Review

The Effects of High Protein Diets on Thermogenesis, Satiety and Weight Loss: A Critical Review

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For years, proponents of some fad diets have claimed that higher amounts of protein facilitate weight loss. Only in recent years have studies begun to examine the effects of high protein diets on energy expenditure, subsequent energy intake and weight loss as compared to lower protein diets. In this study, we conducted a systematic review of randomized investigations on the effects of high protein diets on dietary thermogenesis, satiety, body weight and fat loss. There is convincing evidence that a higher protein intake increases thermogenesis and satiety compared to diets of lower protein content. The weight of evidence also suggests that high protein meals lead to a reduced subsequent energy intake. Some evidence suggests that diets higher in protein result in an increased weight loss and fat loss as compared to diets lower in protein, but findings have not been consistent. In dietary practice, it may be beneficial to partially replace refined carbohydrate with protein sources that are low in saturated fat. Although recent evidence supports potential benefit, rigorous longer-term studies are needed to investigate the effects of high protein diets on weight loss and weight maintenance.

Key teaching points:

- Although authors of some fad diets have advocated increasing dietary protein for weight loss, not until recently have studies begun to investigate the effects of high protein diets on weight loss.
- Convincing evidence exists that protein exerts an increased thermic effect when compared to fat and carbohydrate. Evidence is also convincing that higher protein diets increase satiety when compared to lower protein diets.
- Higher protein diets may facilitate weight loss when compared to a lower protein diet in the short term (within 6 months). But long-term data are limited.
- Exchange protein for carbohydrates has been shown to improve blood lipids, and in epidemiologic studies, higher protein diets have been associated with lower blood pressure and reduced risk of coronary heart disease.
- Although the optimal amount and sources of protein cannot be determined at this time, the weight of evidence suggests that in dietary practice, it may be beneficial to partially replace refined carbohydrate with protein sources that are low in saturated fat.

INTRODUCTION

Obesity in America has reached epidemic proportions. More than half of the US adult population is considered overweight with a body mass index of 25 or greater, and a third is obese (BMI $\geq$30) [1]. The co-morbidities associated with obesity are of major public health concern and include cardiovascular disease, diabetes and certain forms of cancer [2].

Although obesity is known to be a disorder of energy balance, a true understanding of its causes and treatment remains elusive. It is generally agreed that hypo-caloric diets would reduce body weight. However, the composition of fat, carbohydrate, and protein in dietary regimens remains an area of great controversy. The Recommended Daily Allowance for protein is 0.8 g/kg and the typical American consumes 1.2 g/kg or about 15% of dietary energy as protein [3]. Advocates of high protein diets often recommend that protein intakes meet or exceed 25% of dietary energy. One theory is that higher protein diets enhance weight loss due to an increased dietary thermogenesis, increased satiety and a decreased subsequent energy intake. This review will examine in depth current evidence on the effects of high protein diets on thermogenesis, satiety and weight loss.

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Methods

Relevant articles were identified by a search of the Medline database (National Library of Medicine, Bethesda, MD) using keywords such as "high protein diet and weight loss" and "ketogenic diet and weight loss." Additional published reports were obtained by cross matching the references of relevant articles. The selection of articles was restricted to those in the English language. A total of 50 articles were included in this review.

Each study in this review includes both a relatively higher protein and a lower protein diet and compares the effects of each on a variety of outcomes (total weight change, total body fat change, satiety and subsequent energy intake after an isocaloric preload). When a high protein diet was compared to more than one other diet (ie high carbohydrate and high fat), focus was placed on the comparison between the high protein diet and the high carbohydrate diet. This was done to address the current controversy between high protein diets and low-fat high-carbohydrate diets in the treatment of obesity. A meta-analysis was attempted for those studies that included standard errors or standard deviations of the mean difference. However, the level of heterogeneity ($p < 0.001$) among the study designs made the inclusion of a summary estimate inappropriate. Therefore, this review will be more qualitative in nature.

Thermogenesis

One possible reason for the reported success of high protein diets may relate to their greater thermic effect. The thermic effect of a food is the increase in energy expenditure above baseline following consumption. It further can be defined as the energy required for digestion, absorption, and disposal of ingested nutrients. This thermic effect seems to be influenced by the composition of food consumed. In general, the typical thermic effect of protein is 20%–35% of energy consumed and for carbohydrate, this number usually falls between 5% and 15% [4]. The thermic effect of fat is a subject of debate. Some have found that fat has a lower thermic effect compared to carbohydrate [5], while others have found no difference between the two [6].

Fifteen studies were identified and included in this review concerning thermogenesis [4–18] (Table 1). The thermic effect of food was measured in a variety of ways. Six of these investigations calculated the thermic effect of food as a percentage of ingested energy [4,6,12,15–17]. The difference in thermic effect between the higher protein and the lower protein diets ranged from 0.8% of energy to 22% of energy, with protein always exerting the higher effect. In an investigation by Luscombe [12] the higher protein preload exerted a significantly higher percentage of ingested energy at baseline compared to a high carbohydrate preload but did not differ after 16 weeks on an energy restricted or energy balanced diet. Another 3 studies represent the thermic effect in kilojoules [7,8,10]. In each of these investigations, the higher protein meal exerted a significantly higher thermic effect than the higher fat or higher carbohydrate meals.

In addition, Johnston [9] found that a diet with 30% from protein had a thermic effect of 34 kj/hour higher than a diet consisting of 15% protein. Mikkelson [14] found that a 29% pork diet increased 24-hour energy expenditure by 3.9% compared to a high carbohydrate diet with 11% protein. Leblanc [11] found that a 97% protein diet caused an oxygen consumption of 31 mL O2/kg/min while a 1% protein feeding resulted in an oxygen consumption of 17 mL O2/kg/min. However, this level of protein is unrealistic. Zed [18] found significantly increased oxygen consumption for a high protein meal compared to a high carbohydrate meal. In both normal and obese subjects, Swaminathan [5] found significantly higher mean metabolic rates for a high protein preload compared to high fat and high carbohydrate preloads. Finally, Luscombe [13] found that the thermic effect per kilocalorie of energy produced over resting metabolic rate was significantly higher for protein than for carbohydrates at baseline (0.064 *vs.* 0.05 kcal/kcal^{-1} energy consumed/2 hours^{-1}, $p = 0.003$).

