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Thermodynamics and Metabolic Advantage of Weight Loss Diets

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ABSTRACT

Published reports show that low carbohydrate weight loss diets provide a metabolic advantage, a greater weight loss per calorie consumed compared to isocaloric high carbohydrate diets. These reports have not been refuted but rather largely ignored, presumably because of the apparent violation of the laws of thermodynamics ("a calorie is a calorie"). In this review, we show that there is no such violation of thermodynamic laws. Energy utilization of different diets depends on the chemical pathway taken and a metabolic analysis of the efficiency of different pathways reveals large differences. Likewise, thermogenesis produced by diets of different macronutrient composition varies widely. We present a plausible mechanism that depends on the inefficiency of metabolic cycles and, in particular, protein turnover. A low carbohydrate diet makes demands on protein turnover for gluconeogenesis. From a theoretical point of view, energy balance between two diets is to be expected only if the subjects have the same final physiologic state, and only if all of the changes contributing to the energy, heat, work and chemical effects are known. Most diet experiments do not conform to this ideal. There is no theoretical contradiction in metabolic advantage and no theoretical barrier to accepting reports describing this effect.

INTRODUCTION

WEIGHT REDUCTION clearly requires a negative energy balance: calorie expenditure must exceed intake. The quantitative relation between caloric intake and the affected weight loss, however, is a more subtle problem. The extent to which weight loss is linear with caloric intake and, in particular, how macronutrient composition affects energy consumption are unresolved questions. The question bears on the current popularity of low carbohydrate and low glycemic index weight loss diets. Proponents of such diets suggest that they provide a metabolic advantage, that is, there is greater weight loss if carbohydrates are low compared to isocaloric diets of different macronutrient composition.[1–4] Although the effect has been experimentally demonstrated, the idea of a metabolic advantage has been frequently criticized as a violation of the laws of thermodynamics, and it is frequently claimed that "a calorie is a calorie."[5–8]

In this review, we tabulate some of the experimental demonstrations of metabolic advan-

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tage. We show that the apparent loss in energy in such studies can be accounted for by differences in pathways and metabolic cycles and that this will appear as a thermogenic effect as well as changes in body composition. We propose a plausible mechanism for metabolic advantage on low carbohydrate diets. Finally, we provide a brief thermodynamic analysis and show that, in fact, there is no barrier to accepting the published results.

REVIEW OF EXPERIMENTAL LITERATURE

There is a greatly renewed interest in low carbohydrate weight loss diets and several recent experiments have shown them to be effective and, in some comparison trials, better than high carbohydrate diets[3,7–27] (for reviews, see references[2,3,5]). In such experiments, however, the low carbohydrate diet is usually *ad lib* and differences in weight loss may be due to differences in caloric intake. Several literature reports have compared isocaloric diets, however, and there is often an apparent metabolic advantage in low carbohydrate diets, defined as an increased weight loss per calorie compared to similar diets with higher carbohydrate levels.[8,11,15,17–25] Examples of this effect are shown in Table 1. It should be noted that the term low carbohydrate diet has no precise definition and there is no minimum RDA for carbohydrate. Low carbohydrate diets are usually considered to provide less than 50% of calories, while *very* low carbohydrate diets or low carbohydrate ketogenic diets (LCKD) are considered to provide less than 50 g/day or less than 10% of calories (Atkins diet phase 1 = 20 g[1]).

Metabolic advantage has an odd history. One of the earliest demonstrations is the work of Kekwick and Pawan.[19] Their results showed dramatically that weight loss in 12 obese patients was strongly dependent on macronutrient composition. They further demonstrated that weight loss was not due solely to loss of water. Despite the correction, the fact that substantial water was lost in the first two weeks, as well as the short duration may explain why the paper did not spur a large increase in research. In addition, the diets were extreme (carbohydrate, protein or fat were 90% of calories for the different diets studied) and some of the results were sufficiently unusual as to be counter-intuitive, e.g., the 90% fat diet achieved 0.46 g/day against no weight loss for an isocaloric diet with 90% carbohydrate (Table 1).

Until the recently renewed interest in low carbohydrate diets, only a small number of studies have been carried out and, like Kekwick and Pawan's work, they have been largely ignored rather than disproved. Although not comprehensive, Table 1 summarizes several of the major studies in the literature.

