Controversies Surrounding High-Protein Diet Intake: Satiating Effect and Kidney and Bone Health[1,2]

Marta Cuenca-Sánchez,[3] Diana Navas-Carrillo,[4] Esteban Orenes-Piñero[3]*

[3]Department of Biochemistry and Molecular Biology–A, Murcia Biomedical Research Institute, University of Murcia, Campus of Lorca, Lorca, Spain; and [4]Department of Surgery, Hospital de la Vega Lorenzo Guirao, University of Murcia, Murcia, Spain.

ABSTRACT

Long-term consumption of a high-protein diet could be linked with metabolic and clinical problems, such as loss of bone mass and renal dysfunction. However, although it is well accepted that a high-protein diet may be detrimental to individuals with existing kidney dysfunction, there is little evidence that high protein intake is dangerous for healthy individuals. High-protein meals and foods are thought to have a greater satiating effect than high-carbohydrate or high-fat meals. The effect of high-protein diets on the modulation of satiety involves multiple metabolic pathways. Protein intake induces complex signals, with peptide hormones being released from the gastrointestinal tract and blood amino acids and derived metabolites being released in the blood. Protein intake also stimulates metabolic hormones that communicate information about energy status to the brain. Long-term ingestion of high amounts of protein seems to decrease food intake, body weight, and body adiposity in many well-documented studies. The aim of this article is to provide an extensive overview of the efficacy of high protein consumption in weight loss and maintenance, as well as the potential consequences in human health of long-term intake. *Adv Nutr* 2015;6:260–266.

Keywords: high-protein diet, weight loss, bone health, kidney dysfunction, satiety

Introduction

The protein content of a diet can be considered in terms of the absolute amount consumed, the proportion of total energy intake, or the amount of protein per body weight. High-protein diets are used for weight loss and maintenance, muscle hypertrophy, and postexercise recovery. The optimal dietary protein intake has been analyzed for over a century. For that reason, several studies involving animal feeding behavior have been carried out to help nutritionists understand and design human protein intake recommendations. Thus, detailed studies by human and animal nutritionists have yielded a vast amount of information for deriving dietary recommendations for human health (1). As observed in human beings, animal protein intake recommendations can vary in different stages of their lives. For example, adult butterflies feed only on nectar, and protein requirements cannot be achieved. Therefore, in the larval stage, the caterpillar must make sure that it acquires enough protein not only to satisfy its immediate needs, but also its future needs (1). However, there has been a huge controversy surrounding optimal dietary protein intake, with contradictory publications on the clinical and metabolic effects of protein intake and the real needs of the human body. Toward the end of the 19th century, protein requirements were calculated simply by estimating the population's mean protein intake, resulting in a recommended dietary protein intake of 118 g/d for adults of average weight and moderate activity level (2). Later, during the 20th century, these values for protein intake were questioned with the use of the novel nitrogen balance technique (3). The researchers using this technique concluded that just half of the 118 g protein/d would be enough to meet all the human body protein requirements. Moreover, it was stated that even smaller amounts would be enough for people "not leading an active out-of-door life" (3). After reviewing the evidence from nitrogen balance studies, the FAO/WHO/UN University Expert Consultation on Energy and Protein Requirements published a report in 1985 (4). This report concluded that the mean protein requirement should be set at 0.6 g/(kg · d), with no differences in recommendations

[1] E Orenes-Piñero is supported by a postdoctoral contract from the Department of Biochemistry and Molecular Biology–A, Murcia Biomedical Research Institute (IMIB), University of Murcia, Campus of Lorca, Lorca, Spain.
[2] Author disclosures: M Cuenca-Sánchez, D Navas-Carrillo, and E Orenes-Piñero, no conflicts of interest.
* To whom correspondence should be addressed. E-mail: eorenes@um.es.

for men and women and higher requirements for the elderly, because protein utilization is less efficient for them (4, 5). Currently, the Institute of Medicine has set the recommended daily intake (RDI)[5] for protein at 0.8 g protein/(kg body weight · d), covering the requirements of 97.5% of the population (6). With the indicated dosage, no kidney problems have been shown in healthy individuals; however, people with kidney disease should reduce their protein consumption.

