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High-protein Weight-loss Diets: Are They Safe and Do They Work? A Review of the Experimental and Epidemiologic Data

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Recommendations for increased consumption of protein are among the most common approaches of popular or fad diets. This review summarizes the effects of dietary protein on satiety, energy intake, thermogenesis, and weight loss, as well as its effect on a variety of health outcomes in adults. In short-term studies, dietary protein modulates energy intake via the sensation of satiety and increases total energy expenditure by increasing the thermic effect of feeding. Whereas these effects did not contribute to weight and fat loss in those studies in which energy intake was fixed, one ad libitum study does suggest that a high-protein diet results in a greater decrease in energy intake, and therefore greater weight and fat loss. In terms of safety, there is little long-term information on the health effects of high-protein diets. From the available data, however, it is evident that the consumption of protein greater than two to three times the U.S. Recommended Daily Allowance contributes to urinary calcium loss and may, in the long term, predispose to bone loss. Caution with these diets is recommended in those individuals who may be predisposed to nephrolithiasis or kidney disease, and particularly in those with diabetes mellitus.

Key Words: dietary protein, energy intake, thermogenesis, weight loss, high-protein diet, urinary calcium loss, bone loss

Introduction

The prevalence of obesity in the United States and other industrialized countries continues to rise despite increased public awareness and efforts to control weight.[1] However, there remains no scientific consensus on dietary and other causes of the rising prevalence of obesity, or on optimal methods for weight loss and prevention of weight regain. In the absence of scientific unity on this issue, non-scientific prescriptions for weight loss have flourished and are frequently attempted by individuals wishing to lose weight. Many of these have focused on dietary protein and have advocated consumption of high-protein or high-protein, high-fat diets. The purported benefits of such diets include weight loss, amelioration of hunger, and prevention, reduction, or even resolution of several chronic diseases. This review focuses on evidence for the safety and effects of high dietary protein on energy regulation and is the fourth[2–4] in a series from our laboratory on the influence of different dietary factors on weight gain and weight control.

The current recommended dietary allowance (RDA) for protein is 0.8 g/kg,[5] although the typical U.S. American consumes approximately 1.2 g/kg protein daily or 15% of total energy intake.[6] There are no standard definitions for high-protein diets, but based on the data summarized in this review, we propose that intakes of $\geq$25% energy in weight-stable individuals or $\geq$1.6 g/kg ideal body weight in those in negative energy balance be defined as high, and $\geq$35% energy in weight-stable individuals or $\geq$2.4 g/kg ideal body weight in those in negative energy balance be considered extremely high.

Effects of Protein on Satiety and Energy Intake

A number of studies have been conducted to examine the effects of dietary protein on hunger, satiety, energy intake, and body fatness.[7–34] Of eight preload studies that compared subjective hunger and satiety in the hours following consumption of a single high-protein meal and/or a control meal,[9–16] six reported increased satiety with the high-protein diet compared with at least one control diet.[9–12,14,16] Of the two studies that found no

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Table 1. Effect of a High-protein Meal on Later Energy Intake

Author	% Protein C	% Protein HP	Energy Intake C (kcal)	Energy Intake HP (kcal)	% Difference HP/C
Sunkin[7]	6.5	32.0	406.0	382.0	94
Booth[8]	5.0	50.0	330.0	254.0*	77
Porrini[16]	14.8	53.5	1596.0	1385.0*	87
Rolls[12]	0.6	26.5	409.5	300.0*	73
Poppitt[14]	6.0	56.0	602.0	524.0*	87
Stubbs[11]	20.0	59.0	1252.0	1285.0	103
Hill[9]		54.0	900.0	700.0*	78
Crovetti[10]	9.0	68.0	1104.0	1192.0	108
DeGraaf[15]	2.0	70.0	675.0	600.0	89
Barkeling[13]	10.0	43.0	904.0	804.0*	89
Mean	8	51	818	743*	91
Paired t test (Energy Intake)			*$P = 0.030$		

*$P < 0.05$.
C = control, HP = high-protein, kcal = kilocalories.

subjective difference between a high-protein preload and a control, one[15] used liquid breakfasts instead of solid food, which may have influenced the results, and in another study[13] the higher-protein meal was rated more palatable and thus may have influenced subjective satiety. Although not conclusive, the body of evidence from these studies of dietary protein and perceived hunger and satiety suggests that higher-protein meals have the potential to suppress hunger to a greater degree and result in enhanced sensations of satiety. However, it should be noted that not all of these studies controlled for dietary factors other than protein that have the potential to influence hunger and satiety, including fiber content,[4] glycemic index,[2] energy density,[3] variety,[35] and palatability.[36] Whereas all preloads within each study were similar with regard to energy and variety, only a subset used preloads that controlled for energy density[10–12,14] or palatability.[11,16] None of the studies controlled for fiber content or glycemic index. Stubbs et al.,[11] whose study was possibly the most tightly controlled, identified a greater satiety effect of protein, but noted no difference in subsequent energy intake.

