High Incidence of Type 2 Diabetes in Peroxisome Proliferator–Activated Receptor γ2 Pro12Ala Carriers Exposed to a High Chronic Intake of *Trans* Fatty Acids and Saturated Fatty Acids

RAUL EDUARDO PISABARRO, MD[1]
CARLOS SANGUINETTI[2]
MARIO STOLL, MD[3]
DANIEL PRENDEZ[4]

One of the most frequent polymorphisms of peroxisome proliferator–activated receptor (PPAR)γ2 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 PPARγ 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/m^2), 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 PPARγ2 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 PPARγ locus. From the biological point of view, it is plausible for *trans* FAs to have the same effect as SFAs in activat-

From the [1]Department of Endocrinology and Metabolism, University of the Republic, Montevideo, Uruguay; the [2]Department of Molecular Biology, University of Science, University of the Republic, Montevideo, Uruguay; the [3]Department of Clinical Genetics, University of the Republic, Montevideo, Uruguay; and the [4]Department of Nutrition, University of the Republic, Montevideo, Uruguay.

Address correspondence and reprint requests to Raul Eduardo Pisabarro, MD, Domingo Cullen 693, Montevideo CP 11100, Uruguay. E-mail: clibarro@netgate.com.uy.

Received for publication 30 April 2004 and accepted in revised form 31 May 2004.

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.

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

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

Data are means ± 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 noncarriers. 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 PPARα 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.

References

1. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl M-C, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES: The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76–80, 2000
2. Mancini FP, Vaccaro O, Sabatino L, Tufano A, Rivellese AA, Riccardi G, Colantuoni V: Pro12Ala substitution in the peroxisome proliferator–activated receptor-γ2 is not associated with type 2 diabetes. *Diabetes* 48:1466–1468, 1999
3. Hegele RA, Cao H, Harris SB, Zinman B, Hanley AJ, Anderson CM: Peroxisome proliferator-activated receptor-gamma2 P12A and type 2 diabetes in Canadian Oji-Cree. *J Clin Endocrinol Metab* 85: 2014–2019, 2000
4. Evans D, de Heer J, Hagemann C, Wendt D, Wolf A, Beisiegel U, Mann WA: Association between the P12A and c1431t polymorphisms in the peroxisome proliferator activated receptor gamma (PPAR gamma) gene and type 2 diabetes. *Exp Clin Endocrinol Diabetes* 109:151–154, 2001
5. Luan J, Browne PO, Harding A-H, Halsall DJ, O'Rahilly S, Chatterjee VKK, Wareham NJ: Evidence for gene-nutrient interaction at the PPARγ locus. *Diabetes* 50: 686–689, 2001
6. Mazzei ME, Puchulo MR, Rochaix MA: *Tabla de Composición Química de los Alimentos:Centro de Endocrinología Experimental Aplicada (CENEXA)*. Buenos Aires, Argentina,Fundación para la Promoción de la Educación y la Investigación en Diabetes y Enfermedades de la Nutrición (FEIDEN), 1995
7. U.S. Department of Agriculture: *Nutritive Value of Food*. Washington, DC, U.S. Govt. Printing Office, 1998
8. Kriska AM, Caspersen CJ: Paffembarger physical activity questionnaire. *Med Sci Sports Exerc* 29:S83–S88, 1997
9. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 27 (Suppl. 1): S1–S10, 2004