This evidence suggests that diets higher in protein exert a larger effect on energy expenditure than diets lower in protein. A logical question is whether or not this difference is enough to affect body weight. In the Johnston investigation [9], it was estimated that the average difference between the high and low protein diet for their subjects was 126 kj a day. For Crovetti [7], this number was 168 kj after 7 hours, and for Robinson [15] it was 251 kj after 9 hours. In a recent review of high protein diets, Eisenstein and Roberts [19] estimated that for a 8,374 kj diet with 30% protein compared to 15% protein, there would be an increase of 96 kilojoules a day due to thermic effect. Although these numbers seem small, with chronic consumption, they could become clinically significant. If energy expenditure were increased by 168 kj a day, one would expect a weight loss of 1.9 kg a year (168 kj $\times$ 365 $=$ 61,320 kj/32,238 kj $=$ 1.9 kg). These numbers might be underestimated as most studies were conducted for a period of only 6 or 7 hours and many believe that the thermic effect of protein continues on for a longer amount of time.

A main reason for the difference in the thermic effects of food may be due to the fact that the body has no storage capacity for protein and thus it needs to be metabolically processed immediately. The synthesis of protein, the high ATP cost of peptide bond synthesis as well as the high cost of urea production and gluconeogenesis are often cited reasons for the higher thermic effect of protein [14,15].

An interesting theory concerning thermogenesis as it relates to protein intake is the Stock Hypothesis [20]. Stock cites 12 human overfeeding studies to support the view that diets high in protein increase thermogenesis in an effort to homeostatically waste energy when fed an unbalanced diet. This would make sense from an evolutionary perspective in that such an

Table 1. Randomized Trials Of High Protein Diets And Thermogenesis

Reference	Population	Design	Diet	Control	Duration	Result
Crovetti 1997 [7]	10 normal female	Randomized crossover trial	68% protein, 19% fat, 13% carb.	10% protein, 21% fat, 69% carb or 9% protein, 70% fat, 21% carb.	7 hours	HP 261 kj, HF 97 kj, HC 92 kj, $p < 0.001$
Dauncey 1983 [8]	6 normal; 4 female, 2 male	Randomized crossover trial	37% protein, 48% fat, 15% carb.	3% protein, 48% fat, 49% carb.	28 hours	24 hour energy expenditure; HP 8659 kj, LP 7735 kj, $p < 0.001$, HP 12% higher
Johnston 2002 [9]	10 normal females	Randomized crossover trial	30% protein, 30% fat, 40% carb.	15% protein, 25% fat, 60% carb.	2.5 hours	HP averaged 34 kj/hour higher for both lunch and breakfast compared to LP, $p < 0.05$, twice the thermic effect.
Karst 1984 [10]	12 normal males	Randomized crossover trial	2 MJ protein	2 MJ carb. or fat	7 hours	HP 529 kj, HC 99 kj, HF 66 kj, $p = 0.001$
Leblanc 1990 [11]	6 normal male	Randomized crossover trial	97% protein, 3% fat	1% protein, 35% fat, 64% carb.	2 hours	HP 31 mL O2/kg/min, LP 17 mL O2/kg/min, $p < 0.05$
Luscombe 2003 [12]	36 obese hyperinsulinemics 10 male, 26 female	Randomized trial	32% protein, 14% fat, 54% carb.	10% protein, 13% fat, 77% carb.	3 hours	Baseline-HP 9.1% of ingested energy LP 7.1% of ingested energy, $p = 0.009$. After 16 weeks-HP 8.6% of ingested energy LP 7.8% of ingested energy, $p = 0.3$
Luscombe 2002 [13]	26 obese type 2-diabetics; 15 Female, 11 Male	Randomized trial	41% protein, 13% fat, 46% carb.	12% protein, 19% fat, 69% carb.	2 hours	HP .064 kcal/kcal^{-1} energy consumed/2 h^{-1} LP .05 kcal/kcal^{-1} energy consumed/2 h^{-1}, $p = 0.003$
Mikkelson 2000 [14]	12 obese males	Randomized crossover trial	Soy-28% protein, 29% fat, 43% carb. Pork-29% protein, 29% fat, 42% carb.	11% protein, 28% fat, 61% carb.	24 hours	Pork *vs.* HC increased 24 hour expenditure by 3.9%, $p < 0.001$. Soy *vs.* HC increased by 1.9%, $p = 0.05$. Both proteins increased 24 hour energy expenditure significantly
Nair 1983 [6]	5 lean, 5 obese, 8 female, 2 male	Randomized trial	100% protein	100% fat or 100% carb.	157.5 minutes	HP 15% of energy, HF 7%, HC 6%, $p < 0.01$
Robinson 1990 [15]	7 normal males	Randomized crossover trial	70% protein, 15% fat, 15% carb.	15% protein, 15% fat, 70% carb.	9 hours	Increase above resting metabolic rate; HP 31.2%, HC 21.6%, $p < 0.001$. Thermic effect—HP 9.6%, HC 5.7%, $p < 0.01$
Schutz 1987 [16]	7 elderly males	Randomized crossover trial	14% protein, 27% fat, 59% carb.	5% protein, 31% fat, 64% carb.	4 hours	HP 6.5% of energy, LP 3.5%, $p < 0.025$
Steiniger 1987 [17]	8 normal males, 17 obese (11 males, 6 females)	Randomized trial	1 or 2 MJ protein	2 MJ hydrolyzed starch	10 hours	HP 30% of ingested energy in normal, 20% in obese, LP 8% in normal, 4% in obese, $p < 0.01$
Swaminathan 1985 [5]	11 normal (8 female, 3 male), 11 obese (8 female, 3 male)	Randomized trial	1.67 MJ protein	1.67 MJ carb. or 1.67 MJ fat	120 minutes	Mean metabolic rate; lean; HP 4.22 kj/min, HF 3.84 kj/min, HC 4.08 kj/min, $p < 0.05$. Obese; HP 5.71 kj/min, HF 4.45 kj/min HC 5.02 kj/min, $p < 0.05$
Westerterp 1999 [4]	8 normal female	Randomized crossover trial	30% protein, 10% fat, 60% carb.	10% protein, 60% fat, 30% carb.	36 hours	HP 14.6% of energy, LP 10.5% of energy, $p < 0.02$ (1295 kj/day *vs.* 931 kj/day)
Zed 1986 [18]	8 females (4 obese, 4 lean)	Randomized crossover trial	87% protein, 5% fat, 8% carb.	1% protein, 7% fat, 92% carb.	5.5–7.5 hours	O2 consumption increased 30% after HP which was 2–3 times that of HC, $p < 0.05$

