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Protein and Coronary Heart Disease: The Role of Different Protein Sources

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Abstract Meat protein is associated with an increase in risk of heart disease. Recent data have shown that meat protein appeared to be associated with weight gain over 6.5 years, with 1 kg of weight increase per 125 g of meat per day. In the Nurses' Health Study, diets low in red meat, containing nuts, low-fat dairy, poultry, or fish, were associated with a 13% to 30% lower risk of CHD compared with diets high in meat. Low-carbohydrate diets high in animal protein were associated with a 23% higher total mortality rate whereas low-carbohydrate diets high in vegetable protein were associated with a 20% lower total mortality rate. Recent soy interventions have been assessed by the American Heart Association and found to be associated with only small reductions in LDL cholesterol. Although dairy intake has been associated with a lower weight and lower insulin resistance and metabolic syndrome, the only long-term (6 months) dairy intervention performed so far has shown no effects on these parameters.

Keywords Red meat · Chicken · Fish · Vegetable protein · Soy · Heart disease · Type 2 diabetes · Epidemiology · Interventions · Blood pressure · Lipids · Dairy · Insulin resistance · Blood pressure

Introduction

Meat protein has been associated for many years with heart disease and type 2 diabetes, and data supporting this

P. M. Clifton (⊠) Baker IDI Heart and Diabetes Institute, Level 3, 195 North Terrace, GPO Box 884, Adelaide 5000, Australia e-mail: Peter.clifton@bakeridi.edu.au association continues to accumulate. Vegetable protein has been associated with protection from heart disease, but new trial data over the past 3 to 4 years have suggested soy is not as efficacious at lowering low-density lipoprotein (LDL) cholesterol as previously believed, and the US Food and Drug Administration (FDA) is currently reconsidering the soy claim.

Epidemiology

Meat Protein and Body Weight

Obesity is associated with an increased risk of cardiovascular disease (CVD), so any association between protein and weight would impact on CVD risk. In the Diogenes study from five European countries in the EPIC project, 89,432 participants were followed for 6.5 years. Higher intakes of total protein, animal protein (red meat, processed meat, chicken, but not fish or dairy) were associated with weight gain, especially in women. There was no association with plant protein. No clear association was shown with waist circumference [1•]. In the whole EPIC cohort, a total of 103,455 men and 270,348 women aged 25 to 70 years were recruited between 1992 and 2000 in 10 European countries. Total meat consumption was positively associated with weight gain in men and women, in normalweight and overweight subjects, and in smokers and nonsmokers [2•]. After adjustment for estimated energy intake, an increase in meat intake of 250 g/d was estimated to lead to a 2-kg higher weight gain after 5 years (95% CI: 1.5, 2.7 kg). Positive associations were observed for red meat, poultry, and processed meat. It is not clear why no associations were shown for fish or dairy protein, but fish consumers in general are more focused on health.

Coronary Heart Disease and Protein Type

In the 26-year follow-up of the Nurses' Health Study (NHS), higher intakes of red meat, red meat excluding processed meat, and high-fat dairy were significantly associated with elevated risk of coronary heart disease (CHD). Higher intakes of poultry, fish, and nuts were significantly associated with lower risk. It was calculated that if participants replaced red meat with nuts, low-fat dairy, poultry, or fish it would lead to a 13% to 30% lower risk of CHD, with fish being the best replacement option [3••].

Data were not quite so clear cut in the Health Professionals' Follow Up Study (HPFU) of 43,960 men followed for up to 18 years with 2959 incident cases of ischemic heart disease (IHD). The risk ratio (RR) of IHD was 1.08 (*P* for trend=0.30) comparing the top with the bottom quintile of percentage of energy from total protein. Risk ratios for animal and vegetable protein were 1.11 (*P* for trend=0.18) and 0.93 (*P* for trend=0.49), respectively. In a healthy subgroup free of hypertension, hypercholesterolemia, and diabetes at baseline, the RR of IHD was 1.21 (*P* for trend=0.02) for total protein, 1.25 (*P* for trend=0.02) for animal protein, and 0.93 (*P* for trend=0.65) for vegetable protein [4•].

