Diet composition and energy balance in humans

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Diet composition and energy balance in humans[1–3]

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ABSTRACT Inpatient metabolic studies of human subjects were performed to obtain data on important nutritional issues. It was shown that wide variations in the ratio of carbohydrate to fat do not alter total 24-h energy need. Studies of the fatty acid composition of plasma low-density lipoproteins during low-fat feeding indicated that there can be considerable lipogenesis from carbohydrate in humans during isoenergetic feeding. The energy cost of this conversion must be small or be counterbalanced by other changes in energy metabolism because measured energy need was unaltered by fat-to-carbohydrate ratios. Energy need was, however, markedly varied by changes in body weight. Subjects at their usual body weights who had experimentally induced increases in body weight became inefficient and required a higher energy intake for weight maintenance. The reverse occurred with a reduction in body weight. The set point at which energy storage is defended is clearly different in obese persons. *Am J Clin Nutr* 1998;67(suppl):551S–5S.

KEY WORDS Lipogenesis, dietary carbohydrate, adipose tissue, obesity, humans, diet composition, energy balance

INTRODUCTION

We are in the throes of an epidemic of obesity that is worsening despite increasingly dire warnings of the adverse health consequences of being obese. A variety of educational programs emphasizing dietary restriction and increased physical activity have been unable to stem the tide. Although this failure might be attributed to inadequacy of the educational programs, an alternative view is that potent biological factors are at work that are not yet understood and that hobble the public in its efforts to lose weight. Our interest is focused on what biological factors may be important in the production of obesity.

For as long as individuals have dealt with obesity as a medical problem, dietary alterations have been advocated. Nearly all researchers agree that some degree of energy restriction is required for weight reduction, but opinions differ as to which dietary mix, if any, is most effective for weight reduction. Some time ago, carbohydrate was thought to be the particular culprit and therefore diets rich in carbohydrate were believed to generate obesity. Now, reduction in fat intake and a pari passu increase in carbohydrate is widely recommended for the prevention and treatment of obesity (1). Furthermore, there is evidence that dietary fat may have adverse health effects other than obesity. For example, dietary fat has been implicated in the development of some malignancies (1).

EFFECTS OF DIET ON ENERGY BALANCE

We therefore examined some aspects of energy metabolism related to carbohydrate and fat in the diet and also the relation of energy expenditure to fat storage. Several years ago, we examined data that had been accumulated at The Rockefeller University Hospital over four decades of formula feeding, comparing the exact energy requirements for weight maintenance as a function of the components of the diet. We showed that the carbohydrate-to-fat ratio could vary widely with little or no alteration in the energy requirement for weight maintenance. The results of a 13-wk study in which an individual was fed a formula diet extremely rich in carbohydrate and low in fat for a period of 38 d and, thereafter, for a longer time, a diet rich in fat and low in carbohydrate are shown in **Figure 1**. Weight varied little during the study and average energy intake was the same throughout. The details of this technique of feeding and calculations derived from the data shown in Figure 1 are described elsewhere (2). The reason for emphasizing these findings is that under the strict conditions imposed by hospitalization and feedings of a formula diet, energy needs are the same over long periods of time even though carbohydrate-to-fat ratios vary. Similar data were accumulated in 15 subjects.

It must be emphasized that in such studies individuals are not given an opportunity to select the type of food consumed, nor do they select the amount of food. The virtue of the study is the demonstration that under conditions of strict dietary control and over long periods of time, different isoenergetic mixtures can fulfill the requirements for weight maintenance. However, a low-fat diet might be particularly satisfying and lead to the intake of less energy than would be the case with a high-fat diet. Such an analysis was not the point of this study.