The general effect in Table 1 is clear but there is an insufficient number of experiments to define a quantitative relation between macronutrient composition and metabolic efficiency. Also, not all studies comparing high and low carbohydrate diets have found differences that were considered significant.[26,27] From the standpoint of scientific method, however, a single study that shows a disparity serves as a counter example to the doctrine of "a calorie is a calorie." Lean, for example, found that a women on a 1200 kcal low carbohydrate diet (CHO/fat/protein = 35:35:30) lost 6.8 kg compared to 5.6 kg on an isocaloric diet (58:21:21) an effect that they judged not to be significantly different. A subgroup of postmenopausal women, however, showed a difference of 7.7 kg (low carbohydrate) vs. 4.7 kg[17] (Table 1). In comparing weight loss diets, it seems reasonable that the results should be given in kcal; a reasonable conversion method is to use the calorimeter values (weighting fat lost by 9/4 compared to lean mass lost). Table 1 shows that when this correction is applied, some of the studies show the same difference in kcal as in total weight, but some do not. Two of the diet comparisons,[20,26] judged the same on the basis of weight lost appear different when kcal are calculated. Interestingly, one of these, Golay's study, is frequently quoted as a counter example to metabolic advantages.[5,7]

Exercise can have an effect on the emergence of a metabolic advantage in hypocaloric diets. Layman found that isocaloric diets produced similar reductions in body weight, but the introduction of exercise led to an advantage in weight loss for a high protein diet compared to one of high carbohydrate (Table 1). On the

TABLE 1. SUMMARY OF STUDIES ON ISOCALORIC REDUCING DIETS

	Diet description	kcal	n	Time	CHO	Fat	Protein	Weight loss (kg/d)	Weight loss (kg)	Fat loss	Lean mass loss	kcalories loss	Low CHO/high CHO % diff kg	Low CHO/high CHO % diff kcal
Brehm, 2003 (ref. 15)	low FAT	1245	20	3 mo	54	28	18		4.2	2.5	0.8	25.7		
	low CHO	1156	22	3 mo	15	57	28		7.6	4.3	2.8	49.9	44.7	48.5
	low FAT	1247	20	**6 mo**	53	29	18		2.0	2	0.7	20.8		
	low CHO	1302	22	**6 mo**	30	46	23		4.8	4.8	2	51.2	58.3	59.4
Samaha, 2003 (8)	low-fat	1576	68	6 mo	51	33	16		1.9					
	low-CHO	1630	64	6 mo	37	41	22		5.8					
Layman, 2003 (20-21)	CHO	1660	12	10 wk	58	26	16		(7.0)	4.7	1.2	47.1		
	PROT	1670	12	10 wk	41	29	30		(7.5)	5.6	0.9	53.9	6.7	12.6
	CHO	1700	12	10 wk	58	26	16		(5.8)	5.0	0.8	47.9		
	PROT	1700	12	10 wk	41	29	30		(7.2)	7.0	0.2	63.3	19.4	24.4
	CHO + exercise	1700	12	**16 wk**	58	26	16		6.7	5.6	1.1	54.7		
	PROT + exercise	1700	12	**16 wk**	41	29	30		9.8	8.8	0.4	81.0	31.5	32.5
Sondike, 2003 (11)	low FAT	1100	14	12 wk	56	12	32		4.1					
	low CHO	1830	16	12 wk	8	60	32		9.9					
Baba, 1999 (9)	High CHO	0.8 RER	6	4 wk	58	30	12		6.0	6.3	0	56.7		
	High Protein	0.8 RER	7	4 wk	25	30	45		8.3	7.1	0.2	64.7	27.7	12.4
Lean, 1997 (17)	High CHO	1200	57	6 mo	58	21	21		(5.6)	2.5	3.1	34.9		
	Low CHO	1200	35	6 mo	35	35	30		(6.8)	2.9	3.9	41.7	17.6	16.3
	High CHO - subgroup	1200	23	6 mo	58	21	21		4.7					
	Low CHO - subgroup	1200	23	6 mo	35	35	30		7.7					
Golay, 1996 (26)	45 % CHO	1000	21	6 wk	45	26	29		(7.5)	7	0.5	65.0		
	15 % CHO	1000	22	6 wk	15	53	32		(8.9)	9	0	81.0	15.7	19.8
Golay, 1996 (27)	45 % CHO	1200	37	12 wk	45	26	29		(8.6)	7.2	1.4	70.4		
	25 % CHO	1200	31	12 wk	25	45	29		(10.2)	8	2.2	80.8	15.7	12.9
Rabast, 1981 (23)	1. High carbohydrate	1340	7	28 d	70	10	20		9.5					
	2. High corn oil	1340	7	28 d	10	70	20		11.4					
	3. High butterfat	1340	7	28 d	10	70	20		12.9					
Rabast, 1978 (20)	I. High CHO	1000	45	30 d	70	10	20		9.8					
	II. CHO-restricted	1000	45	30 d	10	70	20		14.0					
Young, 1971 (18)	A. 104 g. CHO	1800	2	9 wk	23	51	26		11.9					
	B. 60 g. CHO	1800	3	9 wk	13	61	26		12.8					
	C. 30 g. CHO	1800	3	9 wk	7	68	26		16.2					
Kekwick, 1957 (19)	CHO	1000	14	5-9 d	90	6	4	0.00						
	FAT	1000	14	5-9 d	4	90	6	0.26						
	PROT	1000	14	5-9 d	2	8	90	0.46						

