\Delta I_{30}/\Delta G_{30}$, no resultaron significativamente diferentes entre los dos grupos estudiados. Tanto los hombres como las mujeres familiares de diabéticos Tipo 2, presentaron elevación de los niveles de triglicéridos con una disminución de la HDL-C en los hombres. No se observó otra anormalidad en el perfil lipídico. En las mujeres familiares de diabéticos Tipo 2 se encontró correlación entre el índice de masa corporal (IMC) y el cociente cintura-cadera (CCC) con los pliegues y con diferentes parámetros del metabolismo de los carbohidratos. Esto no se

observó en los hombres. En las mujeres de este grupo, el HOMA-IR se encontró asociado con los pliegues, presión arterial sistólica y varios parámetros lipídicos; mientras que el HOMA-FCB se corrrelacionó con VLDL-C. Se concluye que los familiares en primer grado de diabéticos Tipo 2, adultos, venezolanos de origen hispánico, presentaron en etapas tempranas de su vida, diversos parámetros del sindrome metabólico como hiperinsulinemia, obesidad, dislipidemia y elevación de la presión arterial. Estas alteraciones fueron mas evidentes en las mujeres, en quienes se demostró una asociación significativa entre el IMC, CCC y HOMA-IR con la PAS, PAD, insulina basal, relación insulina/glucosa, TG y HDL-C.

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INTRODUCTION

Hyperinsulinemia and impaired insulin action appear to be familial and predictive of Type 2 diabetes onset (1-4). First degree relatives of non-insulin dependent diabetic patients have a 40% lifetime risk of developing diabetes; this risk becomes greater when there are two o more diabetic family members (5)

It is well recognized that obesity, hypertension, dyslipidemia and abnormal glucose tolerance coexist in the same individuals (6,7), hyperinsulinemia and insulin resistance are common factors associated with these conditions, and together this clustering of cardiovascular and risk factors is known as Syndrome X or metabolic syndrome (5). On the other hand, some reports suggest that inherited hyperinsulinemia could result in a higher prevalence of lipid abnormalities among members of Type 2 diabetes pedigrees (3,6,8,9).

Indirect evidence for the genetic role in the origin of Type 2 diabetes is provided by the marked differences in the prevalence of this disorder among different ethnic groups residing in the same geographic areas. Among hispanics, Haffner and col. have found (1) that Mexican Americans with proportionally higher degree of north american genetic admixture have a higher prevalence of Type 2 diabetes; besides the same group have reported hyperinsulinemia or insulin resistance in Mexican Americans without diabetes (10). However, Gonzalez-Ortiz and col (11) did not find differences in insulin sensitivity in young mexicans with a strong family history of Type 2 diabetes compared with those without family history.

Insulin resistance and other metabolic abnormalities can precede and predict IGT and Type 2 diabetes in high risk populations, and being high levels of insulin a characteristic of our general hispanic (Venezuelan) population (9,12,13), the purpose of this investigation was to identify early metabolic defects in a group of

healthy first degree relatives of Type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

We studied 46 first degree relatives of Type 2 diabetic patients from nine hispanic (Venezuelan) families with two or more members with the disease as defined by the National Diabetes Data Group criteria (14). These subjects (29 women and 17 men) were compared with 22 control subjects (12 women and 10 men) who had no familiy history of diabetes.

All subjects underwent resting blood pressure and anthropometric measurements (height, weight, subscapular (SC) and tricipital (TC) skinfolds and waist and hip circumference (WHR). Body mass index (BMI) was calculated as weight/height^2. Obesity was defined as having a BMI of 25 or more kg/m^2. WHR was a measure of upper body adiposity and the ratio SC/TC skinfolds or Centrality Index (CI) was chosen as a measure of central adiposity.

After a 12-hour overnight fast, blood samples were obtained to measure serum lipids and lipoproteins, glucose and insulin, after which a 75g oral glucose tolerance test (OGTT) was performed and blood was drawn at 30,60 and 120 min for the determination of serum glucose and insulin concentrations. The insulin/glucose ratio from fasting values (I_0/G_0) was taken as an indirect evidence of insulin resistance. Insulin secretion rate was calculated as (30-0 min)serum insulin/ (30-0 min) serum glucose ($\Delta I_{30}/\Delta G_{30}$), which Philips and col. (15) demonstrated to highly correlate with direct measurements of stimulated insulin secretion.

