Is a calorie a calorie?[1–4]

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ABSTRACT
The aim of this review was to evaluate data regarding potential thermodynamic mechanisms for increased rates of weight loss in subjects consuming diets high in protein and/or low in carbohydrate. Studies that compared weight loss and energy expenditure in adults consuming diets high in protein and/or low in carbohydrate with those in adults consuming diets low in fat were reviewed. In addition, studies that measured the metabolizable energy of proteins, fats, and carbohydrates were reviewed. Diets high in protein and/or low in carbohydrate produced an ≈2.5-kg greater weight loss after 12 wk of treatment. Neither macronutrient-specific differences in the availability of dietary energy nor changes in energy expenditure could explain these differences in weight loss. Thermodynamics dictate that a calorie is a calorie regardless of the macronutrient composition of the diet. Further research on differences in the composition of weight loss and on the influence of satiety on compliance with energy-restricted diets is needed to explain the observed increase in weight loss with diets high in protein and/or low in carbohydrate. *Am J Clin Nutr* 2004;79(suppl): 899S–906S.

KEY WORDS Weight loss, energy metabolism, protein, Atkins diet

INTRODUCTION

High-protein diets, low-carbohydrate diets, and combined high-protein and low-carbohydrate diets have been highly popularized, and this is particularly true of the Atkins diet (1). This is not an entirely new phenomenon because both the high-protein diet and the protein-sparing modified fast have been popular in the not-too-distant past (2–9). As a consequence of this more recent interest, however, several controlled trials were performed to test the efficacy of these diets (10–18). Despite the initial skepticism of many investigators, these recent studies found that high-protein and/or low-carbohydrate diets do yield greater weight losses after 3-6 mo of treatment than do low-fat diets (10–13).

We identified 9 studies of free-living adults in which weight losses in subjects consuming diets high in protein and/or low in carbohydrate were compared with those in subjects consuming diets high in carbohydrate and/or low in fat (**Table 1**). Of these studies, 6 lasted ≥12 wk. On average, consumption of the high-protein and/or low-carbohydrate diets resulted in 12-wk and 24-wk weight losses that were 2.5 ± 1.8 ($\bar{x}$ ± SD) and 4.0 ± 0.4 kg greater, respectively, than those that resulted from consumption of the high-carbohydrate and/or low-fat control diets. If these weight losses are assumed to have the typical composition of 80% fat and 20% fat-free mass (19), then this difference in weight can be estimated to reflect a 19 500–31 300-kcal difference in energy balance, or 186–233 kcal/d. These findings, however, are enigmatic because the energy intakes of the treatment groups in most studies were similar. This has caused several investigators to ask whether a calorie is indeed a calorie or whether a calorie is dependent on the macronutrient composition of the diet. We herein review the possible explanations for this difference in energy balance.

THERMODYNAMICS

A calorie, by its simplest definition, is a unit of energy and is equivalent to 4.184 absolute J. In the popular press and in the labeling of food products in the United States, a food calorie actually refers to a kilocalorie, or 1000 cal. That is, 1 food cal equals 1 kcal, or the amount of energy needed to raise 1 kg water from 15 to 16 °C.

From a thermodynamic viewpoint, a calorie is of course a calorie. The first law of thermodynamics states that energy can be neither created nor destroyed, but only transformed. Thus, the human body is constantly transforming energy—in this case, kilocalories—by combusting foodstuffs to produce heat. Although this concept is widely held today, our knowledge of life as a combustion process is limited to the last 2–3 centuries and arose from a very old and fundamental question. Because humans and animals are warm and animal heat is the essence of being alive, that question, as variously phrased, was, What is the innate fire, the vital force, animal heat (20)? The Greek philosophers Plato, Aristotle, and Hippocrates and the Roman physician Galen thought that the innate fire was in the heart and that it was somehow related to food, but the scientific answer to this question arose, in part, only in the latter half of the 18th century from the work of Lavoisier in France (21, 22). Lavoisier's experiments involved the first-ever animal calorimeter, a device used to measure heat production. The outer shell of the calorimeter was packed with snow, which melted to maintain a constant

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TABLE 1

Comparison of weight losses attained with consumption of high-protein (HP) and/or low-carbohydrate (LC) diets with those attained with consumption of high-carbohydrate (HC) and/or low-fat (LF) diets[1]

