

Rev Biomed 1999; 10:107-128.

Symposium on obesity (Second Part).

Symposium

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6) DIET COMPOSITION AND BODY WEIGHT REGULATION

B J Rolls

In this paper I will briefly examine the evolution of theories about the effects of diet composition on the regulation of food intake and body weight. I will then review the evidence regarding the usefulness of high-carbohydrate/low-fat diets for weight loss, weight maintenance, and prevention of weight gain.

Over the years, various macronutrients in food (carbohydrate/sugar or fat) have been targeted as either the cause of obesity or the solution to successful weight loss in obese individuals. Low-carbohydrate diets (including low-sugar diets), high-fiber diets and low-fat diets have all been "in vogue" at different times. These diet plans have been especially popular among dieters when they are so called Afree@ diets, such that dieters are

allowed to eat as much as they like of certain groups of foods and calorie intake per se is not limited.

Background summary. In the 1950's and 60's, several weight loss diets were based on carbohydrate restriction, with free intake of foods high in protein and fat. These diets were based on the premise that carbohydrates, sugar in particular, have low satiety value and that sugar creates some sort of "artificial appetite". Some also suggested that fat may have metabolic benefits over carbohydrate and protein. Any enhanced weight loss demonstrated on these diets was likely due to electrolyte loss and shifts in water balance. Further, a diet with such severe carbohydrate restrictions is not likely to be followed for long periods of time (8).

Current thought is that fat restriction should be advocated for body weight control. Many nutritionists and other health care professionals are advocating the permanent adoption of low-fat diets to achieve weight loss and successful weight maintenance at lower body weights. It has been suggested that a low-fat diet alone, independent of

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Received November 10, 1998; Accepted December 4, 1998.

This paper is also available at <http://www.uady.mx/~biomedic/rb991026.html>

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any conscious energy restriction, will result in significant weight loss that can be maintained. As a result, a new type of Afree@ diet has emerged, this one allowing free consumption of fat-free or low-fat foods.

Evidence from epidemiology for a relationship between diet composition and body weight. In epidemiological studies, information is collected about dietary habits of populations in the natural environment (9, 21). Survey studies have used various measures of self-reported food intake, such as the 24-hour recall, food diaries (2 to 7 days), or food frequency questionnaires, to determine the usual intake of energy and various nutrients in the population being studied. Based on these self-reports of intake, many researchers have found a modest positive association between measures of overweight and the percentage of fat in the diet (6, 24, 41). Some data (24) suggest that the relationship between dietary fat and degree of overweight may be independent of the relationship between dietary fat intake and overall energy intake. Although one study (24) reported a greater intake of added sugars in obese individuals, another found that the prevalence of overweight and obesity was progressively lower with increasing consumption of total carbohydrate, total sugars and added sugars (4). A recent survey in Britain confirms that consumption of added sugars is negatively associated with body mass index (10). On the other hand, diets low in dietary fiber are associated with higher body weights (24).

Longitudinal survey studies have looked specifically at the role of diet composition in the maintenance of a stable body weight over time. Several of these studies indicate that a high-fat diet is associated with weight gain, although this relationship was influenced by age, gender and prior weight change (6, 16, 19).

In general, the results from survey studies have led to the suggestion that there is a causal relationship between dietary fat intake and obesity. Although these studies suggest interesting relationships, by their nature, they are not able to

show causality. In several studies the data suggested a relationship between dietary fat and obesity independent of total energy intake, but interpretation of self-reported food intake data should be made with caution due to the possibility of large sources of error and systematic bias. It has been shown that food intake, in general, is underreported (33) and that self-reports of food intake become less accurate as dietary intake increases. Lichtman and colleagues (20) have confirmed that obese individuals are especially prone to under-reporting their food intake. Such underreporting may help to explain why it has been difficult to demonstrate a relationship between BMI and total energy intake, although it is likely that such a relationship exists.

In addition to the problems inherent in self-reported food intake, some of these studies fail to control for likely confounding variables such as activity level and smoking status. The failure to account for level of physical activity is a particular problem since it is likely to be fat balance rather than fat intake per se that leads to body weight gain. Studies just accounting for fat intake are only measuring half the fat balance equation and therefore reduce the probability of finding a relationship between diet composition and BMI.

Dietary interventions: Reductions in dietary fat without restrictions in total energy intake.

There are many examples of dietary intervention studies aimed at reducing dietary fat (without conscious food restriction) in non-obese individuals in order to reduce health risks for certain diseases. In these studies, baseline fat intake ranged from 35-41% of energy from fat. Following the intervention, fat intake was reduced to 13%-32% of calories. When dietary fat intake was reduced, spontaneous energy intake was usually reduced (2, 14, 17), and body weight declined. Even when total energy intake was not significantly affected (as assessed by diet records) by interventions emphasizing an increase in either total carbohydrates from all sources (37) or high-fiber

carbohydrates (29), spontaneous weight loss still occurred. Weight loss ranged between 1-3 kg in studies lasting less than three months (14), and 1-6 kg in studies lasting from six months to two years (2, 17). Where data are available at intermediate time points (17), the weight loss appeared to occur within the first three to six months and then remained fairly stable for the remainder of the study. This provides a good estimate of the time necessary to produce a new steady state of energy and macronutrient balance after a change in diet composition.

One of the longest and most thoroughly documented intervention trials has been the Women's Health Trial (35). In the vanguard group, 303 women, between the ages of 45 and 69, participated. The treatment consisted of a comprehensive dietary and behavioral program to lower fat intake from a mean baseline of 39% to 20% of energy intake. According to food records, this goal was achieved, with a reduction in fat intake to approximately 22% of calories and a 25% reduction in energy intake during the first 12 months. Although weight loss was neither encouraged or discouraged, the authors noted that many women used the program as an opportunity to lose weight (1.9 kg was lost at the end of two years). Data analysis suggested that change in percent of energy from fat was more strongly predictive of weight change than were changes in total energy intake, although the average energy intake reported is so low (1300-1350 kcal/day at 6, 12 and 24 months), one might question the accuracy of this data.