Diet descriptions as in original papers. n = number of subjects in the study. Time values in bold indicate the same experimental group as the immediately preceding population for longer durations. Groups of values in parentheses are considered by authors to be not significantly different. Values for Kekwick and Pawan estimated from graphic data. Values in the last two columns (low CHO/high CHO% difference) are calculated as (100 × (low CHO value − high CHO value)/(low CHO value)) with values taken as either kg mass lost or kcal lost. RER = resting energy requirement.

other hand, for trained athletes on high energy diets, body mass and tissue distribution are largely independent of the macronutrient composition of the diet.[28]

Recently, Brehm[15] compared low carbohydrate and high carbohydrate diets. The low carbohydrate diet was an *ad libitum* diet based on the Atkins diet but the actual consumption of calories was approximately the same as that for the fixed caloric values for the carbohydrate diet based on the American Heart Association guidelines. Weight loss was greater on the low carbohydrate diet and there was a similar greater ratio of fat loss to lean body loss. Perhaps most striking is the work of Sondike with adolescents.[11] The diets studied were *ad libitum* with the low carbohydrate group (LC) restricted to <20 g carbohydrate for 2 weeks, <40 g for 2 weeks, and the low fat (LF) group, to <30 g of fat. If the outpatient food records are accurate, the experimental calories consumed turned out to be greater for the LC group than the LF group but the LC group lost significantly more weight (Table 1).

A nonlinear dependence on weight change is not restricted to low carbohydrate diets. An unusual example is a study of the scheduling of the large meal of isocaloric diets. Keim et al.[29] showed that, whereas weight loss was slightly greater with large morning meals, large evening meals produced a substantial reduction in fat mass. Also, on *hyper*caloric diets, Kasper[30] demonstrated a nonlinear effect on weight gain of added fat.

Is metabolic advantage in conflict with the laws of thermodynamics? If not, how does it occur? Where does the energy go? In the next section we consider the effect of macronutrient composition on thermogenesis. We then examine the metabolic origins of energetic differences of different hypocaloric diets. We consider one plausible explanation for the missing energy: thermogenesis due to different metabolic pathways for different diets. We also present a theoretical explanation from elementary thermodynamics.