In addition to the above studies, changes in the satiety effects of protein over time have been studied. Long et al.[37] reported that the satiety effect of dietary protein varied inversely with regular protein intake over a 13-day dietary manipulation period that compared 0.75 $g \cdot kg^{-1} \cdot day^{-1}$ with 1.96 $g \cdot kg^{-1} \cdot day^{-1}$ protein intake. Whereas there appears to be evidence for effects on perceived satiety, there is a paucity of evidence for longer-term effects and the stability of such effects.

The question of whether dietary protein influences short-term ad libitum energy intake has also been examined. Ten studies measured energy intake after consuming higher-protein and control preloads (Table 1). Studies were included in the analysis only if time from preload to the test meal was >1 hour (range 1.5–7 hours); this is because the amount of a test meal consumed within 1 hour from the time of the preload may be dictated by the cephalic response to a meal.[38] Energy intake following the higher-protein preload was lower in eight out of ten of the studies reviewed, and mean energy intake was nine percent less than with the lower-protein preload ($P = 0.03$). In many of these studies, however, the higher-protein preloads contained a proportion of protein energy that was extremely high (≥35%), and the relevance of the findings to diets that are typically consumed is therefore uncertain.

Three studies with a control group have also assessed the influence of protein on ad libitum energy intake beyond a single meal (Table 2). In two of the studies[17,18] (conducted for 24 hours and 3 days, respectively) there was no effect of protein level on energy intake, and mean values were very similar. The other study[19] was conducted for 6 months, and observed a significant 18% lower energy intake with the higher-protein diet. The reasons for the differences between the studies are not known, although it is possible that study duration was important. In addition, there may have been unmeasured differences between groups in some of the studies that could have influenced the results. For example, the study design for the long-term study allowed the subjects to choose foods consistent with their group randomization from a store set up by the investigators. It is possible that the nature of the available foods reduced dietary variety in the high-protein group, which could have had an independent effect on energy intake.[35]

Table 2. Longer-term Effects of Dietary Protein on Energy Intake

Author	% Protein C	% Protein HP	Energy Intake C	Energy Intake HP	% Difference HP/C
Johnstone[18]	9	38	3647	3652	100
Skov[19]	12	25	2605	2139*	82
Stubbs[17]	20	60	4161	4153	100
Mean	14	41	3471	3315	95
Paired t test (Energy Intake)			$P = 0.419$		

$*P < 0.05$.
C = control, HP = high-protein.

Table 3. Thermic Effect of Feeding (TEF)

Author	Duration (hours)	Diet	TEF %
Crovetti[10]	7.0	68% P, 19% F, 12% C	11.0
		69% C, 21% F, 10% P	4.0
		70% F, 21% C, 9% P	4.2
Swaminathan[20]	1.5	100% P	6.3
		100% C	3.3
		100% F	1.0
		12% P, 33% F, 55% C	5.4
Welle[21]	4.0	100% P	10.3
		100% C	7.3
		100% F	6.5
Schutz[22]	4.0	14% P, 59% C, 27% F	6.5
		5% P, 64% C, 31% F	3.5
Robinson[23]	9.0	77% P, 7% F, 16% C	11.5
		77% C, 7% F, 16% P	8.0
Karst[24]	6.0	100% P	20.7
		100% C	4.7
Nair[25]	2.6	100% P	15.0
		100% C	6.0
		100% F	7.0
Westerterp[26]	24.0	29% P, 61% C, 10% F	14.6
		9% P, 30% C, 61% F	10.5
Hendler[27]	3.0	95% P, 2% C, 3% F	4.0
		41% P, 55% C, 4% F	5.8
Steiniger[28]	6.0	100% P	22.0
		100% C	5.7

