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The role of protein in weight loss and maintenance[1–5]

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ABSTRACT

Over the past 20 y, higher-protein diets have been touted as a successful strategy to prevent or treat obesity through improvements in body weight management. These improvements are thought to be due, in part, to modulations in energy metabolism, appetite, and energy intake. Recent evidence also supports higher-protein diets for improvements in cardiometabolic risk factors. This article provides an overview of the literature that explores the mechanisms of action after acute protein consumption and the clinical health outcomes after consumption of long-term, higher-protein diets. Several meta-analyses of shorter-term, tightly controlled feeding studies showed greater weight loss, fat mass loss, and preservation of lean mass after higher-protein energy-restriction diets than after lower-protein energy-restriction diets. Reductions in triglycerides, blood pressure, and waist circumference were also reported. In addition, a review of the acute feeding trials confirms a modest satiety effect, including greater perceived fullness and elevated satiety hormones after higher-protein meals but does not support an effect on energy intake at the next eating occasion. Although shorter-term, tightly controlled feeding studies consistently identified benefits with increased protein consumption, longer-term studies produced limited and conflicting findings; nevertheless, a recent meta-analysis showed persistent benefits of a higher-protein weight-loss diet on body weight and fat mass. Dietary compliance appears to be the primary contributor to the discrepant findings because improvements in weight management were detected in those who adhered to the prescribed higher-protein regimen, whereas those who did not adhere to the diet had no marked improvements. Collectively, these data suggest that higher-protein diets that contain between 1.2 and 1.6 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1} and potentially include meal-specific protein quantities of at least $\sim$25–30 g protein/meal provide improvements in appetite, body weight management, cardiometabolic risk factors, or all of these health outcomes; however, further strategies to increase dietary compliance with long-term dietary interventions are warranted. *Am J Clin Nutr* doi: 10.3945/ajcn.114.084038.

Keywords: appetite control, compliance, high protein, satiety, weight management

INTRODUCTION

Substantial evidence exists that supports the consumption of increased dietary protein (ranging from 1.2 to 1.6 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1}) as a successful strategy to prevent or treat obesity through reductions in body weight and fat mass concomitant with the preservation of lean mass (1–4). The effectiveness of these diets may be due, in part, to modulations in energy metabolism and appetitive signaling leading to reduced energy intake. Furthermore, improvements in cardiometabolic risk factors were also observed with higher-protein diets (1–4). However, one point of contention is the feasibility of adhering to a higher-protein diet for periods >1 y (5, 6).

The purpose of this article is to provide an overview of the literature that explores the mechanisms of action after acute protein consumption and the clinical health outcomes after long-term, higher-protein diets. Acceptability and compliance to the chronic consumption of increased dietary protein are also considered. Last, novel recommendations for protein quantity and timing of consumption to achieve improvements in weight management are discussed.

MECHANISTIC OUTCOMES WITH ACUTE PROTEIN CONSUMPTION

Thermic effect of food and resting energy expenditure

Higher-protein diets have been promoted to increase energy expenditure through increased postprandial thermogenesis

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and resting metabolism. In general, dietary protein requires 20–30% of its usable energy to be expended for metabolism and/or storage, whereas carbohydrates require 5–10% and dietary fats require 0–3% (7). Previous reviews confirmed that dietary protein consistently elicits a greater postprandial thermic effect of food (TEF)[6] than do carbohydrates or fats (8, 9). Furthermore, in a recent meta-analysis, protein intake was shown to be positively associated with TEF after adjustment for covariates ($r = 0.43$, $P = 0.009$), such as sex, caffeine intake, and dinner energy intake (10). Although differences in TEF are evident after the consumption of lower- compared with higher-protein meals, the actual energy differential is modest, highly variable, and difficult to quantify, and hence, probably has minimal impact on weight loss and weight maintenance.

During weight loss, higher-protein diets also prevent a decline in resting energy expenditure (REE) (8, 9). Wycherley et al. (11) evaluated 24 randomized controlled trials comparing higher- with lower-protein energy-restricted diets. Of the 24 studies, only 4 included REE analysis. Although both diets reduced REE, the higher-protein diets led to a greater preservation of REE [mean difference (MD): +142 kcal/d; 95% CI: 16, 269 kcal/d; $P < 0.03$] (11). The mechanism by which dietary protein preserves REE during energy restriction is likely due to the concomitant retention of lean mass observed with higher-protein diets (discussed in subsequent sections) (11). These data show a significant positive effect of increased protein consumption on energy metabolism.