However, because the acceptable macronutrient distribution range (AMDR) set by the Institute of Medicine is 10–35% of total energy intake, intake values over 35% should be considered to be high-protein diets (6). It is important to note that the quantity of protein that should be consumed to achieve optimal muscle and bone health seems to be different than the requirement to prevent a deficiency (7). In fact, dietary proteins have many other functions besides synthesizing body proteins. They play an important role in satiety, cellular signaling, and thermogenic and glycemic regulation in the body, and, interestingly, it is when protein intake is above the RDI when these metabolic processes are most evident (8). The Institute of Medicine has not established a protein tolerable upper intake level because of insufficient scientific evidence. However, the risk of adverse effects for the healthy population at the upper level seems to be very low (9). At any rate, the AMDR upper value of 35% does not match the RDI of 0.8 g/(kg · d) given that, if a 70-kg man consumed 2500 kcal/d and 35% of that came from protein, he would be eating ~219 g protein/d, or ~3.0 g/(kg · d), which is almost 4 times the RDI for protein. Thus, a moderate consumption of 1.5 g/(kg · d) can be included in the acceptable protein intake range for most individuals.

Although it is believed that there is no risk of adverse effects when healthy people consume high-protein diets, the lack of long-term studies should be taken into account. All these findings highlight the importance of analyzing the effect of long-term high protein intake on human health. However, high-protein meals and foods are thought to have a greater satiating effect than high-carbohydrate or high-fat meals. For that reason, the aim of this manuscript is to provide an extensive overview of the role of high-protein diets in weight loss, because they have been shown to have a satiating effect through several metabolic pathways. Furthermore, the role of long-term high dietary proteins in bone health and kidney damage will be thoroughly discussed.

Methods

Published data for this review were identified by search and selection in the PubMed database. Reference lists from relevant articles and reviews of high-protein diets and nutritional adequacy published up to July 2014 were also used. A combination of keywords such as "high-protein diet," "weight loss," "bone health," "kidney damage," and "satiating effect" were used. The search was narrowed to studies published in English and Spanish and conducted in either humans or animals. Bibliographies of all selected articles and review articles of high-protein diets and/or human health were checked for other relevant articles.

[5] Abbreviations used: AMDR, acceptable macronutrient distribution range; BMD, bone mineral density; CKD, chronic kidney disease; GLP-1, glucagon-like peptide 1; GFR, glomerular filtration rate; IGF-1, insulin-like growth factor 1; NTS, nucleus tractus solitarius; PYY, peptide YY; RDI, recommended daily intake.

Physiology of Satiety by Dietary Proteins

High-protein meals and foods are thought to have a greater satiating effect than high-carbohydrate or high-fat meals; however, the poor palatability of proteins does not seem to be the main mechanism explaining this fact. Protein intake induces complex signals, with peptide hormones being released from the gastrointestinal tract and blood amino acids and derived metabolites being released in the blood. Protein intake also stimulates metabolic hormones that communicate information about energy status to the brain (10). These signals often are disconnected from the hedonic components of feeding that involve peripheral sensory components. They also involve brain regions influencing reward and motivation, such as the mesolimbic system and nucleus accumbens. However, it is difficult to understand the precise function of each pathway because of the complex integration of signals (10).

Gastrointestinal Satiety Hormones

The most important satiety signals generated in the gastrointestinal tract are cholecystokinin in the duodenum, peptide YY (PYY), which is secreted by L cells in the distal segments of the gut, and glucagon-like peptide 1 (GLP-1) in the ileum (**Table 1**).

Cholecystokinin. Secreted by duodenal and ileal cells when nutrients enter the lumen, cholecystokinin causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively (Table 1). It also binds to specific receptors (cholecystokinin-1R) located on vagal sensory terminals transmitting to the nucleus tractus solitarius (NTS), leading to a sensation of fullness. Some experiments have shown that exogenous cholecystokinin elicits satiety and reduces meal size in different species (11). Intravenous infusion of physiologic doses of cholecystokinin-33 in humans significantly reduced the size of a single-food test meal, as well as the degree of postprandial hunger (12).

PYY. Positively correlated with the number of calories consumed, $PYY_{3–36}$ is mainly secreted by L cells in the distal segments of the gut (Table 1). A $PYY_{3–36}$ deficiency has been identified in obese subjects (13). Moreover, peripheral infusions of the peptide reproducing postprandial concentrations are able to substantially reduce caloric intake in subjects under investigation (13). PYY is hypothesized to act at the hypothalamus via vagal pathways afferent to the NTS and its effect might be mediated by excitement of pro-opiomelanocortin neurons and activation of anorexigenic circuits (14). Despite these observations, further investigation is needed on the potential use of PYY for weight reduction.