Because there is likely to be an obligate requirement for fatty acids as substrates for the energy needs in some organs, it could be argued that a high-carbohydrate diet would lead to a shrinkage in fat storage, because fatty acids inadequate in amount in the diet would have to be removed from the fat storage depots. This would not be the case, however, if it were possible for individuals to convert carbohydrate to fat. Recently, a series of observations were made indicating the likelihood that the second

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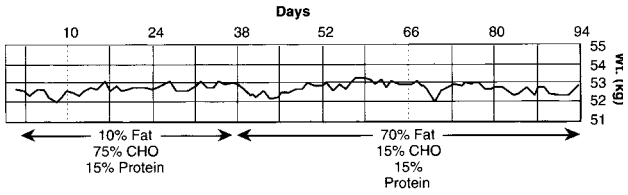

FIGURE 1. The unchanging energy need when a hospitalized patient is fed liquid diets varying widely in fat-to-carbohydrate ratio. The patient was a 64-y-old woman fed 7322 kJ/d. CHO, carbohydrate. For details, *see* reference 2. Reproduced with permission from the American Society for Clinical Nutrition.

scenario occurs in humans (3). It was assumed, as shown in **Figure 2**, that plasma VLDL triacylglycerol fatty acids derive from hepatic sources and that there are three donors for hepatic fatty acids: dietary fat, adipose tissue, and lipogenesis of fatty acids from carbohydrate. To study the possibility that lipogenesis occurs with isoenergetic diets low in fat and high in carbohydrate, we gave several human subjects formula or solid food in which the fatty acid composition of the diet matched that of the subjects' adipose tissue. In particular, the amount of dietary linoleic acid (18:2) was closely matched with concentrations found in adipose tissue. Because linoleic acid cannot be synthesized from carbohydrate in mammalian tissue, any significant lipogenesis must lead to a decline in the amount of 18:2 in VLDL, presumably derived from hepatic sources and therefore mimicking hepatic fatty acid composition. When diets high in carbohydrate and low in fat were fed, VLDL showed a sharp decline in 18:2 and an increase in palmitic acid (16:0).

Documentation for the existence of significant lipogenesis from carbohydrate in humans is provided in **Figure 3**. This was also confirmed in studies in which subjects were administered [^{13}C]acetate and it was shown that acetate was incorporated into VLDL palmitate during feeding of a high-carbohydrate, low-fat diet (3).

It is clear, therefore, that the major components of the dietary mixture are altered by internal biochemical processes. When a very-low-fat diet is fed, the organism makes fat and the ultimate mixture available for metabolic events is different from that eaten. This establishes a degree of interchangeability of dietary

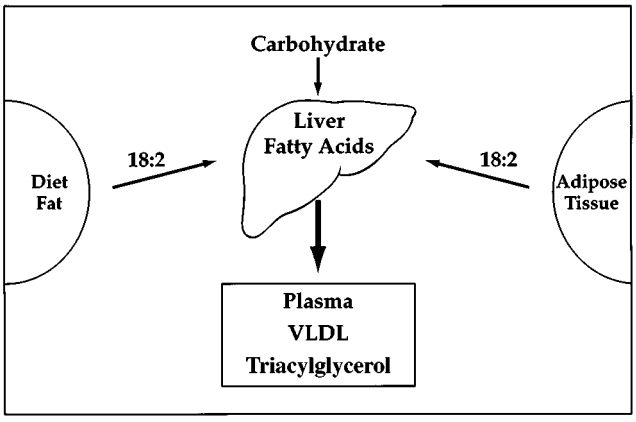

FIGURE 2. The fatty acid composition of plasma VLDL triacylglycerols is hypothesized to originate in liver from three sources as shown. For details, *see* reference 3.