Appetite

There are 2 dimensions to proteins effects on appetitive sensations. First, there may be a protein-specific appetite originating from the hypothesized homeostatic regulation of dietary protein to meet bodily needs/requirements. Second, dietary protein has stronger nonspecific satiety properties than do dietary fat or carbohydrates (12, 13), which may lead to reductions in daily energy intake (14, 15).

Protein-specific appetite

A protein-specific appetite purportedly exists to maintain protein requirements and to prevent excess protein consumption (16). This concept is summarized by the protein leverage hypothesis, which suggests that a protein-specific appetite will stimulate the drive for increased food intake when the protein density of the diet is limited but will reduce intake of diets with higher protein density (17). This hypothesis suggests a mechanism linking dietary protein intake and energy balance. There have been 3 direct tests of the hypothesis.

Gosby et al. (17) completed a randomized crossover study involving three 4-d ad libitum diets containing 10%, 15%, or 25% of energy as protein. When the protein content of the diet was lowered from 15% to 10%, daily energy intake increased by 12 ± 4.5% (+259 kcal/d; $P < 0.05$). However, despite the additional energy consumed, dietary protein remained lower than what was consumed in the 15% diet (−3% of energy, −75 g protein over 4 d). When the protein content of the diet increased from 15% to 25%, energy intake remained unchanged. By using a similar design, Martens et al. (18) compared 12-d ad libitum diets consisting of 5%, 15%, or 30% of intake as protein. No change in energy intake was observed between the 5% and 15% protein diets; however, energy intake was lower (−576 ± 103 kcal/d) after the 30% than after the 15% protein diet (18). In a second trial of comparable design, this group used a different predominant protein source (beef compared with soy or whey with α-lactalbumin) and obtained similar results (19). Thus, whereas the Martens et al. trials confirmed the satiety value of protein, no study in humans has tested and shown the convergence of protein intake from diets with higher and lower relative protein content. Whether the time course of these trials was adequate to observe an effect is unclear. In a recent analysis of 38 ad libitum feeding trials, the percentage of dietary protein was negatively associated with total daily energy intake ($F = 6.9$, $P < 0.0001$). This observation was noted only when protein intakes were between 10% and 20%, and anything above this amount resulted in no further reductions in daily intake. Taken together, there is some evidence that supports the concept of protein-specific appetite; however, the data are inconclusive for the protein-leverage hypothesis because no single study has reported data supporting both sides of the protein leverage.

Nonspecific appetite

Ingestive behavior is a complex system composed of homeostatic, hedonic (i.e., reward), and behavioral/environmental inputs. Clarification of the interactions between these drivers is just beginning to emerge. From 2000 to the present, much has been learned about the peripheral hormonal signals and central targets that influence energy intake (20–22). Dietary protein is an effective stimulus for the release or inhibition of many of these peptides (23–25). Ghrelin reportedly enhances hunger, initiates eating, and increases energy intake (26–28). The responsiveness of ghrelin release to specific nutrients is still under study, but there is evidence of an effect of protein (25, 29). Peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) are associated with satiety and reduce subsequent food intake (23, 24). Both PYY and GLP-1 are stimulated by the ingestion of various dietary components, particularly dietary protein (23, 24, 30). There is also evidence of a dose-response relation between protein quantity and the magnitude of PYY and GLP-1 responses (30).

Importance of satiety

There is substantial industry and consumer interest to identify specific foods, diets, or both that lead to enhanced satiety as a mechanism to promote healthy eating and improved weight management (31). One popular dietary strategy is to increase the consumption of dietary protein. Although the data are not fully consistent, compared with dietary carbohydrates or fats, the consumption of protein has stronger satiety effects (12, 32). Higher-protein ad libitum diets have led to unintentional weight

[6] Abbreviations used: Diogenes, Diet, Obesity and Genes; GLP-1, glucagon-like peptide 1; MD, mean difference; PYY, peptide YY; REE, resting energy expenditure; TEF, thermic effect of feeding; VLCKD, very-low-carbohydrate (ketogenic) diet; WMD, weighted mean difference.

loss caused from reductions in daily energy intake, which may have occurred as a result of increased satiety (14, 15).

A challenge with this line of research is determining the "best" index of satiety (or overall appetite) (33, 34). Although postprandial appetitive sensations and hormonal responses are associated with and may lead to alterations in subsequent energy intake (23, 24, 35–38), they do not consistently track with each other. More work is needed to identify the most important indexes of appetite (hunger, satiety) and associated markers (appetitive sensations, gut hormones) for weight management over the long term.