Two additional studies, the Lifestyle Heart Trial (25) and the Waianae Diet Program (36), suggest that reducing dietary fat to approximately 7 to 10% of total calories will result in significant weight loss. However, achieving this degree of dietary fat reduction requires extreme diet and lifestyle changes and this degree of fat reduction is not recommended by most health professionals. Maintaining diet palatability at this level of dietary fat also requires substantial effort in meal planning

and preparation. It is likely that only the most highly motivated individuals would be able to maintain this type of diet regime for any length of time.

For obese individuals, adoption of a low-fat diet in the absence of conscious caloric restriction also can result in modest weight loss over a period of a few months (15, 23, 34). As in lean individuals, such diets are associated with a spontaneous reduction in energy intake. On the other hand, instructing overweight people to restrict both fat and calories was shown to be a more effective strategy for weight loss than instructing them to only restrict fat (32). The availability of many new low-fat, high-calorie foods may undermine diets which emphasize restriction of fat alone. Whether the enhanced weight loss achieved with caloric restriction will be maintained over the long run is not clear. Certainly it has been demonstrated that most people regain weight that is lost on calorie-restricted diets (5). This indicates that the focus of weight management programs should be on maintenance of weight loss rather than on the weight loss itself.

Macronutrient composition and efficiency of weight loss when caloric intake is constant.

Many weight loss diets combine caloric restriction with recommendations about the amount of fat that should be consumed. A key question is whether changes in the composition of the diet have additional effects on weight loss beyond those of the caloric restriction. In a study where a 1200 kcal weight loss diet contained 10, 35 or 45% of calories from fat, with variations in both protein and carbohydrate, there was no significant difference in total weight loss or in loss of lean body mass over a 10-week period (1). Several recent studies have also found that weight loss on calorie-restricted diets was related to energy intake and not nutrient composition (11, 12, 31). However, in one intervention, caloric restriction combined with a goal of 20% calories from fat was more effective for both weight loss and weight maintenance than just restricting calories (27). The variability in these

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studies could depend upon a number of factors including the level of caloric restriction, the amount of physical activity and the motivation of the participants. In summary, the available data suggest that the fat:carbohydrate ratio does not have a large impact on weight loss in a calorie-restricted diet designed to promote slow weight loss. However, diet composition can be important for weight maintenance.

Effect of macronutrient composition on efficiency of weight gain. While a clear role for nutrient composition in calorie-restricted weight loss diets has not been defined, diet composition can influence weight gain when excess energy is consumed. Studies in which individuals were purposely overfed showed that weight gain was more rapid on a high-fat diet than on an equicaloric high-carbohydrate diet (7, 13). It is not likely that perfect energy balance is achieved on a day-by-day basis, but rather that periods of positive energy balance are compensated for by periods of negative energy balance. The abundant availability of high-fat, energy-dense foods will increase the probability of occurrence of periods of positive energy balance, and the excess dietary fat will be very efficiently stored as body fat. Reductions in the percent of energy from dietary fat could decrease or, perhaps, prevent episodes of positive energy balance and weight gain.

Maintenance of Weight Loss. Although maintaining weight loss once it is achieved is difficult, there are few data on the influence of diet composition on this critical phase of weight control. In a recent study, obese subjects who had been in either rapid or slow weight loss programmes were randomized to two different weight maintenance regimes (40). In one they were instructed to restrict energy intake, in the other they were given a leaflet which advised them to eat less fat and more complex carbohydrates without restriction of total calories. After a year on the maintenance programs, the ad libitum group

maintained a better weight loss (13.2 kg) than the fixed energy group (9.7 kg). At the end of a second year the pattern was similar. The authors conclude that an ad libitum, low-fat, high complex carbohydrate diet was superior to fixed energy intake for maintaining weight after a major weight loss.

Is Energy Density the Key? Two studies conducted at Cornell University (18, 22) are frequently cited as indicating that ad libitum consumption of low-fat foods can reduce fat intake and produce weight loss. In both studies, women were offered diets in which every food item had a fixed proportion of fat and carbohydrate. The low-fat diets included commercially available reduced-fat foods, primarily margarines, salad dressings, and mayonnaise, as well as traditionally low-fat foods. As the proportion of dietary fat increased in the diets, so did the energy density (i.e. kcal/g).

In the first study (22), the women were fed three diets ad libitum for 14 days: 15-20, 30-35, or 45-50% of calories from fat. Daily energy intake increased significantly as the proportion of fat increased in the diet, but, by calculation (30), the weight of the food eaten did not significantly differ between the diets. Over the two-week periods the diets did not produce any significant weight changes.

In a second study (18) the intervention period was extended to 11 weeks and only two levels of dietary fat were used: 20-25% and 35-40% of total calories. Weight loss was seen with both diets, but food consumption was less and weight loss was greater on the low-fat diet. Over the course of the study, there was a trend for the subjects on the low-fat diet to compensate by increasing the weight of food consumed. However, there were no significant differences between the two diets in weight of food consumed.

The results of these studies point to the energy density of the diet as an important determinant of energy intake. When given diets differing systematically in macronutrient composition,

participants ate the same weight of food in all conditions. Generally, energy density increases with the amount of dietary fat (28), so that if volume of food eaten is constant, more total energy will be consumed with high-fat vs low-fat diets.

The results from two additional recent studies (38, 39) confirm that subjects adopt a strategy of eating a constant weight of food when diet composition is manipulated. When subjects were fed diets with increasing amounts of fat and energy density (20, 40 and 60% fat) for 7 or 14 days, they ate a virtually identical amount of food on each diet. Because they ate the same amount of food on each diet, there was a stepwise increase in energy intake as dietary fat increased. Thus, energy density rather than fat content of the diet appeared to be the major factor influencing total energy intake.

In order to separate the effects of energy density on food intake from the effects of macronutrients, high-carbohydrate and high-fat diets should be compared that are of equal energy density and equal palatability. In one study (42), in which intakes of liquid diets with the same energy density but differing in the proportions of fat and carbohydrate were compared, the mean daily energy intake remained constant between conditions. Thus, fat and carbohydrate appeared to be equally satiating when the energy density of the diet was matched.

That energy density is a critical determinant of caloric intake has been demonstrated in a study in which the proportion of fat was held constant in three equally palatable diets which differed in energy density. When lean, young women were allowed free access for 2 days to each of these diets in turn, it was found that they ate the same weight of food in each condition so that energy intake was directly related to the energy density of the diets (3).