The 2-hour area under the curve (AUC) for glucose and insulin was calculated as in (16). The HOMA method (17) was used to calculate insulin resistance (IR) and beta cell function.

Total cholesterol (Chol) and triglycerides (TG) concentrations were measured using commercial kits (Sigma Diagnostics, USA). High density lipoprotein (HDL) was isolated after precipitation of apolipoprotein B containing lipoproteins, using phosphotungstate Mg++. The supernatant HDL-C was measured as described above. Serum VLDL-C and LDL-C were obtained from electrophoresis in agarose gel (18). Serum glucose was measured by the glucose oxidase method (Sigma Diagnostics, USA) and serum insulin concentration was determined using a solid phase radioimmunoassay (Diagnostic Products, USA).

According to previous reports in Venezuela (19) and to guidelines from the International Diabetes Federation (20) dyslipidemia was defined as having any of the following lipid abnormalities: TG > 150 mg/dl (1.69 mmol/L); Chol > 200 mg/dl (5.2 mmol/L); LDL-C > 130 mg/dl (3.35 mmol/L), VLDL-C > 30 mg/dl (0.88 mmol/L) and HDL-C <45 mg/dl (1.16mmol/L) in women and HDL-C < 35 mg/dl (0.9mmol/L) in men.

Statistical analysis

The results are expressed as means ± S.E. and were analyzed using the STATMOST 3.0 system for the Welchs Student t-test or the Mann Withney U test for non-parametric values when comparing variables. Significance in correlations was asessed by the Spearman coefficient correlation (r). The ANOVA test was used to compare glucose and insulin responses. Significance was accepted at the $p < 0.05$ level.

RESULTS

Clinical and anthropometric findings

In the group of relatives of Type 2 diabetic patients (n=46, ages ranging 18 to 66 years) we found that although the BMI and WHR were similar to the control group, the TC and SC skinfolds were significatively higher, with no alterations of the CI (Table I). Also, the diastolic blood pressure (DBP) was comparatively higher in the relatives.

If we separate the group by gender, the anthropometric measures show that the WHR became significatively different among men, but having the Type 2 diabetes relatives a lower ratio, while the skinfolds did not differ from the controls; so, the skinfolds increase observed in the whole group of relatives, was due mainly to larger values in women (Table I).

The elevation in the DBP was significantly only in men relatives; although the mean value for the DBP was not abnormally high we found two individuals with values of 100 mmHg. Same was true for the SBP, finding two individuals with values of 150 mmHg and one with 160 mmHg.

Among women relatives, none presented values over 130 mmHg for SBP or over 90 mm Hg for DBP.

It is worthwhile to mention that 13/17 men (77%) were obese (BMI over 25 kg/m^2) while among women obesity was present in 18/29 (62%).

Carbohydrate metabolism

In relation to parameters from the carbohydrate metabolism, none of the relatives had glucose intolerance (IGT). Their glycemic values never went over 11.1 mmol/L during the OGTT test or over 7.8 mmol/L at 2 h (Fig. 1). The profile of the curve revealed that the insulin response was higher in relatives at all points, being the response of females statistically different at 30 and 60 min, while in males the difference was significative at 60 and 120 min (Fig. 2)

For the relatives, as a whole, the glucose-stimulated insulin response was elevated, resulting in significatively higher insulin areas and fasting insulin/glucose ratio (Table II).

The HOMA values for IR were not statistically different, neither the HOMA beta cell function, nor the $\Delta I_{30}/\Delta G_{30}$ ratio.

