Protein, body weight, and cardiovascular health

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ABSTRACT
Widespread popularity of high-protein diets has drawn controversy as well as scientific interest. By reducing intake of carbohydrates and increasing consumption of fats and proteins, such diets are thought to increase satiety, facilitate weight loss, and improve cardiovascular risk factors. In recent years, many randomized controlled studies have compared the effects of higher-protein diets on weight loss and cardiovascular risk factors with those of lower-protein diets. The aim of this review was to provide an overview of experimental and epidemiologic evidence regarding the role of protein in weight loss and cardiovascular risk. Emerging evidence from clinical trials indicates that higher-protein diets increase short-term weight loss and improve blood lipids, but long-term data are lacking. Findings from epidemiologic studies show a significant relationship between increased protein intake and lower risk of hypertension and coronary heart disease. However, different sources of protein appear to have different effects on cardiovascular disease. Although optimal amounts and sources of protein cannot be determined at this time, evidence suggests a potential benefit of partially replacing refined carbohydrates with protein sources low in saturated fats.

KEY WORDS High-protein diets, weight loss, cardiovascular risk factors, coronary heart disease, low-carbohydrate diets, blood lipids

INTRODUCTION
Today, ≈66% of Americans are overweight, and 33% are considered clinically obese (body mass index ≥30 kg/m²) (1). The rapid increase in the prevalence of obesity, combined with a lack of effective dietary and pharmacologic treatments, has fueled demand for alternative dietary approaches, in particular, high-protein diets. In recent years, high-protein diets gained widespread popularity before scientific evidence on their safety or efficacy. Advocates of such diets often recommend protein intakes at or above 25% of total energy, amounts that are substantially higher than the average consumption of protein in the US diet.

Proponents of several popular diets (especially the Atkins Diet) have long claimed that higher amounts of dietary protein not only facilitate weight loss but also improve cardiovascular risk factors. In recent years, more than a dozen clinical trials have examined the effects of higher-protein diets on weight loss compared with diets lower in protein (2–16). Epidemiologic studies have also assessed the effects of dietary protein on blood pressure and cardiovascular disease. In this review, we provide an overview of experimental and epidemiologic evidence on the role of protein in weight loss and risk of cardiovascular disease.

PROTEIN AND BODY WEIGHT
Recently, Halton and Hu (17) reviewed 15 randomized controlled studies of a higher-protein diet compared with a lower-protein diet on weight loss, which lasted for between 7 d and 1 y and used a wide variety of macronutrient ratios and methodologic designs (2–16). Seven of these investigations found a statistically significant decrease in total body weight for the higher-protein diets (5, 6, 8, 12, 13, 15, 16). Samaha (12) randomized 64 obese patients to receive counseling on maintaining a high-protein, low-carbohydrate diet (22% protein) and 68 to receive counseling on consuming a low-fat, high-carbohydrate diet (16% protein). After 6 mo, the high-protein, low-carbohydrate group lost significantly more weight (5.8 vs 1.9 kg; P = 0.002). However, at 12 mo, weight loss was not significantly different between the two groups (18). Skov (13) found that obese subjects randomized to a high-protein intake (25% of energy) lost significantly more weight (8.8 vs 5.1 kg) and fat (7.6 vs 4.3 kg) after 6 mo compared with those on a low protein diet (12% of energy). Brehm (6) conducted a randomized trial on 42 obese females. Twenty received a low-fat dietary regimen (17% protein), whereas 22 received a low-carbohydrate diet (23% protein). After 6 mo, the higher-protein group had lost significantly more weight (8.5 vs 3.9 kg; P < 0.01). Yancy (16) conducted a trial on 119 overweight men and women for 6 mo. Those consuming a higher-protein, low-carbohydrate diet (26% protein) lost significantly more weight than those consuming a lower-protein diet (19%) (12.9% of body weight vs 6.7% of body weight; P < 0.001). Foster (8) randomized 33 obese patients to receive counseling on following the Atkins diet and 30 to receive counseling on a conventional low-fat diet (15% protein). The Atkins group lost significantly more weight at 3 and 6 mo but not at 1 y.