In a review performed for the American Dietetic Association, Craig and Mangels [5] showed, as has been noted many times before, that a vegetarian diet is associated with a lower risk of death from IHD. Vegetarians also appear to have lower LDL cholesterol levels, lower blood pressure, and lower rates of hypertension and type 2 diabetes than non-vegetarians. Furthermore, vegetarians tend to have a lower body mass index and lower overall cancer rates. Features of a vegetarian diet (other than vegetable protein) that may reduce risk of chronic disease include lower intakes of saturated fat and cholesterol and higher intakes of fruits, vegetables, whole grains, nuts, soy products, fiber, and phytochemicals.

CHD and Low-Carbohydrate Diets

Low-carbohydrate diets contain a higher proportion of protein and, depending on the associated degree of caloric restriction, may contain more protein in grams. In the NHS and HPFU 20- to 26-year follow-up, there were 12,555 deaths [6••]. The overall low-carbohydrate score was associated with a modest increase in overall mortality in a pooled analysis (hazard ratio [HR] comparing extreme deciles, 1.12 [P<0.05, P for trend=0.136). However the *animal* low-carbohydrate score was associated with higher all-cause mortality (pooled HR comparing extreme deciles, 1.23 [P<0.05, P for trend=0.051) and cardiovascular mortality (corresponding HR, 1.14 [P<0.05, P for trend=

0.029). A higher *vegetable* low-carbohydrate score was associated with lower all-cause mortality (HR, 0.80, *P* for trend \leq = 0.001) and cardiovascular mortality (HR, 0.77, *P* for trend<0.001).

Blood Pressure

In the Circulatory Risk in Communities Study [7], a population-based, cross-sectional study of 7585 subjects (3499 men and 4086 women) from 40 to 69 years of age living in five communities in Japan, blood pressure was inversely related to total and animal proteins. Dietary intakes of total, animal, and plant protein were estimated by a single 24-hour dietary recall. A 25.5-g/d increment in total protein intake was associated with a decrease in systolic blood pressure of 1.14 mm Hg (P<0.001) and in diastolic blood pressure of 0.65 mm Hg (P<0.001), and a 19.9-g/d increment in animal protein intake was associated with a decrease in systolic blood pressure of 1.09 mm Hg (P< 0.001) and in diastolic blood pressure of 0.41 mm Hg (P=0.003). A 13.1-g/d increment in plant protein intake was associated with a decrease in diastolic blood pressure of 0.57 mm Hg (P<0.001). These findings are consistent with the 28% reduced risk of cerebral hemorrhage from the intake of eggs, dairy products and fish [8].

In the US Health Professionals Follow up Study total, animal or vegetable protein intake was not related to stroke rate [9].

Type 2 Diabetes

As type 2 diabetes mellitus (T2DM) at least doubles the risk of CVD, then a consideration of the association of protein sources and T2DM is important. In the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study of 146 South Indians living in San Francisco, 28% developed T2DM. There was a 70% increase in odds of having T2DM with highest protein intake after full adjustment [10]. No association with protein type was shown. A 2-hour glucose tolerance test, frequently sampled intravenous glucose tolerance test, and HbA1C were obtained at the follow-up examination in 880 participants in the Insulin Resistance Atherosclerosis Study (IRAS), in which 144 developed T2DM over 5 years [11•]. All dietary patterns that contained a wide variety of protein sources, such as red meat, low-fiber bread and cereal, dried beans, eggs, cheese, and cottage cheese, led to a 4.5-fold increase in risk of T2DM even after adjustment for body mass index (BMI), which was higher in people with this dietary pattern [11•].