Separating by gender, the same picture was observed, a glucose-stimulated hyperinsulinemia was present in men as in women, with

TABLE I
CLINICAL AND ANTHROPOMETRIC CHARACTERISTICS IN RELATIVES OF TYPE 2 DIABETIC PATIENTS AND CONTROL SUBJECTS WITHOUT FAMILY HISTORY OF DIABETES

	TOTAL		WOMEN		MEN	
	Relatives n = 46	Controls n = 22	Relatives n = 29	Controls n = 12	Relatives n = 17	Controls n = 10
Age (years)	35.6 ± 1.7	34.8 ± 2.2	35.2 ± 2.0	35.4 ± 3.4	36.3 ± 3.2	34.0 ± 2.8
BMI (Kg/m^2)	25.9 ± 0.5	24.7 ± 0.5	26.0 ± 0.8	23.9 ± 0.8	25.8 ± 0.6	25.6 ± 0.7
WHR	0.9 ± 0.01	0.9 ± 0.03	0.8 ± 0.01	0.82 ± 0.01	1.0 ± 0.01 [c]	1.05 ± 0.01
SC (mm)	24.6 ± 1.0 [a]	18.1 ± 1.4	25.9 ± 1.4 [b]	17.1 ± 2.2	22.1 ± 1.3 [c]	19.3 ± 1.8
TC (mm)	20.9 ± 1.2 [b]	14.7 ± 1.3	23.6 ± 1.2 [b]	16.1 ± 2.1	15.6 ± 1.8	13.0 ± 1.5
CI	1.3 ± 0.1	1.35 ± 0.1	1.1 ± 0.1	1.09 ± 0.08	1.7 ± 0.2	1.7 ± 0.3
SBP (mmHg)	120.2 ± 1.8	120.7 ± 1.8	116.7 ± 1.6	119.2 ± 2.4	126.2 ± 3.7	122.5 ± 2.9
DBP (mmHg)	78.5 ± 1.2	73.9 ± 1.3	76.7 ± 1.3	73.3 ± 1.9	81.8 ± 2.3[c]	74.7 ± 2.0

Data are expresed as mean ± SE.
BMI = Body mass index; WHR = Waist / hip ratio; SC = Subscapular skinfolds; TC = Tricipital skinfolds; CI = Centrality index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.
[a] $p < 0.0005$, [b] $p < 0.002$, [c] $p < 0.05$, in relation to their respective controls.