THERMOGENESIS

Thermogenesis (thermic effect of feeding) refers to heat generated in digestion and metabolism after feeding. Studies of macronutrient effects on thermogenesis show a substantially greater effect of protein compared to carbohydrate or fat.[31–34] Robinson,[32] for example, determined rates of energy expenditure and protein turnover during a continuous hourly feeding over a 9-h period of high-protein (HP) or isocaloric high-carbohydrate (HC) meals. Thermogenesis in the HP group (9.6% of energy intake) was much greater than the HC group (5.7%). Nitrogen turnover was similarly greater for HP (58.2 g) compared to HC (27.4 g), and the results could be rationalized in terms of greater protein synthesis. As discussed below, we see energetically expensive protein turnover as a likely source of metabolic advantage on low carbohydrate diets, and the primary variable, the need for gluconeogenesis. There may also be a contribution due to the level of protein per se, independent of, or more likely, synergistic with carbohydrate content. A recent study[31] found a 100% increase in thermogenesis with an 1800 kcal low fat diet with high protein (CHO/fat/protein = 47:29:24) compared to an isocaloric high carbohydrate diet (59:29:12). The high protein diet would be considered only moderate carbohydrate in comparison with an LCKD. Similarly, a high protein/high carbohydrate diet (61:10:29) produced greater thermic effect than a high fat diet (30:61:9).[35] Results of a study of thermogenesis that demonstrates the strong effect of macronutrients on thermogenesis is shown in Table 2 taken from the work

TABLE 2. EFFECT OF MACRONUTRIENTS ON THERMOGENESIS

	O_2 consumption (mL/min)		
	Before	*After test meal*	*ΔE (kJ/6 h)*
Starch			
1 MJ	266	274	62
2 MJ	268	279	99
4 MJ	265	291	223
Protein			
1 MJ	272	313	290
2 MJ	278	353	529

Data from Karst.[35] Indirect calorimetry data over 6 h after test meals of the indicated composition and energy. The protein meal was casein and the starch was a hydrolysis product. Egg white and gelatin (at 1 MJ) gave results similar to casein (data from Karst[35] not shown). Starch (1 MJ) was also similar to the starch hydrolysis product.

of Karst et al.[35] The table indicates that the response to a 2-MJ meal of protein was more than five times greater than the response to an isocaloric carbohydrate meal. In these studies, no thermic effect of dietary fat was found.[35]

CHEMICAL CHANGES AND THE EFFECT OF PATH

The caloric value of food is the free energy *change* ΔG (approximated by the change in enthalpy, ΔH, measured in the calorimeter) for a particular process:

$$\text{Food} + O_2 \rightarrow CO_2 + H_2O$$

Although we traditionally express calories in terms of mass (1 g carbohydrate = 4 kcal; 1 g fat = 9 kcal), these relations only apply to the reaction with oxygen with no other products or reactants. If an ingested macronutrient undergoes some other reaction *in vivo*, e.g., conversion from amino acid to carbohydrate, or multiple metabolic cycles before oxidation, then calories cannot be directly substituted for mass. For example, the value of 4 kcal/g of protein contains a correction to the experimental calorimeter value for ureagenesis. In considering differences in diet, we want to compare two metabolic processes such as the oxidation of glucose directly or a *cycle* in which glucose is incorporated in glycogen and then later released by hydrolysis and then oxidized. Such cycles of opposing pathways are analogous to the futile or substrate cycles for individual pathways (e.g., kinase-phosphatase pairs),[36,37] although, far from futile, they are a major method by which living systems adopt metabolic processes to changing conditions, and they can be a major consumer of energy.

To estimate the impact of path on bioenergetics, we must know the energy of each process that is involved. In Table 3, we calculated the yield of ATP for metabolic sequences, using standard biochemical pathways.[36,38] We then calculated the yield for oxidation of a typical protein using percentage composition from a standard text.[36] Finally, we calculated yields for carrying out individual pathways leading to oxidation. The results are shown in Table 4 and Figure 1. The assumptions in these calculation are given in the legend to Table 4. A much more comprehensive series of such calculations including tissue differences was given by Jungas,[39] and there is general agreement with our calculations. We converted the ATP values to kcal/g for comparison with traditional nutritional values. It can be seen in Table 4 that the oxidation of carbohydrate, TAG and an average protein, calculated on this basis, provide energy of 1.54, 3.68, and 1.32 kcal/g. This represents an efficiency of about 40% compared to the usual calorimeter (Atwater) values for these macronutrients. The ratios of 4:9.55:3.4 are in reasonable agreement with the calorimeter values given the number of assumptions. For the calculation of energy expended in metabolic cycles for individual macronutrients, relative values are expected to be more accurate. The effect of path is best seen by considering simple examples.