APPETITE AND SUBSEQUENT FOOD INTAKE AFTER HIGHER-PROTEIN MEALS

Despite the large number of randomized, acute meal, crossover-design studies published over the past 20 y, to our knowledge, there are no systematic reviews or meta-analyses to date comparing the effects of normal-protein with higher-protein meals on markers of appetite, satiety, and subsequent food intake. Thus, as a first step in summarizing the existing data, the following inclusion criteria were applied to the existing literature: *1*) acute feeding trials of ≥120 min; *2*) comparison of lower-fat (<40% of meal as fat), isocaloric normal-protein with higher-protein mixed meals with a protein differential of ≥10 g protein between meals; and *3*) repetitive, postprandial assessments of appetitive sensations, hormonal responses, and/or subsequent food intake. Twenty-four studies met the criteria and are summarized in **Table 1**.

Only 6 (35%) reported greater reductions in postprandial hunger after the higher-protein meals than after the lower-protein meals, whereas 11 (55%) showed significant increases in postprandial fullness. Seven (37%) reported greater reductions in postprandial ghrelin, and 7 (47%) showed a greater increase in either PYY or GLP-1. Although the majority of these studies (17 of 24; 71%) reported at least one beneficial alteration in appetite indexes after higher- than after lower-protein meals, only 3 studies (18%) observed a reduction in subsequent food intake at the next eating occasion. Although the positive findings were inconsistent across studies, it is important to note that none of the studies reported a weakening in appetite control or increased subsequent meal energy intake after the higher-protein meals compared with the lower-protein meals. Restated, the studies found either improvements with higher-protein meals or no differences between the meals. Several dietary factors might have contributed to the inconsistent results.

The consumption of beverages generally elicits a weaker satiety response and less dietary compensation at the next eating occasion in comparison with solid foods (58, 59). This effect was also observed when dietary protein was consumed in a beverage instead of consumed in solid form (60, 61). Thus, it is possible that the blunted satiety response from beverages might ameliorate protein-related effects. Of the 24 studies examined, 3 included beverages; however, 5 studies (45, 47, 50–52) incorporated semisolids (e.g., custards, yogurts), which might have also obscured the findings.

Protein quality (source) varied within and across studies. Although the impact of protein quality on appetite control and food intake is poorly characterized, there are data, albeit inconsistent, that show protein-source effects. In some (62, 63), but not all (64–66), studies the consumption of whey protein elicited a greater reduction in postprandial hunger and a greater increase in postprandial satiety than consumption of casein and/or soy. The contribution of protein quality on these outcomes is further supported by the Veldhorst et al. (50, 51) studies that compared higher- with lower-protein meals but included different types of protein. In one study, greater reductions in postprandial ghrelin and increases in postprandial fullness and GLP-1 responses were observed after the higher-protein whey meals than after the lower-protein whey meals, whereas the second study found no differences in postprandial ghrelin or GLP-1 concentrations after the higher-protein casein meals when compared with the lower-protein casein meals. Because many studies incorporated a mixture of proteins and typically vary these proteins within and between the lower- and higher-protein meals, it is difficult to determine the actual contribution of protein quantity due to the protein quality effects.

Another confounding factor concerns the potential for a protein quantity threshold effect. Several articles reported a specific meal-related protein threshold of ~25–30 g protein that is necessary to stimulate protein synthesis (67–69). Whether a similar threshold exists for satiety is not known. As shown in Table 1, the quantity of protein included within the higher-protein meals ranges from 20 to 207 g/meal. However, all but 2 of the studies included protein quantities well above the 25–30-g protein synthesis threshold. Because of the varied experimental designs and the few studies that contained lower protein quantities, it is not possible to accurately perform a breakpoint analysis. Nonetheless, neither of the studies that included <25 g protein had a satiety effect. Although preliminary, data from several of Leidy's previously published acute trials (70) permit comparison of 15, 20, 25, and 30 g protein/meal interventions. Postprandial fullness was significantly higher after a 30-g protein meal than after the other lower-protein versions (70) and provides support for a potential satiety threshold at this quantity. Future dose-response research including smaller quantities of protein is needed to identify an absolute protein threshold specific to satiety.

The last discussion focuses on whether there is a ceiling effect for dietary protein such that additional protein consumption in a meal is not accompanied by further increases in satiety. The most appropriate study to address this point is that of Belza et al. (30), which observed dose-dependent increases in postprandial fullness, GLP-1, and PYY responses and decreased postprandial hunger and ghrelin responses after the consumption of 24, 44, and 88 g protein/meal. Several other studies (13, 40) compared even larger quantities of protein (i.e., 58 compared with 185 g; 46 compared with 178 g) and found graded appetitive responses with the higher-protein versions (Table 1). Although these study designs do not allow for a direct examination for a protein ceiling, it is clear that fairly large ranges of protein quantity elicit graded satiety effects after a meal.