It is difficult to reduce the energy density or the fat content of a diet without increasing dietary fiber intake. This raises the question of how fiber in foods might interact with the overall energy density of the diet to affect food intake. In "Eat More, Weigh Less, (26) Ornish suggests that 33% more food will need to be consumed for maintenance of energy

intake after a reduction in dietary fat from 40 to 10% of calories. This is true if one considers a straight gram for gram substitution of carbohydrate for fat, but many high-carbohydrate foods are also high in fiber and/or water. In order to maintain caloric intake with such a 30% reduction in dietary fat, it would likely require an increase in food weight that greatly exceeds the 33% estimate. Thus, it is not surprising that a severe reduction in dietary fat consistently results in an initial decrease in energy intake and body weight.

Conclusions. Available data suggest that obesity is more strongly related to consumption of a high-fat diet than to consumption of a high-carbohydrate diet. However, total energy ingested in relation to level of physical activity also plays an important role in body weight regulation. Many athletes, for example, maintain a low body weight and body fat content while eating a high-fat diet. They balance the high fat intake with a high level of fat oxidation.

Currently, the most popular method for weight reduction is to reduce consumption of dietary fat. Reducing the fat content of the diet without energy restriction or an increase in physical activity is a relatively inefficient method of weight loss. When weight loss does occur on a low-fat diet, it is usually associated with a spontaneous reduction in energy intake which may relate to the decrease in palatability of the available foods. A number of studies show that weight loss over periods of several weeks is not dependant on the nutrient composition of the diet as long as total energy is reduced. However, limiting fat intake and increasing carbohydrate and fiber intake during weight loss is advisable for at least two reasons. First, it will allow dieters to consume a greater, and perhaps more satisfying, volume of food. Second, because a low-fat diet is important in order to avoid periods of positive energy balance leading to weight gain, it establishes dietary patterns which can help to maintain body weight.

It is likely that excessive intake of fat is related to its high energy density. Substantial research

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indicates the importance of the energy density of the diet to energy intake and body weight regulation. Consumption of a high energy density diet increases the chances that positive energy balance (and weight gain) will occur. A spontaneous reduction in energy intake consistently occurs when the energy density of the diet, as a whole, is reduced. A diet of low energy density is usually characterized as low in fat and high in complex carbohydrates and fiber. Fruits, vegetables and grain products are likely to be the mainstays of a low energy density diet. In addition, many fat- and sugar-reduced foods, that are also reduced in calories, are currently available on the market. These products can be helpful for weight loss and/or weight maintenance in that they increase the range of foods available that are of low energy density. It is important to note, however, that the substitution of only a few low-energy foods may not reduce daily energy intake and is unlikely to be of benefit in weight control. An emphasis should be placed on reducing the energy density of the total diet and on finding palatable low-fat, high-carbohydrate foods which help individuals sustain dietary change. A low-fat (or low-energy), high-carbohydrate diet could be more effective in preventing obesity or in maintaining weight loss than in producing weight loss.

Guidelines for practice. In the interest of developing more effective methods for helping people achieve and/or maintain a healthy body weight, several guidelines can be formulated from the diverse literature regarding the effect of diet composition on food intake and body weight.

**For weight loss, the critical aspect of a diet is the reduction in energy intake. Thus, a weight reduction diet can be designed around the preferred food patterns and nutritional needs of individuals. A diet of low energy density is a good choice because it requires the development of eating habits conducive to weight maintenance.

**Maintenance of a desirable body weight is most likely to be achieved on a low-fat diet of low energy density. Episodes of positive energy balance are minimized on such a diet, and, when they do occur,

dietary fat is not readily available for efficient deposition into adipose cells.

**Adoption of a diet of low energy density will likely lead to a spontaneous reduction in energy intake that will be helpful to achieve weight loss or weight maintenance. The energy density of the diet may best be reduced by a combination of the following:

- * reduction in dietary fat
- * increase in intake of high-fiber, low-energy foods, namely fruits and vegetables
- * reduction in intake of energy-dense foods, regardless of their composition
- * reduction in alcohol consumption

7) THE BENEFITS OF PHYSICAL ACTIVITY IN OBESITY TREATMENT

JO Hill.

Physical activity in the theoretical framework of energy balance.

An individual maintaining a constant body weight and body composition must be in a steady-state where the amount of total energy ingested is equal to the amount of total energy expended. In addition, over some period of time, the composition of the energy ingested must equal the composition of substrate oxidized (1). Any disruption of energy and nutrient balance elicits compensatory responses to restore these balances. Conditions necessary for energy and nutrient balance are illustrated in table 1. Any disruption of energy and nutrient balance elicits compensatory responses to restore these balances. Physical activity directly affects the right side of table 1.

Table 1

ENERGY & NUTRIENT BALANCE	
E IN	= E Expend
PRO IN	= PRO ox
CHO IN	= CHO ox
FAT IN	= FAT ox

There are clear theoretical reasons why level of physical activity should be important in body weight regulation. First, physical activity is a major factor determining total level of energy expenditure. Increases in physical activity will increase total energy expenditure and decreases in physical activity will reduce total energy expenditure. Unless such changes are accompanied by compensatory changes in energy intake, body weight will change.

Physical activity is also a major determinant of fat balance, and obesity is a result of positive fat balance. Protein and carbohydrate balances appear to be well maintained acutely, even following challenges to body weight regulation (e.g. diet and exercise alterations). Fat oxidation and intake, however, are not acutely responsive to changes in each other. Because total fat oxidation varies directly with body fat mass (2), increases or decreases in the body fat mass may be required to reestablish fat balance. Changes in physical activity provide another means of altering fat oxidation, so that the higher one's level of physical activity, the less body fat mass is required to maintain fat balance at any given fat intake. Similarly, increasing physical activity without a change in fat intake will increase fat oxidation above fat intake and produce negative fat balance and loss of body fat mass.

Is a low level of physical activity a risk factor for development of obesity?

The recent report from NHANES shows that the prevalence of obesity has increased over the past 8 years in U.S. adults from about 25% to 33% (3). A similar increase in pediatric obesity was also found (4). A reduction in physical activity is certainly one factor that could have contributed to the increased prevalence of obesity.