HP = high protein diets, HC = high carbohydrate diets, HF = high-fat diets.

increase in thermogenesis would help ensure an adequate supply of nutrients while avoiding the risks to survival associated with excess weight gain.

An area of research worth mentioning concerns the theory that the obese have a blunted thermic effect in general and to fat in particular. Three studies [21–23] have found differences in the thermic effect of food comparing the lean with the obese while 3 studies have not [24–26]. Several review articles have also addressed this hypothesis [27,28]. Conclusions on this theory await further research.

Satiety

A variety of investigations have examined the effect of high protein diets on satiety. Typically, these studies presented one of several preloads with varying protein content to each subject on separate occasions in a crossover design. For several hours following the consumption of the preload, subjective satiety ratings were measured repeatedly. Of 14 studies that compared high protein to at least one other macronutrient, 11 found that the protein preload significantly increased subjective ratings of satiety (Table 2) [29–42].

Many of the studies that found a higher satiety with protein utilized a very high protein preload (40% or higher). Rolls [38] studied 10 normal women in a crossover design. Five isocaloric preloads were presented to each woman on separate occasions; a high protein preload (75% protein), as well as a high fat, high starch, high sucrose and a mixed preload. Ratings of hunger decreased and satiety increased significantly after 2 hours for the high protein and high starch preloads compared to the others ($p < 0.05$).

Poppitt [36] studied 12 lean women in a crossover design. Four standard lunches were served on 4 separate days with the addition of 1 MJ protein, carbohydrate, fat or alcohol. Subjects were significantly less hungry after the protein preload ($p < 0.05$). Johnson [34] studied 14 normal men and women. Isoenergetic preloads were presented that were high in either protein (76%), carbohydrate (86%) or fat (89%) for 2 calorie levels (628 kj and 1,256 kj). Both the high protein and high carbohydrate preload significantly decreased hunger compared to the high fat preload after 90 minutes ($p < 0.05$).

Stubbs [40] studied 16 normal men in a crossover design after consuming an isocaloric breakfast that contained 60% of energy as either fat, protein, carbohydrate or a mixture of the three. Subjects were significantly less hungry before lunch on the high protein and mixed meals in comparison to the high fat and high carbohydrate preload ($p < 0.001$).

Three relevant studies that also found a higher satiating effect of high protein preloads had small sample sizes. Johnstone [35] studied 6 men on 3 occasions, feeding them isoenergetic amounts of protein, fat and carbohydrate (40% of calories). On subjective ratings of hunger, the high protein diet was found to be more satiating than either high carbohydrate or high fat ($p < 0.05$). Stubbs [39] studied 6 healthy men, feeding them 3 isocaloric preloads; high protein (59% protein), high carbohydrate (18% protein) and high fat (21% protein). Over 24 hours, the high protein preload significantly suppressed hunger to a greater extent than the high fat and high carbohydrate meals ($p = 0.045$). Westerterp-Plantenga [42] found a statistically significant increase in 24 hour satiety among 8 normal women consuming both a high protein diet (29% protein) and a high fat diet (9% protein).

Two studies that found significantly increased satiety with protein preloads utilized a lower percentage of protein (less than 40%). Vanderwater [41] conducted a study on 80 subjects. Forty received a low protein meal consisting of either a bacon lettuce tomato sandwich (11% protein) or strawberry yogurt (20% protein). Forty subjects received a high protein meal consisting of either a ham sandwich (33% protein) or high protein yogurt (43% protein). The higher protein meals decreased hunger compared to the low protein meals using a subjective 145 mm line scale ($p < 0.05$). Hill [32] investigated 13 healthy young men and women. A high protein preload (33% protein) and a high carbohydrate preload (15% protein) were presented in a crossover design. At both 5 minutes and 60 minutes, the high protein preload resulted in a significant decrease in desire to eat ($p < 0.05$).

Furthermore, Holt [33] studied 41 subjects in groups of 11–13 men and women. Each tested 38 different foods and satiety was rated every 15 minutes for 2 hours. Protein, along with fiber and water were significantly and positively correlated with satiety scores ($r = 0.37$, $p < 0.05$). Porrini [37] conducted a crossover investigation of 12 normal men, feeding them a high protein meal (meatballs) and a low protein meal (pasta with tomato sauce) at 2 different calorie levels. Fullness and satiety measures were significantly higher for the high protein preload compared to the low protein preload ($p < 0.05$).

In contrast, three studies did not find such an effect. Barkeling [29] found no difference in satiety after serving 20 normal women isocaloric lunch meals containing 43% protein or 10% protein. However, it was noted that the high protein meal was rated more palatable and this could have biased the results. There is evidence that more palatable foods are related to a faster return of hunger and desire to eat [39]. DeGraaf [30] and Geliebter [31] similarly found no difference in subjective ratings of appetite when varying the protein content of preloads. However, the subjects in these investigations wore noseclips to eliminate the odor of the preloads. This combined with the fact that the preloads were in liquid form makes it difficult to generalize these findings.

A recent investigation by Long [44] looked at the satiety of protein as a function of daily protein intake. In this investigation, subjects were divided by protein intake (1.96 g/kg/day *vs.* 75 g/kg/day) and followed for 13 days. Long found that those with the chronically higher protein intake were less satiated by a high protein meal when compared to those with lower protein intake.