GLP-1. GLP-1 is another peptide hormone released in the gastrointestinal tract after food consumption (Table 1). It

TABLE 1 Physiology of the satiating effect of a high-protein diet[1]

Agent	Location of synthesis	Mechanism of action	Satiating effect	Reference
CCK	Duodenum and ileal cells	Releases digestive enzymes and bile from the pancreas and gallbladder, respectively	Binds to specific receptors (CCK-1R) located on vagal sensory terminals transmitting to the NTS a sensation of fullness	11, 12
$PYY_{3–36}$	L cells in the gut	Reduces caloric intake; concentration is positively correlated with the number of calories consumed	Acts at the hypothalamus via vagal pathways afferent to NTS; effect is mediated by excitement of POMC neurons and activation of anorexigenic circuits	13, 14
GLP-1	Ileum	Delays gastric emptying and accentuates glucose-induced stimulation of insulin synthesis and secretion, suppressing glucagon secretion	Activates the vagus nerve, conveying satiety signals through afferent fibers to the NTS	15–17
Neuropeptides and amino acid precursors	Ventral tegmental area; accumbens nucleus	High-protein diet reduces reward-driven eating behavior through the activation of specific brain regions in the corticolimbic system	Serotonergic pathways and transmitters are involved in the reward circuit, influencing the brain availability of their amino acid precursors; a high-protein diet promotes a reduction in brain activation responses to food stimuli in the limbic regions related to food motivation (i.e., hippocampus, amygdala, anterior cingulated, and parahippocampus)	10, 20, 21

[1] CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; NTS, nucleus tractus solitarius; POMC, pro-opiomelanocortin; PYY, peptide YY.

delays gastric emptying and accentuates glucose-induced stimulation of insulin synthesis and secretion, suppressing glucagon secretion at the same time. Its infusion in rats decreased body weight under certain experimental conditions (15). A significant decrease in ad libitum caloric intake in lean and obese subjects was shown in a meta-analysis of 7 studies (16). GLP-1 has a very limited half-life (1–3 min), because it is quickly turned off by the enzyme dipeptidyl peptidase IV. Thus, the clinical use of this molecule is lamentably limited (17).

The release of some of these gastrointestinal hormones activates the vagus nerve, conveying satiety signals through afferent fibers to the NTS. Structural and functional changes in neuronal circuits that control food intake can occur when a high-protein diet is consumed (17). Long-term ingestion of protein reflects the synaptic plasticity of the satiety pathway. This neuronal plasticity was observed in a study in mice in which, after intragastric loads of both sucrose and protein, different subpopulations of neurons in the NTS were activated (18). Moreover, in a rat model experiment ($n = 32$), after a high-protein diet, the activation of noradrenergic neurons and the increased expression of cellular FBJ murine osteosarcoma viral oncogene homolog in the NTS mediated by cholecystokinin was observed (19).

Brain Reward System

Recent studies have examined the nonhomeostatic mechanisms related to ingestive behavior. Besides stimulating satiety centers such as the NTS and the arcuate nucleus, protein intake also seems to diminish brain reward mechanisms (10). The central mesolimbic reward system generates a sensation of pleasure and promotes the motivation for food consumption through its activation. However, its inactivation decreases the hunger sensation (10). Reward mechanisms are influenced by energy composition and protein content, in addition to the organoleptic properties of the meal. The influence of nutrient composition on neural responses to food stimuli has been demonstrated by MRI studies in humans and animals (10). Mice that were adapted to a high-protein diet had lower basal activation in the hypothalamus associated with lower orexin neuron activity, compared with mice that were adapted to a high-carbohydrate diet (20).

