Is a low leptin concentration, a low resting metabolic rate, or both the expression of the “thrifty genotype”? Results from Mexican Pima Indians1–3

Caroline S Fox, Julian Esparza, Margery Nicolson, Peter H Bennett, Leslie O Schulz, Mauro E Valencia, and Eric Ravussin

ABSTRACT

Background: The high prevalence of obesity and type 2 diabetes in some populations is believed to be the expression of a “thrifty genotype,” which conferred survival advantages during periods of harsh environmental conditions, but has become a liability in industrialized environments of abundance. Low plasma leptin concentrations and a low metabolic rate may be the phenotypic expression of this genotype.

Objective: We hypothesized that plasma leptin concentrations and resting metabolic rate would be lower in Mexican Pima Indians not yet exposed to an affluent lifestyle than in non-Pima Mexicans living in the same environment.

Design: We studied 208 nondiabetic Pima Indians (105 women and 103 men) living a traditional lifestyle in a remote, mountainous area of northwest Mexico and 183 nondiabetic non-Pima Mexicans (90 women and 93 men) living in the same environment. A subset of 40 (17 women and 23 men) Pima Indians and 40 (19 women and 21 men) non-Pima Mexicans was selected for studies of energy metabolism with a ventilated-hood system.

Results: Leptin concentrations were strongly correlated with percentage body fat in both groups (r = 0.83, P < 0.0001). There was no significant difference in plasma leptin concentration between groups in absolute value (P = 0.90) or after adjustment for percentage body fat, waist circumference, age, and sex (P = 0.40). Similarly, there was no significant difference in resting metabolic rate between groups in absolute value (P = 0.27) or after adjustment for fat-free mass (P = 0.32).

Conclusions: These results do not support the hypothesis that hypoleptinemia, a relatively low resting metabolic rate, or both are expressions of the thrifty genotype. Am J Clin Nutr 1998;68:1053–7.

KEY WORDS Pima Indians, thrifty genotype, leptin, resting metabolic rate, obesity, indirect calorimetry, diabetes

INTRODUCTION

The high prevalence of obesity and type 2 diabetes in some populations has been proposed to be the expression of a “thrifty genotype.” The thrifty genotype has been postulated to confer a survival advantage during periods of starvation by favoring the accumulation of fat stores in times of abundant food (1), possibly by increasing food intake, decreasing energy expenditure, or both. Low plasma leptin concentrations and a low metabolic rate may both represent the phenotypic expression of such a genotype.

Since the positional cloning of the ob gene (2), much interest has focused on the extent to which leptin is involved in the pathophysiology of human obesity (3). Two subjects of Pakistani origin with congenital leptin deficiency were described recently to be morbidly obese, insulin resistant, and hyperphagic (4). Leptin may have evolved to protect mammals against starvation and may be the physiologic link between starvation and reproductive capability, thermogenesis, and the stress response (5). Cross-sectional studies in humans indicate that low plasma leptin concentrations are associated with low daily energy expenditure (6) and low sympathetic nervous system activity (7), both of which are known to be associated with weight gain (8, 9). Furthermore, insufficient signaling from leptin is likely to be associated with hyperphagia (4).

A low resting metabolic rate (RMR) may also be an adaptive mechanism for survival in periods of famine. Although a relatively low RMR is a predictor of body weight gain in conditions of plenty (8, 10), the loss of 10–20% of body weight resulting from underfeeding results in a decrease in energy requirements (11). During seasons of heavy physical work and decreased food supplies, Gambian men have a decreased RMR, indicating their ability to develop important energy-conserving mechanisms when necessary (12).

Whether leptin deficiency, a low metabolic rate, or both are predisposing factors for the degree of obesity seen in some genetically predisposed populations is not known. The US Pima Indians are one of the best examples of a population likely to have an increased frequency of such a thrifty genotype because they have a high prevalence of obesity (13) and type 2 diabetes.

1 From the Phoenix Epidemiology and Clinical Research Branch, Phoenix, AZ; Centro de Investigacion en Alimentacion y Desarrollo, Hermosillo, Mexico; AMGEN, Thousand Oaks, CA; and the University of Wisconsin, Milwaukee.
2 Supported in part by grant NIH-DK-49957.
3 Reprints not available. Address correspondence to E Ravussin, Lilly Research Laboratories, Lilly Corporate Center, Drop Code 0545, Indianapolis, IN 46285. E-mail: Eric_Ravussin@lilly.com.
4 Received February 27, 1998.
5 Accepted for publication May 29, 1998.
(14) when exposed to affluent conditions. However, when living in such an environment, Pima Indians do not exhibit a low metabolic rate (15, 16) or low plasma leptin concentrations (17), probably as a result of weight gain. Our prospective studies have shown that in response to weight gain, metabolic predictors of the development of obesity tend to become normal for the new body weight (18).

In the present study, we investigated whether low plasma leptin concentrations and a relatively low RMR were characteristic of Mexican Pima Indians living a traditional lifestyle compared with non-Pima Mexicans living in the same environment. Because of the restrictive environment, Mexican Pima Indians are extremely lean compared with their American counterparts (19) and are likely to manifest physiologic mechanisms promoting metabolic efficiency and weight gain.