In summary, the evidence supports that meals higher in

Table 2. Randomized Trials Of High Protein Diets And Satiety And Subsequent Energy Intake

Reference	Population	Design	Diet	Control	Duration	Compliance	Result-Subsequent energy intake	Results-Satiety
Araya 2000 [47]	35 children, 18 females, 17 males	Randomized trial	47% protein, 40% fat, 13% carb.	12% protein, 20% fat, 68% carb.	3.5 hours	Supervised	HP 1,087 kj, HC 1,255 kj, $p < 0.05$	—
Barkeling 1990 [29]	20 normal females	Crossover trial	43% protein, 21% fat, 36% carb.	10% protein, 21% fat, 69% carb.	4 hours	Instructed not to eat during study period	HP 1,262 kj, HC 1,419 kj, $p < 0.05$	No significant difference in satiety.
Booth 1970 [49]	15 normal males and females	Crossover trial	High protein spread (30 grams cheese)	Low protein spread (no cheese)	2.5 hours	Supervised	HP 1,063 kj, LP 1,382 kj, $p < 0.05$	—
DeGraaf 1992 [30]	29 normal females	Crossover trial	70% protein, 3% fat, 27% carb.	1% protein, 99% carb.	Ad lib intake recorded for rest of day	Pre-load supervised, intake by food record.	HP 8,499 kj, HC 8,499 kj ns	No significant difference in satiety
Geliebter 1978 [31]	12 normal males	Crossover trial	100% protein	100% carb.	70 minutes	Supervised	HP 4,918 kj, HC 4,971 kj (ns)	No significant difference in satiety
Hill 1986 [32]	13 normal males and females	Crossover trial	41% protein, 29% fat, 30% carb.	15% protein, 33% fat, 52% carb.	1 hour	Supervised	—	HP significantly increased satiety.
Holt 1995 [33]	41 healthy subjects	Controlled trial	38 different foods varying in macronutrient content	38 different foods varying in macronutrient content	2 hours	Supervised	—	Protein correlated positively with satiety r = .37, $p < 0.05$.
Johnson 1993 [34]	14 normal (8 females, 6 males)	Crossover trial	76% protein, 24% fat	13% protein, 1% fat, 86% carb.	90 minutes	Supervised	HP 2,684 kj, HC 2,822 kj, $p < 0.01$	HP significantly increased satiety.
Johnstone 1996 [35]	6 normal males	Crossover trial	37% protein, 29% fat, 34% carb.	11% protein, 29% fat, 60% carb.	15 days	Inpatient for 12 days	HP 13,770 kj, HC 12,690 kj (ns)	HP significantly increased satiety.
Long 2000 [44]	14 normal males and females	Controlled trial	Test meal; 35% protein, 32.5% carb. 32.5% fat. 13 day dietary manipulation; .75 g/protein/kg body wt or 1.96 g/kg body wt	—	13 hours for satiety test. 13 days for dietary manipulation	Food intake supervised for satiety test. Food records and protein provided for manipulation.	—	Significant correlation between protein and satiety r = .36. After 13 days of dietary manipulation, LP satiety significantly greater than HP suggesting satiety effect of protein varies inversely with habitual intake.
Ludwig 1999 [48]	12 Obese teen males	Crossover trial	30% protein, 30% fat, 40% carb.	16% protein, 20% fat, 64% carb.	5 hours	Supervised	HP 3,199 kj, HC 5,799 kj, $p = 0.01$	—
Poppitt 1998 [36]	12 normal females	Crossover trial	60% protein, 20% fat, 20% carb.	12% protein, 20% fat, 68% carb.	90 minutes	Supervised	HP 2,195 kj, HC 2,502 kj protein lowest, $p < 0.05$	HP significantly increased satiety.
Porrini 1995 [37]	12 normal males	Crossover trial	56% protein, 25% fat, 19% carb.	17% protein, 27% fat, 56% carb.	2 hours	Supervised	HP 1,834 kj, HC 3,396 kj, $p = 0.0028$	HP significantly increased satiety.
Porrini 1997 [46]	14 normal males	Crossover trial	54% protein, 45% fat, 1% carb.	15% protein, 79% fat, 6% carb.	2 hours	Instructed not to eat during study period	HP 5,799 kj, HF 6,682 kj (ns)	—
Rolls 1988 [38]	10 normal females	Crossover trial	75% protein, 25% fat	22% protein, 8% fat, 70% carb.	2 hours	Supervised	HP 1,256 kj, HC 1,570 kj, $p < 0.05$	HP significantly increased satiety.
Stubbs 1996 [39]	6 normal males	Crossover trial	59% protein, 19% fat, 22% carb.	18% protein, 21% fat, 61% carb.	5 hours	Supervised	HP 11,120 kj, HC 11,141 kj (ns)	HP significantly increased satiety.
Stubbs 1999 [40]	16 normal males	Crossover trial	60% protein, 20% fat, 20% carb.	20% protein, 20% fat, 60% carb.	24 hours	Supervised	HP 17,379 kj, HC 17,178 kj (ns)	HP significantly increased satiety.
Teff 1989 [50]	32 normal males	Crossover trial	71% protein, 10% fat, 19% carb.	100% carb.	3 hours	Supervised	HP 5,234 kj, HC 5,497 kj (ns)	—
Vanderwater 1994 [41]	40 normal males and females	Crossover trial	43% protein, 6% fat, 51% carb.	20% protein, 6% fat, 74% carb.	2 minutes	Supervised	—	HP significantly increased satiety.
Westerterp-Plantenga 1999 [42]	8 normal females	Crossover trial	29% protein, 10% fat, 61% carb.	9% protein, 61% fat, 30% carb.	24 hours	Supervised	—	HP significantly increased satiety

HP = high protein diets, HC = high carbohydrate diets, HF = high-fat diets.

protein tend to increase satiety when compared to meals lower in protein, at least in the short term. Whether this has a long-term effect on energy intake will be explored later in this review. There are, however, some methodological issues concerning this type of research. Satiety appears to be influenced by a wide variety of factors including palatability, food mass, energy density, fiber and glycemic index. When using real foods, it is difficult if not impossible to control for all of these influences at the same time while still delivering different amounts of protein.