Study (reference)	Subjects	HP and/or LC diet	HC and/or LF diet	Length of study	Mean weight loss
				wk	
Ad libitum energy intake[2]					
Foster et al, 2003 (10)	63 obese men and women aged ≈44 y (49 completed 12 wk, 42 completed 24 wk, and 37 completed 52 wk)	Total dietary energy intake not reported; subjects instructed to follow Atkins diet (1). Intake ad libitum.	Total dietary energy intake not reported; men and women instructed to consume 1500–1800 and 1200–1500 kcal/d, respectively; both 15%P, 25%F, 60%C.	52	HP diet for 12 wk, 6.7 kg; HC diet for 12 wk, 2.6 kg; difference: $P = 0.001$ HP diet for 24 wk, 6.9 kg; HC diet for 24 wk, 3.1 kg; difference: $P = 0.02$ HP diet for 52 wk, 4.3 kg; HC diet for 52 wk, 2.4 kg; difference: $P = 0.26$
Samaha et al, 2003 (13)	132 severely obese men and women aged 54 ± 9[3] y (79 completed 24 wk)	1630 ± 894 kcal/d (22%P, 41%F, 37%C); intake ad libitum.	1576 ± 760 kcal/d (16%P, 33%F, 51%C); intake fixed.	24	HP diet, 5.8 ± 8.6 kg; HC diet, 1.9 ± 4.2 kg; difference: $P = 0.002$
Skov et al, 1999 (11)	50 overweight and obese men and women aged 18–55 y (46 completed 24 wk)	0–12 wk, 2055 kcal/d (25%P, 29%F, 46%C); 12–24 wk, 2223 kcal/d (24%P, 29%F, 47%C); intake ad libitum.	0–12 wk, 2533 kcal/d; 12–24 wk, 2677 kcal/d; both phases 12%P, 29%F, 59%C; intake ad libitum.	24	HP diet for 12 wk, 7.5 kg; HC diet for 12 wk, 5.0 kg; difference: $P < 0.02$ HP diet for 24 wk, 8.7 kg; HC diet for 24 wk, 5.0 kg; difference: $P = 0.0002$
Brehm et al, 2003 (12)	53 obese women aged 31–59 y (42 completed 24 wk)	12 wk, 1156 kcal/d (28%P, 57%F, 15%C), 24 wk, 1302 kcal/d (23%P, 46%F, 30%C); intake ad libitum.	12 wk, 1245 kcal/d (18%P, 28%F, 54%C); 24 wk, 1247 kcal/d (18%P, 29%F, 53%C); intake fixed.	24	HP diet for 12 wk, 7.6 ± 0.7 kg; HC diet for 12 wk, 4.2 ± 0.8 kg; difference: $P < 0.001$ HP diet for 24 wk, 8.5 ± 1.0 kg; HC diet for 24 wk, 3.9 ± 1.0 kg; difference: $P < 0.001$
Fixed energy intake[4]					
Luscombe et al, 2003 (16)	36 obese men and women aged 34–65 y	Energy restriction for 12 wk, 1520 kcal/d energy balanced for 4 wk, 1928 kcal/d; both phases 27%P, 27%F, 45%C.	Energy restriction for 12 wk, 1592 kcal/d (16%P, 27%F, 57%C) energy balanced for 4 wk, 1968 kcal/d (15%P, 28%F, 57%C).	16	HP diet, 7.9 ± 1.1 kg ($\bar{x}$ ± SEM); HC diet, 8.0 ± 0.7 kg; difference: NS
Luscombe et al, 2002 (18)	32 obese men and women aged ≈63 y (26 completed 8 wk)	Energy restriction for 8 wk, 1585 ± 42 kcal/d ($\bar{x}$ ± SEM; 28%P, 28%F, 45%C); energy balanced for 4 wk, 1844 ± 78 kcal/d (28%P, 28%F, 43%C).	Energy restriction for 8 wk, 1583 ± 62 kcal/d ($\bar{x}$ ± SEM; (16%P, 26%F, 55%C); energy balanced for 4 wk, 1777 ± 130 kcal/d (16%P, 26%F, 56%C).	12	HP diet, 4.9 ± 0.4 kg ($\bar{x}$ ± SEM); HC diet, 4.3 ± 0.7 kg; difference: $P = 0.6$
Layman et al, 2003 (15)	24 overweight women aged 45–56 y	1670 ± 47 kcal/d ($\bar{x}$ ± SEM; 30%P, 29%F, 41%C)	1659 ± 40 kcal/d ($\bar{x}$ ± SEM; 16%P, 12%F, 58%C)	10	HP diet, 7.5 ± 1.4 kg ($\bar{x}$ ± SEM); HC diet, 7.0 ± 1.4 kg; difference: NS
Baba et al, 1999 (14)	13 obese men	≈1790 kcal/d (45%P, 30%F, 25%C)	≈1763 kcal/d (12%P, 30%F, 58%C)	4	HP diet, 8.3 ± 0.7 kg ($\bar{x}$ ± SEM); HC diet, 6.0 ± 0.6 kg; difference: $P < 0.05$
Piatti et al, 1994 (17)	30 obese women aged 40 ± 3 y (25 completed 3 wk)	800 kcal/d (45%P, 20%F, 35%C)	800 kcal/d (20%P, 20%F, 60%C)	3	HP diet, 4.5 ± 0.4 kg ($\bar{x}$ ± SEM); HC diet, 6.4 ± 0.9 kg; difference: NS