Shorter studies with smaller sample sizes have produced mixed results. Baba (5) conducted a wk randomized trial on 13 obese male subjects with hyperinsulinemia. Seven men received...
a high-protein diet (45% protein), whereas the other six received a high-carbohydrate diet (12% protein). After 4 wk, the high-protein group lost significantly more weight than the high-carbohydrate group (8.3 vs 6 kg; P < 0.05). Worthington (15) conducted a randomized trial on 21 overweight females. Eleven women received high-protein, low-carbohydrate diets (49% protein), whereas 10 received a diet lower in protein and higher in carbohydrate (21% protein). After 2 wk, the high-protein group lost significantly more weight (5.5 vs 3.95 kg; P < 0.05). However, several other studies found no significant difference in weight loss comparing higher- and lower-protein diets (4, 9, 11, 14). Recently, Dansinger et al (19) reported that four popular diets (Atkins, Ornish, Weight Watchers, and Zone) produced similar but modest weight loss at 1 y. However, the study was not designed to compare the efficacy of these diets because overall adherence rates were very low. The authors found that increased adherence was an important determinant of weight loss for all diets.

Overall, there is some evidence that high-protein diets enhance weight loss compared with lower-protein diets in the short term (within 6 mo). Possible mechanisms include an increased satiety, decreased subsequent energy intake, and carbohydrate displacement with higher-protein diets. It is likely that several of these mechanisms work together and are related to each other (Figure 1).

There is convincing evidence that high-protein diets increase satiety in short-term studies (17). Higher-protein diets may also reduce subsequent energy intake. Skov et al (13) found that free living subjects randomized to a high-protein diet consumed an average of 8956 kJ/d compared with a mean of 10 907 kJ/d for those on a low-protein diet. These data, which are consistent with those from other ad libitum studies, (17) support findings that high-protein diets produce greater satiety and lower subsequent energy intake than do diets with less protein.

A higher thermogenesis for protein is a possible mechanism as well. A main reason for the difference in the thermic effects of foods higher in protein compared with those higher in carbohydrates or fats may be attributable to the fact that the body has no storage capacity for protein, and thus it needs to be metabolically processed immediately. The synthesis of protein, the high ATP cost of peptide bond synthesis, as well as the high cost of urea production and gluconeogenesis are possible reasons for the higher thermic effect of protein (20, 21). However, most of feeding studies were of too short a duration to be conclusive.

Displacement of carbohydrates, especially refined carbohydrates, by dietary protein may also contribute to greater short-term weight loss seen in high-protein diets. Emerging evidence suggests that high glycemic, refined carbohydrates decrease satiety and increase subsequent energy intake (22). In a recent study, Pereira et al (23) found that resting energy expenditure decreased less with a hypocaloric low-glycemic load diet than with an isocaloric low-fat high-glycemic load diet, after a10% weight loss in both diets. These findings suggest that reducing glycemic load may be useful in weight maintenance.

PROTEIN AND BLOOD LIPIDS

Experimental studies in rabbits or rat suggested that cholesterol-free, purified diets containing proteins of animal rather than vegetable sources were hypercholesterolemic and atherogenic (24). However, this cholesterol-raising effect was not observed in other species of animals (eg, pigs) or humans (25, 26). On the contrary, exchanging animal protein for carbohydrates in human diets significantly reduced LDL cholesterol and triacylglycerol levels and increased HDL cholesterol levels (27). In a crossover study (28), subjects with moderate hypercholesterolemia were randomly assigned to either high-protein (23% energy) and low-carbohydrate (53% energy) diet or low-protein (11% energy) and high-carbohydrate (65% energy) diet for 4–5 wk. Intakes of dietary fat, cholesterol, and fiber were kept constant. The main sources of protein were turkey, cottage cheese, beef, fish, and ham. Exchanging protein for carbohydrate significantly reduced LDL cholesterol (by 6.4%) and triacylglycerol (by 23%) levels and increased HDL (by 12%). Favorable effects on plasma lipids of substitution of protein for carbohydrates were also observed among subjects with familial hypercholesterolemia (29) and normolipidemia (30).

Jenkins (31) conducted a 1 mo study of a high-wheat protein diet (27% energy from protein) compared with a control diet (16% energy protein) and found significant decreases in triacylglycerol and oxidized LDL cholesterol on the higher-protein diet. A recent study by Samaha (12) compared a low-carbohydrate, high-protein Atkins diet (22% energy from protein) with a low-fat diet (16% energy from protein) on severely obese subjects. The higher-protein group had significantly lower triacylglycerols compared with the lower-protein group (−20 vs −4%; P = 0.001) at 6 mo. However, the higher-protein group lost more weight, and this may have accounted for these differences. At 12 mo, although weight loss was no longer statistically different between the two groups, participants in the higher-protein and low-carbohydrate diet experienced great reduction in triacylglycerol levels but less decline in HDL cholesterol levels compared with the low-fat group (18). In addition, Farnsworth (7) and Skov (13) found a significant decrease in triacylglycerols with higher-protein diets, whereas Parker (10) found a significantly lower LDL cholesterol level with a higher-protein diet.

