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Dietary fat and obesity: a review of animal, clinical and epidemiological studies

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Abstract

The First Law of Thermodynamics provides a framework for understanding the imbalance between energy intake and expenditure that produces obesity, but it does not help understand the role of genetics, the regulation of food intake, the distribution of body fat, the mechanisms by which diets work or the mechanism by which portion control has gotten out of control. In animals, increasing dietary fat increases body fat, and it is unlikely that humans escape this important biological rule. In epidemiological studies, increasing dietary fat is associated with increased prevalence of obesity probably by increasing the intake of energy dense foods. In the National Weight Loss Registry, three things were associated with weight loss: continued monitoring of food intake, lowering dietary fat intake, and increased exercise. The relation of dietary fat is most evident when physical activity is low. The speed of adaptation to dietary fat is increased by exercise. When dietary fat is reduced, weight is lost, but weight loss eventually plateaus. The rate of weight loss during the initial phase is about 1.6 g/day for each 1% decrease in fat intake. When dietary fat is replaced with olestra to reduce fat intake from 33% to 25% in obese men, weight loss continues for about 9 months reaching a maximum of nearly 6% of body weight and a loss of 18% of initial body fat. In the control group with a 25% reduced-fat diet, weight loss stopped after 3 months and was regained over the next 6 months, indicating the difficulty of adhering to a conventional low-fat diet. Thus, dietary fat is an important contributor to obesity in some people.
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1. Introduction to the first law of thermodynamics

The current epidemic of obesity undeniably reflects an imbalance of energy intake and expenditure. Put another way, "portion control is out of control". The First Law of Thermodynamics accurately describes the consequences of an imbalance between energy intake and expenditure: when there is either an increase in energy intake, a reduction in energy expenditure or a combination of both body fat stores will increase. In spite of its descriptive accuracy, the First Law of Thermodynamics fails to explain the mechanisms involved in producing and maintaining the disequilibrium. For example, the First Law does not explain how we regulate food intake, how genetic factors influence the susceptibility to obesity, the gender differences in fat storage, whether fat is deposited or mobilized from visceral or subcutaneous fat or how the diet influences energy balance.

For the present discussion, we will take an epidemiological approach to the problem, using food and other environmental factors as the precipitating agents, the processing of nutrients in the body as the host factors, and obesity as the outcome variable similar to the disease one gets from being bitten by an insect that carries an infectious parasite. Fig. 1 is a schematic presentation of the epidemiological model we are using.

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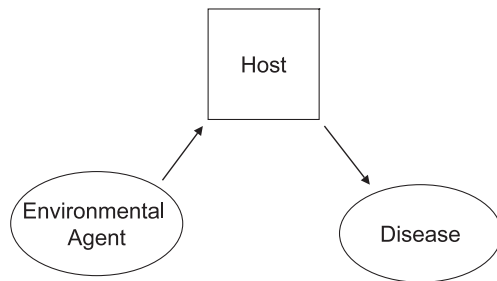
Epidemiological Model

Fig. 1. Epidemiological model.

A number of dietary factors could play a role in the development of human obesity. Among the most important of these is the macronutrient composition of the diet. We will focus this discussion on dietary fat. In addition, however, there are trace elements, toxins, the social setting in which the food is provided, and the overall level of physical activity of the host considered as possible elements in the host's response to food. We will address the question of whether the reduction of fat intake is effective in reducing obesity in industrialized countries. We will also ask whether increasing fat intake is playing a role in the development of obesity in populations where a traditionally low-fat diet is being replaced by a higher-fat diet. Finally, we will discuss the effect of exercise on fat oxidation and the replacement of dietary fat with indigestible fat substitutes.

It is important to place the role of dietary fat in its proper context. Fat intake must be seen through its effects on total energy intake. For example, it is well known that a high-fat diet is highly palatable, and this often leads to over-consumption of tasty foods, a loss of portion control. Lowering dietary fat is one of the effective strategies in people who have successfully kept their weight off [1], and

it was one of the effective strategies in the Diabetes Prevention Program lifestyle intervention [2].