The mechanisms by which protein may affect satiety remain elusive. Satiety is a complicated interaction of psychological, behavioral and physiological mechanisms. One theory was developed by Mellinkoff in 1956 and is termed the aminostatic hypothesis [45]. Since amino acid concentrations are correlated with a reduction in appetite, Mellinkoff believed there to be a satiety center in the brain. In this hypothesis, the center is sensitive to serum amino acid levels and once levels reach a certain point, hunger would cease. It would seem to make sense that the control of amino acids would be a priority considering their importance for tissue growth and maintenance coupled with their potential for toxicity at very high levels. However, there is little evidence to support this hypothesis.

Another possible mechanism is a relationship between satiety and dietary induced thermogenesis. In the investigation by Westerterp-Plantenga [42], differences in satiety over a period of 24 hours was significantly correlated with differences in 24 hour dietary induced thermogenesis (r = 0.8, $p < 0.01$). This area requires further investigation.

Subsequent Energy Intake

Taking the question one step further, several investigations have examined whether high protein meals will significantly influence subsequent energy intake compared to lower protein meals. The methodological procedure of this type of research is very similar to that of studies on satiety. Two isocaloric preloads differing in protein content were presented to each subject on separate occasions and then several hours later, subjects were given free access to food and instructed to eat until full. Most of these investigations were of a crossover design, so subjects received both preloads and thus acted as their own control.

Of 15 studies identified, 8 showed a significant decrease in energy intake after the higher protein preload (Table 2). A meta-analysis was not feasible due to a lack of inclusion of standard errors or standard deviations of the difference between the high and low protein preloads for the majority of studies.

Several of the investigations that found a decreased energy intake with high protein preloads utilized a very high percent of energy from protein (50% or greater). Johnson [34] studied 14 males and females in a crossover design. Subjects were presented with 3 isocaloric preloads on separate occasions; pasta (13% protein), chicken (76% protein) or whipped cream (2% protein). Post load energy consumption averaged 2,684 kj, 2,822 kj, and 3,408 kj for the chicken, pasta and whipped cream preloads respectively (for protein intake *vs.* high fat group intake, $p < 0.01$).

In a crossover design, Poppitt [36] manipulated the macronutrient composition of a test meal on 4 separate occasions in 12 lean women. Isocaloric lunches were served with the addition of 1 MJ of protein, fat, or carbohydrate. The high protein group's energy intake was significantly less than the high fat and high carbohydrate preloads at an ad lib lunch meal ($p < 0.05$).

Porrini conducted two studies on subsequent energy intake. Twelve males consumed both a low protein (17% protein) and a high protein (56% protein) lunch of equal calories. Food intake was significantly higher after the low protein preload at an ad lib buffet (1,834 kj *vs.* 3,396 kj, $p = 0.0028$) [37]. Later, Porrini [46] conducted a crossover study on 14 normal men feeding them an omelet either high in protein (54% protein) or low in protein (15% protein) and found no significant differences between the two groups.

Rolls [38] conducted a cross-over trial on 10 normal females serving them 5 different isocaloric preloads; pasta (6.6% protein), cream cheese (2% protein), chicken (55.6% protein), lemon sorbet (1.8% protein) and a mixed confectionary (3.6% protein). At a subsequent ad lib meal, the high protein preload resulted in the consumption of significantly fewer calories than all of the preloads except for the high starch ($p < 0.01$).

Three investigations that found a decreased subsequent intake with protein utilized a high protein preload of less than 50% protein. Araya [47] provided 35 children two isocaloric lunches, one high in protein (47% protein) the other low in protein (12% protein). At an ad lib lunch, the children consuming the high protein preload consumed an average of 1,087 kj compared to 1,255 kj for the low protein group ($p < 0.05$).

Barkeling [29] conducted a crossover trial on 20 normal females. Isocaloric lunches were served that were high in protein (43% of energy) or low in protein (10% of energy). Four hours after lunch an ad lib dinner was served. Subjects ate 12% fewer calories after the higher protein preload ($p < 0.05$).

Ludwig [48] conducted an investigation on 12 obese adolescent males. Five hours after consumption of a low glycemic high protein preload (30% protein, 30% fat, 40% carbohydrate) subjects consumed significantly fewer calories than when consuming a low protein high glycemic preload (16% protein, 20% fat, 64% carbohydrate). The difference in intake was striking with the lower protein group consuming 2,600 more kilojoules ($p = 0.01$). Furthermore, Booth [49] conducted a crossover trial on 15 normal males and females. Lunch was served containing either a high protein spread or without it. Two to three hours later, an ad lib supplement was provided. Total caloric intake for the supplement was significantly lower for the high protein preload ($p < 0.05$).

In contrast, DeGraaf [30] and Geliebter [31] found no significant differences in subsequent energy intake after administering preloads varying in protein content. Again, the use of nose clips and liquid preloads make the testing conditions unusual. Johnstone [35] found no significant differences in ad lib intake across the 3 preloads varying in protein content.

Stubbs and colleagues conducted two investigations on this topic. First, they fed 6 men a breakfast comprising 3.1 MJ of protein, fat or carbohydrate on separate occasions. There were no significant differences in intake among the preloads after 5 hours [39]. Later, 16 normal men were fed a breakfast and 2 hours later a snack comprising 80% of resting metabolic rate as either protein, fat or carbohydrate in a crossover design. Ad lib intake was monitored for the rest of the day and there were no significant differences in energy intake among the preloads [40]. Finally, Teff [50] found no significant differences in subsequent energy intake between a high and low protein preload after 3 hours. It is important to note that the preloads were not isocaloric (HP 879 kilojoules, LP 1,675 kilojoules). This may explain the null results.

It is not easy to interpret these results because of a wide variety of designs and subjects used in these studies. Similar to the satiety research, energy intake is affected by a wide variety of factors including palatability, food mass, energy density, fiber and glycemic index. Although most researchers tried to make the preloads as equal as possible in this regard, this is a nearly impossible task and may have affected energy intake independent of protein.