In general, these data confirm a modest satiety effect with protein-rich meals but do not support an effect on energy intake at the next eating occasion. Because most of these studies did not assess changes in daily energy intake, it is unclear as to whether the satiety effects of protein might affect eating behavior across the entire day or beyond. A recent trial examined the effects of a higher-protein breakfast on daily intake in habitual breakfast-skipping young adults (55). Compared with a lower-protein

TABLE 1
Summary of the tightly controlled acute feeding trials comparing lower- with higher-protein meals[1]

	Acute meals							Perceived sensations, (%)		Hormonal responses, (%)			
	Lower-protein		Higher-protein										
First author, year (reference)	Protein, g	Protein source	Protein, g	Protein source	Energy, kcal	Meal type	Postprandial period, min	Hunger	Fullness/ satiety	Ghrelin	PYY	GLP-1	Subsequent meal energy content, (kcal)
Stubbs, 1999 (39)	66	Plant	207	Animal	1400	Solid	120	↓ (45)	↑ (10)	—	—	—	Ø
Stubbs, 1996 (40)	58	Mixed	185	Mixed	1400	Solid	240	Ø	↑ (10)	—	—	—	Ø
Batterham, 2006 (13)	46	Mixed	178	Mixed	1100	Solid	180	↓ (58)	—	Ø	↑ (21)	Ø	—
Brennan, 2012 (41)	28	Mixed	127	Mixed	1130	Solid	180	↓ (37)	↑ (49)	↓ (28)	Ø		↓ (148)
Foster-Schubert, 2008 (25)	13	Dairy (no eggs, whey)	100	Mixed	500	Beverage	180	Ø	Ø	↓ (38)	—	—	—
Belza, 2013 (30)	24	Mixed	88	Mixed	700	Solid	240	↓ (25)	↑ (19)	↓ (10)	↑ (14)	↑ (20)	Ø
Barkeling, 1990 (42)	16	Plant	64	Animal	600	Solid	240	Ø	Ø	—	—	—	↓ (38)
van der Klaauw, 2013 (43)	20	Mixed (no pork)	60	Mixed	400	Solid	240	Ø	Ø	Ø	↑ (28)	↑ (20)	Ø
Boelsma, 2010 (44)	17	Whey	59	Whey	675	Beverage	240	Ø	Ø	↓ (4)	—	—	Ø
Blom, 2006 (45)	19	Dairy	57	Dairy	400	Semisolid	180	Ø	Ø	↓ (45)	—	↑ (66)	Ø
El Khoury, 2010 (46)	14	Mixed	55	Mixed	550	Beverage	240	—	—	Ø	Ø	—	—
Vozzo, 2003 (47)	25	Dairy	51	Dairy	700	Semisolid	180	Ø	—	—	—	—	Ø
Leidy, 2010 (48)	26	Mixed (no pork, eggs)	46	Mixed	700	Solid	600	Ø	↑ (6)	Ø	↑ (20)	—	—
Leidy, 2010 (49)	26	Mixed	46	Mixed	500	Solid	240	—	Ø	Ø	Ø	—	↓ (131)
Belza, 2013 (30)	24	Mixed	44	Mixed	700	Solid	240	↓ (15)	↑ (6)	Ø	↑ (7)	↑ (10)	Ø
Veldhorst, 2009 (50)	15	Whey	38	Whey	600	Semisolid	240	—	↑ (12)	↓ (38)	—	↑ (60)	Ø
Veldhorst, 2009 (51)	15	Casein	38	Casein	600	Semisolid	240	—	↑ (36)	Ø	—	Ø	Ø
Veldhorst, 2009 (52)	15	Soy	38	Soy	600	Semisolid	240	—	↑ (36)	Ø	—	Ø	Ø
Al Awar, 2005 (53)	20	Dairy	36	Dairy	400	Solid	180	—	—	Ø	—	—	—
Smeets, 2008 (54)	14	Pork	35	Pork	350	Solid	180	—	↑ (10)	Ø	Ø	Ø	—
Leidy, 2013 (55)	13	Mixed (no beef, eggs)	35	Mixed	350	Solid	480	Ø	↑ (9)	Ø	Ø	—	Ø
Leidy, 2007 (29)	17	Mixed (no pork)	28	Mixed	400	Solid	195	↓ (17)	Ø	↓ (8)	—	—	—
Makris, 2011 (56)	12	Mixed	24	Mixed	350	Solid	240	Ø	Ø	—	—	—	Ø
Karhunen, 2010 (57)	3	Plant	20	Plant	300	Solid	120	Ø	Ø	Ø	Ø	Ø	Ø