In breakfast-skipping adolescent girls, the inclusion of breakfast resulted in a reduction in brain activation responses to food stimuli in limbic regions related to food motivation (i.e., in the hippocampus, amygdala, anterior cingulate cortex, and parahippocampus). Reductions in these areas were also reported after breakfasts with a higher protein content (21). Therefore, a high-protein diet seems to reduce reward-driven eating behavior through the activation of specific brain regions in the corticolimbic system. However, serotonergic pathways, several neuropeptides and transmitters such as dopamine (secreted in the ventral tegmental area), opioid receptors, and γ-aminobutyric acid (synthesized in the accumbens nucleus) seem to be involved

in the reward circuit that influences the brain availability of their amino acid precursors (10) (Table 1). The results of these studies ensure that further investigations of the interactions between the homeostatic and hedonic controls of protein intake will take place.

High-protein Diets and Weight Management

High-protein diets are thought to produce increased satiety, enhanced weight loss, diminished cardiovascular disease risk factors, and improved body composition (22). The effects of weight loss with ad libitum diets with varying amounts of protein have been well documented by many investigators in previous meta-analyses and large well-controlled dietary studies (23, 24). Greater weight loss on a high-protein diet was mainly attributed to the typical satiating effect of these diets and the reduction in carbohydrate intake (23). In addition, controlled studies comparing single macronutrient intakes have shown that protein content is an important factor that affects the amount of food eaten (24, 25). In a study conducted in 19 subjects consuming diets ad libitum for 12 wk, it was observed that a high-protein diet led to greater satiety and was associated with a reduction in energy consumption of 441 ± 63 kcal/d ($P < 0.001$), a reduction in body weight of 4.9 ± 0.5 kg ($P < 0.001$), and a reduction in fat mass of 3.7 ± 0.4 kg ($P < 0.001$) (25). These observations showed that an increase in dietary protein from 15% to 30% of energy at a constant carbohydrate intake produced a sustained decrease in ad libitum caloric intake that may have been mediated by the central nervous system, which further resulted in substantial weight loss. Moreover, a systematic review and a meta-analysis were performed comparing high-protein diets (25–35% of total energy) and isocaloric standard-protein diets (26). In this study, 24 trials including 1063 individuals with a mean diet duration of 12.1 ± 9.3 wk showed that a prescribed high-protein diet produced more favorable changes, including reductions in body weight (−0.79 kg; 95% CI: −1.50, −0.08 kg), fat mass (−0.87 kg; 95% CI: −1.26, −0.48 kg), TGs (−0.23 mmol/L; 95% CI: −0.33, −0.12 mmol/L), and fat-free mass (−0.43 kg; 95% CI: −0.09, −0.78 kg). Furthermore, greater satiety with high-protein diets was reported in >60% of the studies (26). It is widely accepted that the effect of high protein intake on satiety is mainly because of the oxidation of amino acids fed in excess. However, there is a substantial difference when comparing types of protein. In such a comparison, the satiety effect is higher with ingestion of specific "incomplete" proteins (vegetal) than animal proteins (27). On the other hand, thermogenesis induced by diet is higher for proteins than for other macronutrients. Specifically, diet-induced thermogenesis increases after protein ingestion by ~30%, but only by 10% after carbohydrate ingestion and 5% after fat ingestion. Once again, the increase in energy expenditure is different depending on the source of the diet proteins. This effect is higher with animal proteins containing larger amounts of essential amino acids than with vegetable proteins (27). As observed in these studies, the satiating effect of proteins could be an important factor for weight loss.

Dietary Protein and Bone Health

Aging leads to progressive bone loss, which may result in osteoporosis. This is becoming an epidemic disease, with 1 in 4 women >70 y of age having at least one fracture in their lifetime (28). The global increase in individuals suffering from osteoporosis means that modifiable factors such as nutrition are of paramount importance. An increase in protein recommendations to >0.8 g/(kg · d) for the aging population may be beneficial, because protein utilization is less efficient in the elderly, and age-related bone loss is progressive and can lead to osteoporosis and fracture risk (4, 5).

High-protein diets could positively affect calcium and bone homeostasis through their effects on calcium absorption, bone turnover, and production of insulin-like growth factor 1 (IGF-1). It has been shown that higher protein consumption increases intestinal calcium absorption (29–32). The amount of calcium absorbed from the intestine has been inversely correlated with the amount of parathyroid hormone released, which may benefit bone health by attenuating bone resorption (29, 30). In a study comparing women on a 10 d high-protein diet (1.5 g/kg) with those on a 10 d low-protein diet (0.5 g/kg), a substantially lower concentration of parathyroid hormone in subjects on the high-protein diet was observed (30). Another explanation for the increase in calcium absorption can be found in the fact that protein induces gastric acid secretion. The acidic pH in the stomach (1–3) allows calcium ionization and subsequent absorption. Two studies confirm these findings (31, 32). In one study, it was shown that patients with achlorhydria absorbed less calcium than did control subjects with normal gastric acid production (31). In the second study, a significant decrease in calcium absorption was identified in women after they ingested a proton pump–inhibiting drug (32).