[1] P, dietary protein; F, dietary fat; C, dietary carbohydrate. Intakes of P, F, and C are expressed as percentages of total energy intake.
[2] For at least one intervention group.
[3] $\bar{x}$ ± SD (all such values) unless otherwise noted.
[4] For both intervention groups.

temperature of 0 °C around an inner shell filled with ice. In the core of the inner shell was a wire cage housing a guinea pig. As the ice melted from the heat produced by the guinea pig, the water flowed out of the calorimeter and was collected and weighed. Each kilogram of melted ice water represented 80 kcal heat given off by the animal. Lavoisier noted that, in 10 h, the guinea pig melted 0.37 kg ice, thus producing 29.6 kcal heat (0.37 kg × 80 kcal heat/kg). He concluded, "la respiration est donc une combustion." That is, respiratory gas exchange is a combustion, like that of a candle burning.

Across the English Channel, Crawford was also conducting experiments on the heat of combustion in animals. Crawford noted that a given portion of pure air is "altered" by the respiration of an animal and that the extent of this alteration is nearly equal to that produced by combustion of an amount of wax or charcoal that used the same volume of oxygen during combustion. That is, the amount of heat produced per unit of oxygen consumed is nearly the same for animal catabolism as it is for the combustion of inanimate material (23). Lavoisier further concluded that a flame and an animal both consume oxygen, which combines with organic substance to release water and carbon dioxide. Thus, Lavoisier and Crawford showed that from a purely thermodynamic point of view, a calorie is indeed a calorie.

METABOLIZABLE ENERGY

The human body, however, is not a perfect engine, and thus the thermodynamics may not be so pure. It is now known that the energy liberated from the combustion of a food is not identical to the energy available to the body from consumption of that food. This is the concept of "metabolizable energy," or the difference between the gross energy (as measured by bomb calorimetry) of consumed food and the energy contained in feces and urine (also measured by bomb calorimetry) (24). The systematic investigation of the gross energy content of food and of the availability of that energy can be credited to Rubner in Germany and to Atwater in the United States. Both scientists' work is described in detail by Widdowson (25). Using a bomb calorimeter, Rubner measured the heats of combustion of many different proteins, fats, and carbohydrates found in individual foods. He thus determined the energy density of dietary fat to be 9.3 kcal/g on the basis of the mean combustion values for olive oil (9.384 kcal/g), animal fat (9.372 kcal/g), and butterfat (9.179 kcal/g). The energy density of dietary carbohydrate (specifically of starch and sugar in a mixed diet) was determined to be 4.1 kcal/g on the basis of the average combustion values for glucose (3.692 kcal/g), lactose (3.877 kcal/g), sucrose (3.959 kcal/g), and starch (4.116 kcal/g), which were weighted for their average contribution to a mixed diet. Rubner, however, made no allowance for fecal losses in deriving his calorie-conversion factors for fat and carbohydrate. He did, however, conclude that the heat of combustion of protein in a bomb calorimeter is higher than the energy value available to the host because the body oxidizes protein only to urea, creatinine, uric acid, and other nitrogenous end products, which can themselves be further oxidized in a bomb calorimeter. From urinary and fecal combustion in one subject, Rubner determined that the loss of energy from the nitrogenous substances in urine and feces totaled 23% of energy intake, 16.3% from meat sources and 6.9% from vegetable sources. Thus, meat and vegetable protein differed in their metabolizable energy densities: the former provided 4.23 kcal/g and the latter provided 4.30 kcal/g (after correction for the heat of combustion of nitrogenous end products in urine and losses of nitrogen in feces). Assuming that 60% of dietary protein was from animal sources and 40% from vegetable sources and recognizing that the energy content of wheat and rye protein ("the most important sources of vegetable protein") was overestimated by 7.9% because of the higher nitrogen content in wheat and rye protein than in animal protein, Rubner suggested that 4.1 kcal/g be used as an average factor for determining the energy content of dietary protein. Thus, Rubner showed that a calorie is a calorie; however, he also showed that the human body cannot extract all the calories liberated from combustion of a food and that macronutrients differ according to their chemical composition in the number of calories per unit of weight.