In the Whitehall II study, *burgers and sausages* were part of a dietary pattern that increased the risk of T2DM by 50% after full adjustment [12]. In the Nurses Health Study, the multivariate relative risk (RR) for the comparison of extreme deciles of low-carbohydrate diet score based on total carbohydrate, animal protein, and animal fat was 0.99 but the RR for a low-carbohydrate diet score based on total carbohydrate, vegetable protein, and vegetable fat was 0.82 (*P* for trend=0.001 [ie, vegetable protein was protective against diabetes]) [13]. In a meta analysis of 12 cohort studies, the estimated summary RR and 95% CI of T2DM comparing high versus low intake was 1.17 (P=not significant because fewer studies had total meat) for total meat (1.21, P<0.05) for red meat, and 1.41 (P<0.05) for processed meat [14••].

In the Potsdam cohort of the EPIC study, substituting protein or polyunsaturated fatty acid (PUFA) for carbohydrate reduced the risk of diabetes by 23% for each 5% energy substitution with protein and by 17% for substitution with polyunsaturated fat [15]. This finding was contrary to many of the above studies.

Legumes

Villegas et al. [16] examined legume intake in 64,227 women with no history of T2DM, cancer, or cardiovascular disease at study recruitment for an average of 4.6 years in the Shanghai Women's Health study. They observed an inverse association between quintiles of total legume intake and three mutually exclusive legume groups (peanuts, soybeans, and other legumes) and T2DM incidence. The multivariate-adjusted relative risk of T2DM for the upper quintile compared with the lower quintile was 0.62 (95%) CI, 0.51-0.74) for total legumes and 0.53 (95% CI, 0.45-0.62) for soybeans. The association between soy products (other than soy milk) and soy protein consumption (protein derived from soy beans and their products) with T2DM was not significant. The same study also showed a clear monotonic dose-response relationship between soy food intake and risk of total 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. The inverse association was more pronounced for nonfatal myocardial infarction (RR=0.14; 95% CI, 0.04–0.48 for the highest versus the lowest quartile of intake; P for trend=0.001). The number of cases, however, was very low (43 nonfatal and 14 fatal myocardial infarctions) [17].

Dairy

Dairy is an interesting food group containing foods that can be consumed in their full-fat natural form or as a low to zero fat protein and mineral mix. The latter is clearly not associated with CVD and there is variable evidence about the role of dairy saturated fat in increasing CVD risk, even though in interventions it elevates LDL cholesterol, suggesting other components may mitigate the risk from the saturated fat, such as the blood pressure–lowering effect of protein and calcium, the fat binding effects of calcium, and fermentations products in yogurt. This area has been recently reviewed [18•, 19].

Mozaffarian et al. [20•] found in the Cardiovascular Health Study that higher trans-palmitoleate (16:1 t) levels were associated with slightly lower adiposity and, independently, with higher high-density lipoprotein (HDL) cholesterol levels (1.9% across quintiles; P=0.040), lower triglyceride levels (-19.0%; P<0.001), a lower total cholesterol to HDL cholesterol ratio (-4.7%; P<0.001), lower C-reactive protein levels (-13.8%; P=0.05), and lower insulin resistance (-16.7%, P<0.001). Transpalmitoleate was also associated with a substantially lower incidence of diabetes, with multivariate hazard ratios of 0.41 (95% CI, 0.27–0.64) and 0.38 (95% CI, 0.24–0.62) in quintiles 4 and 5 versus quintile 1 (P for trend<0.001). Whole-fat dairy consumption was most strongly associated with higher trans-palmitoleate levels.

High Protein Interventions to Reduce CVD Risk

Assessing the effect of vegetable protein interventions compared with animal protein interventions is difficult because the former may increase PUFA and fiber (eg, nut and legume sources but not soy) whereas the latter can have a very variable amount of saturated fat, and these of course are essential elements of these two differing protein sources. Although no studies have examined just the effect of the proteins per se, this is not relevant to normal consumption of these protein sources.

