Metabolic Differences and the Development of Obesity

Eric Ravussin

Studies, such as those on Pima Indians, have shown that metabolic factors are involved in the development of obesity and that being overweight is not simply a result of "sloth and gluttony." However, the environment also affects the development of obesity. Among individuals in a given environment, the variability in body size is influenced by genetically determined responses to that environment. People with a low metabolic rate (adjusted for body size and composition) are prone to weight gain, whereas those with a high level of spontaneous physical activity are less likely to become obese. Similarly, individuals with a high 24-hour respiratory quotient (RQ) are more likely to gain weight than those with a low RQ. Insulin sensitivity (not insulin resistance) is another metabolic predictor of obesity. Genetic linkage studies suggest a number of genes are linked to the development of obesity. By sibling-pair linkage analysis, tumor necrosis factor-alpha (TNF-α) was found to be linked to the percentage of body fat, and other studies have shown that fat cell production of TNF-α is greater in obese individuals.

THE REAL CHALLENGE facing the treatment of obesity is to prevent patients from regaining lost weight. Many obese patients manage to lose weight, but few maintain the weight loss. One reason that the treatment of obesity is often unsuccessful in the long term is the belief that obesity is the patient's fault.[1] Obese patients are still assumed to lack will power and exhibit poor attitudes toward food and physical activity. "Sloth and gluttony" are viewed as the major reasons for their weight regain. However, overweight populations, such as the Pima Indians, suggest that obesity is a disease and that inherited metabolic factors, as well as environmental factors, are involved in weight gain.

PIMA INDIANS

The Pima Indians of Arizona have the highest prevalence of obesity and non–insulin-dependent diabetes mellitus (NIDDM) in the world.[2,3] By the age of 35 years, about half the population has NIDDM. Another population of Pima Indians living in Mexico probably split from the Arizona group about 400 to 600 years ago. These two populations appear to have a similar genetic background, although they live in very different environments. A recent study compared the weight and body mass index (BMI) of the two populations: for each of the Mexican Pimas, 10 Arizona Pimas were matched for age and gender and then compared for BMI.[4] There was a significant difference in BMI between the two populations, with the Arizona Pimas having, on average, a BMI 10 kg/m^2 greater among females and 6 kg/m^2 among males than the Mexican Pimas (Fig 1). The primary reason for this difference in BMI appears to be related to the different environmental conditions in which these two populations live.

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0026-0495/95/4409-0105$03.00/0

GENES AND ENVIRONMENT

Data from studies on twins,[5] adoption studies,[6] and combined twin and adoption studies[7] suggest that the genetic component of obesity accounts for 40% to 80% of an individual's BMI. However, these data were collected in developed countries, where the environmental influences are likely to be consistent. The role of genes in determining BMI may therefore be inflated in these studies.

When whole populations are studied, the prevalence of obesity appears to be largely determined by environment. Among individuals in a given environment, variability in body size is largely influenced by genes. Favorable changes in the environment, due to public-health campaigns for example, may reduce the prevalence and incidence of obesity in the population as a whole.

METABOLIC PREDICTORS OF WEIGHT GAIN (RMR AND RQ)

The Pima Indians were studied to identify early metabolic predictors of body weight gain[8] and diabetes.[9] In these studies, the body composition of the individuals was assessed by hydrodensitometry. Carbohydrate metabolism was measured by an oral glucose tolerance test and a euglycemic hyperinsulinemic glucose clamp, and energy expenditure was measured by a ventilated hood system or a respiratory chamber.[10]

Total energy expenditure increased as body weight increased in both men and women, although at any given weight there was variability in energy expenditure of about 500 to 700 kcal/d.[1] A positive correlation between resting metabolic rate and fat-free mass was found in another study.[11] However, after adjustment for differences in fat-free mass, fat mass, age, and sex, most of the remaining variance was found to aggregate in families, indicating a genetic background to resting metabolic rate.[11] After adjustment for the above covariates, a low relative metabolic rate was a predictor of body weight gain.[12]

The respiratory quotient (RQ) is used to determine the amount of energy derived from carbohydrate and fat. A high RQ has been shown to predict future weight gain in Pima Indians[13] and whites.[14] In a study of weight gain over 3 years, individuals with a high RQ were more likely to gain weight than those with a low RQ (Fig 2). Studies have shown that 24-hour RQ may vary among individuals in a

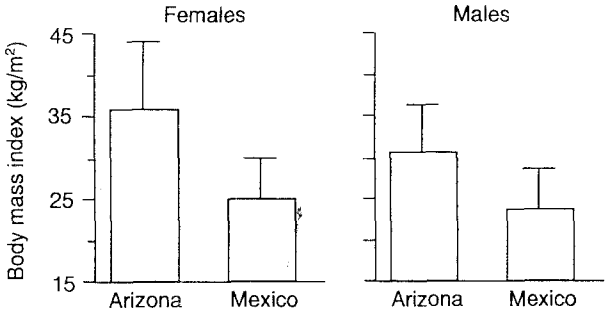

Fig 1. Effect of environment. Thirty-five subjects (19 females/six males) of Pima heritage, living a traditional lifestyle in northern Mexico, were compared with sex- and age-matched Pima Indians in Arizona. Pimas in Mexico were lighter (means ± SD, 64.2 ± 13.9 *v* 90.2 ± 21.0 kg; *P* < .0001).

population, but is fairly constant within any one individual. RQ is a familial trait, probably genetically determined and, like metabolic rate, predicts subsequent weight change.