It is known that low-fat, high-carbohydrate diets reduce LDL if substituted for saturated or trans fats, but these diets also reduce HDL levels and raise fasting triacylglycerols (32). However, the observed apparent benefit of exchanging protein for carbohydrate cannot be simply attributed to displacement of carbohydrate in the diet because LDL cholesterol levels were also reduced in metabolic studies. A high-protein diet may decrease triacylglycerol secretion by hepatocytes (33). Rats fed with a
protein-deficient diet (8% energy) had slight hypercholesterolemia and increased activity of liver β-hydroxy-β-methylglutaryl coenzyme A reductase compared with controls (16% casein diet) (34). These rats also exhibited increased susceptibility of lipoprotein to peroxidation.

PROTEIN AND BLOOD PRESSURE

Higher consumption of dietary protein has been inversely associated with blood pressure in several observational studies and animal experiments (35). Liu et al (36) conducted a meta-analysis of nine cross-sectional studies and found significant inverse associations between dietary protein and systolic and diastolic blood pressure in both men and women. Only two longitudinal studies examined the associations between dietary protein intake and blood pressure. In the Coronary Artery Risk Development in Young Adults study (37), higher protein intake was inversely associated with changes in systolic and diastolic blood pressure in multiethnic groups during 7 y of follow-up. In a 3-y follow-up study of the 662 participants in the Dietary Intervention Study in Children (38), protein intake was significantly associated with lower blood pressure in separate analyses of each nutrient, but the association became nonsignificant when other nutrients were adjusted for in the models. In the Dietary Approach to Stop Hypertension trial (39), whereas fruits and vegetables independently lowered blood pressure, the combination diet with relatively high-protein intake (18% energy) and increased intakes of fruits and vegetables lowered blood pressure even further. However, because the intervention altered overall eating patterns instead of single nutrients, it is not possible to disentangle the effects of protein from those of other nutrients.

PROTEIN AND CORONARY HEART DISEASE (CHD)

Ecological studies suggest a positive association of CHD mortality rates with animal protein consumption (r = 0.78) and an inverse association with vegetable protein consumption (r = −0.40) (40). This result should be interpreted with caution because the countries with a higher protein intake also have higher intakes of saturated fat and cholesterol and lower intake of fiber. Previous prospective cohort studies have primarily focused on dietary fats, and only a few examined the association with protein intake. A significant positive association between protein intake and CHD was seen in one study (41), but this was not adjusted for intake of specific types of fat. Hu et al (42) specifically examined the relationship between protein intake and risk of CHD in the Nurses’ Health Study. After controlling for age, smoking, total energy intake, percentages of energy from specific types of fat, and other coronary risk factors, the relative risk (RR) of CHD comparing highest quintile (median, 24% energy) with lowest quintile (median, 15% energy) of total protein intake was 0.74 (95% CI, 0.59−0.94).

Recently, Kelemen et al (43) reported that a higher consumption of vegetable protein was associated with a significantly decreased CHD mortality compared with equivalent amount of energy from carbohydrates or animal protein in the Iowa Women’s Health Study.

PROTEIN AND STROKE

Mortality rates from cerebrovascular disease (stroke) are much higher in some Asian countries (including Japan and China) than in countries in North America or Europe. Data suggest that some aspects of the Asian diet (eg, very low animal fat and protein and relatively high salt) may be associated with high rates of stroke (especially hemorrhagic) in some Asian countries (44).

A significant decline in the incidence of stroke in Japan in the past decades has been attributed to increased consumption of animal products, including meat, eggs, and dairy, as well as improved pharmacologic treatment of hypertension (45). A similar decreasing trend in stroke rate, accompanied by increased consumption of animal products, has also been observed in China (46).

Prospective investigation of protein consumption and stroke is limited. During 14-y follow-up of the women in the Nurses’ Health Study cohort, Iso et al (47) found that animal protein intake was inversely associated with risk of intraparenchymal hemorrhage (RR in the highest vs lowest quintiles, 0.32; 95% CI, 0.10−1.00; P = 0.04). Lower consumption of saturated fat was associated with increased risk of hemorrhagic stroke, especially among hypertensive women. These data may help explain a heightened risk of hemorrhagic stroke in populations (eg, Asians) with very low consumption of animal fat and protein and very high intake of carbohydrates.