P = protein, F = fat, C = carbohydrate

Thermogenesis

Another potential mechanism by which high dietary protein could promote weight loss is through increasing energy expenditure. If a measurable increase in energy expenditure occurred as a result of eating a high-protein diet and was not counterbalanced by a corresponding increase in the desire to eat or hunger that promoted increased energy intake, body weight would fall. Research in this area has focused on the increase in energy expenditure after eating, which is known as the thermic effect of feeding (TEF); TEF typically accounts for 10 to 15% of total energy expenditure averaged over 24 hours.[39]

Table 3 summarizes 10 studies that assessed TEF in relation to dietary composition and used at least two diets differing in protein content but controlled for other dietary variables. A mixture model regression analysis was performed to determine the relative contribution of macronutrients to TEF, which yielded the following equation:

$$\text{TEF}(\%\ \text{energy intake}) = 0.132\text{P} + 0.051\text{F} + 0.054\text{C}$$

$$(r^2 = 0.331, P = 0.005),$$

where P = protein (g), F = fat (g), C = carbohydrate (g).

In this analysis, which combined studies using isolated macronutrients with those using mixed meals, protein contributed approximately twice as much to the estimated TEF as fat or carbohydrate. In addition, because the contribution of fat and carbohydrate to the TEF was similar, for any fixed protein level, TEF was essentially unaffected by the proportions of fat and carbohydrate. Although confirmatory studies are needed, this initial analysis suggests that protein exerts a more significant effect on energy expenditure. For example, if an individual consuming a 2000 kcal/day weight-loss diet was to substitute a high-protein diet (30% protein, 30% fat, 40% carbohydrate) for a typical recommended U.S. diet (15% protein, 30% fat, 55% carbohydrate), the above equation predicts an increase in energy expenditure of 23 kcal/day, which is approximately equivalent to an increase of 0.8% of the total energy expenditure (TEE) for a typical individual. On theoretic grounds, this small increase in energy expenditure would result in additional weight loss of 0.09 kg/month. These observations and calculations demonstrate that high-protein diets are associated with a significant increase in TEF, but it is quantitatively small and as such is expected to have only a limited influence on body weight even if energy intake is unaffected by the increase in energy expenditure. Other studies, although not providing enough information to calculate TEF, corroborate the finding that protein has a higher thermogenic effect.[40,41]

A potential mechanism for these results is described by Robinson et al.,[23] who found that whereas 36% of TEF in a high-carbohydrate meal accounted for a postprandial increase in protein synthesis, 68% of the TEF from a high-protein meal was due to protein synthesis, suggesting that an increase in protein synthesis following consumption of higher-protein meals may help to explain the increased TEF. By contrast, whereas the sympathetic nervous system seems to play at a partial role in the TEF of carbohydrate, Welle et al.[21] found no significant alteration in plasma norepinephrine levels after ingestion of protein and fat meals.

The potential effects of dietary protein on the other major components of energy expenditure, i.e., resting energy expenditure (REE) and energy expenditure for physical activity, have received little attention to date. Whitehead et al.[42] found during a 7-day weight-loss study that a diet with 36% protein was associated with a smaller decline in 24-hour energy expenditure and sleeping metabolic rate than either of two 15%-protein isocaloric diets. Similarly, Baba et al.[33] reported a smaller decrease in REE following weight loss with a high-protein diet compared with a control diet (-384 vs. -132 kcal, $P < 0.05$). In this case, however, the effects of differences in TEF between protein and other macronutrients may have contributed because details of the conditions of REE measurement were not provided.

Weight Loss

Several research groups have investigated the question of whether the short-term effects of high-protein diets on satiety, energy intake, and TEF translate into enhanced weight loss during dieting. However, several of the studies either provided insufficient study details to evaluate the study design or made it difficult to evaluate whether the effects seen were due to high protein intake or another aspect of the study design.[43–55] We therefore summarized only the eight available studies longer than 2 weeks duration (variable and transient diuresis during the initial period of negative energy balance makes weight loss results hard to interpret for shorter periods of time), which had a control group consuming a lower-protein diet and provided essential study details. Tables 4 and 5 summarize the studies, with the diets separated by whether energy intake was ad libitum and whether they were ketogenic.