There were some methodological differences between the studies that showed a decrease in energy intake after high protein preloads, compared with lower protein version, and those that did not. For example, in two of the studies that showed no effect, the study was conducted in a whole body calorimeter chamber, which does not reflect real life conditions [35,39]. Similarly, two other studies not showing an effect used nose clips and/or anesthesia to eliminate taste from the preloads [30,31]. Again, this does not reflect everyday normal eating behaviors. In the study by Teff [50], the preloads were not isocaloric, which certainly could affect the results.

Overall, the weight of evidence suggests that higher protein intakes cause a decreased subsequent energy intake although the results are not entirely consistent. It appears that, the closer the methodology was to real life situations (real food *vs.* liquid, sense of taste unaltered, free living *vs.* whole body calorimeter), the more likely it was for protein to exert a significant decrease in subsequent energy intake. The majority of studies identified in this review did find a decreased subsequent energy intake with a higher protein preload. More research is needed in this area, with better agreement with regards to methodology across studies in order to shed further light on this question.

Total Weight Loss

Fifteen studies have been identified that measured absolute weight lost (Table 3) [12,13,51–63]. These investigations lasted for between 7 days and one year and the majority of them were randomized controlled trials of fixed energy intake. There were a wide variety of macronutrient ratios and methodological designs that make the research, as a body of work, difficult to summarize. Seven of these investigations found a statistically significant decrease in total body weight for the higher protein diets [52,53,55,59,60,62,63].

Of the 7 studies that found a significantly greater weight loss with a higher protein diet, 5 were of a longer duration (6 months or longer). Samaha [59] conducted a randomized trial on 132 obese subjects. Sixty-four received counseling on maintaining a high protein, low carbohydrate diet (22% protein) while 68 received counseling on consuming a low fat, high carbohydrate diet (16% protein). After 6 months, the high protein, low carbohydrate group lost significantly more weight (5.8 *vs.* 1.9 kg, $p = 0.002$).

Skov [60] found that in 60 free living overweight men and women, those randomized to a high protein intake (25% of energy) compared to a low protein intake (12% of energy) lost significantly more weight (8.8 *vs.* 5.1 kg) and fat (7.6 *vs.* 4.3 kg) after 6 months. Of note in this investigation is the fact that the high protein group averaged 8,956 kj/day while the low protein group averaged 10,907 kj/day. This is the likely cause of the difference in weight lost.

Brehm [53] conducted a randomized trial on 42 obese females. Twenty received a low fat dietary regimen (17% protein) while 22 received a low carbohydrate diet (23% protein). After 6 months, the higher protein group had lost significantly more weight (8.5 kg *vs.* 3.9 kg, $p < 0.01$). Yancy [63] conducted a trial on 119 overweight men and women for 6 months. Those consuming a higher protein, low carbohydrate diet (26% protein) lost significantly more weight than those consuming a lower protein diet (19%) (12.9% of body weight *vs.* 6.7% of body weight, $p < 0.001$).

Foster [55] examined the Atkins diet in a randomized trial of 63 obese males and females. Thirty-three received counseling on following the Atkins diet and 30 received counseling on a conventional low fat diet (15% protein). The study lasted for 1 year. The Atkins group lost significantly more weight at 3 months and 6 months, but not at 1 year.

Two studies that found an increased weight loss with higher protein diets were of a shorter duration, lasting only several weeks. Baba [52] conducted a four week randomized trial on 13 obese male subjects with hyperinsulinemia. Seven men received a high protein diet (45% protein) while the other 6 received a high carbohydrate diet (12% protein). After 4 weeks, the high protein group lost significantly more weight than the high carbohydrate group (8.3 *vs.* 6 kg, $p < 0.05$). Worthington [62] conducted a randomized trial on 21 overweight females. Eleven women received high protein, low carbohydrate diets (49% protein) while 10 received a diet lower in protein and higher in carbohydrate (21% protein). After 2 weeks, the high protein group lost significantly more weight (5.5 kg *vs.* 3.95 kg, $p < 0.05$).