TABLE 2
Atwater factors for heat of combustion, coefficient of availability, and "available energy" for nutrients in a mixed diet

Macronutrient	Heat of combustion	Coefficient of availability	Available energy
	kcal/g	*%*	*kcal/g total nutrients*
Protein	5.65	92	4.0[1]
Fat	9.40	95	8.9
Carbohydrate	4.10	97	4.0

[1] Corrected for unoxidized material in the urine, ie, (5.65 kcal/g × 0.923) − 1.25 kcal/g.

With Bryant, Atwater extended Rubner's work by studying the availability of the other macronutrients. Data from human digestion experiments were combined with other data in the literature to devise "coefficients of availability" (defined as intake minus fecal excretion divided by intake) for protein, fat, and carbohydrate. Atwater and Bryant applied these coefficients of availability to the heat of combustion of "mixed" diets that were typical of the time (consisting of foods such as beef, butter, ginger snaps, parched cereal, rye bread, baked beans, and canned pears) and were consumed by 3 adult male subjects. The foods consumed, as well as the subjects' urine and feces, were collected and analyzed for nitrogen and fat content; the difference between total organic matter and the sum of protein and fat was taken to represent carbohydrate. An additional correction was made for protein: for each gram of nitrogen in urine, there was sufficient unoxidized matter to yield an average of 7.9 kcal, or 1.25 kcal/g absorbed protein (7.9 divided by 6.25). Thus, after correction for the coefficient of availability, 1.25 kcal/g was subtracted from the heat of combustion of protein. The calculated availability of the mixed diets agreed closely with the actual availability as found by experiment.

The energy values obtained by Atwater and Bryant's experiments, to which we refer today as the Atwater factors, are presented in **Table 2**. The metabolizable energy values in the right column, ie, 4, 9, and 4 kcal/g protein, fat, and carbohydrate, respectively, are more appropriately known as the Atwater general factors for metabolizable energy and were proposed for application to mixed diets of similar composition to those used in Atwater's experiments. With the use of the Atwater general factors, metabolizable energy is calculated as $4.0P + 9.0F + 4.0\text{TC}$, where P is protein ($P = 6.25 \times$ nitrogen; in g), F is fat (in g), and TC is total carbohydrate (in g, calculated by dry weight difference). Not only have these factors been applied to the total amounts of protein, fat, and carbohydrate in a mixed diet, as Atwater and Bryant had intended, but they have also been used, and continue to be used, in assessing the energy value of individual foods.

At first glance, calculated metabolizable energy would appear to be equivalent to measured metabolizable energy. The work of Atwater and Bryant, however, clearly showed that these factors were average values. Although the general factors could be used to calculate the metabolizable energy of a mixed diet, they were in error to some degree for almost any particular single food item. This error results from differences in chemical structure that can alter the gross energy per unit weight by up to several percent and, to a slightly larger degree, from differences in availability. Thus,

TABLE 3

Comparison of gross energy and measured and calculated metabolizable energy between 2 diets with different fiber content that were fed to 12 healthy, free-living men for 5 wk[1]