In a study from China, 30 obese adults were randomized to two groups [21]. The soy-based low-calorie group consumed soy protein as the only protein source, and the traditional low-calorie group consumed two-thirds animal protein and the rest plant protein in a 1200-kcal/d diet for 8 weeks. The decrease in body fat percentage in the soy group (2.2%; 95% CI, 1.6–2.8) was greater than that in the traditional group (1.4%; 95% CI –0.1 to 2.8), although not significantly so. Serum total cholesterol concentrations, LDL cholesterol concentrations, and liver function parameters decreased in the soy-based group and were significantly different from measurements in the traditional group (P<0.05). No significant change in serum triacylglycerol levels, serum HDL cholesterol levels, and fasting glucose levels was found in the soy or traditional group.

In a small study with 28 participants with high LDL cholesterol, whole bean soy milk and soy protein isolate was compared to dairy milk for 4 weeks each with 4 weeks washout between phases [22]. A 25-g dose of daily soy

protein from soy milk (800 mL/d) led to a modest 5% lowering of LDL-C relative to dairy milk among adults with elevated LDL cholesterol. The effect did not differ by type of soy milk, and neither did soy milk significantly affect other lipid variables, insulin, or glucose.

In a test of a vegetarian, reduced-carbohydrate diet, a total of 44 overweight hyperlipidemic men and women consumed either 1) a low-carbohydrate (26% of total calories), high-vegetable protein (31% from gluten, soy, nuts, fruit, vegetables, and cereals), and vegetable oil (43%) plant-based diet, or 2) a high-carbohydrate lacto-ovo vegetarian diet (58% carbohydrate, 16% protein, and 25% fat) for 4 weeks each in a parallel study design [23]. The study food was provided at 60% of calorie requirements. Weight loss was similar for both diets (approximately 4.0 kg). However, reductions in LDL cholesterol concentration and total cholesterol to HDL cholesterol and apolipoprotein B to apolipoprotein A-I ratios were greater for the low-carbohydrate compared with the highcarbohydrate diet (-8.1% [P=0.002], -8.7% [P=0.004], and -9.6% [P=0.001], respectively). Reductions in systolic and diastolic blood pressure were also seen (-1.9%) [P= 0.052] and -2.4% [P=0.02], respectively). This was almost certainly due to the high polyunsaturated fat rather than the higher amount of vegetable protein. It is a pity there was not an animal protein intervention group or that fat source and amount was not matched between groups.

A complete contrast was the 12-month, animal-based Atkins diet performed at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Australia, which showed that despite a weight loss of over 14-kg, LDL cholesterol rose by 0.6 mmol/L because of the 15% of energy as saturated fat. Although triglyceride fell dramatically as did blood pressure, and blood glucose and HDL rose, an adverse cardiovascular outcome from this diet would be expected as flow-mediated dilatation worsened [24•, 25].

In a small, underpowered study of 18 participants that lasted for 5 months, Aldrich et al. [26] compared three treatment groups: control diet (CD; 55% carbohydrate/15% protein/30% fat), mixed protein (40% carbohydrate/30% protein/30% fat), or whey protein (WP; 40% carbohydrate/ 15% mixed protein/15% whey protein/30% fat). No statistically significant differences in total weight loss or total fat loss were observed between treatments; fat loss in the leg and gynoid regions was greater (P<0.05) in the WP group than the CD group, but this may not be beneficial. A decrease in systolic blood pressure was significantly greater (P<0.05) in the WP group compared with the CD group, which is in keeping with other weight steady studies of dairy protein.

In another small study of 35 obese men for 8 weeks, Abete et al [27] compared a high-mixed protein diet to a high-legume diet and a high-fatty fish diet and a control weight-loss diet. The high-protein diet and high-legume diet achieved greater body weight reduction ($-8.4\%\pm1.2\%$ and $-8.3\%\pm2.9\%$, respectively), as compared to the control diet ($-5.5\%\pm2.5\%$; P=0.042). Total and LDL cholesterol levels were significantly improved by the legume diet (P<0.05), whereas mitochondrial oxidation was specifically activated by the high-protein diet and high-legume diet at the end of the study.