Studies have been performed to assess the possible underlying physiological mechanism for the variability in RQ between individuals. RQ is related to the activity of lipoprotein lipase (LPL)[16] and beta-hydroxyacyldehydrogenase (BOAC).[17] Both enzymes are involved in the uptake and oxidation of triglyceride and fatty acid in muscle and adipose tissue. High activity of lipoprotein lipase in the muscle is associated with a low RQ.[16] Similarly, a high activity of BOAC in the muscle predicts a low RQ.[17]

Studies have shown that post-obese individuals have a high RQ, although they may not have a low metabolic rate after adjusting for body composition or body size.[18,19]

INSULIN RESISTANCE

Studies in adult Pima Indians have shown that insulin sensitivity, measured by glucose disposal during a euglycemic hyperinsulinemic clamp, decreases with increasing body weight.[20] Surprisingly, patients with higher insulin sensitivity were found to be more likely to gain weight than those who were insulin-resistant.[21] Insulin resistance seems also to be genetically determined[22] and is known to increase with obesity; it may therefore be viewed as a metabolic adaptation that counteracts further weight gain (Fig 3).

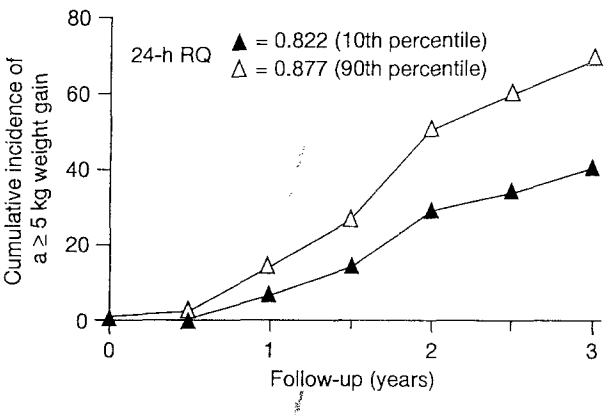

Fig 2. High 24-hour RQ as a predictor of body weight gain.

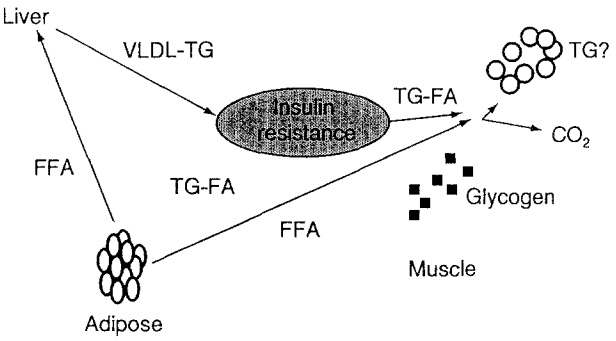

Fig 3. Insulin resistance: an adaptation for weight maintenance. FFA, free fatty acid; TG-FA, triglyceride fatty acid; VLDL-TG: Very–low-density lipoprotein tryglyceride. (Adapted with permission.[14] © by The Lancet Ltd, 1992.)

PHYSICAL ACTIVITY

Physical activity levels also predict future weight gain. The ratio of total energy expenditure (as determined by the doubly labeled water method) divided by basal metabolic rate has been used as an index of physical activity. From a review of studies performed using the doubly labeled water method, energy expended through physical activity was found to vary tremendously among individuals.[23] In another study, males with a high level of spontaneous activity have been shown to be less likely to gain weight.[24] Levels of spontaneous activity may be related to the level of sympathetic nervous activity[25] and seem to run in families.[24]

GENES

A number of genes are believed to contribute to the development of obesity. Studies in genetically engineered animal models and linkage studies in animals and humans have identified a number of possible obesity genes.[26]

Tumor Necrosis Factor-Alpha

The gene expressing tumor necrosis factor-alpha (TNF-α) is one of the possible obesity genes. TNF-α expression is elevated in rodent models of obesity. TNF-α suppresses the expression of certain genes in mouse adipocytes. In the *fa/fa* rat, in vivo neutralization by a soluble TNF-α receptor results in decreased insulin resistance. Increased plasma levels of TNF-α also increase serum triglyceride and very–low-density lipoprotein levels in rats and humans.

Genetic linkage studies indicate that the gene for TNF-α is linked to the percentage of body fat.[27] Northern blotting and mRNA analysis indicate that TNF-α expression is elevated in obese patients. Obese patients produce more TNF-α in their fat cells than lean individuals.[28]

Mitochondrial DNA

Mitochondria are responsible for cellular respiration and therefore regulate energy metabolism. For these reasons, mitochondria are thought to play a role in controlling energy balance. Some of the mitochondrial proteins involved in energy metabolism are encoded by mitochondrial DNA. Nonsilent point mutations in mitochondrial DNA are significantly associated with a low or high resting

metabolic rate in 246 Pima Indians.[29] Specific mitochondrial genes or mutations in genes may yield a susceptibility to the development of obesity.

SUMMARY

Obesity cannot always be attributed to a lack of will power, poor behavior, or "sloth and gluttony." Inherited metabolic factors have been shown to play a role in the etiology of obesity. At least part of the etiology of obesity is the result of a genetic predisposition to weight gain. The genes involved must encode proteins that can regulate energy intake or energy expenditure. The environment also plays a role in the development of obesity, either by compounding a genetic tendency toward weight gain or by mitigating it. Body shape is a product of both our parents and our environment.

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