	High-fiber diet[2]		Low-fiber diet[3]	
	Value	Difference from measured metabolizable energy	Value	Difference from measured metabolizable energy
	kcal/d	*kcal (%)*	*kcal/d*	*kcal (%)*
Gross energy	3069 ± 448[4]	360 (13.3)	3032 ± 490	249 (8.9)
Measured metabolizable energy	2709 ± 402		2783 ± 461	
Metabolizable energy (Atwater general factors)	2925 ± 427	216 (8.0)	2894 ± 468	111 (4.0)
Metabolizable energy (Atwater specific factors)	2892 ± 422	183 (6.8)	2927 ± 5472	144 (5.2)

[1] Adapted from reference 29.
[2] Containing 37 g fiber and 14% of energy from protein, 33% from fat, and 53% from carbohydrate.
[3] Containing 16 g fiber and 14% of energy from protein, 36% from fat, and 50% from carbohydrate.
[4] $\bar{x}$ ± SD (all such values).

although a calorie is still a calorie from a thermodynamic point of view, calculations of the metabolizable energy of a diet that are obtained by using the Atwater general factors are not exact and could thus introduce an error in the calculated metabolizable energy content of a particular food or diet. In recognition of this, a modification of the general factors, the Atwater specific factors, was devised in the mid-1950s for specific classes of foods to account for the differences in the average digestibility of different food groups and thus reduce this potential for error (26).

The Atwater general factors, however, continue to be commonly used. In 1970 Southgate and Durnin (27) tested the Atwater general factors and determined that they were still valid, with one exception. Large amounts of unavailable dietary carbohydrate resulted in increased excretion of fecal fat, nitrogen, and energy, and these findings were subsequently confirmed by other researchers (28–31). Thus, Southgate and Durnin (27) found that the Atwater protein and fat factors overestimate the energy derived from these constituents. Others have since found that the Atwater general factors overestimate the measured metabolizable energy of mixed diets, especially those high in dietary fiber, by a mean (±SD) of 6.7 ± 4.4% (range: 1.2–18.1%) (28–30, 32–35). The reasons hypothesized to explain the effect of dietary fiber on metabolizable energy are many. Dietary fiber may decrease the transit time of food in the intestine (resulting in less time for digestion and absorption), increase bulk and water-holding capacity (reducing the rate of diffusion of digestion products toward the intestinal mucosal surface for absorption), or cause mechanical erosion of the mucosal surface (leading to increased endogenous material) (29, 36). Wisker and Feldheim (28) also note that in contrast with the energy content of protein and fat, the energy content of dietary fiber is liberated by fermentation. Thus, factors affecting the microbial degradation of dietary fiber—the chemical structure of nonstarch polysaccharides, the solubility and degree of lignification of the fiber components, and physiologic factors such as the composition of the colon microflora and the transit time—may affect metabolizable energy (28). This may be the reason why the Atwater general factors were found to overestimate measured metabolizable energy to a greater extent for diets high in nonavailable fiber than for diets high in available fiber (overestimations of 7.0% and 2.6%, respectively; $P < 0.05$) (35). Together, findings from the above studies show that not all dietary carbohydrates provide 4 kcal/g.

The differences between the general Atwater factors, the specific Atwater factors, and true metabolizable energy might explain some of the difference in weight loss observed after consumption of 2 diets with different fiber content. For example, Miles et al (29) carefully determined the metabolizable energy of 2 diets, one with 16 g fiber and one with 37 g fiber (**Table 3**). If the energy intakes in this study were extrapolated downward to 2 weight-loss diets each providing 1500 metabolizable kcal/d, one high and the other low in fiber, the Atwater general and specific factors would overestimate the measured metabolizable energy of the high-fiber diet by 120 and 102 kcal, respectively. Similarly, for the low-fiber diet, the Atwater general factors would overestimate metabolizable energy intake by 60 kcal, and the Atwater specific factors by 78 kcal. Thus, if a weight-loss study is performed and the energy intake of the 2 diets is calculated on the basis of the macronutrient content of the diets and the Atwater general factors, the 2 diets would differ in measured metabolizable energy by ≈60 kcal/d (120 − 60). If one assumes that weight loss averages 80% fat by weight, then this error could account for a difference in weight loss of 0.008 kg/d, or 0.6 kg over 12 wk. If the energy intakes were calculated by using the Atwater specific factors or tabulated food values from the US Department of Agriculture *Agriculture Handbook no. 8* (37), which are based on the Atwater specific values, then the 2 diets would differ by 24 kcal/d (102 − 78), and the weight-loss effect would be 0.003 kg/d, or 0.3 kg over 12 wk. This error, however, does not bring into question the thermodynamics of a calorie being a calorie, but it does point to the limits of our ability to determine the exact metabolizable energy intake from a given diet.