IGF-1 modulates bone homeostasis by promoting osteoblast activity (33) and stimulating renal phosphate resorption (34). There is a huge amount of evidence of the positive effect of IGF-1 on human bone health. This includes a decrease in the urinary bone resorption markers deoxypyridinoline and *N*-telopeptide (35), a decrease in proximal femur bone mineral density (BMD) loss in the elderly with a recent hip fracture, and a positive association with BMD in several skeletal structures (36). Dietary protein benefits bone health through IGF-1 secretion. A positive correlation between protein consumption and serum IGF-1 concentration has been established (35). Moreover, the quality and quantity of the ingested protein may influence serum IGF-1 concentration, because a higher concentration was identified in subjects consuming high-quality protein (i.e., from milk sources) (35).

Despite all these findings, the beneficial role of high-protein diets on bone health remains controversial. Some authors support the hypothesis that dietary protein may support calcium metabolism and bone health through several mechanisms; for instance, by increasing IGF-1 or higher intestinal calcium absorption (29–36). Conversely, other

investigators have observed that high-protein diets seem to be harmful to bones, because kidneys may not be able to completely neutralize the acid load remaining from amino acid metabolism, requiring buffering by bone as a result of that limitation (37, 38).

It is well documented that an increase in dietary protein leads to greater calcium urinary excretion. However, the origin of this urinary calcium remains controversial. Some authors believe that in some conditions (i.e., with a hyperproteic diet), the lungs and kidneys are not able to handle this acidification; thus, an additional buffer could be necessary. Therefore, carbonate would be released from the skeleton to provide this buffer and, in consequence, calcium would be released together with carbonate (37). However, some authors have shown with the use of both the in vivo and in vitro mouse model that metabolic acidosis also induces the depletion of mineral phosphate from the bone matrix (39). Moreover, it has been observed that phosphate release could be used predominantly to buffer the additional protons and help restore the pH toward normal. Thus, as observed by these authors, chronic metabolic acidosis decrease bulk bone phosphate to a greater extent than bone carbonate (39). It has been reported that increasing fruit and vegetable consumption would be a practical way to counteract the acidity generated by protein consumption, reducing calciuria and, hence, improving calcium balance (38).

Interestingly, it is also believed that dietary protein intake is directly related to endogenous acid production; however, the amount necessary to affect bones remains unclear. The lungs regulate pH by excreting a metabolic by-product called carbon dioxide; so does kidney buffering, by excreting excess hydrogen ions (primarily known as ammonium). Thus, both of them work together in a normal homeostatic response to regulate blood pH. Because dietary protein is consumed with each meal, divided several times, there is enough time for acid neutralization. Moreover, it has been shown that the pH of extracellular fluid is ~7.36 and the activation of osteoclast resorption requires an extracellular pH <7.2. Therefore, this situation does not seem likely to occur after a high-protein meal, because under changing protein conditions, blood pH remains stable (40).

A significant positive association between protein intake and BMD has been shown by many epidemiologic studies. The Iowa Women's Health Study featuring a cohort of 41,837 women aged 55–69 y showed an inverse relation between protein intake and hip fracture risk. Hip fracture was correlated with a lower protein intake ($P = 0.01$). Moreover, the risk of hip fracture significantly increased ($P = 0.006$) with lower protein intake when it was segregated into quartiles. Therefore, increased dietary protein seems to be correlated with decreased risk of hip fracture (41). Isotopic studies have shown greater calcium absorption and retention in subjects consuming higher protein diets, especially when calcium is consumed below the minimum requirements (29). One study used dual stable isotopes to evaluate calcium balance in healthy pre- and postmenopausal women (29). The effect of a 2 wk dietary intervention in which participants consumed a moderate- [1.0 g/(kg · d)] or high- [2.1 g/(kg · d)] protein diet while consuming a low amount of calcium (800 mg/d) was analyzed. The results showed significantly greater intestinal calcium absorption ($P < 0.001$) and a significant increase in urinary calcium ($P < 0.001$). No effect on biochemical markers of bone turnover was observed between the 2 diets. Importantly, significantly lower urinary calcium from bone origin was detected with the high-protein diet ($P < 0.001$) (29). Therefore, hypercalciuria after a high-protein meal seems to be from increased intestinal calcium absorption.