METABOLIC CYCLES

If we consider 100 g of fatty acid in a cell, and assume complete oxidation to CO_2 and water, we expect theoretical 900 kcal, or 368 kcal based on yield of ATP (Table 4). If, instead of directly oxidizing the fatty acid, we convert it to the CoA derivative and synthesize TAG for storage, and at some later time—perhaps due to changes in levels of insulin or other hormones—we hydrolyze the TAG and oxidize the fatty acid, we have accomplished the same thing by a different metabolic route. It costs 7 ATP to synthesize TAG and some energy has been lost in the cycle. For TAG, this represents about 2% loss (Table 4).

The limited losses in the fatty acid-TAG-fatty acid cycle agrees with the general perception of fat as an efficient fuel.[35,40] Similarly, in the cycle of conversion of glucose to glycogen, followed by glycogenolysis and oxidation has a cost of 2 ATP, or about 5% of calories compared to direct oxidation of the glucose. Again, the efficiency is high although, in both cases, multiple cycles due to insulin fluctuations might make a significant difference.

Protein turnover is a drastically different cycle from the TAG and glycogen metabolic cycles.

TABLE 3. CALCULATION OF ENERGY FOR OXIDATION OF AMINO ACIDS

Amino acid	*Mass*	*Yield of oxidation ATP/mole*	*Yield kcal/g*	*Occurrence average protein (%)*	*Corrected for synthesis (−4 ATP)*	*Yield kcal/g*	*Corrected for cycle (−6 ATP)*	*Yield kcal/g*
Glycine	75	7	0.68	7.2	3	0.29	1	0.1
Alanine	89	14	1.15	7.8	10	0.82	8	0.66
Valine	117	31	1.93	6.6	27	1.68	25	1.56
Leucine	131	38	2.12	9.1	34	1.89	32	1.78
Isoleucine	131	40	2.23	5.3	36	2.01	34	1.89
Glutamic acid	147	23	1.14	6.3	19	0.94	17	0.84
Aspartic acid	133	14	0.77	5.3	10	0.55	8	0.44
Glutamine	146	20	1.00	4.3	16	0.80	14	0.70
Asparagine	132	11	0.61	4.3	7	0.39	5	0.28
Proline	115	29	1.84	5.2	25	1.59	23	1.46
Tyrosine	181	40	1.61	3.2	36	1.45	34	1.37
Phenylalanine	165	37	1.64	3.9	33	1.46	31	1.37
Tryptophan	204	41	1.47	1.4	37	1.32	35	1.25
Serine	105	14	0.97	6.8	10	0.70	8	0.56
Threonine	119	15	0.92	5.9	11	0.67	9	0.55
Cysteine	121	14	0.84	1.9	10	0.60	8	0.48
Methionine	149	17	0.83	2.2	13	0.64	11	0.54
Lysine	146	33	1.65	5.9	29	1.45	27	1.35
Arginine	174	25	1.05	5.1	21	0.88	19	0.80
Histidine	155	18	0.85	2.3	14	0.66	12	0.57
Average protein			1.32			1.00		0.96

Yield in moles ATP/mole amino acid oxidized. It is assumed that the $\Delta G^{0\prime}$ for hydrolysis of ATP is −7.3 kcal/mole.[36,38] Standard free energies are used rather than ΔG values,[46] since concentrations of metabolites vary. Yield from coenzyme oxidation is assumed to be 3 ATP for NADH (mitochondrial transport assumed isoenergetic) and 2 ATP for reduced flavins. Oxidation of nitrogen is calculated, for amino acids that carry out transamination, by assuming transfer to Glu by the action of glutamate dehydrogenase, transport by glutamine and urea cycle coupled to TCA cycle. Values are divided by 2 to give net cost of −1 ATP. Reactions that produce ammonia directly start with glutamine transport. Pathways for amino acid oxidation used the preferred pathways as indicated in standard texts.[36,38]