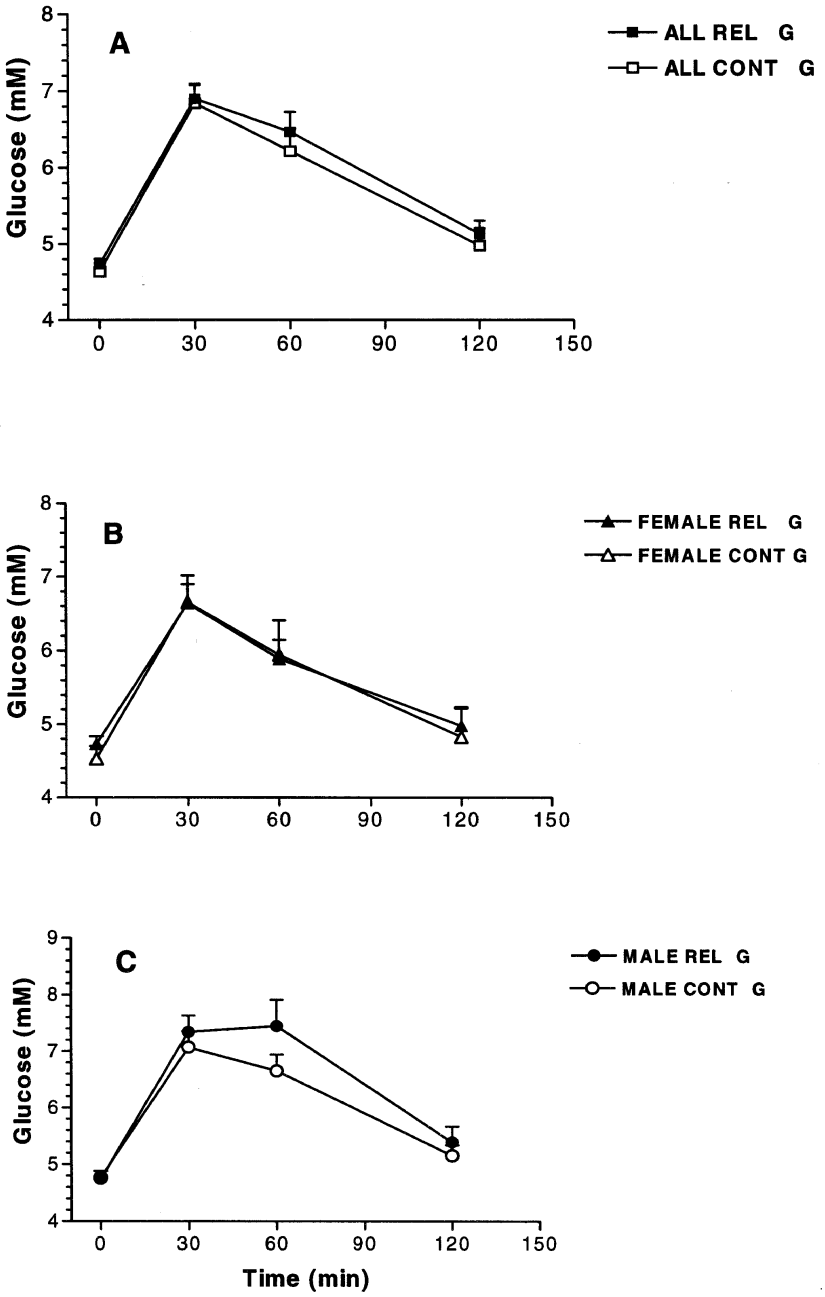

Fig. 1. Glycemic responses to a 75 g OGTT in all relatives (A) and female relatives (B) and male relatives (C) of Type 2 patients compared with control subjects.