SUBJECTS AND METHODS

Maycoba is located in the mountains of northwest Mexico, in the eastern region of the state of Sonora, 340 km southeast of Hermosillo. According to a 1990 census, 601 Pima Indians reside in this area. In 1995, a population survey to determine the prevalence of obesity and type 2 diabetes was initiated in this Mexican community.

Subjects surveyed

All persons of Maycoba and its surrounding area aged ≥20 y were invited to participate in the population survey. Subjects arrived at the clinic in the morning after a 10–12-h fast. Height and weight were measured with a portable stadiometer (Holtain Stadiometer, Holtain, United Kingdom) and a battery-operated electronic scale. Waist circumference was measured with subjects in the supine position. Body composition was assessed by bioelectrical impedance analysis (model BIA-103; RJL Systems, Detroit). After subjects completed a questionnaire on their present health status, a 75-g oral-glucose-tolerance test was performed. Only nondiabetic subjects, according to World Health Organization criteria (20), were included in this study. Leptin concentrations were measured in the fasting plasma sample collected before glucose ingestion.

Body composition was calculated from bioelectrical resistance by using equations developed in US Pima Indians (21). Plasma glucose concentrations were measured by using the glucose oxidase method (EXPRESS 550; Ciba-Corning, Oberlin, OH) and plasma insulin concentrations were measured by automated immunoassay (Concept 4; ICN, Horsham, PA). Plasma leptin concentrations were measured in duplicate in a solid-phase sandwich enzyme immunoassay with affinity-purified polyclonal and monoclonal antibodies. The leptin concentration was calculated from standard curves generated for each assay by using recombinant human leptin. The sensitivity of the method is 90 ng/L. Studies were approved by the Institutional Review Boards of the University of Wisconsin and the Centro de Investigacion en Alimentacion y Desarrollo in Hermosillo, Mexico.

Subjects in whom energy metabolism was studied

A subset of 40 healthy, full-blooded Mexican Pima Indians and 40 healthy non-Pima Mexicans was invited to come twice (1 wk apart) to the clinic in a fasting condition for studies of energy metabolism. Subjects rested comfortably on a bed for 10 min, after which RMR was measured over 30 min by using a Deltatrac metabolic cart (SensorMedics Corp, Yorba Linda, CA) as described previously (22). The RMR measurement was repeated under fasting conditions 1 wk later. Results represent the mean of the 2 measurements.

Statistical analyses

Statistical analyses were performed by using the programs of the SAS Institute (Cary, NC). Logarithms of insulin and leptin concentrations were used to normalize distributions. Pearson product-moment correlations were used to determine associations among variables. General linear regression models (analysis of covariance) were used to compare leptin concentrations and RMR between ethnic groups (Mexican Pima Indians and non-Pima Mexicans) after adjustment for significant determinants such as percentage body fat, waist circumference, age, and sex (for leptin), and fat-free mass, fat mass, age, and sex (for RMR). All results are presented as means ± SDs unless specified otherwise.

RESULTS

The characteristics of the 208 Pima Indians (105 women and 103 men) and the 183 non-Pima Mexicans (90 women and 93 men) are shown in Table 1. By design, all subjects were nondiabetic. Pima Indians were not significantly different from non-Pima Mexicans with respect to body mass index, waist circumference, and age, but were shorter, lighter, and had higher percentage body fat and higher fasting glucose concentrations.

Leptin concentrations

Body mass index (r = 0.69, P < 0.0001), waist circumference (r = 0.62, P < 0.0001), and percentage body fat (r = 0.87, P < 0.0001) were all strongly correlated with leptin concentration. After adjustment for percentage body fat, the leptin concentration remained positively correlated with waist circumference (P < 0.0001) and became negatively correlated with age in non-Pima Mexican and Pima Indian women and men (P < 0.0001).

The relation between the leptin concentration and percentage body fat in Pima Indians and non-Pima Mexicans is depicted in Figure 1. After adjustment for percentage body fat, waist circumference, age, and sex, there was no significant difference in leptin concentration between Pima Indians and non-Pima Mexicans (Table 2). The model was similar when men and women were analyzed separately (data not shown). Neither fasting insulin nor fasting glucose was significant in the model, and thus both were excluded.