Of the seven fixed–energy intake studies summarized in Table 4, two used a liquid formula,[29,30] two were comprised of a very limited variety of foods (e.g., boiled turkey and grape juice),[27,31] and the remainder had a more varied menu.[32–34] The amount of protein in the summarized diets varied considerably, but weight loss and fat loss did not differ between control and higher-protein diets either in all studies combined or in the studies separated by whether or not they were ketogenic. Combined, these studies strongly suggest no effect of high-protein intake on body fat loss or body weight change during negative energy balance when energy intake is fixed. The combination of no difference in weight or fat loss suggests no difference in lean body mass loss.

Other studies have investigated the potential for a specific nitrogen-sparing effect of high dietary protein during weight loss. Hoffer et al.[56] compared two isocaloric diets (500 kcal), one at 1.5 $g \cdot kg^{-1} \cdot day^{-1}$protein and the other at 0.8 $g \cdot kg^{-1} \cdot day^{-1}$ protein plus 0.7 $g \cdot kg^{-1} \cdot day^{-1}$ carbohydrate. After 3 weeks of adaptation to the diets, nitrogen balance was zero for the higher-protein diet and -2 g/day for the diet at the RDA level of protein ($P < 0.05$). By contrast, Vazquez et al.[29] (Table 4) compared similar protein amounts (50 g vs. 70 g or 0.8 g/kg ideal body weight [IBW] vs. 1.1 g/kg IBW) while varying the carbohydrate content to assess the interaction between protein and ketosis. The nitrogen-sparing effect of increased carbohydrate significantly surpassed that of protein. This finding is supported by Howard et al.,[57] who examined the effect of amino acids alone and supplemented with glucose on nitrogen balance and found that mean cumulative nitrogen balance over a 5-day study period was -12.4 g on amino acids alone and $+0.5$ g when glucose was added. Combined, these studies do not support a role for high dietary

Table 4. Weight Loss Studies with Fixed Energy Intake

Author	Duration (weeks)	% Protein		Weight loss (kg)		Fat loss (kg)		Change in LBM (kg)	
		Control	HP	Control	HP	Control	HP	Control	HP
				Ketogenic					
DeHaven[31]	5.5	50.0	100.0	8.0	10.2*	7.8	7.7	−0.2	−2.5*
Hendler[27]	3.0	41.0	95.0	8.9	8.7	6.8	7.1	−2.1	−1.6
Vazquez[29]	4.0	35.0	46.0	8.8	8.5	7.1	7.1	−1.7	−1.4
Yang[30]	9.1	51.8	98.0	23.5*	20.4	12.3	13.6	−11.2*	−6.8
Mean		44.5	84.8	12.3	12.0	8.5	8.9		
Paired t test				$P = 0.768$		$P = 0.326$			
				Nonketogenic					
Vazquez[29]	4.0	34.0	43.0	8.9	7.6	8.0	6.9	−0.9	−0.7
Piatti[32]	3.0	20.0	45.0	6.4	4.5	3.3	3.2	−3.0*	−1.4
Baba[33]	4.0	12.0	45.0	6.0	8.3*	6.3	7.1	+0.3	−1.0*
Alford[34]	10.0	15.0	30.0	4.8	6.4	2.8	4.5		
Mean		20.3	40.8	6.5	6.7	5.1	5.4		
Paired t test				$P = 0.877$		$P = 0.626$			
All Studies									
Mean		**33**	**63**	**9.4**	**9.3**	**6.8**	**7.2**		
Paired t test				$P = 0.904$		$P = 0.303$			

*$P < 0.05$.
LBM = lean body mass, kg = kilograms, HP = high-protein.

Table 5. Weight Loss Study with Ad Libitum Energy Intake

	High-carbohydrate *(n = 25)*	**High-Protein** *(n = 25)*
Duration (weeks)	27	27
Average BMI	30.8	30.0
Diet composition	12% P, 58% C, 30% F	25% P, 45% C, 30% F
Average Energy Intake (kcal/day)	2605	2139*
Weight loss (kg)	5.1	8.9*
Fat loss (kg)	4.3	7.6*

*$P < 0.05$.
BMI = body mass index (kg/m^2). Source: Skov.[19]

protein in preventing loss of lean tissue during negative energy balance, provided that dietary protein intake at least meets the RDA.