TABLE 4. EFFECT OF PATH ON THE ENERGETICS OF OXIDATION

Macronutrient and path	*Mass*	*Yield ATP/mole*	*Yield kcal/g*	*Inefficiency (%)*
AA (AVE PROTEIN) → CO_2			1.32	—
AA → PROTEIN → AA → CO_2 (1)		4 ATP (synth)	1.08	18.2
AA → PROTEIN → AA → CO_2 (2)		6 ATP (cycle)	0.96	27.3
GLUCOSE → CO_2	180	38	1.54	—
GLUCOSE → glycogen → GLUCOSE → CO_2	180	36	1.46	5.3
2 Ala → GLUCOSE → CO_2	178	30	1.23	20.2
PALMITATE → CO_2	256	129	3.68	—
TAG (3 × C-16) → CO_2	806	406	3.68	—
3 PALMITATE → TAG → PALMITATE → CO_2	806	399	3.61	1.8
PALMITATE → Ketone Body → CO_2	256	121	3.45	6.2

The same assumptions as in Table 3 are used to calculate direct oxidation or oxidation through indicated path. For amino acid oxidation: (1) Correction of 4 ATP for synthesis (hydrolysis assumed exergonic). (2) Correction of 6 ATP for synthesis and hydrolysis via the ubiquitin-proteasome system. Inefficiency is calculated by dividing the value for each path by the path for direct oxidation (and conversion to % and subtraction from 100).[36,38]

Each elongation step of ribosomal protein synthesis requires 2 ATP for aminoacyl-tRNA synthesis and 2 GTP for elongation factors. Also, unlike digestion, protein breakdown through the ubiquitin-proteasome system is an energy requiring process. ATP-dependent proteases require 2 ATP's per hydrolyzed bond although uncoupling occurs in some cases. Glycogen is a homopolymer from which monomers may be removed one at a time and TAG is a relatively small molecule. On the other hand, an entire protein must be hydrolyzed to obtain energy from a particular amino acid. The calculation in Table 2 shows a 27% energy loss in converting a mole of amino acids to protein and back. This is a minimum estimate. Data from *in vivo* studies summarized by Young[41] suggest much higher values.

Protein turnover fulfills several goals in the life of the cell providing for removal of damaged proteins and supplying amino acids for specialized products. It is also a component of gluconeogenesis, supplying alanine directly and via transamination. The impact of carbohydrate deprivation on gluconeogenesis is probably a major energy cost translating into metabolic advantage.

GLUCONEOGENESIS

Under normal conditions, there is an obligate requirement for glucose for brain, CNS, and red blood cells. This is estimated at 100 g/day for brain and about 35 g/day for RBC. Although a truly ketogenic diet may reduce this need substantially, 50 g/day is probably an absolute minimum. The effect of this obligate demand for glucose can be illustrated by a simple imaginary example. If we consider the early stages of a 2000-kcal low carbohydrate ketogenic diet (CHO/fat/protein = 8:52:40) and a reduced obligate need to 100 g due to some ketone bodies, we have to ask where the remaining required

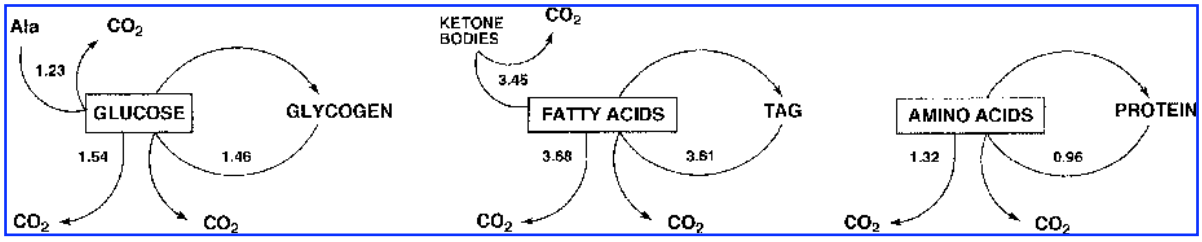

FIG. 1. The effect of path on energy of oxidation (kcal/g) of macronutrients. Schematic of processes for direct oxidation (single arrows) or indirect processes (multiple arrows). Values from Table 4.