ENERGY EXPENDITURE

A second potential mechanism through which diets differing in macronutrient composition can produce differences in energy balance and hence weight loss is a change in energy expenditure. For example, if a particular diet were to increase energy expenditure relative to another diet, then for the same energy intake, energy balance would be more negative for the former diet, and weight loss would probably be greater. Although the most important consideration of energy expenditure with regard to energy balance is total energy expenditure, it is also helpful to look at the components of energy expenditure, ie, resting metabolic rate, the thermic effect of food, and energy expended in physical activity, to understand the mechanism through which macronutrients can alter energy expenditure.

One difficulty in comparing the effects of macronutrients on energy expenditure is the problem of being unable to manipulate only one macronutrient at a time under the experimental restriction of eucaloric feeding. Ten studies of energy expenditure measured in a whole-room calorimeter have been performed; in these studies, protein intake was held constant, and the percentages of energy from fat and carbohydrate were varied (38–47). The fat content of the low-fat diets used in these studies ranged from 3% to 20% of energy, and the fat content of the high-fat diets ranged from 40% to 60% of energy; the protein content was held at 10%, 15%, or 20% of energy. When the protein content was held constant and fat was substituted for carbohydrate, the mean 24-h energy expenditure of the control groups did not differ. Two studies (43, 46) also included a postobese subgroup, in whom 24-h energy expenditure decreased 75–80 kcal/d after consumption of the high-fat diet. When the results of all 10 studies were averaged, the difference in 24-h energy expenditure between the high-carbohydrate and high-fat diets was not different from zero ($\bar{x} \pm$ SD: -19 ± 54 kcal/d).

Resting or sleeping metabolic rates were reported in 7 of these studies (41–47) and were found not to differ between the 2 diets ($\bar{x} \pm$ SD: -21 ± 77 kcal/d). The thermic effect of food was measured in 2 studies (43, 45) and was 58 kcal/d lower with the high-fat diet in one study (45) and tended to be higher with the high-fat diet in the other (43). This topic was also reviewed by Eisenstein et al (48); the average effect of replacing fat (50% of energy) with carbohydrate was 40 kcal/d. Another study was performed in which total energy expenditure was measured by doubly labeled water, and thus the study provided greater freedom for the subjects to expend energy in physical activity (49). This was a crossover study comparing diets in which the protein content was held at 10% of energy, and the carbohydrate content was set at either 7% or 83% of energy. Energy expenditure was measured with doubly labeled water in the free-living participants. Under these conditions, total energy expenditure for the low-carbohydrate diet was 365 kcal/d lower than that for the low-fat diet, but resting metabolic rate and the thermic effect of a meal did not differ significantly between the 2 diets, which indicates that the difference in total energy expenditure was due to a reduction in the energy expended in physical activity.

Although the above studies provide some evidence of a change in the thermic effect of food when fat is substituted for carbohydrate, the magnitude of this change is usually small, and the direction is opposite to the one that would be required to explain a greater weight loss after consumption of a low-carbohydrate diet. This change in the thermic effect of a meal, however, did not translate into a lower total energy expenditure, except when the carbohydrate intake was reduced to a ketogenic level (7% of calories). The reason for this decrease is unknown, but the authors speculated that it was due to reduced physical activity that was secondary to low glycogen stores.