2. Dietary fat intake in animal studies

As a rule, experimental animals eating low-fat diets do not become obese. The major exceptions are animals with genetic forms of obesity or brain damage, and animals treated with drugs or certain peptides. Development of obesity in animals eating high-fat diets is the expected outcome [3,4]. Whether the animals are susceptible or resistant to obesity when eating high-fat diets has a strong genetic component. Some strains of mice and rats are exquisitely susceptible to developing obesity when eating high-fat or high-fat, high-carbohydrate diets (A/J and C57/BL mice and the Osborne–Mendel rat). Other strains of mice (SWR) and rats (S5B/Pl) are resistant to developing obesity when fed similar diets. When animals are exposed to several levels of dietary fat, there is a dose–response curve with a threshold of about 25% dietary fat. This suggests that levels of dietary fat needs to exceed 25% in the diet before obesity develops [5].

2.1. Epidemiologic studies

Ecologic studies are the most basic type of epidemiologic investigation. They do not indicate a causal relationship, but they can provide an insight into the diet–disease relationship in different populations. Fig. 2 shows the association between the proportion of energy from fat (obtained from the national food balance data) with the prevalence of overweight (body mass index, BMI, of 25 kg/m^2 or greater) among the adult participants of nationally representative surveys from 20 countries [6]. A weighted regression
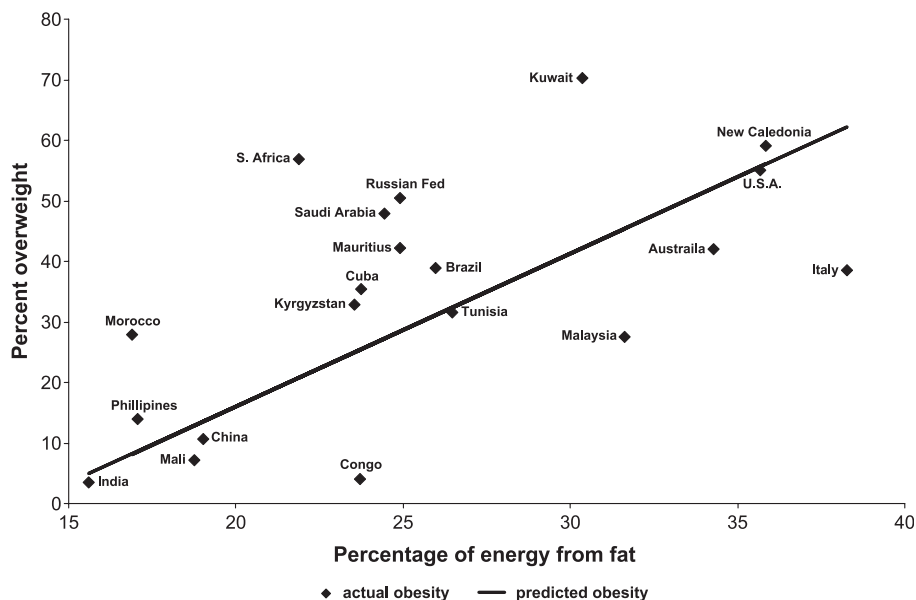

Fig. 2. Fat intake vs. population.

analysis shows a significant positive association between fat consumption and the proportion of the population who are overweight. This suggests that halting the increase in dietary fat in many countries where the diet is traditionally low in fat may be an effective strategy to prevent an increase in obesity. Migration studies provide additional evidence. Re-analysis of the Ni-Hon-San migration study [7], where 8006 Japanese men living in Honolulu were compared with 2183 men living in Hiroshima and Nagasaki, shows that while the total energy intake was only slightly higher in Honolulu than Hiroshima and Nagasaki, the percentage of energy from fat was two times greater in Honolulu. The mean BMI and subscapular skinfold thickness were also greater in men living in Honolulu and more of these men were obese. The Leeds Fat Study [8] shows that when the frequency distribution of BMI among individuals who consumed a higher-fat diet (>45% of energy) was plotted, the tail was skewed to the right as compared to those who consumed a lower-fat diet (<35% of energy), and the proportion of obese individuals was about 19 times higher among those who consumed higher-fat diets than those who consumed lower-fat diets. However, there were also a number of individuals who consumed a higher-fat diet but whose BMI was normal, suggesting that other factors, including genetic susceptibility, must play a role. Another ecologic study used the time-trend analysis to examine obese individuals and their past diet [9]. Among 377,200 Danish military recruits from the years 1943–1974, there was a marked parallel between the percentage of energy from fat and the subsequent development of obesity. Studies conducted among the Pima Indians in the United States [10] produce similar results. Obviously, the association between high-fat intake and subsequent obesity is compounded by other factors, most notably the declining trend in physical activity.