Table 3. Randomized Trials Of High Protein Diets On Weight And Fat Loss

Reference	Population	Design	Diet	Control	Duration	Compliance	Result
Alford 1990 [51]	35 older females	Randomized trial	30% protein, 45% fat, 25% carb.	15% protein, 75% carb., 10% fat	10 weeks	Food records, weekly counseling	Wt loss—HP 6.4 kg, LP 4.8 kg (ns), fat loss—HP 4.5 kg, LP 2.8 kg (ns)
Baba 1999 [52]	13 obese male hyper-insulinemic	Randomized trial	45% protein, 30% fat, 25% carb.	12% protein, 30% fat, 58% carb.	4 weeks	Food provided, diet records, counseling	Wt loss—HP 8.3 kg, LP 6 kg ($p <$ 0.05), fat loss—HP 7.1 kg, LP 6.3 kg (ns)
Brehm 2003 [53]	42 obese females	Randomized trial	23% protein, 46% fat, 31% carb.	17% protein, 31% fat, 52% carb.	6 months	Counseling, food records	Wt loss—HP 8.5 kg, LP 3.9 kg ($p <$ 0.01), fat loss—HP 4.8 kg, LP 2.0 kg ($p < 0.01$)
Farnsworth 2003 [54]	57 overweight 14 male, 43 female	Randomized trial	27% protein, 44% carb., 29% fat	16% protein, 57% carb., 27% fat	16 weeks	Supplied 60% of energy, counseling, checklists	Wt loss—HP 7.8 kg, LP 7.9 kg (ns), fat loss—Both 6.9 kg
Foster 2003 [55]	63 Obese; 20 male, 43 female	Randomized trial	Atkins; protein not specified	15% protein, 60% carb., 25% fat	1 year	Counseling, Instructional Books	Wt loss—After 1 year; HP 4.3 kg, LP 2.5 kg (ns) After 6 months HP 6.9 kg, LP 3.1 kg ($p > 0.05$)
Layman 2003 [56]	24 overweight females	Randomized trial	30% protein, 41% carb., 29% fat	16% protein, 58% carb., 26% fat	10 weeks	Received food for 4 weeks, 6 weeks on own, food records	Wt loss—HP 7.53 kg, LP 6.96 kg (ns), fat loss—HP 5.6 kg, LP 4.7 kg (ns)
Luscombe 2003 [12]	36 obese hyperinsulinemics 10 male, 26 female	Randomized trial	27% protein, 45% carb., 28% fat	16% protein, 57% carb., 27% fat	16 weeks	Supplied 60% energy, counseling, food records	Wt loss—HP 7.9 kg, LP 8.0 (ns), fat loss—both 6.8 kg
Luscombe 2002 [13]	26 obese type 2-diabetics; 15 Female, 11 Male	Randomized trial	28% protein, 30% fat, 42% carb.	16% protein, 29% fat, 55% carb.	12 weeks	Urea/creatinine ratio, 24 h recall	Wt loss—HP 4.9 kg, LP 4.3 kg (ns), fat loss—both 4.5 kg (ns)
Parker 2002 [57]	54 type 2-diabetics; 35 Female, 19 Male	Randomized trial	30% protein, 30% fat, 40% carb.	15% protein, 25% fat, 60% carb.	12 weeks	Supplied 60% energy, record, interviews	Wt loss—HP 5.2 kg, LP 5.2 kg (ns), fat loss—women on HP lost more total fat (5.3 *vs.* 2.8 kg, $p < 0.009$)
Piatti 1994 [58]	25 obese glucose intolerant females	Randomized trial	45% protein, 35% carb., 20% fat	20% protein, 60% carb., 20% fat	21 days	Hospital admission	Wt loss—HP 4.5 kg, LP 6.4 (ns), fat loss—HP 3.2 kg, LP 3.3 kg (ns)
Samaha 2003 [59]	132 obese; 109 males, 23 females	Randomized trial	22% protein, 37% carb., 41% fat	16% protein, 51% carb., 33% fat	6 months	Counseling and 24-hour recall	Wt loss—HP 5.8 kg, LP 1.9 kg ($p =$ 0.002)
Skov 1999 [60]	65 overweight, 50 females, 15 males	Randomized trial	25% protein, 30% fat, 45% carb.	12% protein, 30% fat, 58% carb.	6 months	Urinary Nitrogen Excretion	Wt loss—HP 8.9 kg, LP 5.1 kg ($p <$ 0.001) Caloric intake—HP 8,956 kj, LP 10,907 kj Fat loss—HP 7.6 kg, LP 4.3 kg, $p <$ 0.0001
Whitehead 1996 [61]	8 overweight, 6 female 2 male	Randomized crossover trial	36% protein, 32% fat, 32% carb.	15% protein, 32% fat, 53% carb.	7 days	Food provided, questionnaire, urinary nitrogen	Wt loss—HP 2.06 kg, LP 2.33 kg (ns)
Worthington 1974 [62]	21 overweight female	Randomized trial	49% protein, 45% fat, 6% carb.	21% protein, 47% fat, 32% carb.	2 weeks	Inmates	Wt loss—HP 5.5 kg, LP 3.95 kg, $p <$ 0.05
Yancy 2004 [63]	119 overweight, 91 female, 28 male	Randomized trial	26% protein, 68% fat, 8% carb.	19% protein, 29% fat, 52% carb.	6 months	Food records, group meetings, urinary ketone assessment	Wt loss—HP 12 kg (12.9% of body weight) LP 6.5 kg (6.7% of body weight) $p < 0.001$

HP = high protein diets, LP = low protein diets.

Of the 8 studies that found no significant difference in weight loss comparing higher and lower protein diets, half of them were of a relatively short duration (10 weeks or less) and small sample size (6–35 subjects) [51,56,58,61]. Alford [51] conducted a randomized trial on 35 older females. After 10 weeks, there was no significant difference in weight loss between the high carbohydrate (15% protein) and the low carbohydrate (30% protein) groups.

Layman [56] conducted a randomized trial on 24 overweight females for 10 weeks. Twelve received a high protein diet (30% protein) while 12 received a high carbohydrate diet (16% protein). By the end of follow-up, there were no significant differences in weight lost between the two groups.

Piatti [58] randomized 10 glucose intolerant females to a diet that was high in protein (45% protein) and 15 to a diet high in carbohydrate (20% protein) for 3 weeks. There were no significant differences in weight loss between the two groups. Whitehead [61] conducted a randomized crossover trial on 8 overweight subjects for one week. Four diets were tested, one of which was high in protein (36% protein) and one low in protein (15% protein). There were no significant differences in weight lost among the two diets.

Four of the 8 studies that did not find an increased weight loss with higher protein diets were of a relatively longer duration, lasting 12 weeks or more [12,13,54,57]. Farnsworth [54] randomized 29 subjects to a standard protein diet (16% protein) and 28 subjects to a high protein diet (27% protein). After 16 weeks, there were no significant differences in total weight lost.

Luscombe [12,13] conducted 2 randomized weight loss trials and in both found no significant difference in weight lost between high protein and low protein groups. Finally, Parker [57] randomized 26 type-2 diabetics to a high protein diet (30% protein) and 28 to a low protein diet (15% protein) for 8-weeks of energy restriction and then 4-weeks of energy balance. There were no significant differences in weight lost between the two groups.

Overall, there is some evidence that high protein diets enhance weight loss compared to lower protein diets in the short term. It is important to realize that not all of the diets were isocaloric. In fact, all 5 of the investigations that utilized an ad lib dietary intake found significantly increased weight loss with the higher protein regimen [53,55,59,60,63]. This includes only the first 6 months of the Foster study [55] due to the very high drop out rates of this 12 month investigation. Therefore, the mechanism by which protein enhances weight loss may be through increased satiety and a decreased subsequent energy intake. When the diets are isocaloric, the evidence is not convincing.

There has also been recent interest concerning the hypothesis that increasing dietary protein after weight loss has a beneficial effect on weight regain and/or weight maintenance. Westerterp-Plantenga [64] found that increasing protein from 15% of energy to 18% of energy during weight maintenance resulted in a 50% lower body weight regain, which consisted solely of fat-free mass. This is an interesting observation that awaits further research.