Negative relationships between measures of physical activity (usually self-reports) and indices of obesity (usually body mass index or BMI) are seen in most data sets obtained from the general US population (5). The relationship appears to be similar in men and women, and across all ages and

ethnic groups (5).

Further, studies in which subjects are followed over time suggest that changes in physical activity are associated with changes in body fatness (6,7,8). In these studies, self-reported physical activity and BMI were recorded at baseline and at follow-up (2-10 years later). In all studies, the level of physical activity was negatively related to BMI at baseline, and level of physical activity at follow-up was negatively related to change in BMI from baseline to follow-up. In 2 of these studies (7,8) the level of physical activity at baseline was negatively related to change in BMI from baseline to follow-up. Finally, all studies suggest a negative relationship between change in level of physical activity and change in BMI.

Are increases in physical activity useful in treatment of obesity?

Substantial weight loss can be produced by exercise alone. This is illustrated in the study by Lee et al. (9) where overweight men were drafted into the Singapore army and subjected to 20 weeks of supervised vigorous exercise. The average loss of body weight in this study was 12.5 kg in 20 weeks. Subjects were free to consume as much food as they desired. While the study by Lee et al. (9) represents an extreme physical activity program, it does illustrate that physical activity alone can produce weight loss. Less intense physical activity programs will produce slower weight loss and may require much longer time periods to observe significant changes in body weight.

Increases in physical activity will increase to the right side the energy balance equation shown in table 1. This will produce negative energy balance, negative fat balance, and weight loss unless subjects increase the left side of the equation (i.e. energy intake). While we can accurately estimate the effects of a given increase in physical activity on energy expenditure, we know little about effects of such changes on energy intake. Thus, we still do not have a good ability to predict the effects of

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a given increase in physical activity on weight loss. Table 2 illustrates some estimated effects of increasing physical activity on body weight, depending of how the increase in physical activity affects energy intake.

Studies from Peter Wood and colleagues (10, 11) show that adding physical activity to caloric restriction programs can increase the amount of weight and fat loss. In one study (10), men and women were randomly assigned to a control group, a group receiving food restriction alone (diet only) or a group receiving diet and physical activity (diet & exercise). After 1 year, men in the diet and exercise group lost about 4 kg more of body fat and body weight than subjects in the diet only group. This suggests that energy intake compensation may have been in the order of 50%

of total calories expended in physical activity. For women, the differences were less and were only about 1 kg of total body weight and 1.5 kg of body fat. This could suggest that caloric compensation was greater in women than men.

Many studies have reported that the combination of physical activity and energy restriction do not lead to any greater weight loss than energy restriction alone. However, a careful examination of such studies shows them to be of short duration and of questionable power to detect the expected additional effects of physical activity on body weight.

There are reports in the literature that adding physical activity to energy restriction minimized loss of fat-free mass and maximizes loss of body fat (12). Unfortunately, most such studies are short in

Table 2
Potential Impact of adding 5 hr/wk of Moderate Exercise on Body Weight.

No Compensation		
<u>Length of Program</u>	<u>Caloric Deficit</u>	<u>Weight Loss</u>
12 Weeks	16,800 kcal	1.9-2.2 kg
20 Weeks	28,000 kcal	3.1-3.7 kg
52 Weeks	72,800 kcal	8.1-9.7 kg
25% Compensation		
<u>Length of Program</u>	<u>Caloric Deficit</u>	<u>Weight Loss</u>
12 Weeks	12,600 kcal	1.4-1.7 kg
20 Weeks	21,000 kcal	2.3-2.8 kg
52 Weeks	54,600 kcal	6.1-7.3 kg
50% Compensation		
<u>Length of Program</u>	<u>Caloric Deficit</u>	<u>Weight Loss</u>
12 Weeks	8,400 kcal	0.9-1.1 kg
20 Weeks	14,000 kcal	1.5-1.9 kg
52 Weeks	36,400 kcal	4.0-4.8 kg

Assumes the energy expended in exercise is 280/hour above resting and that weight loss comes entirely from body fat.

duration and involve small numbers of subjects. Weight loss produced by physical activity includes substantial reduction of visceral adipose tissue (13). However, it is not clear whether weight loss produced by exercise alone or exercise combined with energy restriction includes a greater proportion of visceral adipose tissue reduction than weight loss produced by energy restriction alone. While loss of visceral adipose may be affected by physical activity it may also vary due to gender and age.

It is also unclear whether men and women show a similar reduction in visceral adipose tissue with weight loss and particularly with exercise. Wing & Jeffery (14) assessed waist-to-hip ratio (WHR) in men and women participating in a 6 month behavioral weight loss program. They found a greater reduction in WHR in men vs women at the end of the program and at the 12 month follow-up period. However, at the 18 months follow-up period, the results were reversed, with women showing a greater reduction in WHR than men. Schwartz et al. (15) examined body fat loss due to endurance exercise training in young and elderly men. They found greater loss of visceral adipose tissue younger vs older men.

Despite the relative small effects of exercise on acute loss of body weight and body fat mass, the benefits of physical activity for body weight and body fat regulation become apparent when long-term maintenance of body weight losses is examined. Subjects who are most successful in maintaining a body weight reduction are those who engage in regular physical activity (16,17).

What type of physical activity is best in obesity treatment?

Aerobic vs Resistance

Both aerobic and resistance exercise have been used successfully in weight reduction programs and although the latter may preserve or increase fat-free mass, both seem to reduce body fat similarly when total dose of activity is considered (18). Further, a variety of aerobic activities have been successfully used in weight reduction studies.

While moderate intensity exercise uses proportionally more fat than high intensity, there is some suggestion that exercise of greater intensity is associated with lower BMI than exercise of moderate intensity (19). It should be realized that moderate intensity aerobic exercise must be performed for a longer period of time to produce as much fat oxidation as high intensity aerobic exercise. It is not possible with the available data to conclusively separate effects of intensity from effects of total amount of physical activity.

Continuous exercise or short-bouts of activity?

A great deal of new information suggests that short bouts of activity may be just as effective for body weight regulation as longer bouts. Jakicic et al. (20) demonstrated similar weight loss in overweight subjects given an exercise program consisting of the same dose of activity either as 30 minute or 10 minute bouts of exercise.