A longitudinal survey in China also suggests that the increase in fat intake led to an increase in body weight [11,12]. The potential confounders in the relation of diet to BMI (e.g., age, sex, physical activity, and smoking) were taken into account. To test the hypothesis that fat has an independent effect on body weight, the effect of change in absolute amount of energy from fat was examined while controlling for the effect of change in energy from the non-fat sources (i.e., protein and carbohydrate). Similarly, the effect of change in the percentage of energy from fat was examined while controlling for total energy intake. In both cases, a significant effect of fat intake on BMI was found: a 100 kcal increase in fat intake was associated with about 0.05 and 0.01 unit increase in BMI in adolescents and adults, respectively. In contrast, a 100 kcal increase in protein and carbohydrate intake combined was associated with an increase of only 0.01 and 0.0007 BMI unit in adolescents and adults, respectively. Similar results were seen when fat intake was expressed as the percentage of total energy intake. These findings suggest that the energy from fat may have a greater effect on body weight than energy from non-fat sources. They are consistent with the
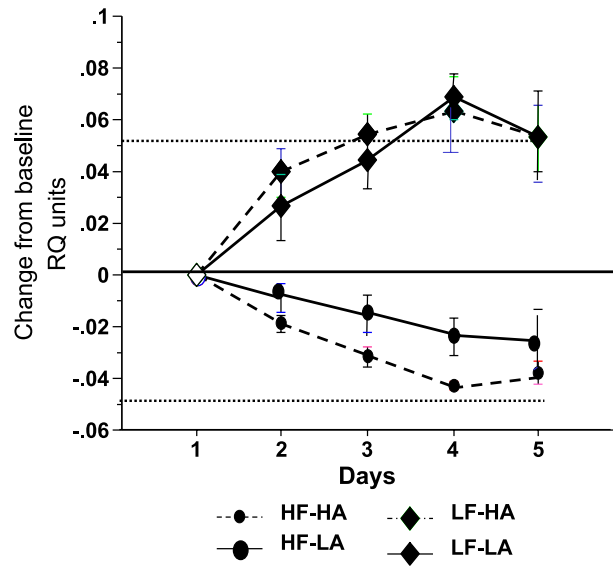

Fig. 3. Exercise and fat intake.

view that the increase in fat intake may put a significant fraction of the population at risk of obesity, especially those who are genetically predisposed to the condition [3,4,9,13,14].

3. Exercise

The relation of fat intake in the population to levels of physical activity was suggested in the study from Gothenberg [13]. In this study, the 6-year weight gain was related to fat intake only in the subjects with the lowest level of physical activity. To explore the relationship of physical activity to fat intake, we have turned to the controlled setting of clinical investigation. The effect of exercise on the adaptation to an acute increase in dietary fat or carbohydrate is very instructive. Fig. 3 shows the response to a high-fat diet in healthy young men who lived in a metabolic chamber for 5 days. The upper two lines show that within 2 days, a low-fat (20%), high-carbohydrate (65%) diet reaches the expected new equilibrium, and this rate of adaptation is not affected by exercise. In contrast, the adaptation to the high-fat diet (50%) low carbohydrate (35%) was slower, and when the men were sedentary, they had still not fully adapted by the end of 5 days. The importance of exercise on the rate of adaptation to this high-fat diet is clear, and suggests an important public health message: get moving—the more the better.