There are fewer studies of the effect of changes in the percentage of energy from protein on total energy expenditure than there are of the effect of changes in total energy intake. The effect of changes in the percentage of dietary energy from protein on the thermic effect of food has been reviewed recently (48). On the basis of a meta-analysis, it was concluded that the thermic effect of food increases ≈7 kcal/1000 kcal of ingested food for each increase of 10 percentage points in the percentage of energy from protein. Thus, if a subject is instructed to consume a 1500-kcal/d energy-restricted diet with 35% of energy from protein, then the thermic effect of food will be 21 kcal/d higher than if protein contributes only 15% of the dietary energy. Two studies also showed that a high-protein diet is associated with a higher resting metabolic rate. Mikkelsen et al (50) provided participants with a eucaloric diet having 29% or 11% of energy from protein and found that the resting metabolic rate was 51 kcal/d higher with the 29% protein diet. Whitehead et al (47) instructed participants to consume a diet that was energy restricted by ≈50% and that had either 36% or 15% of energy from protein; the sleeping metabolic rate was 44 kcal/d higher with the high-protein diet. These investigators also measured 24-h energy expenditure by using a room calorimeter and reported that expenditure was 71 kcal/d higher with the high-protein diet ($P < 0.05$), which was in agreement with the increase in sleeping metabolic rate and the predicted increase in the thermic effect of food.

Thus, although substituting carbohydrate for fat in the diet does not appear to alter total energy expenditure, increasing protein intake to 30–35% of energy does increase energy expenditure. The increase, however, is only ≈70 kcal/d, or 2.7% of a median 2550-kcal/d total energy expenditure for an adult. If the difference in energy expenditure is assumed to be proportionally reduced with a 1500-kcal/d energy-restricted diet, then the increase in energy expenditure with the higher protein diet would be 41 kcal/d. Given identical energy intake, however, this would increase weight loss by ≈0.04 kg/wk, or 0.44 kg over a 12-wk course of weight-loss treatment. Note, however, that no measurements have been made by using doubly labeled water in free-living subjects to determine whether changes in energy expenditure from physical activity occur. Inclusion of measures of total energy expenditure in future studies is recommended to provide these data.

IS A CALORIE A CALORIE?

The effects of metabolizable energy and diet-induced changes in energy expenditure indicate that having 2 groups of subjects consume 2 different energy-restricted diets could introduce a different energy imbalance. Should this, however, be considered evidence that a calorie is not a calorie when comparing macronutrients? Dietary intakes calculated by using the Atwater general factors of 4, 9, and 4 kcal/g protein, fat, and carbohydrate, respectively, may be in error with respect to metabolizable energy content. This is particularly true for a high-fiber diet, in which incomplete absorption of the fiber reduces the metabolizable energy provided to the body. This is because the Atwater general factors are not exact constants for calculation of metabolizable energy. Indeed, that is one reason why the food tables from the US Department of Agriculture are calculated by using the Atwater specific factors. As reviewed above, however, even these latter values have been found to overestimate metabolizable energy by 3–7%, particularly when the fiber content of the diet is high. However, this overestimation would lead to a prediction of only a 0.2–0.6-kg weight difference over a 12-wk treatment for a 21-g difference in fiber intake. In addition, diets that are specially formulated from a small number of foods or from isolated proteins, fats, and carbohydrates can also differ in metabolizable energy from the metabolizable energy content calculated by using the Atwater factors because, as stated above, the Atwater factors are average values for a mixed diet, and individual nutrients do deviate from the mean by a few percent. These effects, however, should not be interpreted as a thermodynamic advantage of one diet over another. The difference in energy can be totally explained by the increase in fecal energy, and the reality is that the difference is actually an error in calculating the metabolizable energy of the diets.

Of course, the increased energy expenditure associated with increased protein intake also does not violate the laws of thermodynamics, because the energy is conserved. It does, however, come close to the spirit of the argument that a calorie is not a calorie, because feeding diets that induce a difference in energy expenditure can introduce a difference in energy balance and thus a difference in weight loss. Of the macronutrients, only protein has been found to have this effect, but the magnitude of this effect is small and perhaps accounts for a 0.8-kg difference in weight loss between diet treatments over 12 wk. This difference in predicted weight loss could only account for one-third of the average greater weight loss of 2.5 kg reported for a 12-wk high-protein and/or low-carbohydrate weight-loss diet and thus should not be taken as evidence that a calorie is not a calorie.