Only one study[19] compared a high-protein diet with a control diet in order to evaluate weight loss on a high-protein diet when energy intake is ad libitum. That study examined the effects of higher dietary protein intake (25% vs. 12% energy intake) on weight loss in obese subjects and found that weight and fat loss were significantly greater in the high-protein group (Table 5). The results are consistent with a weight loss–promoting effect of higher-protein diets mediated by increased satiety and decreased energy intake (see previous section). However, the possibility cannot be discounted that unmeasured differences existed between the groups (for example in dietary variety, which is known to independently influence energy intake and body fatness),[35] which would help explain the results as well as the differences in dietary protein. By contrast with the findings of the above study, a recent large observational cross-sectional study[58] found a strong, positive association between dietary protein intake and higher body mass index (BMI, kg/m^2) even after adjusting for variables such as energy intake and physical activity. Therefore, in individuals consuming self-selected diets, the contribution of dietary protein to body weight is far from straightforward and additional longer-term studies in this area are needed.

Health Consequences of High Dietary Protein

High-protein intake has been suggested to adversely effect calcium homeostasis, renal function, and cancer risk. However, as with the effects of protein on body weight, there remains substantial controversy.

Dietary Protein and Bone

Data from short-term studies indicate that increased protein intake is associated with increased renal calcium excretion, negative calcium balance,[59–65] and bone resorption.[66] The studies reviewed demonstrated calciuretic effects at 2 $g \cdot kg^{-1} \cdot day^{-1}$ (102–193 g/day) when compared with control diets containing 0.7 to 1.0 $g \cdot kg^{-1} \cdot day^{-1}$ (39–95 g/day). Mechanisms proposed to explain protein-induced bone resorption and calciuresis have primarily focused on the acid load imposed by increased protein intake. High-protein diets have been proposed to increase exogenous acid load and to result in a chronic low-grade metabolic acidosis,[60,67,68] which may result in increased osteoclastic or decreased osteoblastic activity,[69] an increase in urinary calcium excretion, and a negative calcium balance.[70] This effect appears to be primarily due to animal proteins, which are higher in the acid-generating sulfur-based amino acids than in vegetable protein, and are thought to be the primary cause of increased calciuria.[59,62,71–77] The importance of sulfur-containing amino acids as the causative mechanism for urinary calcium loss is highlighted by direct comparisons with ingestion of soy protein that has relatively few sulfur-containing amino acids and does not induce hypercalciuria.[78] However, the total protein content of the diet was found to correlate strongly with sulfuric acid production, and correlations with animal protein content are only marginally stronger.[60]

By contrast with the relatively consistent data from short-term studies suggesting negative effects of high–animal protein intake on bone, long-term data from epidemiologic studies are conflicting. Some studies suggest that there is an increased risk of fractures or osteoporosis with increasing levels of dietary protein,[79–83] whereas other studies have observed a positive association between dietary protein intake and increased bone mineral content or decreased fracture risk.[84–86] Important issues that likely contribute to the apparent conflicting results include the age, menopausal status, and nutritional status of subjects. Undernutrition, which includes inadequate protein nutriture, appears to increase risk for osteopenia or fracture.[87] Conflicting results in part may also reflect differing levels of control for effects of other food groups or specific nutrients influencing bone health such as calcium, sodium, and other ions.[88–91] It is also possible that detrimental effects of a high–animal protein diet could be counterbalanced by consumption of foods (such as fruits and vegetables) or supplements high in either potassium or bicarbonate,[59,64,67,73,78,79,92] an effect presumably mediated by increased buffering capacity. There is additionally some evidence, albeit controversial,[93] that bone loss may be attenuated by appropriate calcium supplementation,[94,95] as well as by the higher phosphorus levels often found in high-meat diets.[62,96,97] Therefore, consumption of high-protein diets potentially has adverse effects on bone, especially when the majority of protein is from animal sources and when low intakes of acid-buffering foods such as fruits and vegetables are consumed. Further, the upper level of protein intake consistent with minimal adverse effects on bone has not been established, and the extent to which adverse effects may be minimized by choice of protein sources and dietary intake of potassium, bicarbonate, calcium, and phosphorus is not known.