4. Overconsumption of palatable high-fat diets

Unlike protein and carbohydrate, fat stimulates excess energy intake through its high palatability and lack of satiating power [15]. Periodic exposure to high-fat meals, particularly when hungry, may be sufficient to lead to

overconsumption of energy with obesity as the result [16]. Several approaches have been used to examine the effect of macronutrients on satiety and on subsequent food intake. Overfeeding studies that compare high-fat with high-carbohydrate diets indicate that metabolic adaptations to changes in fat in the diet are slow compared to adjustment to carbohydrate which are almost immediate [17–21]. However, it appears that the ability to reduce food intake to compensate for the food eaten earlier is impaired when the subsequent foods are high in fat [22,23] and especially when they are high in both fat and sugar [8,24]. These findings point to one reason why sweet, high-fat foods can lead to obesity: people tend to overconsume them.

5. Can a reduction in dietary fat prevent or reverse obesity?

5.1. Animal experiments

Two major findings from animal experiments are noteworthy: first, a high-fat diet induces an increase in the number of fat cells or adipocytes, and second, replacing a high-fat with a low-fat diet may, but does not always, reverse obesity. Both mice and rats increase their number of fat cells after eating a high-fat diet for an extended time, and these cells remain after dietary fat is reduced [25–29]. Rats fed a high-fat diet did not return to their baseline weight when switched to a lower-fat diet [29]. After being fed the high-fat diet for longer than 7 months, the animals did not lose their weight to the control levels [30,31]. The extent to which genetic factors are involved in the increase in the number of fat cells and of weight gain after switching from a high-fat to a low-fat diet has not yet been determined. These data suggest that the increase in fat intake may be

particularly important in inducing obesity, whereas a reduction in dietary fat has less of an effect on weight loss, and that they may operate through different metabolic pathways.

5.2. Effect of fat reduction on weight loss in overweight subjects

Several intervention trials have examined the effect of a low-fat diet with or without energy restriction in overweight subjects [32–48], and these have been reviewed [6,49–51], and a meta-analysis performed by Astrup et al. [52,53]. The rate of weight loss was generally greater when the low-fat diet was combined with reduction in total energy intake. These studies show that apart from energy restriction, a low-fat diet alone is effective in inducing weight loss in overweight subjects, with an observed mean weight loss of about 1.8 kg/month. Although the rate of weight loss on an ad libitum, low-fat, high-carbohydrate diet may not be as rapid as that induced by energy restriction (calorie counting), the diet has been found to provide greater satiety and, subsequently, the compensation for the decrease in energy intake is not complete, i.e., energy intake remains decreased [29,43,44,54]. Even in studies where the goal is to maintain a constant energy intake, the total energy intake is often unintentionally reduced when a low-fat diet is consumed [36]. Among the obese subjects, about 23% of the initial reduction in total energy intake is not compensated for. Despite the fact that compliance tends to decrease over time, a low-fat, high-carbohydrate diet is still one of the most effective tools in weight maintenance [54,55]. Consumption of reduced-fat products leads to a lower energy consumption, suggesting that this may make it easier to maintain a long-term energy deficit and hence slow down the rate of weight gain or regain [56]. In at least one study, the ad
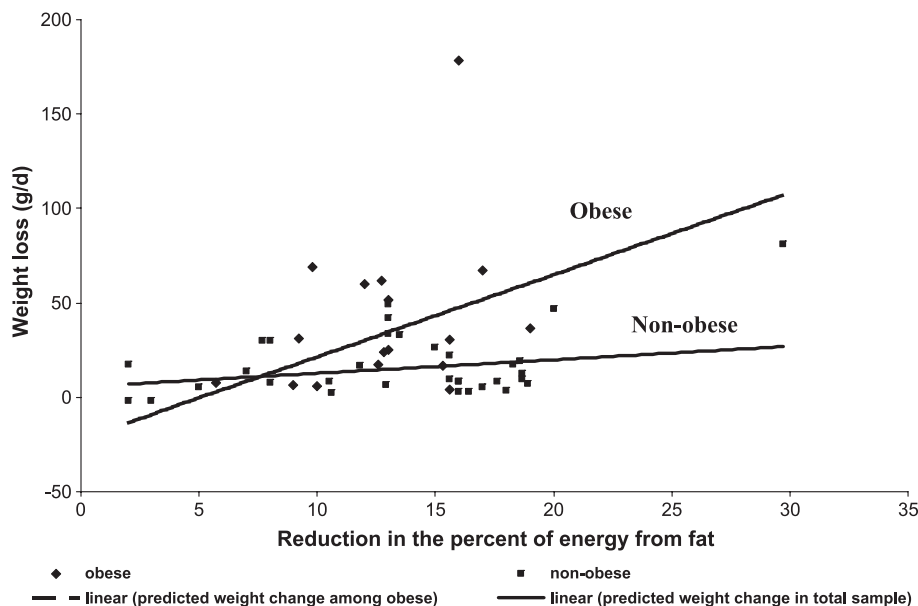