How often should overweight individuals engage in physical activity?

Little data are available regarding how frequency of physical activity impacts upon body weight regulation. Most experts recommend that people exercise 3-5 days/week, and while such recommendations are reasonable, we have no data at present to allow determination of optimum frequency of exercise for body weight regulation.

Enjoying physical activity

One of the most important characteristics of a physical activity program is that it should be fun. Physical activity only provides benefits for weight maintenance if it is regular and chronic. The benefits of physical activity are lost quickly after the activity is discontinued. Thus, if overweight subjects find physical activity that they enjoy, this will increase the likelihood that the activity will become a permanent part of the subject's life.

How to get overweight subjects physically active?

1. Reduce sedentary activity

Energy expenditure is near its lowest level when people are sedentary. Thus, the first strategy for

increasing energy expended in physical activity is to reduce sedentary activity. Any non-sedentary activity will increase energy expenditure above sedentary levels. A good start is to reduce the amount of time spent watching television or working on a computer.

2. Increase lifestyle activities

Another way to increase daily energy expenditure is to become more active in daily life. This can be accomplished by walking instead of driving, taking stairs instead of elevators and engaging in hobbies such as gardening.

3. Participate in regular exercise

Overweight individuals should be encouraged to find a type of exercise they enjoy and to plan to engage in this exercise on a regular basis. Specific advantages and disadvantages of different types of exercise for body weight management are discussed above. The most important factor in choosing a regular exercise, however, is to choose one the subject enjoys.

Summary.

While it has not been definitively shown that a low level of physical activity causes obesity, the two are closely linked with a strong theoretical basis for suspecting that a low level of physical activity is a risk factor for obesity. Highly active populations have a lower prevalence of obesity than sedentary populations, and the higher one's level of physical activity, the less likely that BMI will increase over time. Maintaining a high level of physical activity helps to reduce body fatness and to avoid future increases in body fatness. Increases in physical activity, either alone or in combination with dietary modification, can reduce body fat content. However, the public needs to have reasonable expectations regarding the magnitude and rapidity with which increases in physical activity can reduce body fatness. With moderate increases in physical activity, this is likely in the range of 2-6 kg/year, with 60-80% of the weight loss coming from body fat. Whether or not increases in physical activity preferentially reduce visceral adipose tissue

is unclear.

At present the most important characteristic of physical activity for body weight regulation is how much you do - or total dose. The best advice to the public is to find enjoyable physical activities in which to participate on a lifelong basis. Time spent in sedentary activities should be minimized and efforts should be made to increase physical activity in daily living. Maintaining an active lifestyle is a major benefit in maintaining a healthy body weight, and maintaining a healthy body weight is one way to lower risk of cardiovascular disease.

8) TREATMENT FOR HIGH - RISK OBESITY : THE BENEFITS OF WEIGHT LOSS

F X Pi-Sunyer.

Obesity is associated with a number of health hazards, including insulin resistance with hyperinsulinemia, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, stroke, gall bladder disease, and cancer. Other adverse conditions include respiratory insufficiency, sleep apnea, heart failure, gout and osteoarthritis. Where the fat is distributed in the body is also important, with increased health risk occurring if more is placed in the upper body or centrally. It is thought that it is the fat deposited intra-abdominally that is the primary risk. The risk of central fat distribution is additive with the risk of total burden of fat, making for a synergism that enhances risk considerably (14, 15). Weight loss reduces many of these health hazards both by decreasing total fat burden and by decreasing the amount of central fat. Changes in waist circumference with a given amount of weight are reflective of changes in visceral fat, and occur in both men and women, with a somewhat greater effect in men (20).

Hypertension improves with weight loss in overweight persons. The Framingham study showed that blood pressure decreased with weight

loss (8). In men, a 15% decrease in weight was associated with a 10% decrease in systolic blood pressure. McMahon and colleagues (12) reported a 1 mm decrease in systolic and diastolic blood pressure per kg of weight loss among a group of obese women. Similar beneficial effects were reported by Neaton et al (13) in the treatment of mild hypertension study, by the Cardia study and by Rocchini (17) in adolescents.

Obesity leads to insulin resistance, which is characterized by an elevation of circulating insulin and by a diminished ability to oxidize and store glucose. With weight loss, insulin sensitivity increases, insulin secretion, if impaired, improves, hepatic glucose production decreases, and glucose disposal improves (5). Blood glucose levels decrease in both normoglycemic and hyperglycemic persons who receive hypocaloric diets. These levels improve within days after starting a weight loss program and before there is major body compositional change, suggesting that just the change in caloric intake can make a substantial impact on glucose homeostasis (6). Over the long term, as insulin sensitivity improves, there is an improvement in prevailing glucose levels that is reflected in a decrease in glycated hemoglobin. Similar results, showing an improvement of glucose control in type 2 diabetic patients losing weight has been reported by Liu et al (9). In an interesting longitudinal study in Sweden, a group of persons with impaired glucose tolerance were followed for 7 years. They were randomized into three groups: no therapy, weight loss, and weight loss plus sulfonylurea. The two intervention groups had much lower incidence of progression to diabetes mellitus (18).

The dyslipidemia associated with obesity is characterized by an elevation of triglycerides and a decrease in high-density lipoprotein cholesterol (3). Total and low-density lipoprotein cholesterol are sometimes elevated, but are often normal. The ratio of LDL to HDL cholesterol is usually elevated, however, resulting in a greater atherogenic risk. In addition, the LDL particles, although not

elevated, are nevertheless qualitatively different, showing a shift to smaller denser particles that are much more atherogenic (1). As weight loss supervenes, both free fatty acid flux and hyperinsulinemia decrease, causing a decrease in VLDL production. Also, weight loss results in an enhancement of lipoprotein lipase activity at the adipose tissue level, increasing triglyceride clearance. Weight loss also increases HDL cholesterol levels. Even small weight losses of 5% to 10% will have this result (12).