[1] n = 24 studies. Higher-protein compared with lower-protein meals: ↑, increased; ↓, reduced; Ø, no difference; —, not assessed. GLP-1, glucagon-like peptide 1; PYY, peptide YY.

breakfast, the higher-protein version led to less energy consumed throughout the day, particularly from high-fat/high-sugar evening snacks (55).

CLINCIAL OUTCOMES WITH CONTROLLED HIGHER-PROTEIN DIETS OF ≤1 y

Three recent meta-analyses examined the effects of higher-protein diets on body weight management and cardiometabolic outcomes. As previously described, Wycherley et al. (71) performed a meta-analysis with 24 tightly controlled feeding trials that compared higher-protein with lower-protein energy-restriction diets of 12 ± 9 wk in duration. It included 1063 overweight and obese individuals between 18 and 80 y of age. The higher-protein diets contained between 27% and 35% of daily energy intake as protein (1.07–1.60 g protein · kg^{-1} · d^{-1}), whereas the lower-protein diets contained 16–21% protein (0.55–0.88 g protein · kg^{-1} · d^{-1}) (71). Despite a similar energy deficit, the higher-protein diets led to greater weight loss (MD: −0.79 kg; 95% CI: −1.50, −0.08 kg; $P < 0.03$) and fat loss (MD: −0.87 kg; 95% CI: −1.26, −0.48 kg; $P < 0.001$) compared with the lower-protein diets (71). The higher-protein diets also preserved more lean mass during energy restriction than did the lower-protein diets (MD: +0.43 kg; 95% CI: 0.09, 0.78 kg; $P < 0.01$) (71). Although fasting glucose, fasting insulin, blood pressure, and total, LDL, and HDL cholesterol were not different between diets, fasting triglycerides were lower in the higher-protein diets than after the lower-protein diets (MD: −0.23 mmol/L; 95% CI: −0.33, −0.12 mmol/L; $P < 0.0001$).

Similar findings were reported in a meta-analysis in individuals with type 2 diabetes (4). Nine controlled-feeding studies of 4–24 wk in duration with 418 participants were analyzed (4). The higher-protein diets contained between 25% and 32% of energy as protein, whereas the lower-protein diets contained 15–20% of energy as protein. Compared with the lower-protein diets, the higher-protein versions led to greater weight loss (MD: −2.08 kg; 95% CI: −3.25, −0.90 kg; $P < 0.05$), greater reductions in glycated hemoglobin concentrations (MD: −0.52%; 95% CI: −0.90%, −014%; $P < 0.05$), and greater reductions in systolic and diastolic blood pressure [MD (95% CI): −3.13 (−6.58, −0.32) mm Hg ($P < 0.05$) and −1.86 (−4.26, −0.56) mm Hg ($P < 0.05$), respectively].

Last, Santesso et al. (72) extended these findings to include both energy restriction and ad libitum feeding studies in adults who varied in age, health status, and daily energy intake. In this meta-analysis, 74 randomized controlled trials were included comparing higher-protein (16–45% of energy intake as protein) with lower-protein (5–23% of energy intake as protein) diets. The higher-protein diets led to greater weight loss (MD: −0.36 kg; 95% CI: −0.56, −0.17 kg; $P < 0.001$), greater reductions in BMI (in kg/m^2; MD: −0.37; 95% CI: −0.56, −0.19; $P < 0.001$), and greater reductions in waist circumference (MD: −0.43 cm; 95% CI: −0.69, −0.16 cm; $P < 0.001$) than the lower-protein diets.

The magnitude of change in many of these outcomes is modest but holds possible clinical relevance in light of the increased prevalence of obesity, type 2 diabetes, metabolic syndrome, and sarcopenia in the elderly. However, these benefits may be realized only if the increase in actual protein intake or the increased percentage of protein consumed within the diet can be sustained over the long term.

CLINICAL OUTCOMES WITH LONG-TERM HIGHER-PROTEIN DIETS OF ≥1 y

One critical aspect of body weight management is the prevention of weight regain after weight loss. This section discusses the current, but limited, evidence exploring whether increased dietary protein is a significant factor for long-term success with weight loss and the prevention of weight regain. Cardiometabolic risk factors are also considered.