Resting metabolic rate

The characteristics of the subset of subjects in whom energy metabolism was studied [40 Pima Indians (17 women and 23 men) and 40 non-Pima Mexicans (19 women and 21 men)] are also shown in Table 1. Pima Indians were not significantly different from non-Pima Mexicans with respect to age, height, weight, percentage body fat, and fat mass. Fat-free mass (r = 0.86, P < 0.0001) and weight (r = 0.75, P < 0.0001) were strongly correlated with RMR. The relation between RMR and fat-free mass in Pima Indians (r = 0.93, P < 0.0001) and non-Pima Mexicans (r = 0.80, P < 0.0001) is depicted in Figure 2. After adjustment for fat-free mass, there was no difference in RMR between Pima Indians and non-Pima Mexicans (7272 compared with 7188 kJ/d, P = 0.32; Table 3). When fat mass, age, and sex (all nonsignificant covariates) were included in the model, similar results were achieved.
Entire population

Leptin deficiency is associated with obesity, diabetes, hyperphagia, and low energy expenditure in animals (24–26), all traits of the thrifty genotype. In humans, 2 subjects with congenital leptin deficiency were found to be morbidly obese, insulin resistant, and hyperphagic (4). Short-term starvation (17) and weight-loss studies (27–30) consistently result in a decrease in leptin concentration out of proportion to the decrease in fat mass, suggesting a role for leptin in the preservation of adipose tissue. Leptin may have evolved to protect humans and other mammals against starvation and may be the physiologic link between starvation and reproductive capability, thermogenesis, and the stress response (5).

This study confirms the association between leptin concentration and percentage body fat and the independent contribution of

![FIGURE 1. Relation between plasma leptin concentration (log scale) and percentage body fat measured by bioelectrical resistance in nondiabetic Mexican Pima Indians and non-Pima Mexicans.](https://academic.oup.com/ajcn/article-abstract/68/5/1053/4648614)
waist circumference (a measure of central obesity) to the variation in plasma leptin concentration. The results of this study did not show a significant difference in leptin concentration between Mexican Pima Indians and non-Pima Mexicans and therefore do not support the hypothesis that hypoleptinemia is part of the expression of the thrifty genotype. Ethnic variability in leptin concentration has been noted in only one study, in which Indians were found to have higher leptin concentrations than Creole or Chinese populations of Mauritius (31). Our findings are more consistent with those of others who did not detect an ethnic variation in leptin. For example, a difference in leptin concentration was not detected between white, Afro-Caribbean, and Asian subjects with type 2 diabetes (32), African American children and white children (33), or Mexican American adults and non-Hispanic whites (34).

Although a relatively low RMR has been shown to predict subsequent weight gain (8, 10), the loss of 10–20% of body weight achieved by underfeeding results in a decrease in energy requirements (11), suggesting that to preserve fat stores the body becomes more energy efficient in response to a negative energy balance. Studies in Gambian men during the “hungry season” showed that the basal metabolic rate and sleeping metabolic rate were lower and work efficiency was increased, indicating that these Gambian men may have developed important energy-conserving mechanisms to allow them to cope with dwindling food supplies and heavy physical demands (12). Similar mechanisms may have occurred in the Pima Indians and the selection of a thrifty metabolism in Pima Indians in the United States seems likely as a plausible mechanism to explain this population’s high prevalence of obesity and type 2 diabetes. However, RMR was not significantly different in Pima Indians and non-Pima Mexicans. These results do not support the hypothesis that Pima Indians have a low RMR, thus predisposing them to obesity in an affluent environment.

In studies comparing white and African American subjects, RMR was shown to be lower in African American subjects (35) and may be a predisposing factor in the high rates of obesity seen in African Americans. However, there is no evidence of ethnic and racial differences in energy expenditure between Pima Indians and whites (15, 16). Although US Pima Indians have been shown to have lower muscle sympathetic nervous activity than age-matched whites (36), both adults (15) and children (16) had an RMR similar to that in whites.

In summary, we did not detect a significant difference in leptin concentration or RMR between Mexican Pima Indians and non-Pima Mexicans. Our results do not support the hypothesis that hypoleptinemia or a relatively low RMR is part of the

---

**TABLE 2**

Linear regression model for the effect of ethnicity (non-Pima Mexican or Mexican Pima Indian) on log leptin concentration

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$\beta$</th>
<th>$P$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.17</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Percentage fat (%)</td>
<td>0.03</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.013</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Age (y)</td>
<td>-0.01</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td>0.32</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-0.023</td>
<td>0.40</td>
<td>0.81</td>
</tr>
</tbody>
</table>

$n = 195$ women and 196 men. Besides sex and ethnicity, only statistically significant determinants of plasma leptin concentration are reported.

**TABLE 3**

Linear regression model for the effect of ethnicity (non-Pima Mexican or Mexican Pima Indian) on resting metabolic rate

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$\beta$</th>
<th>$P$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2485</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>92</td>
<td>&lt;0.0001</td>
<td>—</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>-84</td>
<td>0.50</td>
<td>0.75</td>
</tr>
</tbody>
</table>

$n = 36$ women and 44 men. Besides ethnicity, only the statistically significant determinant of resting metabolic rate is reported.

---

**FIGURE 2.** Relation between resting metabolic rate and fat-free mass measured by bioelectrical resistance in nondiabetic Mexican Pima Indians and non-Pima Mexicans.
expression of the thrifty genotype, predisposing susceptible populations to obesity and type 2 diabetes.

We thank the members of the Maycoba community for their participation in these studies. Our gratitude also goes to Hortencia Montesinos, Bertha Isabel Pacheco, and Ana Cristina Gallegos for data collection in Mexico.

REFERENCES