Despite the controversy surrounding a high-protein diet and bone health, higher protein intake seems to be beneficial for bone mineralization and maintenance in a healthy population because it increases IGF-1 concentrations and intestinal calcium absorption. However, further investigations should be carried out to clarify the role of long-term high protein intake and bone health.

Kidney Damage

It has been demonstrated that the glomerular filtration rate (GFR) rises after protein consumption is increased (42). This long-term elevation in GFR may be harmful to the kidney. However, although it is well accepted that a high-protein diet is harmful to individuals with existing kidney dysfunction, there is little evidence that a high protein intake is dangerous to healthy individuals (42). The National Kidney Foundation's recommendations for nondialyzed individuals with chronic kidney disease (CKD) are below those for the overall population [0.6–0.75 g/(kg · d)] (43). One study in women with mild renal insufficiency reported a significant association between protein intake and diminished renal function (44). In another cross-sectional study including 599 adult patients diagnosed with stage 3–5 CKD, a significant correlation between high protein intake and a decrease in GFR was reported when compared with normal or low intake (45). The idea that high protein consumption may be detrimental to those with CKD seems obvious and is well accepted. However, hyperfiltration could just be an adaptive mechanism of high protein consumption and may not necessarily be related to a decline in renal function for those individuals with normal kidney function.

With respect to kidney function, characterizing the relation between high protein intake and hydration is of great importance. As a consequence of high protein intake, an increase in solute excretion, such as urea and other nitrogenous wastes, is produced. Thus, more water is needed to avoid dehydration. A recent study analyzed the relation between increased protein intake and hydration indexes in a 12 wk randomized, crossover, controlled diet intervention analysis (46). In the study, individuals consumed several diets containing 3.6 (high), 1.8 (moderate), and 0.8 (low) g protein/(kg · d) for 4 wk. The amount of energy ingested was calculated for each individual according to personal requirements and activity level at baseline. Other features, such as blood urea nitrogen, plasma osmolality,

urine-specific gravity, and estimation of fluid balance, were also evaluated. No changes in fluid intake and fluid balance were reported. Importantly, greater blood urea nitrogen was found with the high-protein diet than with the moderate- or low-protein diet, and urine-specific gravity was significantly higher with the high-protein diet than with the moderate-protein diet. Baseline plasma osmolality was higher with the high-protein diet than with the moderate- or low-protein diet. However, no significant effect on fluid status was reported as a result of increased dietary protein (46). In conclusion, consideration should be given before those at risk of renal disease (i.e., those with diabetes, hypertension, or cardiovascular disease) start a high-protein diet.

Further investigation is needed to clarify the impact of long-term high protein consumption on the GFR in the older population, because the GFR decreases with age. In any case, a rise in protein consumption to 1–1.5 g/kg appears to be safe and even necessary for older individuals with healthy kidney function, because it is well accepted that protein efficiency declines with age. Serum creatinine and hemoglobin $A1_C$ tests for diabetes screening and a urine test for proteinuria are useful screening tools to identify individuals for whom high protein consumption may not be advisable (4).

High-protein diets have also been linked to the risk of kidney stone formation. In one large prospective study in humans, a positive association between animal protein consumption and kidney stone formation was observed (47). Thus, high protein consumption may be unsafe for those with inherited or underlying abnormalities associated with renal disease and development of kidney stones (48). These findings suggest that higher protein consumption could be considered an independent risk factor in the development of kidney stones in predisposed individuals.

