

High Incidence of Type 2 Diabetes in Peroxisome Proliferator-Activated Receptor γ 2 Pro12Ala Carriers Exposed to a High Chronic Intake of *Trans* Fatty Acids and Saturated Fatty Acids

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One of the most frequent polymorphisms of peroxisome proliferator-activated receptor (PPAR) γ 2 is the Ala allele. Its incidence in the expression of obesity, insulin resistance, and type 2 diabetes is controversial (1–4). Recently it was suggested (5) that a gene-nutrient interaction at the PPAR γ locus exists. We hypothesized that when exposed to a chronic environment of high *trans* fatty acid (FA) and saturated FA (SFAs) intake and sedentary lifestyle, 12Ala carriers express more type 2 diabetes at lower BMI and age than subjects without the polymorphism. This could be due to some weakness in the defenses against the ectopic storage of triglycerides, particularly in myocytes and β -cells. The current study is aimed at examining these possible relationships.

RESEARCH DESIGN AND METHODS

This is a pilot study. We have included 56 subjects (40 women and 16 men), all of them Caucasian, who consecutively visited our metabolic department seeking care for overweight and obesity, but not all were overweight or obese. It was a population with a wide age range (21–62 years) and range of BMI (22.3–58.5 kg/m²), ideal for exploring our hypothesis. Criteria for exclusion

were known diabetes, the presence of any other disease or drug that alters glucose and lipid metabolism, and having followed a diet in the last year. Each subject answered a standardized food-frequency questionnaire. Portion sizes were specified for each foodstuff, and subjects were asked how often their consumption of that was in a scale ranging from “never or once a month” to “five or more times a day.” The types of fat commonly used for cooking and at the table were surveyed and registered. The values for the amount of dietary fats in food were obtained from computerized nutritional data, including regional data (6) as well as basic data from the U.S. Department of Agriculture’s *Nutritive Value of Food* (7). Nutritional information from manufacturers and published literature was also taken into account. The intake of total fat, SFAs, and polyunsaturated and monounsaturated FAs was calculated in grams per day. We estimated the daily intake of *trans* FAs in grams, averaging the weekly intake of margarine, pastry, cookies, cakes, packed white bread, shortcakes (extremely popular in Uruguay), as well as those contained in fried food, sandwiches, beef, pork, or lamb. Most of the margarine used in Uruguay is stick margarine, containing close to 30% of *trans* FA and nearly 15%

in shortening, also widely used. The weekly caloric expenditure for physical activity was evaluated through the Paffenbarger Physical Questionnaire (8). Waist circumference and BMI were also registered. Baseline insulin was determined by radioimmunoassay (Diagnosis Products). The Pro12Ala polymorphism of PPAR γ 2 was determined by PCR single-strand conformation polymorphism.

The diagnosis of type 2 diabetes was performed following the new American Diabetes Association criteria (9).

RESULTS— The polymorphism was detected in 21.4% of the sample: 11 heterozygotes and 1 homozygote (Table 1). Fifty percent of Ala carriers had abnormalities in their glucose metabolism: five subjects had type 2 diabetes and one impaired fasting glucose. This significantly differed with the figure of 10.4% detected in Pro12Pro subjects: three subjects had type 2 diabetes and two impaired fasting glucose. Table 1 shows that type 2 diabetes tends to occur at younger ages in Ala carriers than in Pro12Pro carriers and at lower waist circumference, BMI, and insulin levels; but none of them reached significance, perhaps due to the smallness of the sample. The daily intake of total FAs was higher in diabetic Ala carriers than in nondiabetic subjects ($P = 0.010$). The same was true for the intake of SFAs ($P = 0.007$) and, particularly, for *trans* FA ($P < 0.001$).

CONCLUSIONS— To our knowledge, no studies have been published exploring the relationships between the intake of *trans* FAs and type 2 diabetes in Pro12Ala subjects. Luan et al. (5) reported the gene-nutrient interaction at the PPAR γ locus. From the biological point of view, it is plausible for *trans* FAs to have the same effect as SFAs in activat-

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Abbreviations: FA, fatty acid; PPAR, peroxisome proliferator-activated receptor; SFA, saturated FA.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Comparisons between diabetic/impaired fasting glucose (IFG) and nondiabetic subjects according to PPAR γ genotype status

Variable	Non-Ala carriers		P	Ala carriers		P
	Nondiabetic	Diabetic/IFG		Nondiabetic	Diabetic/IFG	
n	39	3/2		6	5/1	
Weight (kg)	90.2 \pm 22.1	127.4 \pm 27.0	0.003	69.5 \pm 13.3	109.3 \pm 14.3	0.001
Waist circumference (cm)	100.5 \pm 20.0	133.8 \pm 12.1	0.002	78.3 \pm 6.1	115.8 \pm 19.9	0.002
BMI (kg/m ²)	32.6 \pm 7.1	41.8 \pm 7.7	0.018	25.8 \pm 3.5	38.0 \pm 7.8	0.006
Age (years)	40.6 \pm 15.1	56.8 \pm 4.9	0.041	27.0 \pm 5.7	48.7 \pm 10.8	0.002
Basal insulinemia (mUI/l)	14.4 \pm 13.0	38.8 \pm 29.9	0.003	10.8 \pm 4.4	26.3 \pm 14.3	0.030
Basal glycemia (mg/dl)	92.0 \pm 8.6	144.8 \pm 38.3	<0.0001	84.7 \pm 10.5	163.3 \pm 60.4	0.010
Energy expenditure (kcal/week)	776.6 \pm 427.8	575.3 \pm 117.3	0.358	1,016.3 \pm 372.7	405.3 \pm 122.0	0.003
SFA (g/day)	39.9 \pm 24.8	36.8 \pm 18.4	0.808	26.7 \pm 5.4	78.4 \pm 36.7	0.007
Trans FA (g/day)	19.0 \pm 13.4	19.3 \pm 13.2	0.964	8.8 \pm 1.4	35.9 \pm 13.4	<0.001

Data are means \pm SD.

ing the steatosis pathways that result in insulin resistance and early dysfunction of the β -cells. It could be possible that carriers who ingest these fats are more susceptible to type 2 diabetes than non-carriers. But the reason why subjects with the Pro12Ala polymorphism may exhibit such lack of control over fat intake is still unclear. Is it possible for PPAR α and γ to exert a central modulation over fat intake, acting as fatty sensors, or is it a casual finding in a small number of Ala carriers? This hypothesis must be tested in future research.

In summary, we found a direct relationship between the intakes of *trans* FA and type 2 diabetes in Ala carriers. Confirmation of this finding will require further research, with larger numbers of subjects, and it could be very important for our clinical practice, considering the high consumption of *trans* FAs by the Uruguayan population.

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