glucose will come from. Glycogen levels are typically lowered and stores appear to be conserved on low carbohydrate ketogenic diets.[42] Gluconeogenesis becomes increasingly important. If we assume 20% of the requirement for gluconeogenesis can be supplied by glycerol, the rest must come from protein. To supply 80 g of glucose will require about 80 g of alanine. Table 4 shows that this process involves a loss of about 20% of the energy when compared to direct uptake and oxidation. This means that the equivalent of an additional 16 g of alanine must be supplied (0.2 × 80 g). If we now assume (long-term) nitrogen balance,[41] then this 16 g must come from additional protein breakdown. A major source of the nitrogen for alanine are branched chain amino acids.[20,21] 16 g of alanine requires the equivalent of about 24 g of branched chain amino acids, or about 4 × 24 = 95 kcal that are lost in running gluconeogenesis. This energy must come from oxidation of fat. Thus, a 2000-kcal diet has actually consumed 2095 kcal, a number that may be compared to popular (and government) recommendations for dieters to reduce intake by 100 kcal/day.[43]

This analysis greatly underestimates the real costs. The major loss of energy, and the presumed contributor to thermogenesis described above, is the need to re-synthesize the proteins that supply branch chain amino acid. Table 4 shows that the calculated cost is between 18% (synthesis) and 27% (cycle: synthesis + breakdown through ubiquitin-proteasome pathway). Such calculations are also probably low. Young has summarized estimates of the costs of protein synthesis and suggests that as much as 4–5 kcal/g are required.[41]

In summary, the need to meet the obligate demand for glucose means that a nominally eucaloric low carbohydrate diet can lead to increased gluconeogenesis from protein. Increased gluconeogenesis will, in turn, lead to protein turnover. Together, these processes will lead to weight loss.

MECHANISM OF METABOLIC ADVANTAGE

The considerations above provide a plausible mechanism for metabolic advantage that draws on work of Jungas,[39] Layman,[20,21] and others. The key feature is energy associated with protein turnover. The major stimulus for protein turnover on a low carbohydrate diet is the need to supply alanine for gluconeogenesis as well as a direct effect of high protein intake due to stimulation of protein synthesis by leucine. Each cycle of protein turnover requires energy that must come from fat oxidation. Such a mechanism is supported by measurement of plasma values of amino acids. Table 5 from the work of Layman[20,21] is a comparison of the plasma levels of amino acids for two isocaloric diets of different macronutrient composition. The higher fasting levels of alanine in the high carbohydrate group are explained by reduced uptake of this amino acid by the liver for gluconeogenesis, a process that is down-regulated by high carbohydrate intake. The postprandial elevation of leucine in the protein group and the reversal of the relative alanine concentrations after a meal are consistent with the increased catabolism in the protein group to supply amino acids for glucose production.

TABLE 5. COMPARISON OF PLASMA VALUES

	Plasma concentration (mmol/L)	
	Protein diet	*Carbohydrate diet*
12-h fasted		
Leucine	102	99
Alanine	324	388
2-h postprandial		
Leucine	181	93
Alanine	485	452

Data from Layman.[21] Subjects received isocaloric diets of ~1700 kcal/day. The Protein and Carbohydrate groups had a CHO/fat/protein ratio of approximately (41:29:30) and (56:26:16) respectively. Postprandial values determined after a 400-kcal breakfast of the indicated macronutrient composition.

THEORETICAL

Historically, the first law of thermodynamics is intimately connected with the study of living organisms,[44] and conservation of energy is a fundamental aspect of metabolism. Because it is frequently invoked in criticisms of the concept of metabolic advantage, we discuss differences in diets in the context of elementary

thermodynamics.[44,45] The discussion is not meant to be comprehensive but rather to point out the areas in which conservation of energy has been misapplied. The first law can be written as follows:

$$\Delta E = q - w \quad (1)$$

Energy consumption is due to heat (q) added to a system minus the measured work (w) done by the system.