Dietary Protein and Kidney Disease

In those with existing renal disease, limiting dietary protein to the RDA level rather than the typical protein intake of U.S. Americans (which is ≈50% greater than the RDA level[6]) is known to slow progression of disease[98] and is associated with a reduced mortality rate.[99] The mechanism by which reduced protein intake delays progression of renal disease is through reduced hyperfiltration, a well-described phenomenon seen early in many forms of renal disease.[98] The question of whether high-protein intake results in adverse effects in healthy persons without renal disease is not well established. Several studies have reported that high-protein intake causes hyperfiltration[61,76,100–102] up to a saturation point of approximately125 g/day.[102] However, *net* hyperfiltration (filtration expressed as a function of renal mass) did not occur when protein intake varied within the range of 70 to 108 g/day because higher protein intakes were associated with increased renal mass.[103] Other measures of renal function have provided inconsistent results. For example, one study observed a positive relationship between microalbuminuria and protein intake in older Caucasians without kidney disease,[104] whereas another study found no such relationship.[103] In evaluating renal clearances of creatinine, urea, and albumin, one study compared these parameters in body builders consuming high-protein diets with well-trained athletes consuming medium-protein diets and found no adverse consequences of protein intakes up to 2.8 g/kg.[105]

In a prospective study of greater than 45,000 men ages 40 to 75 years who were followed for more than 4 years, the intake of animal protein was directly associated with the risk of symptomatic kidney stone formation, or nephrolithiasis.[106] Protein intake has also been associated specifically with uric acid stones[75] and calcium stones.[107] Additionally, a recent trial investigated the effects of a reduced-protein (93 g/day) and reduced-sodium diet versus a reduced-calcium diet on recurrence of nephrolithiasis over 5 years,[108] and found reduced risk for recurrence with the lower-protein and lower-sodium diet. Protein intake data for the reduced-calcium diet are not provided, but differences in animal protein intake are suggested by urea excretion, which remained unchanged in that group but was reduced in the low-protein group. However, Hiatt et al.[109] compared the effects of dietary counseling to decrease protein intake with dietary counseling to consume the usual intake in a trial of individuals who had had calcium oxalate stones for the first time. The investigators found a relative risk of 5.6 of recurrent stones in the low-protein intervention group compared with the control group; however, they did note a greater fluid intake in the control group. Together these studies suggest that there is little clear evidence for adverse effects of high-protein diets on renal function in individuals without renal disease, but further longer-term studies are needed. However, the limited available evidence in conjunction with the effects described in those with renal disease suggests caution in at-risk populations, such as diabetics, those with evidence of renal disease, and patients with previously documented nephrolithiasis.

Dietary Protein and Cardiovascular Risk

Effects of dietary protein on such risk factors for cardiovascular disease as blood pressure and blood lipids have been proposed. However, Obarzanek et al.[110] reviewed the literature prior to 1996 and concluded that intervention studies generally demonstrated no association between blood pressure and dietary protein. One study[111] reviewed by Obarzanek et al. did report increased systolic blood pressure but the protocol was unusual, requiring vegetarians to switch to animal-protein diets for the study, and this may have influenced the results. In a separate weight loss protocol, a very-low-calorie (400 kcal/day) 100%-protein diet resulted in orthostatic hypotension, probably owing to the effects of ketosis and resultant dehydration.[31]

The effects of protein intake on blood lipids are controversial. Jenkins et al.[112] performed a carefully controlled 1-month study of a high–wheat protein diet (27%) compared with a control diet (16%) in hyperlipidemic subjects and found a significant decrease in serum triglycerides and oxidized low-density lipoprotein cholesterol on the high–wheat protein diet. However, other investigators studying dietary protein and weight loss[19,34] found no significant differences in lipid profiles between subjects consuming higher- versus lower-protein diets.

The above studies suggest little or no effect of protein on blood pressure and blood lipids. By contrast, epidemiologic studies have suggested beneficial effects of higher-protein diets on the cardiovascular system. Iso et al.[113] found that the risk for hemorrhagic stroke was increased in the lowest quintiles of animal protein intake in women even after controlling for energy intake and traditional cardiovascular risk factors (median animal protein intake: lowest quintile = 42.7 g/day, highest quintile = 81.6 g/day). Hu et al.[114] reported an inverse association between dietary protein (animal and vegetable) and the risk of ischemic heart disease in women without cardiovascular disease (median total protein intake: lowest quintile = 14.7%, highest quintile = 24.0%). The fact that epidemiologic associations appear to conflict with the short-term metabolic data suggests that the associations may be mediated by other dietary constituents that differ between high- and low-protein diets in individuals consuming self-selected diets, and further research on this issue is needed. It is also important to note that the ranges of protein intakes in the epidemiologic studies are, for the most part, well within the range of acceptable protein intake, and so do not provide support at the present time for high-protein diets and cardiovascular risk reduction.