The first comparisons include chronic very-low-carbohydrate (ketogenic) diets (VLCKDs) because these diets typically contain either higher protein content or a higher percentage of protein within the diet (even if the absolute amount remains unchanged). Bueno et al. (73) completed a meta-analysis comparing long-term (>12 mo), conventional, low-fat customary-protein diets (10–15% of intake as protein) with VLCKDs. The VLCKDs contained ∼20% of intake as protein. Thirteen studies were included in the meta-analysis. Compared with conventional low-fat diets, VLCKDs led to greater weight loss [weighted MD (WMD): −0.91 kg; 95% CI: −1.65, −0.17 kg; $P = 0.02$] and improvements in fasting triglycerides (WMD: −0.18 mmol/L; 95% CI: −0.27, −0.08 mmol/L; $P < 0.001$), HDL cholesterol (WMD: +0.09; 95% CI: +0.06, +0.12 mmol/L; $P < 0.001$), and diastolic blood pressure (WMD: −1.43 mm Hg; 95% CI: −2.49, −0.37 mm Hg; $P = 0.008$) (73). These data are consistent with a view that increased dietary protein, within the context of very-low-carbohydrate and high-fat intakes, improves weight management, reduces cardiometabolic risk factors, and might aid in the treatment of obesity and other disease states over the long term. However, adherence to these diets is quite low as evidenced by the ∼40% dropout rate, the specific role of protein is uncertain, and the high-fat, low-carbohydrate regimen does not coincide with current dietary guidelines and may not be appropriate for all ages, populations, and disease states (73).

Schwingshackl and Hoffmann (74) performed a meta-analysis to examine the effects of low-fat (<30% of intake as fat) diets containing either higher protein (>25% of intake as protein) or lower protein (<20% of intake as protein) on long-term changes in body weight, body composition, and cardiometabolic risk factors. The diets in this meta-analysis were very similar to those in Wycherley et al. (71) but included ≥12 mo of follow-up. No differences in weight loss, fat mass loss, or reductions in waist circumference were observed between diets. No differences in total, LDL, or HDL cholesterol or triglycerides were detected (74).

Recently, Clifton et al. (75) performed a more comprehensive meta-analysis that included 32 studies in 3492 individuals of >12 mo in duration that contrasted weight-loss diets that differed in the percentage of protein. VLCKDs and low-fat diets were permitted and outcomes consisted of changes in body weight and body composition as well as in fasting glucose, insulin, and lipid concentrations. A recommendation to consume a lower-carbohydrate, higher-protein diet was associated with better weight loss, compared with lower-protein diets, but the effect size was small (standardized MD: −0.14; 95% CI: −0.24, −0.04 ; $P = 0.008$). Although lean mass did not differ between diets, fat mass losses were greater after the higher-protein diets

(standardized MD: −0.22; 95% CI: −0.33, −0.11; $P < 0.001$). These effects are equivalent to a difference of ∼0.4 kg. A difference of ≥5% in protein intake between diets at 12 mo was associated with a 3-fold greater reduction in fat mass compared with <5% (0.9 compared with 0.3 kg; $P = 0.038$). Triglyceride and insulin concentrations were also lower after the higher-protein diets.

Last, although the previous meta-analyses do not include the findings from the Diet, Obesity and Genes (Diogenes) Study, it is the largest trial to date comparing lower- with higher-protein diets for weight-loss maintenance and thus merits specific discussion (76–78). This pan-European multicenter trial included 938 adults and 253 children (from the adults in the study). The parents completed an initial 8-wk energy-restriction period. In those families in which at least one parent lost 8% of their initial body weight (average: −11.0 kg), the parents and children then completed 26 wk of weight maintenance with either a higher-protein (25% of intake as protein) or lower-protein (13% of intake as protein) ad libitum diet (76, 77). Glycemic index was also included within these diets but is not included in this discussion. In the adults who completed the study, the higher-protein diet led to less weight regain (MD: −0.93 kg; 95% CI: −0.31, −1.55 kg; $P = 0.003$) than the lower-protein diet did (66). The children who followed the higher-protein regimen had reductions in waist circumference (−2.7 cm; 95% CI: 0.9, 5.1 cm; $P < 0.007$) and LDL cholesterol (−0.25 mmol/L; 95% CI: 0.09, 0.41 mmol/L; $P < 0.007$) compared with those following the lower-protein version (78). Collectively, these data suggest that a modest increase in dietary protein leads to long-term maintenance of weight loss and/or improvements in cardiometabolic risk factors in adults and young people.