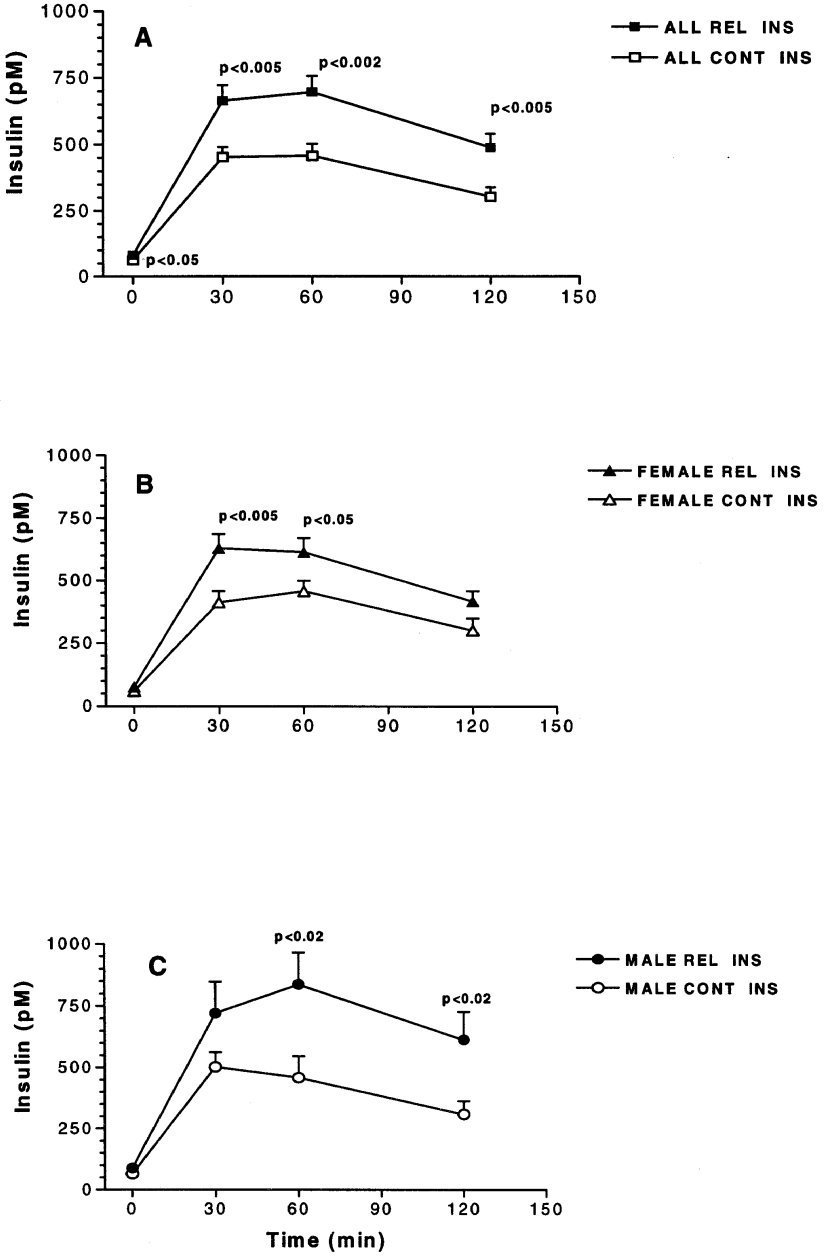

Fig. 2. Insulin responses to a 75g OGTT in all relatives (A) and female relatives (B) and male relatives (C) of Type 2 patients compared with control subjects.

no differences in the measures of IR and beta cell function (Table II).

Lipid metabolism

In relation to lipids (Table III), the main feature encountered was a marked elevation in TG levels in the group of relatives. This feature was evident in men as well as in women.

In general the TG values in the whole group of relatives exceeded the cut off values in 41% of the men (vs none in controls; p=0.026) and 27 % of women (vs 8 % in controls).

The HDL-C values were found significatively lower only in men. In general, 52% of the men relatives had values under 0.9 mmol/L (vs 20% in controls) and 72% of the women relatives had values under 1.19 mmol/L (vs 33% in controls, p = 0.034).

The mean values for the other lipids did not result significatively different, however, in men, 35 and 41% had high Chol (> 5.2 mmol/L) and LDL-C levels (3.35 mmol/L) respectively in contrast with 10% in controls.VLDL-C values were between normal limits in all cases.

Correlation analysis

BMI and WHR were strongly correlated with the skinfolds and several parameters of the carbohydrate metabolism in women, not in men (Table IV and V). On the other hand IR in women was associated with the skinfolds, systolic blood presssure and TG and HDL-C and, beta cell function was associated with VLDL-C (Table IV and V). In men we only found an isolated association of IR with DBP (Table IV). The lack of correlations in men might be due to the fewer numbers of cases, however the Spearman Rank correlation coefficientes were quite lower to the ones observed in women.

DISCUSSION

The results of the present study revealed that the first degree relatives of Type 2 diabetic patients from hispanic (Venezuelan) families, exhibit important metabolic disturbances, early in their lives. The mean age of the studied group was 35.2 y for women and 36.3 y for men, and in them we found already as a predominant alteration, an elevated insulin response to a glucose load, in absence of glucose intolerance in men as well as in women, with an elevation in the fasting insulin/glucose ratio in women.

These indirect signs of IR supports the view of the presence of this feature of the metabolic syndrome in this group of individuals. However, the mean HOMA calculated IR values did not result significatively different, although in 3 cases (2 women and 1 men) the values were over the third quartile for their group.

This characteristic is mentioned in most papers on studies of relatives of Caucasians (2,3,5) or Mexican-Americans (1,16) Type 2 diabetic patients.Leslie and col. (4) found hyperinsulinemia but in the presence of impaired glucose tolerance in a group of young offspring of Type 2 caucasians patients. Haffner

TABLE II

PARAMETERS RELATED TO CARBOHYDRATE METABOLISM IN RELATIVES OF TYPE 2 DIABETIC PATIENTS AND CONTROL SUBJECTS WITHOUT FAMILY HISTORY OF DIABETES