Dietary Protein and Blood Glucose

The glycemic index (GI) is a well-described property of carbohydrate-containing foods that predicts the body's blood glucose response.[115] GI may be important in weight control efforts because it modulates hunger and satiety.[2] Because protein has a minimal short-term effect on blood glucose in comparison with carbohydrate, protein can be used in metabolic studies and weight loss efforts that strive to lower the GI of any particular diet. Although protein produces a lower blood glucose level than carbohydrate, it is known to produce an insulin response.[116] Nuttall et al.[117] found that consumption of 50 grams of animal protein in type 2 diabetics produced an equivalent insulin response to 50 grams of glucose. Protein and glucose together were found to have a synergistic effect on the insulin response in these subjects. However, in another study[118] this group found that in healthy subjects (non-diabetics) the insulin response to protein was attenuated by comparison with the response to glucose, and the two together produced only an additive effect. This agrees with the findings of Wolever and Bolognesi,[119] who noted that, in non-diabetics, varying protein in a mixed meal by ≈100% (11–20% of energy intake) did not have an important effect on the postprandial glucose and insulin response. Therefore, diabetics may be more sensitive to the effects of protein in meals. Indeed, Linn et al.[120] found that in adult-onset insulin-dependent diabetics, those who habitually ate a high-protein diet (1.87 $g \cdot kg^{-1} \cdot day^{-1}$) had an increase in glucose output and a decrease in insulin sensitivity by comparison with those who ate a lower-protein diet (0.74 $g \cdot kg^{-1} \cdot day^{-1}$). Weight-loss studies have shown variable responses to dietary protein in terms of glucose and insulin, including both improved insulin sensitivity with a high-protein diet[32] and no change in 2-hour postprandial blood glucose.[121]

Observational data provide mixed evidence for an association between the development of diabetes mellitus and protein intake. Several trials have found either no association[122,123] or a positive association[124–126] between animal or total protein intake and incident diabetes. However, it remains unclear whether results were attributable to protein or other dietary factors that varied with protein.

Thus, whereas consistent findings of insulin or glucose responses with high-protein diets are lacking in healthy subjects and in weight-loss trials, there is some evidence that in diabetics a high-protein diet may be detrimental to glucose control or insulin sensitivity. This concern, in addition to the potential for adverse renal consequences in this population (see previous section), should alert clinicians to consider avoiding the use of high-protein diets in their diabetic patients.

Dietary Protein and Cancer

Limited human intervention studies on the effect of dietary protein intake on cancer risk have been undertaken, with adverse effects of beef and pork on levels of oxidative DNA damage[127] and soy protein on breast lobular epithelium[128] being suggested. The results of these investigations are broadly consistent with the epidemiologic investigations suggesting a generally positive association between dietary protein and incidence of cancer,[129–140] although some other studies have found no association,[141–146] or even a negative association.[147–150] The question of whether these effects are attributable to protein per se or to other factors associated with meat consumption such as nitrosamines, the method of meat cooking, or saturated fat content has not been well established.

Summary

Dietary protein is the least studied macronutrient in weight loss, yet high-protein diets are widely recommended for weight loss in the popular press. Although there is evidence for short-term increases in satiety and thermogenesis and reduced energy intake, available data on body fat loss with ad libitum consumption of high-protein diets are limited. Specifically, there is currently only one published study documenting the effect of ad libitum consumption of a high-protein diet on body fat loss, although it is not clear how certain aspects of the study design (e.g., differences in variety between diets) may have affected the findings. Combined, the studies suggest that increased amounts of protein may enhance compliance with energy-restricted diets via decreasing hunger and increasing satiety, but the fixed–energy intake studies demonstrate that protein is not likely to have an impact on body composition or otherwise enhance weight loss.

Mounting evidence suggests that protein intakes in excess of two to three times the RDA may have harmful effects on calcium homeostasis and possibly bone mass, particularly if the protein comes primarily from animal sources and if attempts are not made to minimize bone calcium losses by buffering with other dietary elements such as potassium or bicarbonate. Additional potential harmful effects of high-protein intake on kidneys, the cardiovascular system, and carcinogenesis have been suggested but available data remain inconclusive. Current recommendations on the safety of high-protein diets should therefore emphasize the need for more research and should consider recommendations focused on avoidance of high-protein diets for those individuals most at risk of potential adverse effects.

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