Whereas the principle always applies, the application to living systems is not simple. Strictly speaking, equation 1 only applies to closed systems (no exchange of material) that are close to equilibrium and that do not carry out chemical reactions. In fact, living organisms are open systems (take in food and excrete products), are far from equilibrium and, of course, carry out metabolic reactions. In applying conservation laws to living organisms, then, the contribution of the chemical reactions must be included and the second law of thermodynamics must be considered. The appropriate equation (that includes the second law) shows the effect of the change in number of moles of each chemical entity, n_i and the chemical potential, μ_i, the effect of each species on the energy. (Mathematically, $\mu_i = \partial E/\partial n_i$). The correct equation then is

$$\Delta E = T\Delta S - p\Delta V + \Sigma\, \mu_i\, \Delta n_i \quad (2)$$

where S = entropy and in comparison to equation 1, $T\Delta S$ would be equal to q, and $p\Delta V = w$. Application of equation 2 makes it possible to see where metabolic advantage comes from. Two diets of different macronutrient composition may have different values for ΔE ($= E_{final} - E_{initial}$) because they may not wind up in the same energy state. The metabolic paths that they follow may be very different due to differences in hormonal state or enzymatic activity. Thus, although the conservation law holds for each diet separately, they may not be directly comparable. The observed heat q (BMR and thermogenesis) is now due to the entropic change ($T\Delta S$) and some part of the change in chemical bonds ($\Sigma\, \mu_i\, \Delta n_i$). As discussed above, low carbohydrate/high protein diets are associated with greater thermogenesis than those with high content of fat or carbohydrate. Similarly the two diets may differ in the chemical pathways, e.g., number and types of metabolic cycles.

In summary, for comparison of two hypocaloric diets, thermodynamics dictates that one must be careful that the initial and final states are the same for both diets, and, in addition to caloric input and the change in mass, one must know the work performed, the heat generated and the change in chemical composition. Whereas activity can be assumed constant or can be controlled, heat production and chemical changes (body composition and metabolic pathways utilized) are strongly affected by macronutrient composition. Metabolic advantage is seen because different diets lead to different paths (due to hormonal and enzymatic changes) that are not equivalent when correctly compared through the laws of thermodynamics. That one may lead to greater weight loss is the important bottom line.

PRACTICAL CONSIDERATIONS FOR WEIGHT LOSS DIETS

The review presented here indicates that reported metabolic advantage of low carbohydrate diets has a plausible mechanism and is consistent with physical laws. Thus, in the absence of criticism of experimental methodology, there is no reason to disbelieve the published data. Although the decline in body mass on weight loss diets is frequently proportional to caloric intake, a diet that offered the possibility of metabolic advantage would be of great practical value. Such a diet would sensibly provide a psychological benefit in addition to the physiologic advantage, with a higher likelihood of compliance. The need for better strategies for weight loss is accentuated by concern about the current epidemic of obesity. In addition to treatment, an effective long range approach may depend on attacking the causes of this epidemic. These are not completely understood, or at least not generally agreed on. Proponents of controlled carbohydrate strategies point to the correlation between increased total consumption and the decreased percentage of fat and increased percentage of carbohydrate consumption in the population. Another factor that is cited, not necessarily mutually exclusive, is the increased availability of

high volume, high calorie meals. In either case, a low carbohydrate diet that can demonstrate a metabolic advantage would provide a correction—indeed would test the relative importance of the increase in carbohydrate consumption versus the increase in food availability (since food availability is unlikely to change).

There is, of course, more to a reducing diet than its efficiency. There is always some concern about high protein diets and renal function. As discussed by Layman,[21] there is no upper limit (UL) for protein intake, and this problem is still a matter of controversy. For patients with normal renal and liver function, the risks are conjectural and must be balanced against the real and established risk of continued obesity. Other factors, particularly individual responses are also important. In the end, the best diet is the one that a subject can stay on.

What would it take to firmly establish the metabolic advantage? Two aspects of the problem have been presented here: the experimental demonstration of the phenomenon and the role of gluconeogenesis as a likely underlying mechanism. To understand energy balance experimentally will require the study of weight loss diets, and LCKD in particular, with precise measures of food intake, energy expenditure and thermogenesis. Metabolic studies,[20,21,47,48] under the same conditions can be expected to provide evidence on underlying mechanism.

Note added in proof. Since the submission of the manuscript, a well-designed pilot study has been presented providing further evidence for the metabolic advantage (Green P, Willett W, Devescus J, Skaf A. Pilot 12-week feeding weight-loss comparison: Low-fat vs. low-carbohydrate (ketogenic) diets. Obesity Res 2003; 11:A23).

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