	TOTAL		WOMEN		MEN	
	Relatives n = 46	Controls n = 22	Relatives n = 29	Controls n = 12	Relatives n = 17	Controls n = 10
Fasting glucose (mmol/l)	4.7 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.5 ± 0.17	4.7 ± 0.1	4.8 ± 0.1
Fasting insulin (pmol/l)	80.1 ± 6.5	62.3 ± 6.2	76.9 ± 8.5	60.4 ± 9.8	87.9 ± 9.5	64.5 ± 7.6
Glucose area (mmol/l)	2.1 ± 0.3	11.7 ± 0.4	11.4 ± 0.4	11.3 ± 0.7	13.1 ± 0.58	12.2 ± 0.3
Insulin area (pmol/l)	1105.0 ± 89.0[a]	737.5 ± 59.6	1149.9 ± 148.1[b]	714.1 ± 59.3	1295.9 ± 194.8[c]	765.0 ± 114
I_0 /G_0 ratio	16.9 ± 1.3[a]	13.4 ± 1.3	16.0 ± 1.63[b]	13.2 ± 2.13	18.63 ± 2.2	13.4 ± 1.43
ΔI_{30} /ΔG_{30} ratio	375.0 ±100.0	278.2 ± 65.8	431.1 ± 156.7	311.1 ± 112.0	257.9 ± 40	238.0 ± 59.1
HOMA-IR	2.8 ± 0.2	2.29 ± 0.22	2.7 ± 0.3	2.3 ± 0.3	3.08 ± 0.3	2.3 ± 0.3
HOMA-cell	270 ± 27.9	216.1 ± 43.2	254.3 ± 27.1	53.0 ± 80.6	300.0 ± 58.4	175 ± 20.4

Pairwise differences were computed by the Mann-Whitney Test. [a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$, in relation to their respective controls.

TABLE III

PARAMETERS RELATED TO LIPID METABOLISM IN RELATIVES OF TYPE 2 DIABETIC PATIENTS AND CONTROL SUBJECTS WITHOUT FAMILY HISTORY OF DIABETES

	TOTAL		WOMEN		MEN	
	Relatives n = 46	Controls n = 22	Relatives n = 29	Controls n = 12	Relatives n = 17	Controls n = 10
TG	1.7 ± 0.1 [a]	1.05 ± 0.11	1.56 ± 0.17 [b]	0.98 ± 0.16	1.96 ± 0.2 [c]	1.13 ± 0.15
Chol	4.6 ± 0.2	4.48 ± 0.18	4.53 ± 0.2	4.5 ± 0.2	4.76 ± 0.3	4.4 ± 0.3
VLDL - C	0.6 ± 0.1	0.49 ± 0.06	0.52 ± 0.1	0.47 ± 0.1	0.7 ± 0.1	0.5 ± 0.1
LDL - C	3 ± 0.1	2.8 ± 0.16	2.9 ± 0.2	2.7 ± 0.2	3.20 ± 0.3	2.9 ± 0.2
HDL - C	1 ± 0.04	1.12 ± 0.05	1.1 ± 0.05	1.2 ± 0.06	0.83 ± 0.06 [c]	1.0 ± 0.07

Data (mmol/l) are expresed as mean ± S.E. [a] $p < 0.0005$, [b] $p < 0.05$, [c] $p < 0.02$, in relation to their respective controls.

TABLE IV
SPEARMAN RANK CORRELATION COEFFICIENTS AMONG BMI,WHR,IR, β-CELL AND PHYSICAL PARAMETERS IN RELATIVES OF TYPE 2 DIABETICS

		SC	TC	CI	SBP	DBP
BMI	All relatives	0.71[d]	0.50[c]	0.13	0.27	0.34[a]
	Female	0.77[d]	0.63[c]	0.38[a]	0.39[a]	0.33
	Male	0.32	0.43	-0.35	0.08	0.42
WHR	All relatives	0.11	-0.29[a]	0.45[b]	0.49[c]	0.43[b]
	Female	0.42[a]	0.30	0.23	0.46[b]	0.40[a]
	Male	0.16	-0.01	0.09	0.40	0.25
IR	All relatives	0.32[a]	0.31[a]	-0.07	0.35[a]	0.44[b]
	Female	0.37[a]	0.60[c]	-0.17	0.42[a]	0.34
	Male	0.43	0.43	-0.18	0.07	0.51[a]
β-CELL	All relatives	0.03	-0.01	-0.02	-0.02	0.07
	Female	0.10	0.03	-0.11	0.15	0.15
	Male	-0.04	0.04	-0.06	-0.35	0.02