Conclusions

High-protein diets may be appropriate for some individuals, but not for others; hence, specific individual needs, as well as potential negative consequences, must be considered cautiously before such a diet is adopted. The protein content of a diet may be measured using several methods; however, because of the great individual variability in caloric requirements, measuring intake based on the proportion of proteins in total energy intake seems to be the most realistic method. A moderate intake of 1.5 g/(kg · d) may be easily included in the acceptable protein intake range (AMDR 10–35%) for most individuals. However, currently, no objective standard for protein consumption >0.8 g/(kg · d) exists. It is important to distinguish between the amount of protein that is required to optimize bone and muscle health and the amount necessary to prevent a deficiency. It is also important to note that high-protein diets are harmful to CKD patients; however, for healthy kidney patients, in view of the findings of several studies, the consumption of a high-protein diet appears to be more advantageous than deleterious. In addition, dietary protein seems to play an important role in other metabolic processes, such as satiety, cellular signaling, and thermogenic and glycemic regulation in the body. However, this effect becomes important only when consumption is above the RDI; thus, it seems likely that protein intake above the RDI could be advantageous in many situations. Long-term clinical intervention trials in which dietary protein is increased in healthy individuals should be carried out to determine the efficacy and potential negative consequences of a high-protein diet.

Acknowledgments

All authors read and approved the final manuscript.

References

1. Simpson SJ, Raubenheimer D. The nature of nutrition: A unifying framework from animal adaptation to human obesity. Princeton University Press, 2012.
2. Chittenden RH. Physiologic economy in nutrition with special reference to the minimal protein requirement of the healthy man. An experimental study. London: William Heinemann, 1905.
3. Carpenter KJ. Protein and energy. A study of changing ideas in nutrition. Cambridge (United Kingdom): Cambridge University Press, 1994.
4. FAO/WHO/UNU. Energy and protein requirements. Report of a Joint Expert Consultation. World Health Organ Tech Rep Ser 1985;724: 1–206.
5. Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. Am J Clin Nutr 2003;77:109–27.
6. Phillips SM. Dietary protein for athletes: from requirements to metabolic advantage. Appl Physiol Nutr Metab 2006;31:647–54.
7. Wolfe RR. Protein Summit: consensus areas and future research. Am J Clin Nutr 2008;87:1582S–3S.
8. Layman DK. Dietary guidelines should reflect new understandings about adult protein needs. Nutr Metab (Lond) 2009;6:12.
9. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for energy, carbohydrates, fiber, fat, protein and amino acids (macronutrients). Washington (DC): National Academies Press, 2002.
10. Journel M, Chaumontet C, Darcel N, Fromentin G, Tomé D. Brain responses to high-protein diets. Adv Nutr 2012;3:322–9.
11. Geary N. Endocrine controls of eating: CCK, leptin, and ghrelin. Physiol Behav 2004;81:719–33.
12. Lieverse RJ, Jansen JMB, Masclee AM, Lamers CBHW. Satiety effects of a physiological dose of cholecystokinin in humans. Gut 1995;36:176–9.
13. le Roux CW, Batterham RL, Aylwin SJ, Patterson M, Borg CM, Wynne KJ, Kent A, Vincent RP, Gardiner J, Ghatei MA, et al. Attenuated peptide YY release in obese subjects is associated with reduced satiety. Endocrinology 2006;147:3–8.
14. Woods SC. Gastrointestinal satiety signals. An overview of gastrointestinal signals that influence food intake. Am J Physiol Gastrointest Liver Physiol 2004;286:G7–13.
15. Meeran K, O'Shea D, Edwards CM, Turton MD, Heath MM, Gunn I, Abusnana S, Rossi M, Small CJ, Goldstone AP, et al. Repeated intracerebroventricular administration of glucagon-like peptide-1 (7–36) amide or exendin (9–39) alters body weight in the rat. Endocrinology 1999;140:244–50.
16. Verdich C, Flint A, Gutzwiller JP, Naslund E, Beglinger C, Hellstrom PM. A meta-analysis of the effect of Glucagons Like Peptide 1 (7–36) Amide on ad libitum energy intake in humans. J Clin Endocrinol Metab 2001;86:4382–9.
17. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake. Nutr Metab Cardiovasc Dis 2008;18:158–68.
18. Schwarz J, Burguet J, Rampin O, Fromentin G, Andrey P, Tomé D, Maurin Y, Darcel N. Three-dimensional macronutrient-associated Fos expression patterns in the mouse brainstem. PLoS ONE 2010;5: e8974.