OTHER EXPLANATIONS FOR DIFFERENCES IN WEIGHT LOSS

If a calorie is a calorie, then what other factors could account for the reported differences in weight loss between either high-protein or low-carbohydrate diets and low-fat diets? One obvious explanation is a difference in the composition of the weight loss. A greater loss of solids or water from fat-free mass for one treatment than for a second treatment would result in greater weight loss with the former treatment. One particular factor for a low-carbohydrate diet is, of course, the loss of glycogen stores and associated water, which can be as great as 2 kg (51). In this regard, note that the 2 short studies (3 and 4 wk; references 14 and 17 in Table 1) of weight loss with a high-protein and/or low-carbohydrate diet found an ≈2-kg greater weight loss with the high-protein and/or low-carbohydrate diet than with the high-carbohydrate and/or low-fat diet, which is comparable to the average difference in weight loss in the 10–12-wk studies. This suggests that the difference in weight loss is an early event and is not one that increases with time; thus, this difference is more consistent with a rapid loss of extra water than with a loss of fat mass. Furthermore, the one 12-mo study (10) reported that the difference in weight loss between the 2 diets decreased after 3 mo, which is when the participants should have been adding back some carbohydrate to the low-carbohydrate diet (1) and would have been expected to regain the weight lost due to glycogen and water loss. Three studies (11, 12, 15), however, did measure changes in body composition after ≥10 wk of treatment, and the composition of the weight lost with the high-protein and/or low-carbohydrate diet was quantitatively similar to that of the weight lost with the control diet, which reduces the likelihood that the difference in weight loss typically reported is simply water weight.

Participants with lower initial relative fatness lose more fat-free mass per unit of weight loss than do those with higher initial relative fatness (19), and men may lose more fat-free mass per unit of weight loss than do women (52). These differences could confound weight-loss results if the 2 diet treatment groups in a study are not well matched. Because fat loss and preservation of fat-free mass are important goals in the treatment of obesity through weight loss, future comparisons between weight-loss treatments should include a measure of change in body composition to provide more specific information about the quality of the weight loss.

Another important consideration in clinical trials comparing weight-loss treatments is the accuracy of the participants' energy intake data. For studies in which intake is prescribed and actual intake is assumed to equal the prescription or in which intake is calculated from self-reported diaries, actual intakes are almost certainly higher than prescribed or reported intakes (53–57) because participants frequently underreport their energy intake. Even if meals are provided, noncompliance can occur and dietary intakes are likely to be higher than prescribed. However, this higher intake may not be apparent from the diet records because of underreporting and the tendency to report an intake similar to the intake prescription (53, 56).

Finally, there is no reason to speculate that underreporting is any greater for one diet treatment than for another unless there is a difference in satiety between the meals. Preliminary evidence, which was comprehensively reviewed by Yao and Roberts (58) and Eisenstein et al (48), indicates that both protein and a low energy density of the diet increase satiety. Thus, subjects who consume a prescribed diet high in protein or fiber may be more compliant with the diet than are subjects who consume other diets, but this speculation has been confirmed by only one long-term study to date. Skov et al (11) instructed 2 groups of subjects to consume ad libitum amounts of a diet high in protein (25% of energy from protein and 46% from carbohydrate) or high in carbohydrate (12% of energy from protein and 59% from carbohydrate) for 6 mo. The subjects who consumed the high-protein diet reported that they consumed ≈22% fewer calories and subsequently lost 2.7 kg more than did those who consumed the high-carbohydrate diet, which led the authors to conclude that protein had a higher satiating effect than did carbohydrate. Further research into the dietary factors that increase satiety and decrease energy intake in the long term is recommended.

CONCLUSION

We conclude that a calorie is a calorie. From a purely thermodynamic point of view, this is clear because the human body or, indeed, any living organism cannot create or destroy energy but can only convert energy from one form to another. In comparing energy balance between dietary treatments, however, it must be remembered that the units of dietary energy are metabolizable energy and not gross energy. This is perhaps unfortunate because metabolizable energy is much more difficult to determine than is gross energy, because the Atwater factors used in calculating metabolizable energy are not exact. As such, our food tables are not perfect, and small errors are associated with their use.

In addition, we concede that the substitution of one macronutrient for another has been shown in some studies to have a statistically significant effect on the expenditure half of the energy balance equation. This has been observed most often for high-protein diets. Evidence indicates, however, that the difference in energy expenditure is small and can potentially account for less than one-third of the differences in weight loss that have been reported between high-protein or low-carbohydrate diets and high-carbohydrate or low-fat diets. As such, a calorie is a calorie. Further research is needed to identify the mechanisms that result in greater weight loss with one diet than with another.

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