LIMITATIONS

There was variability in the dropout rates across the studies included in the meta-analyses (ranging from 7% to 55%; average: 30 ± 12%). This contributed to large amounts of missing data, and only approximately half of these studies reported intention-to-treat analyses along with completer results. These factors contributed to a high risk of bias in the interpretation of data (74).

In addition, regardless of the protein content of the diets, most of the studies showed poor compliance with the prescribed diets. According to the dietary food records collected in most of the studies, no groups met their prescribed protein content for either diet. The higher-protein diet groups reduced their protein content throughout the study, whereas the lower-protein diet groups increased their protein content, both potentially returning back to their habitual protein intakes at baseline (74). This led to several studies having similar protein contents between diets (79–82). The lack of protein differential between diets was also supported by the validated urinary biomarker data, particularly urinary nitrogen, urea, or the urea:creatinine ratio from 24-h urine collections (83) measured in 9 of the 15 studies included in the Schwingshackl and Hoffmann meta-analysis (74) and 8 of the 32 in the Clifton et al. meta-analysis (75). However, although the participants in these studies were unable to reach the prescribed protein content, the Diogenes study (76, 77) and the Clifton et al. meta-analysis (75) indicated that only an absolute difference in protein intake of 5% was required for a clinically significant effect on weight management.

COMPLIANCE WITH HIGH-PROTEIN DIETS

There are myriad behavioral and environmental factors that contribute to the lack of compliance with and/or adherence to dietary (protein) interventions (84). One factor that is strongly associated with weight loss and prevention of weight regain is attendance to dietary counseling sessions (5). This might be even more critical with higher-protein diets (5). For example, Layman et al. (85) incorporated weekly dietary counseling sessions over a 12-mo period and reported a lower dropout rate in the higher-protein group (36%) than in the lower-protein group (55%). Furthermore, those who completed the study attended 75% of the counseling sessions (85).

The incorporation of family-based dietary strategies also improved adherence to long-term higher-protein diets. As shown in the Diogenes studies (76–78), the parents exhibited relatively low dropout rates, regardless of protein intake; however, the higher-protein diet group had a lower dropout rate than the lower-protein diet group (26% compared with 37%; $P = 0.02$).

Another point is whether increased protein consumption reduces acceptability to diets over the long term. Several studies refute this argument by reporting greater overall satisfaction (i.e., greater palatability, pleasure, enjoyment) and/or motivation with higher-protein diets than with lower-protein diets (42, 86, 87). Although not definitive, potential reasons for the increased acceptability may be due to the satiating effects of protein and anticipated improvements in body weight management (31).

As described above, the lack of adherence to higher-protein diets is typically attributed to behavioral and/or environmental factors. However, the return of protein intakes to habitual quantities has been postulated to be due to a physiologic (nutritional) regulation of protein intake, as proposed by the protein leverage hypothesis previously discussed (17). Although this concept is worth exploring, the existing evidence from high-quality studies in humans fails to support the protein leverage hypothesis (17–19).

PROTEIN QUANTITY

The last remaining question is "How much protein is required to elicit the improvements in body weight management?" The meta-analyses including shorter-term energy restriction and longer-term weight maintenance studies indicate that the quantity of protein necessary to promote improved weight management and cardiometabolic outcomes lies somewhere between 1.2 and 1.6 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1} (which is ∼89–119 g protein/d for women or 104–138 g protein/d for men) (86, 88). However, recent evidence suggests that lower protein quantities (i.e., 0.8 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1}) during energy restriction might be sufficient for body weight and fat mass losses, whereas higher protein quantities (i.e., 1.2 g protein $\cdot$ kg^{-1} $\cdot$ d^{-1}) are required for the preservation of lean mass (89).

To further support a specific protein quantity that is required to elicit improvements in weight management, Bosse and Dixon (90) categorized 25 higher-protein weight-loss studies on the

basis of those who showed successful weight loss compared with those who did not. The change in protein intake (from habitual intake) was compared between groups. An average increase in protein consumption of 28.6% g protein · kg^{-1} · d^{-1} beyond habitual protein intake was needed to elicit significant weight loss (90). Thus, if habitual protein intake in US adults (ages 19–70 y) is, on average, 88 g/d (1.07 g protein · kg^{-1} · d^{-1}), then the addition of only ~25–30 g protein/d [up to 113–118 g/d (~1.38 g protein · kg^{-1} · d^{-1})] would potentially be sufficient to elicit long-term improvements in weight management (90). In addition, under isoenergetic conditions, the increase in protein appears to be the critical component, not the reduction in carbohydrates or fat (91).