The effects of obesity on the heart are multiple and complex. There is an increased stroke volume leading to increased cardiac output; there is an association with hypertension; there is an increased peripheral resistance leading also to increased blood pressure. All of these in turn lead to left ventricular hypertrophy. Following weight reduction, there is a reduction of left ventricular hypertrophy, characterized by a decrease in interventricular septal thickness, posterior wall thickness, left ventricular internal diameter, and left ventricular mass (11, 12). Obese persons have a greater risk for gallstones than do persons of normal weight (4), probably because they produce bile with a higher saturation of cholesterol than do lean controls matched for age, sex, and serum lipid levels (10). In obese persons, biliary cholesterol secretion is greatly increased, yet bile salt secretion remains relatively constant. As a result, bile becomes supersaturated with cholesterol, and nucleation can begin. The nucleation process is abetted by the fact that obese persons have larger, less contractile gall bladders, allowing for a larger and more stagnant reservoir for the supersaturated bile.

The lithogenicity of bile, which is elevated in obese persons (2) is increased further during weight loss. Relatively higher amounts of cholesterol than bile acids and phospholipids are secreted into the bile, resulting in an increase in the lithogenic index for cholesterol crystallization. Although there is a higher risk of gallstone formation during weight loss, the bile has a lower lithogenic index after weight loss than it did when the patient was heavier.

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Thus, risk is reduced once a lower weight is achieved.

Finally, there has been some concern that weight loss may be detrimental to health once obesity has developed. A recent study by Williamson et al (19) has reported that women with obesity-related conditions who intentionally lost weight showed a significant reduction in all-cause mortality, compared with those with no weight change. This large, prospective study is probably the only study to analyze the association between intentional weight loss and mortality. It suggests that even a modest intentional weight loss is associated with an overall increase in life expectancy among obese women.

9) DYSLIPIDEMIA AND OBESITY : EPIDEMIOLOGIC AND CLINICAL ASPECTS

J-P Després.

Clinicians are familiar with the considerable metabolic heterogeneity which can be found among obese patients. This metabolic heterogeneity raises the important problem of defining what is obesity from a medical standpoint. Obesity has been traditionally defined by a high accumulation of body fat. However, a substantial number of individuals who are not markedly overweight will eventually develop premature coronary heart disease and diabetes whereas some obese patients will remain free from these common metabolic complications. In this regard, the development of imaging techniques such as magnetic resonance imaging or computed tomography (1) has allowed to measure with good precision not only the amount of body fat but also its distribution, particularly the amount of adipose tissue located in the abdominal cavity, the so-called intra-abdominal or visceral adipose tissue. Studies that have been conducted in our laboratory have emphasized the importance of visceral adipose tissue as a critical correlate of the metabolic

complications that have been in the past associated with excess fatness per se (for reviews, see 2-4).

Thus, excess visceral adipose tissue accumulation has been associated with hyperinsulinemia resulting from an insulin resistant state, glucose intolerance which may convert to non-insulin dependent diabetes mellitus (NIDDM) among genetically susceptible individuals, hypertriglyceridemia, elevated LDL particle concentration, increased proportion of small-dense LDL particles and reduced plasma HDL-cholesterol concentrations. These metabolic abnormalities have been reported to cluster among individuals with an excess accumulation of visceral adipose tissue, irrespective of the amount of total body fat.

Thus, some insulin resistant dyslipidemic patients who would not be considered as being overweight from the current weight/height standards could benefit from a reduction in atherogenic visceral adipose tissue mass. Irrespective of the patient's body weight, excess visceral adipose tissue accumulation is associated with a cluster of metabolic complications which may contribute to increase the risk of NIDDM and cardiovascular disease.

These features of visceral obesity are reminiscent of the characteristics of the insulin resistance syndrome which have been described by Reaven at the end of the 80's (5). It is also important to emphasize that the insulin resistant-dyslipidemic state of visceral obesity is not frequently associated with marked elevations in plasma cholesterol and LDL-cholesterol levels (2-4). Studies conducted in our laboratory have indicated that the clinician should not be misled by these apparently normal plasma cholesterol and LDL-cholesterol levels. Additional techniques such as gradient gel electrophoresis and the measurement of plasma apo B levels have revealed that visceral obese patients are characterized by a substantial increase in apo B concentrations as well as in the proportion of small, dense LDL particles (6).

The risk of ischemic heart disease associated

with the cluster of metabolic abnormalities found in visceral obesity has been examined in the Quebec Cardiovascular Study, a prospective study in which 2,103 middle-aged male subjects were followed over a period of 5 years. This study indicated that fasting hyperinsulinemia was, among nondiabetic men, an independent risk factor for ischemic heart disease (IHD)(7,8). Furthermore, an elevated apolipoprotein (apo) B concentration, which is another common complication of visceral obesity, was found to be a much better predictor of IHD risk than raised cholesterol or LDL-cholesterol levels (9). Furthermore, this study indicated that fasting hyperinsulinemia associated with increased apo B levels (the synergic combination found in visceral obese patients) was associated with more than 10-fold increase in the risk of ischemic heart disease, emphasizing the atherogenic nature of this cluster of metabolic abnormalities (8). We also recently reported that the presence of small, dense LDL particles was associated with an approximately three-fold increase in IHD risk (10). The IHD risk was further increased in the presence of elevated apo B levels (10). As hyperinsulinemia, elevated apo B and an increased proportion of small, dense LDL particles are abnormalities which are simultaneously found in visceral obese patients, we have examined the atherogenic potential of this triad of new metabolic complications in the sample of men of the Quebec Cardiovascular Study. Unpublished results from our laboratory indicate that hyperinsulinemia combined with elevated apo B was associated with a 20-fold increase in the risk of ischemic heart disease when these metabolic alterations were accompanied by a high proportion of small, dense LDL particles (Lamarche et al, unpublished observations). Thus, this "new triad" of metabolic alterations found in visceral obesity substantially increases the risk of ischemic heart disease, even in pre-diabetic individuals. Considering the high prevalence of visceral obesity in sedentary adult men (about 25%)(4), this cluster of related metabolic abnormalities may represent the most prevalent cause of coronary

heart disease in our affluent societies.