HIGH-PROTEIN FOODS AND CARDIOVASCULAR DISEASE

High-protein animal products (eg, meat, high-fat dairy, and eggs) are also primary sources of saturated fat and cholesterol. Positive relationships between saturated fat, cholesterol, and CHD suggest that regular intake of foods high in saturated fat and cholesterol (eg, red meat and eggs) may increase risk of CHD. However, epidemiologic studies suggest that the effects of protein-rich foods on cardiovascular risk are not entirely driven by saturated fat and cholesterol.

Red meats

There are few data on the direct relationship between intake of red meat and risk of CHD. In a study of California Seventh-Day Adventists (48), higher beef consumption was significantly associated with increased risk of fatal ischemic heart disease in men but not in women. In a case-control study conducted in Italy (49), higher meat and butter consumption was associated with increased risk of myocardial infarction in women. In the Nurses’ Health Study (50), after adjustment for age, consumption of red meat and high-fat dairy products was associated with increased risk of CHD, whereas consumption of poultry/fish and low-fat dairy products was associated with a lower risk. These associations were substantially attenuated in multivariate analyses and became nonsignificant, but the directions of the associations remained unchanged. The ratio of red meat to poultry/fish consumption was more strongly associated with the risk [multivariate RRs across increasing quintiles of the ratio were 1.0, 1.00, 1.13, 1.20, and 1.32 (1.07−1.62); P for trend = 0.001]. In the Iowa Women’s Health Study, higher consumption of red meat was significantly associated with increased CHD mortality (43).

Frequent consumption of processed meat has been consistently shown to increase the risk of diabetes in prospective studies (51–53). Although processed meats are a major component of the so-called “Western” diet pattern in these study populations, these associations have been found to be independent of the
Western pattern (51, 53). Furthermore, although the associations between red meat consumption and diabetes risk were attenuated by controlling for saturated fat intake, processed meats remained significantly associated with risk (53), suggesting that constituents of processed meat other than fatty acids (eg, nitrite or advanced glycation end products) may play a role in the development of diabetes.

Heme iron, present in high amounts in red and processed meats, may also link intake of processed meats to risk of diabetes. Heme iron is readily absorbed in the gut and contributes significantly to body iron stores. A recent study (54) found that in healthy women, higher iron stores (reflected by an elevated ferritin concentration and a lower ratio of transferrin receptors to ferritin) were associated with an increased risk of type 2 diabetes; this relationship was independent of known risk factors for diabetes.

**Poultry and fish**

A recent meta-analysis indicates that frequent intake of fish is associated with reduced risk of coronary death (55). Other recent data link increased consumption of fish with decreased risk of ischemic stroke (56). Similarly, Hu et al (50) found that exchange of poultry or fish for red meat was associated with a significantly decreased risk of CHD.

Compared with red meat, white meat from chicken and fish contains similar amounts of protein but substantially less saturated fat and cholesterol. Although the protection against CHD afforded by fish is most likely attributable to the anti-arrhythmic effect of omega-3 fatty acids, other nutrients, including protein, might also have beneficial effects.

**Eggs**

There is little direct evidence linking egg consumption to increased risk of CHD. In the Nurses’ Health Study and Health Professionals’ Follow-up Study, moderate egg consumption (up to one egg per day) was not significantly associated with risk of either CHD or stroke (57). It is conceivable that beneficial effects of protein and other nutrients (including protein, B vitamins, and minerals) may have counterbalanced the small adverse effects of cholesterol in eggs. However, among diabetic patients, even moderate consumption of eggs and cholesterol was associated with significantly increased CHD risk (58). Insulin resistance and dyslipidemia may magnify the adverse effects of cholesterol in those with diabetes.

**Dairy products**

Cross-sectional studies and small clinical trials have suggested an inverse association between dairy consumption and body weight, hypertension, and insulin resistance syndrome (59, 60), but data from large prospective studies are limited. Recently, the Coronary Artery Risk Development in Young Adults study reported a strong inverse association between dairy consumption and insulin resistance syndrome among young obese adults (61). In the Health Professionals’ Follow-up, we found a modest inverse association between dairy consumption, primarily low-fat dairy, and risk of type 2 diabetes (62). Few epidemiologic studies have examined the relationship between dairy consumption and risk of CHD. In the Nurses’ Health Study (50), the ratio of high-fat dairy to low-fat dairy product consumption was positively associated with the risk of CHD [multivariate RRs across increasing quintiles of the ratio were 1.0, 0.87, 0.94, 1.17, 1.27 (1.04–1.54); P for trend = 0.0004]. Among the dairy products, whole milk consumption was associated with significantly increased risk, whereas greater consumption of skim milk was associated with a nonsignificantly lower risk. These results suggest potential benefits of substituting low-fat for high-fat dairy products in preventing CHD.