The protein quantities proposed above are within the acceptable macronutrient range for protein and allow for the ability to meet the dietary guidelines for other requirements including fruit, vegetables, dairy, and fiber. However, a 2-y study by Jesudason et al. (92) prescribed a 20-g increase in protein intake but achieved a difference of only 16 g/d at 1 y and 13 g/d at 2 y, suggesting a 25–30-g/d increase might be a difficult target to sustain over the long term.

Last, although the current dietary guidelines state the recommendations in terms of daily protein intake, the mechanistic data, particularly with regard to energy metabolism, protein synthesis, and appetite control, examine meal-specific quantities, not daily intake. In these studies, ~25–30 g protein/eating occasion was required to elicit protein-related benefits (29, 55, 67–69). Theoretically, if 4 meals containing 25–30 g protein/meal are consumed throughout the day, the total amount of protein would equate to the quantities shown to elicit body weight/body composition changes described above. Although many Americans consume ≥25 g protein at lunch and dinner, the average consumption of protein at breakfast is well under the 25-g quantity (93). There is evidence that supports unique benefits with increased protein consumption at breakfast for improved satiety and reductions in unhealthy snacking in the evening (55, 94). Future research that explores meal-specific protein quantity and timing of consumption is warranted.

CONCLUSIONS

Higher-protein diets that contain between 1.2 and 1.6 g protein · kg^{-1} · d^{-1} and potentially include meal-specific protein quantities of at least ~25–30 g protein/meal provide improvements in appetite, body weight management, and/or cardiometabolic risk factors compared with lower-protein diets (**Table 2**). Although greater satiety, weight loss, fat mass loss, and/or the preservation of lean mass are often observed with increased protein consumption in controlled feeding studies, the lack of dietary compliance with prescribed diets in free-living adults makes it challenging to confirm a sustained protein effect over the long term.

The authors' responsibilities were as follows—All of the authors participated in Protein Summit 2.0 and were involved in the writing and editing of the manuscript; HJL: developed the draft of the manuscript; HJL, PMC, AA, TPW, MSW-P, NDL-M, SCW, and RDM: reviewed and revised the manuscript accordingly; and all authors: substantially contributed to the completion of the manuscript and read and approved the final version. HJL has current funding from The Beef Checkoff, Egg Nutrition Center, and DuPont Nutrition & Health. She is also on the speaker's bureau for the National Cattlemen's Beef Association. PMC has conducted protein-related research funded by Meal and Livestock Australia and Dairy Australia and published a number of high-protein cookbooks. AA is a consultant/member of advisory boards for the Dutch Beer Knowledge Institute, Global Dairy Platform, Jenny Craig, McCain Foods Ltd, McDonald's, and the Gerson Lehrman Group (ad hoc consultant for clients). He is a recipient of honoraria and travel grants as speaker for a wide range of Danish and international concerns. He has conducted research funded by a number of organizations with interests in the food production and marketing sector. TPW, MSW-P, NDL-M, SCW, and RDM had no conflicts of interest to report. None of the

TABLE 2
Summary of review

Conclusions	Limitations and/or gaps in the current literature
• Higher-protein energy-restriction diets lead to greater weight loss, fat mass loss, and preservation of lean mass along with greater improvements in select cardiometabolic health outcomes, over the shorter term, compared with lower-protein diets. Potential mechanisms of action include the marginal increase in thermogenesis and satiety after the consumption of protein-rich meals.	• Research is needed to examine whether the satiety effects of protein promotes voluntary reductions in energy intake and improved body weight management over the long term.
• Although the long-term data are less consistent, persistent effects of increased protein consumption are evident with respect to weight maintenance and/or the prevention of weight re(gain).	• Dietary compliance appears to be the primary contributor to discrepant findings related to energy balance because improvements in weight management were detected in those who adhered to the prescribed higher-protein regimen, whereas those who did not adhere to the diet had no marked improvements. • Future long-term research including family-based interventions with dietary counseling and meal-specific quantities of protein are warranted.
• Higher-protein diets that contain between 1.2 and 1.6 g protein · kg^{-1} · d^{-1} and potentially include meal-specific protein quantities of at least ~25–30 g protein/meal provide improvements in appetite, body weight management, and/or cardiometabolic risk factors.	• Future research exploring meal-specific protein quantity and timing of consumption are warranted.

sponsors were involved in the design, implementation, analysis, or interpretation of data.

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