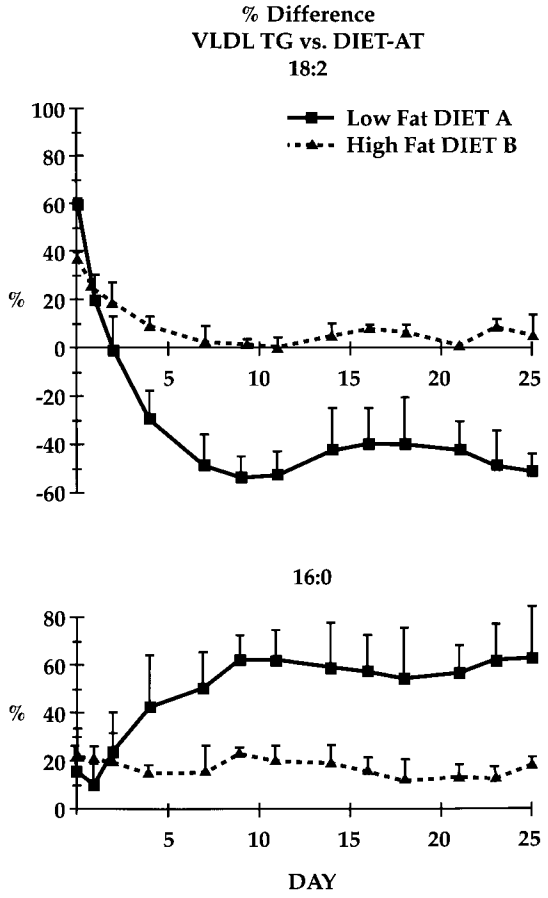

FIGURE 3. Shown is the percentage change in linoleic acid (18:2) or palmitic acid (16:0) in VLDL in a subject fed a formula diet with 10% of energy from fat (diet A) compared with initial values before dietary change on day 0. The rise in 16:0 and decline in 18:2 are taken as evidence for lipogenesis from carbohydrate. Body weight was maintained throughout the study by isoenergetic feeding. For details, *see* reference 3. Reproduced from reference 3 by copyright permission of The American Society for Clinical Investigation.

substances such that the carbohydrate-to-fat ratio of the diet is not the ultimate mixture available to tissues metabolizing fat. The amount of carbohydrate or degree of restriction of fat at which significant lipogenesis develops has yet to be determined. Interestingly, the fat synthesized is of necessity more saturated than fat ordinarily found in the diet. It may well be that in the obese or in those with diabetes or other metabolic disturbances, there are special sensitivities to dietary carbohydrate with respect to conversion of carbohydrate to fat. These important matters must be investigated in detail. It was also shown that the type of carbohydrate fed may also be a factor in lipogenesis because complex carbohydrates are less likely to be converted to fat than simple sugars (4).

In other experiments carried out over the past 10 y in our laboratory, a special relation has been uncovered between the amount of energy storage in adipose tissue and energy expenditure. Before these studies, adipose tissue, particularly the size and cellularity of the depot, was implicated in the regulation of food intake. In adult animals the amount of energy storage is usually sufficiently constant so that energy intake equals energy outgo. It is always the case that any change in energy storage,

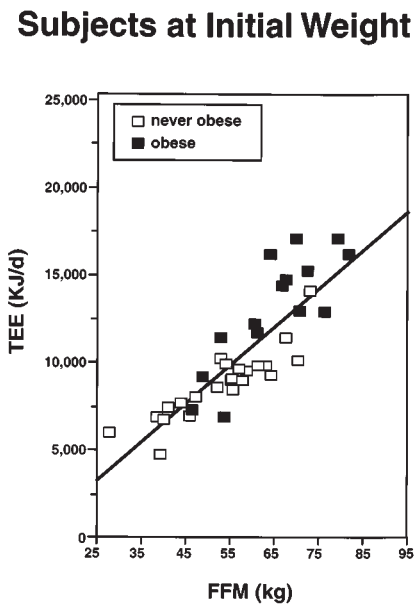

FIGURE 4. The relation of total energy expenditure (TEE), as measured by the amount of energy required to keep weight constant, with fat-free mass (FFM). Both obese and nonobese subjects are shown at their usual weights. For details, *see* reference 6. Reproduced from reference 6 with permission (Copyright 1994 Massachusetts Medical Society. All rights reserved.)