19. Faipoux R, Tome D, Gougis S, Darcel N, Fromentin G. Proteins activate satiety-related neuronal pathways in the brainstem and hypothalamus of rats. J Nutr 2008;138:1172–8.
20. Becskei C, Lutz TA, Riediger T. Blunted fasting-induced hypothalamic activation and refeeding hyperphagia in late-onset obesity. Neuroendocrinology 2009;90:371–82.
21. Leidy HJ, Lepping RJ, Savage CR, Harris CT. Neural responses to visual food stimuli after a normal vs. higher protein breakfast in breakfast-skipping teens: a pilot fMRI study. Obesity (Silver Spring) 2011;19: 2019–25.
22. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.
23. Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int J Obes Relat Metab Disord 1999;23:528–36.
24. Bowen J, Noakes M, Clifton PM. Appetite regulatory hormone responses to various dietary proteins differ by body mass index status despite similar reductions in ad libitum energy intake. J Clin Endocrinol Metab 2006;91:2913–9.
25. Weigle DS, Breen PA, Matthys CC, Callahan HS, Meeuws KE, Burden VR, Purnell JQ. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. Am J Clin Nutr 2005;82:41–8.
26. Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:1281–98.
27. Keller U. Dietary proteins in obesity and in diabetes. Int J Vitam Nutr Res 2011;81:125–33 10.1024/0300–9831/a000059.
28. WHO scientific group on the burden of musculoskeletal conditions at the start of the new millennium. The burden of musculoskeletal conditions at the start of the new millennium. World Health Organ Tech Rep Ser 2003;919:1–218.
29. Kerstetter JE, O'Brien KO, Caseria DM, Wall DE, Insogna KL. The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. J Clin Endocrinol Metab 2005;90:26–31.
30. Kerstetter JE, Caseria DM, Mitnick ME, Ellison AF, Gay LF, Liskov TA, Carpenter TO, Insogna KL. Increased circulating concentrations of parathyroid hormone in healthy, young women consuming a protein-restricted diet. Am J Clin Nutr 1997;66:1188–96.
31. Recker RR. Calcium absorption and achlorhydria. N Engl J Med 1985; 313:70–3.
32. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med 2005;118:778–81.
33. Langdahl BL, Kassem M, Moller MK, Eriksen EF. The effects of IGF-I and IGF-II on proliferation and differentiation of human osteo-blasts and interactions with growth hormone. Eur J Clin Invest 1998;28:176–83.
34. Palmer G, Bonjour JP, Caverzasio J. Stimulation of inorganic phosphate transport by insulin-like growth factor I and vanadate in opossum kidney cells is mediated by distinct protein tyrosine phosphorylation processes. Endocrinology 1996;137:4699–705.
35. Arjmandi BH, Khalil DA, Smith BJ, Lucas EA, Juma S, Payton ME, Wild RA. Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. J Clin Endocrinol Metab 2003;88:1048–54.
36. Schürch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double blind, placebo-controlled trial. Ann Intern Med 1998;128:801–9.
37. Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. Am J Clin Nutr 2003;78: 584S–92S.
38. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997; 336:1117–24.
39. Bushinsky DA, Smith SB, Gavrilov KL, Gavrilov LF, Li J, Levi-Setti R. Chronic acidosis-induced alteration in bone bicarbonate and phosphate. Am J Physiol Renal Physiol 2003;285:F532–9.
40. Bonjour JP. Dietary protein: an essential nutrient for bone health. J Am Coll Nutr 2005;24:526S–36S.
41. Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr 1999;69:147–52.
42. Friedman AN. High-protein diets: potential effects on the kidney in renal health and disease. Am J Kidney Dis 2004;44:950–62.
43. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis 2001;37:S66–70.
44. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 2003;138:460–7.
45. Huang MC, Chen ME, Hung HC, Chen HC, Chang WT, Lee CH, Wu YY, Chiang HC, Hwang SJ. Inadequate energy and excess protein intakes may be associated with worsening renal function in chronic kidney disease. J Ren Nutr 2008;18:187–94.
46. Martin WF, Cerundolo LH, Pikosky MA, Gaine PC, Maresh CM, Armstrong LE, Bolster DR, Rodriguez NR. Effects of dietary protein intake on indexes of hydration. J Am Diet Assoc 2006;106:587–9.
47. Fink HA, Akornor JW, Garimella PS, MacDonald R, Cutting A, Rutks IR, Monga M, Wilt TJ. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. Eur Urol 2009;56:72–80.
48. Hess B. Nutritional aspects of stone disease. Endocrinol Metab Clin North Am 2002;31:1017–30.