Total Fat Loss

Several of the previously mentioned studies also looked at body composition to test the hypothesis that higher protein diets spare the lean body mass of those on energy restricted diets (Table 3). Out of 10 studies identified, most found greater fat loss with the high protein diets in comparison to the lower protein diets, but only three studies found this difference to be statistically significant [53,57,60].

High Protein Diets and Renal Function

There has been some debate as to the safety of high protein diets with regard to kidney function. In populations with established renal disease, it has been shown that limiting protein to the RDA level may slow the progression of disease [65]. Whether or not high protein diets adversely affect kidney function in healthy populations is not clear. In a recent review paper, Eisenstein and Roberts [19] assessed the evidence and came to the conclusion that there is little evidence for adverse effects of high protein diets on renal function in individuals without established renal disease.

For example, several studies have reported that high protein diets cause hyperfiltration up to a saturation point of approximately 125 g/day [66–70], although net hyperfiltration (filtration expressed as a function of renal mass) did not occur when protein intake varied in the range of 70–108 grams a day. These higher protein intakes are related to an increase in renal mass [71].

Other measures of renal function are similarly inconsistent. In evaluating the clearance of creatinine, urea and albumin, one study compared the very high protein diet of body builders to that of athletes consuming moderate protein diets. No adverse effects in the parameters measured were found with protein intake up to 2.8 grams per kilogram [72].

There is evidence that higher protein intakes can significantly increase the risk of kidney stones [73], uric acid stones [74], and calcium stones [75]. However, one study found a significant decrease in calcium oxalate stones with a higher compared to a lower protein group [76].

Taken together, there is little evidence that high protein diets pose a serious risk to kidney function in healthy populations. More susceptible groups such as diabetics and those with existing renal disease should exercise more caution with higher protein intakes.

Blood Lipids and Cardiovascular Disease Risk

Another area of controversy is the effect of high protein diets on blood lipids. Jenkins [77] conducted a one month study of a high wheat protein diet (27%) compared to a control diet (16%) and found significant decreases in triglyceride and oxidized LDL cholesterol on the higher protein diet. A recent study by Samaha [59] compared a low carbohydrate, high protein Atkins diet (22% protein) to a low fat diet (16%) on severely obese subjects. The higher protein group had significantly lower triglycerides compared to the lower protein group (−20% *vs.* −4%, $p = 0.001$). However, the higher protein group lost more weight and this may have accounted for these differences. In investigations included in this review, Farnsworth [54] and Skov [60] found a significant decrease in triglycerides with higher protein diets while Parker [57] found a significantly lower LDL cholesterol level with a higher protein diet. Finally, Wolfe [78] found that the isocaloric substitution of animal protein for carbohydrate significantly raises HDL cholesterol and lowers triglyceride levels.

Other studies looking at high protein diets found no significant differences in blood lipid measures in comparison to lower protein diets [51,60]. While more research is still needed in this area, it appears that higher protein diets at the very least are not harmful to blood lipids in the short term and the exchange of protein for carbohydrate may actually be beneficial for blood lipids.

Limited epidemiological data are available on high protein intake and cardiovascular risk. A prospective cohort study by Hu [79] found that a higher protein intake (24% of calories *vs.* 15% of calories) was associated with a decreased risk of coronary heart disease during 14 years of follow-up. Both animal and plant protein contributed to the lower risk. Iso [80] found that very low levels of animal protein intake were associated with a significantly increased risk of hemorrhagic stroke. This is consistent with ecological data from Japan that suggests a low intake of protein increases the risk of intraparenchymal hemorrhagic stroke [81,82]. Furthermore, in a meta-analysis of cross-sectional investigations, Liu and colleagues found a significant inverse association between dietary protein and blood pressure in both sexes [83]. While more research is needed in these areas, it appears that moderately high protein diets are not harmful to cardiovascular health and may indeed be beneficial.

Conclusion

For years, authors of some fad diets have advocated raising the percentage of dietary protein in the overweight, although not until recently have studies begun to investigate the effects of high protein diets on weight loss. This macronutrient has not been studied extensively enough with regards to its effect on body weight and long-term studies are particularly needed. In the year 2002, Eisenstein and Roberts [19] published an extensive review on the efficacy and safety of high protein diets. We have identified an additional 30 investigations and included them in this review in order to shed more light on this controversial topic.

Convincing evidence exists that protein exerts an increased thermic effect when compared to fat and carbohydrate. The increased amount of energy attributable to this thermic effect is probably too small to have a visible effect on weight loss in the short term, but over periods of months or years, this difference may become significant, both clinically and statistically.

Evidence is also convincing that higher protein diets increase satiety when compared to lower protein diets. This may enhance a dieter's ability to "stick with" a hypocaloric diet over the long term. Evidence is suggestive that higher protein diets decrease subsequent energy intake at the next meal compared to lower protein diets, although the studies are not consistent.

Our review suggests that higher protein diets may significantly increase total weight lost and possibly percentage of fat lost when compared to a lower protein diet in the short term. Possible mechanisms include an increased satiety and decreased subsequent energy intake with higher protein diets. All 5 investigations that utilized an ad lib intake found significantly increased weight lost with the higher protein regimens in the short term studies (6 months or less). A higher thermogenesis for protein is a possible mechanism as well, but the studies included in this review were of too short a duration for this to be conclusive; if it does have an effect, this higher thermogenesis is likely to be noticeable only in the longer term. Another possible mechanism is the displacement of carbohydrate, especially refined carbohydrate, in the diet by dietary protein. There is emerging evidence that high glycemic, refined carbohydrates decrease satiety and increase subsequent energy intake [48]. It is likely that several of these mechanisms are working together and are related to one another.

In conclusion, evidence suggests that higher protein diets may have beneficial effects on weight loss in the short term, although most of the studies have been small and inconclusive. More definitive evidence should wait for the results from ongoing long-term trials. Although the optimal amount and sources of protein cannot be determined at this time, the weight of evidence suggests that in dietary practice, it may be beneficial to partially replace refined carbohydrate with protein sources that are low in saturated fat.

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