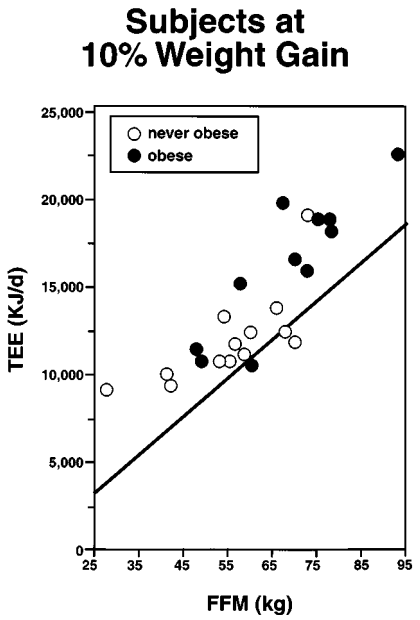

FIGURE 5. A repeat of the data in Figure 5 when subjects were maintained at a constant weight on a plateau 10% above their usual weight. TEE, total energy expenditure; FFM, fat-free mass. Reproduced from reference 6 with permission (Copyright 1994 Massachusetts Medical Society. All rights reserved.).

ΔE, can result only from an inequality of Q (energy intake) and W (energy outgo). Thus, $\Delta E = Q - W$. It is only by transient differences in intake and outgo that increases in storage of fat or an increase in ΔE occurs. The cumulative amount of either Q or W over a lifetime equals 200–400 GJ. Obviously, inequalities between Q and W could not be sustained for long periods of time because this would lead to continuous accretion of obesity or a continuous decline in body weight. An alteration in the total amount of fat storage is accompanied by a change in total energy outgo. My colleagues and I became aware of this when studying individuals who had lost body weight. These persons required less energy for weight maintenance than those at the same weight who had never experienced a period of weight reduction, ie, the energy expenditure of the reduced-obese does not equal that of the never-obese (5).

We analyzed this phenomenon in a study of >50 subjects hospitalized for many months (6). In the course of hospitalization, subjects were studied at their plateau weights, ie, weights maintained as constant as possible by equalizing food intake with energy outgo, and then at plateaus 10% above their initial weight and ≥10% below their initial weight. When weight is altered in this way, subjects who gain weight and maintain a fixed higher amount of weight have an unanticipated increase in body energy expenditure. The expenditure is unanticipated in the sense of being greater than that experienced by an individual at the same body weight and with the same body composition who had never experienced a weight gain. Usual body weight is lawfully related to energy expenditure in a system reminiscent of that described by Kleiber (7) for animal energy expenditure in animals of different sizes. Expenditure is governed by a precise mathematical relation as a logarithmic function of body weight (7). For example, the energy expenditure of a group of individuals at different usual weights is shown in **Figure 4**. Expenditure was measured in a variety of ways, including with use of the doubly labeled water method or the measured energy requirement for weight maintenance. In **Figure 5** is shown the effect of increasing body weight to 10% above usual body weight: a 15–20% unanticipated increase in energy expenditure.

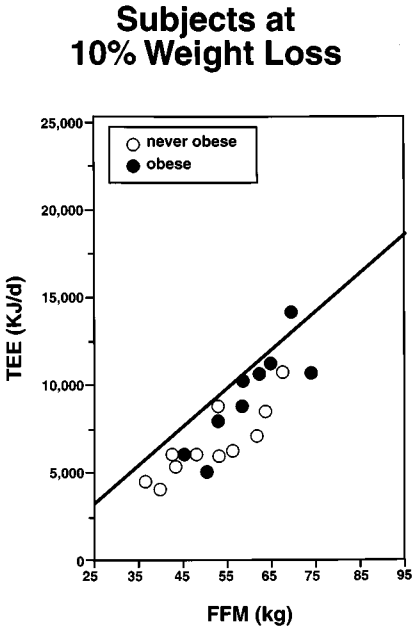

FIGURE 6. A repeat of the data in Figure 5 when subjects were maintained at a constant weight on a plateau 10% below their initial weight. TEE, total energy expenditure; FFM, fat-free mass. Reproduced from reference 6 with permission (Copyright 1994 Massachusetts Medical Society. All rights reserved.).