It therefore appears relevant to prevent visceral adipose tissue accumulation observed with age (11). From a clinical standpoint, it would therefore be important to target our intervention among high risk overweight patients and to focus on obese patients with excess visceral adipose tissue and metabolic complications (4). From a practical standpoint, we have shown that a simple anthropometric measurement such as the waist circumference is a crude but better correlate of the absolute amount of visceral fat than the waist-to-hip ratio which has been commonly used in epidemiological studies (12,13). Recent observations from our laboratory have suggested that waist circumference values of 1 meter and above among individuals below 40 years of age and of 90 cm and above among individuals between 40-60 years of age were associated with an increased likelihood of finding the cluster of metabolic abnormalities of visceral obesity (13). Therefore, emphasis should be placed on the management of body waist rather than weight, and the objective of normalizing body fatness and weight is not always justified from a medical standpoint. Finally, whether the reduction in visceral adipose tissue mass which can be achieved by diet, exercise and pharmacotherapy reduces the incidence of diabetes and cardiovascular disease remains an unresolved issue. Answering this simple question would have tremendous public health implications. The costs of such a study would obviously be considerable but our inaction probably has a much greater impact on our health care expenses.

10) Future Targets for Pharmacologic Treatment of Obesity

LA Campfield.

Explosion in obesity research

An explosion of research into the molecular and

biochemical basis of obesity has greatly expanded the cast of potential characters in the control of body energy balance (1, 4). Not only have five single gene mutations that produce obesity in mice (*ob*, *db*, *fat*, *tub*, *agouti* (MC4 and one in rats - two variants) been cloned (2, 3) but also we have the first two single gene mutations in humans that have been identified (*ob* and PC-1). In addition, we have identified well known molecules that may be important players in the regulation of body fat (CRH, POMC, melanocortins, GLP-L, Pka) (5). Finally, we have also identified novel molecules and receptors that may also play a role in the regulation of body energy balance such as OB protein and the OB protein pathway, urocortin, agouti-related peptide, and melanocyte concentrating hormone (MCH) (6). These new advances have greatly increased the potential points for pharmacologic intervention for the treatment of obesity. These new advances and the rapid pace at which they have come has led to increased optimism that at least some of these new pathways and molecules will provide targets that will lead to a new generation of drugs for the treatment of obesity (1).

Mouse obesity genes

Single gene mutations that produce obesity in mice and rats have received a lot of attention over the last several years (2). These single gene models in mice have been the focus of intense research resulting in the cloning of all five of these mouse genes (Table 1). In mice, four *recessive* (*oblob*, *dbl db*, *fatlfat*, *tubl tub*) and one dominant (*agouti*) single gene mutation have been known and studied for many years (3). In rats, only one single gene mutation is known, although it has apparently appeared two separate times (*fa/fa* or Zucker and *LAIN ff*). Studies have demonstrated that the *fa/fa* or obese Zucker rat was the rat homologue of the *dbl db* mutation in the mouse.

A mutation in the *ob* gene results in severe obesity in mice (*oblob* mice) (2). In December 1994, in a *tour de force* of positional cloning, the laboratory of Dr. J. M. Friedman succeeded in cloning the *ob* gene. A mutation in the *db* gene

results in severe obesity that is phenotypically similar to the *oblob* mice. Following the expression cloning of the OB protein receptor, OB-R, in late 1995 by scientists at Millennium Pharmaceuticals and Hoffmann-La Roche, three groups demonstrated that the *db* gene encodes the OB-R receptor in early 1996 (2,3).

The first mouse obesity gene cloned was *agouti* by the scientists at Glaxo in 1992. They cloned the *agouti* gene and determined that ectopic expression of AGOUTI protein was responsible for the obesity observed in *agouti* mice. At present, we do not have a good understanding of the action of the AGOUTI protein on energy balance. However, AGOUTI antagonism of the melanocortin 3 or/and 4 receptors (MC3-R, MC4R) has been proposed as the mechanism of the obesity in *agouti* mice. Recently, ICV administration of a peptide agonist of MC3-R and MC4-R was reported to decrease food intake in mice. More importantly, scientists at Millennium Pharmaceuticals and Hoffmann-La Roche demonstrated that targeted disruption of the MC4-R locus in mice results in obesity with an interesting metabolic phenotype. These results provide support for the hypothesis that AGOUTI produces obesity by antagonism of the MC4-R receptor.

The two other genes are *fat* and *tub*. A mutation in either of these genes results in a mild form of obesity. The *fat* gene was cloned by scientists at the Jackson Laboratory in 1995. The *fatlfat* mice are obese animals that remained insulin sensitive in spite of marked expansion of the adipose tissue mass. The *fat* mutation results in decreased activity of carboxypeptidase E, an enzyme that is involved in the conversion of prohormones into active hormones. The *tub* gene was positionally cloned by two groups: one group at Millennium Pharmaceuticals and another at Jackson Laboratory in collaboration with Sequana Pharmaceuticals. The biology of the TUB protein is unknown (4).

Therefore, all five single gene mutations resulting in obesity in mice have been cloned and the gene products identified (Table 1). The biology and

Table 1
Genetic models of obesity in mice and rats.

Single gene mutations	Major Site of Expression	Gene Product
MICE		
ob/ob	fat	Ob protein (leptin)
db/db	brain, periphery	OB - R receptor
fat/fat	Brain, periphery	Carboxypeptidase E
tub/tub	Brain	TUB protein
agouti	Ectopic	AGOUTI protein
RATS		
fa/fa or Zucker (rat equivalent of db/db)	Brain, periphery	OB -R receptor
LA/N f/f or corpulent	Brain, periphery	OB - R receptor
POLYGENIC MODELS		
Body fat	?	?
hiperglycemia	?	?

physiology of each of these gene products and a mechanistic understanding of how each protein contributes to the obese phenotype remains to be determined (4).

Potential new drugs for the treatment of obesity

The following lists categorizes the known and newly appreciated or newly discovered molecules involved in the regulation of energy balance according to the expected dominant mode action of a drug for the treatment of obesity based on them (1, 5, 6).