SC = subscapular skinfold; TC = Tricipal skinfold; CI = centrality index; SBP = systolic blood pressure; DBP = diastolic blood pressure. [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; [d] $p < 0.0000$.

and col. (1) mentioned that the increase in fasting insulin values depend on the number of parents affected. In our study, although all individuals came from families where only one parent was affected (66% from the maternal line and 33% from the paternal line), the fasting insulin although not statistically higher than the controls, reached values over 100 pmol/L in 7/13 individuals; values that were well over the third quartile for their group.

Gonzalez-Ortiz and col (11) in a group of healthy young (19-20 y) Mexicans, from Jalisco, Mexico, with a strong family history of Type 2 diabetes in first and second degree of the paternal branch, did not find differences in insulin sensitivity, measured by the insulin tolerance test, fasting insulin values (53.3 vs 54pmol/L) or the insulin/glucose ratio (10.7 vs 10.9)

No abnormal insulin secretion, as assessed by the ratio of the change in insulin to the change in glucose from 0 to 30 min on an OGTT (15) or by de HOMA calculated beta cell function, was observed in the present study. Haffner and col. have demonstrated in the 7-year follow up in the San Antonio Heart Study (21) that Mexican-Americans with increase fasting insulin and decrease $\Delta I_{30}/\Delta G_{30}$ during an OGTT, independently predict the development of Type 2 diabetes in this ethnic group. Besides, for conversion from normal glucose tolerance to IGT, fasting insulin, but not $\Delta I_{30}/\Delta G_{30}$, significantly predict the

TABLE V

SPEARMAN RANK CORRELATION COEFFICIENTS AMONG BMI, WHR, IR , β-CELL FUNCTION AND BIOCHEMICAL PARAMETERS IN RELATIVES OF TYPE 2 DIABETICS

		G0	I0	GA	IA	I0/G0	TG	VLDL-C	HDL-C
BMI	All relatives	0.29[a]	0.42[b]	0.37[b]	-0.11	0.35[a]	0.15	0.08	-0.18
	Female	0.21	0.52[b]	0.47[b]	-0.05	0.41[a]	0.20	0.29	-0.45[a]
	Male	0.34	0.34	0.18	-0.15	0.32	-0.03	-0.35	0.06
WHR	All relatives	0.06	0.32[a]	0.40[b]	0.14	0.30[a]	0.38[b]	0.43[b]	-0.56[d]
	Female	0.14	0.36	0.37[a]	-0.06	0.28	0.36	0.41[a]	-0.30
	Male	0.08	0.17	0.13	0.55[a]	0.19	0.09	0.20	-0.36
IR	All relatives	0.51[c]	0.95[d]	0.53[c]	0.29[a]	0.83[d]	0.44[b]	0.38[a]	-0.48[c]
	Female	0.53[b]	0.93[d]	0.35	0.11	0.77[d]	0.41[a]	0.35	-0.66[d]
	Male	0.30	0.98[d]	0.61[b]	0.59[a]	0.89[d]	0.34	0.34	-0.13
β-CELL Funct.	All relatives	-0.73[d]	0.25	-0.22	-0.04	0.46[b]	0.12	0.42[b]	-0.32[a]
	Female	-0.75[d]	0.28	-0.33	-0.23	0.51[b]	0.21	0.54[b]	-0.30
	Male	-0.59[c]	0.31	-0.09	0.35	0.44	-0.08	0.30	-0.44

G_o = basal glycemia; I_o = basal insulinemia; GA = glycemic area; IA = insulin area.
[a] $P < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; [d] $p < 0.0000$.

conversion to IGT. Our group with normal glucose tolerance but glucose-stimulated hyperinsulinemia, would be at risk of developing, at least, IGT. This risk would be specially important for overweight women since in them BMI was associated with fasting insulin and the I_0/G_0 ratio (Table III).