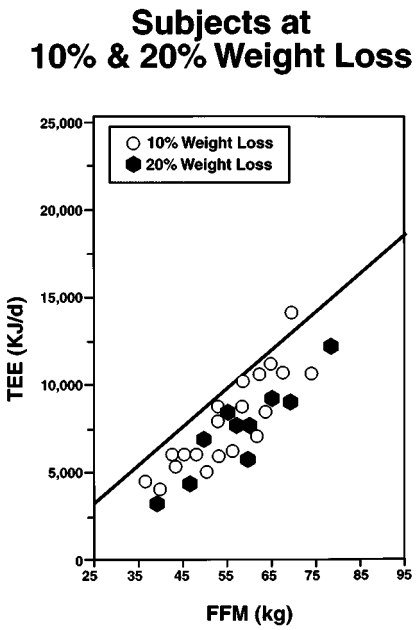

FIGURE 7. A repeat of the data in Figure 5 when subjects were maintained at a constant weight that was 10% or 20% below their initial weight. TEE, total energy expenditure; FFM, fat-free mass. Reproduced from reference 6 with permission (Copyright 1994 Massachusetts Medical Society. All rights reserved.).

Contrariwise, when individuals lose weight to 10% below their usual weight, energy balance declines, as shown in **Figure 6**. As shown in **Figure 7**, further weight loss, to 20% below usual weight, does not lead to any further decrease in energy expenditure. These experiments argue for a set point for each individual relating body fat storage to energy expenditure. Whatever is experienced as the usual or comfortable body weight is that weight at which the Kleiber relation between energy expenditure and lean body mass pertains. With imposed alterations in either

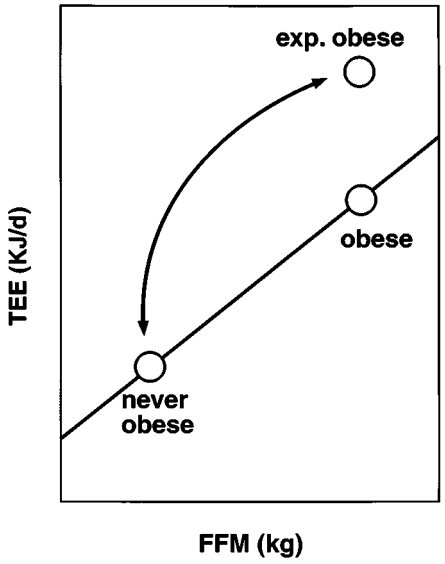

FIGURE 8. A hypothetical schema relating experimental (exp.) obesity to naturally occurring obesity. TEE, total energy expenditure; FFM, fat-free mass.

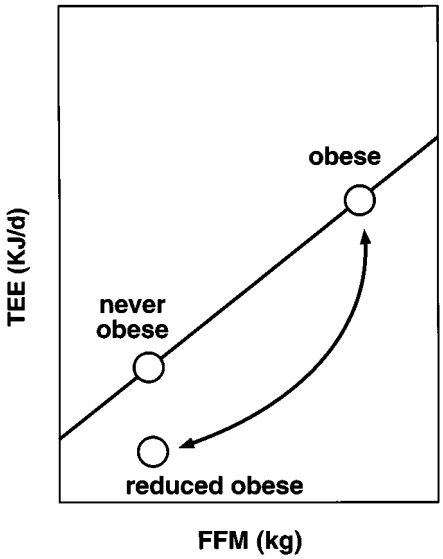

FIGURE 9. A hypothetical schema suggesting one reason for the high recidivism rate after weight reduction. TEE, total energy expenditure; FFM, fat-free mass.

an upward or downward direction, energy expenditure becomes either inefficient or more efficient, acting as a force to oppose the externally imposed changes. It appears that the obese behave exactly the same as the nonobese except that the set point in obese persons is at a higher level of fat storage.