Appetite suppressants:

- * Monoamine neurotransmitter modulators - serotonin (Redux, Merida, Fen/Phen); dopamine, norepinephrine
- * NPY antagonists/ Y5 receptor antagonists
- * MC-4R agonists
- * CRH antagonists/ binding proteins
- * Galanin antagonists
- * Enterostatin agonists
- * CCK agonists

- * OB protein pathway agonists
- * Urocortin antagonists
- * GLP-1 agonists
- * MCH antagonist

Stimulators of energy expenditure:

- * upregulators of UCP2/3/4 expression activity
- * 11-3 adrenergic agonists
- * OB protein pathway agonists

Enhancers of insulin sensitivity:

- * troglitazone and analogs
- * PTPase inhibitors
- * OB protein pathway agonists

Inhibitors of fat absorption:

- * inhibitors of gastrointestinal lipases

Metabolic efficiency partitioning:

- * GH agonists
- * IGFs agonists

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- * OB protein pathway agonists
- * PKa antagonists

Rationale for Targeting OB Protein Pathway for Obesity Treatment

The following observations or experimental finding suggest that the OB protein pathway should be a good source of potential drugs for the treatment of obesity (2, 3) :

- * OB protein is a circulating hormone that is an important controller of body energy storage (body weight and body fat)
- * Acting through the long form of the receptor, it has the following actions:
 - * decreased food intake
 - * increased energy expenditure
 - * increased insulin sensitivity
 - * mobilization of stored triglyceride
 - * decreased body fat
 - * decreased body weight
- * These biological actions of OB protein may provide therapeutic benefits in obese patients.
- * Since OB protein acts at multiple points in the system regulating energy balance, and through multiple neuropeptides within the CNS, the OB protein pathway has advantages over other targets affecting only one aspect of energy balance (e.g. UCP3/4, NPY).
- * In almost all obese humans, OB protein levels are elevated in proportion to body fat. Thus, most obesity is due to a decreased central and/or peripheral sensitivity to elevated OB protein levels. In diet-induced obese mice, the sensitivity to ICV OB protein is reduced; this reduction is reversed by weight loss.
- * Two obese cousins have a mutation in the ob gene with very little mature OB protein in circulation. Although normal weight at birth, both have severe early-onset obesity.

Importance of pharmacologic treatment of obesity.

A consensus has been emerging that the role of pharmacologic treatment of obesity as an adjunct

to behavioral modification and exercise. An useful image is the three legged milking stool. Sound eating behavior and exercise are the two legs that we have been using for many years. But, like a two legged stool, the ability of obese individuals to maintain weight loss over time has been an unstable and rare event. Pharmacologic treatment is the third leg that has been missing. This third leg supports the obese individual's efforts at life style change (sound eating habits and increased physical activity) and can, hopefully, lead to successful maintenance of reduced body fat and increased health over time.

Goals of treatment

Obesity is a complex, increasingly prevalent and an important health problem throughout the world.

Multiple treatment options are needed with documented, medically significant outcomes to assist patients improve compliance to voluntary lifestyle changes that lead to success in *achieving and maintaining* weight reduction

Intervention and/or lifestyle change

What is the most appropriate treatment ?

- * Short-term intervention
 - * single drug
 - * multiple drugs (with different and complimentary mechanisms of action)
- * Long-term intervention
 - * single drug
 - * multiple drugs (with different and complimentary mechanisms of action)
- * Sustained lifestyle changes
- * Interventions leading to sustained lifestyle changes
- * Different Goals for Different Patients - Induction of Weight Loss
- * Weight Maintenance
- * Absence of Weight Gain

Important issues for pharmacological agents

- * Goals of Treatment
- * Induction of Weight Loss

- * Weight Maintenance
- * Absence of weight gain
- * Single versus Multiple Drug Therapies
- * Treatment for Life
 - * Pro
 - * Con
- * Risk / Benefit Analysis:

How Little Efficacy is Acceptable ?

The concept of “metabolic fitness” as an alternate outcome measure

Definition of metabolic fitness: the absence of any metabolic or biochemical risk factor for diseases associated with obesity.

Metabolic fitness would correlate closely with general health status and would improve with risk factor reduction.

Metabolic fitness may provide an alternative, medically oriented goal of the treatment of obesity that does not focus on weight.

Improvements in metabolic fitness may include:

- * medically significant reduction of risk factors
- * restoration of abnormal risk factors to normal ranges
- * reversal of “high normal” or “borderline” parameters
- * prevention of risk factors in overweight individuals
- * Improvements in metabolic fitness, and, thus, in health status, may be independent of weight loss (or poorly correlated with weight loss)

Matching treatments to patients: interface between behavioral and medication-based approaches

- * Separate treatments combined in same patient
- * Combination tailored to patients - “menu approach”
- * Integrated, multifaceted approach-medication supports behavioral change and helps patients to “learn to become successful” at sustaining beneficial voluntary behavioral and life style changes.

Is dosing schedule for medication independent of diet and exercise aspects of the treatment program?

- * Could meal contingent dosing increase compliance to diet?
- * Is once-a-day medication the appropriate goal?

How do rituals and routines associated with aspects of treatment affect compliance to diet and exercise and treatment outcome?

Possible strategy for enhanced self-efficacy for weight maintenance

Combine three modalities or “tools” during the weight loss phase of a treatment program

- * Diet
- * Exercise
- * An antiobesity drug

One of the “tools” is then withdrawn during a supervised and supported weight maintenance phase of the program

During *weight maintenance phase* of a treatment program and after, the patient is instructed to add back the third “tool” when:

- * unacceptable weight gain occurs and
- * to continue its use until weight maintenance is again restored. In this way, individuals may feel that they:
 - * have more control over their weight
 - * may be more successful at responding to, and minimizing weight gain that often follows the end of closely supervised and supported weight management programs

Conclusions.

Additional basic and clinical research focused on intervention combined with paradigm shifts in industry, the research community and regulatory agencies and enhanced industry/regulatory interaction and flexibility will hopefully lead to a safe, effective, multifactorial treatment approach in which patients will “learn to become successful” at sustaining beneficial voluntary behavioral and

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life style changes.

We stand at the edge of this new era in the clinical management of obesity with the recent availability of medications. Whether this hope can be realized for large numbers of obese patients depends on additional research, clinical experience and improved physician education and appropriate health-care professional-patient interactions.

In such a treatment approach, pharmacological treatment would not be "an end in itself" but rather be used to **support, reinforce and sustain** desirable behavioral changes leading to improved health for obese patients.

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