On the other side, the most frequent dyslipidemia encountered in this group of individuals was hypertrigliceridemia with significant decrease in the HDL-C levels, mainly in men. The Chol and LDL-C values, although elevated in relation to controls, did not reach statistical difference. Moreover, an important amount of subjects had lipid values over the cut off levels for dyslipidemia. Fifty-two per cent of men and 72% of women had low HDL-C and 40% of the men relatives had hypercholesterolemia and high LDL-C.

These results are similar to those reported by Haffner and col. in Mexican-Americans (16) and by Laws and col. (3) in obese relatives from caucasians families, however, the latter, did not find differences in HDL-C levels. Schumacher and col. (8) observed not only hypertriglyceridemia and low HDL-C, but also hypercholesterolemia in white normoglycemic members of Type 2 diabetes pedigrees. Stewart and col. (5) found only low HDL-C in their series, with no changes in triglycerides in overweight caucasians Type 2 diabetes relatives. The Mexican group (11) reported only a slight increase in total Chol, however they were dealing with younger subjects.

The other feature of the metabolic syndrome encountered was the increase in blood pressure mainly in men. In a previous report on obese relatives from a single family (9), we found that men exhibited higher blood pressure than women and that the DBP had a positive and significative correlation with fasting insulin levels. This time, the association between fasting insulin and blood pressure, taking the group as a whole, was not significative, however the IR had a possitive correlation with SBP and DBP. Separating by gender, in women appeared a positive and significative relationship between IR and SBP and in men, with DBP.

The effect of fasting insulin concentration as a strong risk factor for hypertension has been demonstrated in both Mexican-Americans and non-hispanic whites for Haffner and col. (6), while Saad and col (22) did not find a relationship between IR and blood pressure in Pima indians or blacks, only in whites. In our venezuelan population we have reported (13) a relationship between fasting insulin and DBP in non-obese young patients with mild to moderate essential hypertension, more evident in males. Laws and col. (3) in obese and Stewart and col. (5) in non-obese but insulin-resistant relatives of Type 2 diabetes caucasians patients, of similar age, did not find modication of blood pressure.

The Kuopic Ischemic Heart Disease Risk Factor Study demonstrated the role of hyprinsulinemia

in incident hypertension and dyslipidemia and suggest that both alterations are associated with insulin metabolism disturbance, independently of obesity and body weight (23).

The Botnia group (24) have stressed the influence of family history of Type 2 diabetes in the body fat distribution. They found that the main difference were in WHR and glucose area in men, while in women, besides these mentioned parameters, SBP and DBP, log insulin and Chol. Our results with a group of similar BMI (although slightly younger) on the contrary, revealed no differences in WHR between women relatives and controls. Moreover, men relatives had a lower WHR than their respective controls. These results indicate a different body fat distribution in this ethnically different population.

In our study, obesity (defined as a BMI of 25 kg/m^2 or over) was present in 77% of the men and 62% of women; BMI in women, not in men, was strongly associated with SC and TC skinfolds,fasting insulin levels and glucose area, SBP and DBP. Same was true for WHR, being this parameter associated in the same manner to TG and VLDL-C. Although IR values were not statistically different between relatives and controls, IR was posssitively associated in women with TG and negatively with HDL-C. Again, only in women beta cell function was positively associated with TG.

The results of the present paper indicate that adult relatives of Type 2 diabetic venezuelan patients from hispanic origin had, early in their lives, several parameters of the metabolic syndrome as hyperinsulinemia, obesity, dyslipidemia and high blood pressure. We emphasize the role of ethnicity and gender respect to the observed abnormalities. Moreover, environmental conditions or habits, might be important since other hispanic populations like the mexicans, or Mexican-Americans, behave differently to this venezuelan population.

These alterations were more evident in women, group in which the association among BMI, WHR and IR were statistical significant with respect to SBP, DBP, basal insulin, I_0/G_0 ratio, and lipids.

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