But what are the consequences of these interesting findings relating adipose tissue mass to energy expenditure? Remember that for maintenance of body weight, energy expenditure and energy intake must be equal; therefore, the speculations that follow deal as much with the relation of adipose mass to energy intake as they do to energy expenditure.

A concept of the pathogenesis of obesity stemming from these findings on energy expenditure and adipose mass is shown in **Figure 8**. The production of experimental obesity by excess food intake or a mixture of excess food intake and reduced physical activity of necessity eventuates in increased fat storage, but this is opposed by a state of inefficiency or enhanced energy expenditure. In the natural course of events, this state would then tend to rectify itself with the consequent disappearance of the experimental obesity. In fact, this may occur often in response to transient overeating during holiday seasons or the availability of unusually tasty and attractive food. Investigators have often commented on the difficulty of producing persistent obesity in humans by excess food intake alone and these findings speak to that phenomenon. One can conclude that although an increase in food intake or decline in energy outgo are thermodynamic essentials for an increase in fat storage, the imposition of positive energy balance by cultural or psychologic events alone is unlikely to be a sufficient and total cause for the production of obesity. Some additional feature is needed that permits the obese person to rejoin the Kleiber line at a higher weight, establishing the usual mathematical relation of energy expenditure to body mass, different from that found in experimental overfeeding. Thus, something is missing from the educational campaigns and the approaches now being used for the prevention of obesity.

Similarly, weight reduction by an increase in energy outgo or a decrease in food intake produces the same departure from the

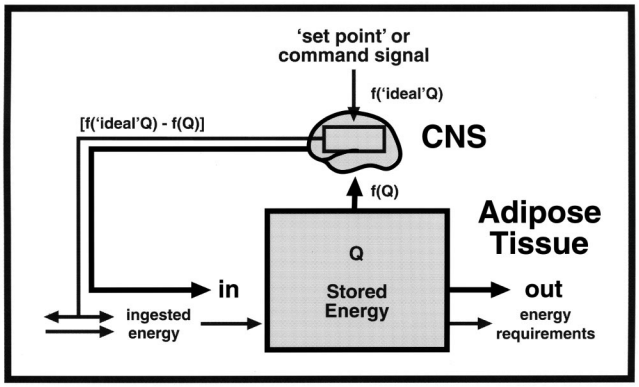

FIGURE 10. A simple model implicating adipose tissue in the regulation of food intake and energy metabolism. CNS, central nervous system. For details, *see* reference 8.

anticipated relation between body mass and energy outgo (**Figure 9**). In some way, reduced weight is experienced as an adverse situation and is all too frequently rectified with return to the original obese body weight. This of course does not mean that the reduction in body weight is not beneficial to health, it simply means that it is extremely difficult to sustain without some additional maneuver dependent on further information not yet available.

A full description of the etiology and pathogenesis of obesity will likely incorporate some mixture of growth and developmental events as well as environmental and psychologic circumstances, interacting with a biological system that sustains body fat storage. That biological system is now beginning to be understood. Perhaps the simplest model is one published nearly 25 y ago (8). **Figure 10** is a simplified version of the model emphasizing a relation between adipose tissue and central nervous system function. The regulatory capacity within adipose tissue for the maintenance of a given level of fat storage has effector arms altering both energy expenditure and food intake.

The control of adipose tissue storage in at least one mouse strain is dependent on the secretion of a peptide from adipose tissue and a receptor system in the hypothalamus. Mutations of the genes controlling elaboration of the peptide or its receptor system can affect fat storage in at least two mouse strains and one rat strain (9–11). These recent demonstrations of the relation of adipose tissue to the central nervous system are being explored vigorously for relevance to human obesity. How this system interacts with features such as cultural events, availability of food, and carbohydrate-to-fat mixtures is our agenda for future research in human obesity. When the molecular genetics of human obesity is understood, then the role of carbohydrate-to-fat ratios in the diet will be reexamined and the relation of dietary fat and carbohydrate in obesity will at last be placed on a firm basis of understanding.

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