**Nuts**

Nuts are high in monounsaturated and polyunsaturated fats. Most nuts are rich in protein, especially arginine, which is the precursor of endothelium-derived relaxing factor, nitric oxide (NO). NO is a potent vasodilator that can inhibit platelet adhesion and aggregation. It has been suggested that the anti-atherogenic effect of nuts might be related, in part, to the arginine-NO pathway (63). Nuts also contain high amounts of magnesium, copper, folic acid, potassium, fiber, and vitamin E.

Several epidemiologic studies suggest a relationship between intake of nuts and protection against CHD (64, 65). Bazzano et al (66) found a significant inverse relationship between legume consumption (including peanuts) and risk of CHD. Data also show a significant association between higher consumption of nuts and peanut butter and lower risk of type 2 diabetes in women (67). Wien et al (68) have shown that the substitution of nuts for carbohydrates improves insulin sensitivity and blood lipids and facilitates weight loss.

**Soy**

A meta-analysis of 38 controlled feeding studies in humans suggested that substitution of soy protein for animal protein significantly decreased total and LDL cholesterol levels (69). However, the effects of soy protein and isoflavones on blood cholesterol in humans are highly variable, and overall effects appear to be modest (70).

Because soy protein, the usual experimental source of vegetable protein, is not commonly consumed in Western populations, it is difficult to examine the effect of this specific protein on CHD in the United States. In a prospective study of ~65 000 Chinese women aged 40–70 y old in the Shanghai Women’s Health Study (71), there was a monotonic inverse relationship between soy food intake and risk of CHD (P for trend = 0.003), with an adjusted RR of 0.25 (95% CI, 0.10–0.63) observed for women in the highest versus the lowest quartile of total soy protein intake. Because of its small number of cases (62 CHD cases and relatively short follow-up (2.5 y), these results need to be confirmed with additional follow-up and larger studies.

**SUMMARY AND CONCLUSIONS**

Experimental data indicate that high-protein diets produce greater short-term (within 6 mo) weight loss; most studies, however, have been small and inconclusive. Clinical trials suggest that the exchange of protein (either animal or plant) for carbohydrates improves blood lipid profiles. Epidemiologic studies have linked high-protein intake with lower risk of hypertension and CHD. In addition, very low levels of animal protein intake have been associated with a significantly increased risk of hemorrhagic stroke.

Studies suggest that different sources of protein have different effects on cardiovascular disease. The effects of white meat from poultry and fish are known to differ from those of red meat from
beef and pork. Diets containing substantial amounts of red meat, and products made from these meats, appear to increase risk of CHD. Data indicate that substitution of white meat (poultry and fish) for red meat provides health benefits. In addition, consumption of animal products may have opposing effects on CHD and hemorrhagic stroke. Thus, dietary recommendations should emphasize both the amount and sources of protein. One should distinguish poultry and fish from beef and pork. Also, eggs and dairy products should be distinguished from meats. There is little evidence that moderate consumption of eggs has material adverse effects on chronic diseases, and moderate consumption of dairy products may have complex effects, including benefits and risks. In countries where hemorrhagic stroke rates are substantially elevated, very low consumption of animal products may not be optimal. In many situations, the partial displacement of the carbohydrate staple source of energy, such as grain products with animal products, may have neutral or beneficial health effect. However, the use of plant source of protein and fat, such as nuts, legumes, soy, and vegetable oils, may provide even greater health benefits and should therefore be considered simultaneously (72).

In conclusion, emerging evidence from clinical trials indicates that higher-protein diets increase short-term weight loss and improve blood lipids, but long-term data are lacking. Findings from epidemiologic studies show an inverse relationship between increased protein intake and lower risk of hypertension and CHD. However, different sources of protein appear to have different effects on cardiovascular disease. Although optimal amounts of protein cannot be determined at this time, evidence suggests that it may be beneficial to partially replace refined carbohydrates with protein sources low in saturated fats.

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