Fig. 4. The effect of a reduction in the percent of energy from fat on grams of weight loss per day.

libitum low-fat, high-carbohydrate diet was shown to be more effective than energy restriction alone in maintaining weight loss over 1 year [54]. This may be due to the fact that simple energy restriction is often associated with extremely poor compliance [44]. Weight loss and lower fat intake were both predictors of weight loss in the Diabetes Prevention Program [2].

We summarize the studies of the effect fat reduction on body weight in Fig. 4. The data depict the relation between the percent reduction in fat energy and the resultant weight change. The predicted weight loss for the entire set of studies is provided. The main explanatory variable was the change in percentage of energy from fat (isoenergetic studies were not included), and the difference in size of the studies was accounted for. The covariates analysis included gender, mean initial body weight, and mean age of the subjects. The regression model showed that those with a higher initial weight lost more weight, as expected. The slope of the regression line suggested that each additional percentage point reduction in dietary fat produced a weight loss of 0.99 g/day (p=0.10) for all studies combined. For obese individuals, the loss was considerably greater at 3.22 g/day (p=0.08). Although the results are not statistically significant, they reiterate the importance of dietary fat reduction in obesity. Among the obese subjects, a 10% decrease in fat (e.g., from 36% to 26% of total energy) was associated with weight loss of 32 g/day. A subsequent meta-analysis of the effect of changes fat intake on weight loss showed comparable results [49].

5.3. Effect of indigestible fat substitutes

Fat substitutes such as sucrose polyester (e.g., Olestra®) have been used to facilitate research on the degree to which covert changes in dietary fat alter total energy intake and macronutrient selection. Short-term studies of the substitution of indigestible fat substitutes for dietary fat show two patterns of adaptation. When 20 or 30 g of olestra was substituted for fat in a single breakfast meal, there was energy compensation over the next 24–36 h in healthy young men [57,58]. When fat intake was lowered from 40% to 30% of energy by substituting olestra for fat at the noon or the evening meal, there was no energy compensation over the next 24 h [59]. However, when Olestra substitution lowered the fat intake from 30% to nearly 20% of energy over three meals, healthy subjects felt less satisfied and compensated for nearly 75% of the energy deficit over the next day [60].

To explore these effects further, a 9-month feeding trial was performed. Forty-five overweight men with a BMI of about 30 kg/m^2 were randomized to one of three diets, a control diet with 33% fat, a reduced-fat diet with 25% fat, and a diet in which olestra reduced available fat from 33% to 25%. During the first 3 months, all three groups lost weight. For the next 6 months, the body weight of the 15 men on the control diet stabilized, with no further change in body fat. The men eating the 25% reduced fat diet actually began to regain weight, indicating that they were not adhering to the diet. The men eating the olestra-substituted diet continued to lose weight overt the entire 9 months. By the end of the study they had lost nearly 20% of their body fat [60]. Leptin decreased in relation to body fat. These observations indicate that loss of body fat and a decrease in leptin provide only weak signals for increasing body fat. They also suggest that there are signals from the GI track that play a very important long-term role in maintaining body fat stores.

From these studies, we conclude that dietary fat is one of the factors involved in the current epidemic of obesity. Higher-fat diets make it more difficult to control energy intake. Reducing dietary fat has modest effects in lowering body fat, but not more so than other strategies for reducing energy intake. However, preventing the rise in fat in the diet of developing countries might be important in reducing the rate at which obesity is developing worldwide.

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