Dairy Protein

Wennersberg et al. [28..] performed an intervention study in 2009 in 121 overweight participants who had some traits of the metabolic syndrome. Participants took either 3 to 5 servings of dairy per day or continued on their habitual diet for 6 months. Total milk and yogurt increased by 248 mL/d whereas cheese increased by only 20 g/d and butter did not change significantly. Protein, fat, and sugar all increased but there was no change in energy intake. No effects were seen on body weight or body composition, blood pressure, markers of inflammation, endothelial function, adiponectin, or oxidative stress in either the milk or the control groups. There was a modest unfavorable increase in serum cholesterol concentrations in the milk group (P=0.043). Among participants with a low calcium intake at baseline (< 700 mg/d), there was a significant treatment effect for waist circumference (P=0.003).

Vegetable Protein

In a review on soy, Xiao [29] noted that the Nutrition Committee of the American Heart Association has assessed 22 randomized trials conducted since 1999 and found that isolated soy protein with isoflavones (ISF) slightly decreased LDL cholesterol but had no effect on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. The other effects of soy consumption were not evident.

Ferdowsian and Barnard [30], in a review of plant-based diets and plasma lipids, included 27 randomized controlled and observational trials. Of the four types of plant-based diets considered, interventions testing a combination diet (a vegetarian or vegan diet combined with nuts, soy, and/or fiber) demonstrated the greatest effects (up to 35% plasma LDL cholesterol reduction), followed by vegan and ovolacto vegetarian diets. Interventions allowing small amounts of lean meat demonstrated less dramatic reductions in total cholesterol and LDL levels.

In a large (91 men and women) Australian study, 24 g/d of soy protein with or without 70 to 80 mg/d of isoflavones had no effect on LDL cholesterol in either the nonequol producers or the 30 subjects who produced equol. [31]. Equol producers have intestinal bacteria that convert the

isoflavone daidzein to equol, which is more biologically active than the parent compound.

In a randomised, controlled study, Campbell et al. [32] noted that in 62 women soy consumption over 12 months produced no significant differences in LDL cholesterol or triglyceride levels compared with control foods; however, a significant increase in apolipoprotein B levels (105.5 \pm 5.9 mg/dL vs 120.21 \pm 5.9 mg/dL; *P*=0.002) and a significant decrease in apolipoprotein A levels (189.36 \pm 10 mg/dL vs 173.21 \pm 10 mg/dL; *P*=0.009) were seen.

In a review on nuts and peanuts, Kris-Etherton et al. [33] noted that the LDL cholesterol–lowering response of nut and peanut studies is greater than expected on the basis of blood cholesterol–lowering equations that are derived from changes in the fatty acid profile of the diet. Thus, in addition to a favorable fatty acid profile, nuts and peanuts contain other bioactive compounds (such as arginine, phenolics, resveratrol) that may explain their multiple cardiovascular benefits.

Blood Pressure

A review by Altorf-van der Kuil [34] reported that most observational studies showed no association or an inverse association between total dietary protein and blood pressure or incident hypertension. Results of biomarker studies and randomized controlled trials indicated a beneficial effect of protein on blood pressure. This beneficial effect may be mainly driven by plant protein, according to results in observational studies. Data on protein from specific sources (eg, from fish, dairy, grain, soy, and nut) were scarce. There was some evidence that blood pressure in people with elevated pressure and/or older age could be more sensitive to dietary protein. However, meat-based interventions also lower blood pressure compared with carbohydrate [35].

In the PREMIER study of 810 participants followed for 18 months, dietary plant protein was inversely associated with both systolic and diastolic blood pressure in cross-sectional analyses at the 6-month follow-up (P=0.0045 and 0.0096, respectively). Fruit and vegetable intake was also inversely associated with both systolic and diastolic blood pressure cross-sectionally at 6 months (P=0.0003 and 0.0157, respectively) [36]. Animal and plant protein each comprised approximately 66% and 34%, respectively, of the total daily protein intake at baseline, and the overall pattern remained relatively constant over time and was little influenced by the intervention (DASH and usual diets). However, sex, race, age, and body weight status all influenced contribution patterns from different food groups significantly [37].

In a large (176 participants), 18-month weight loss trial, use of a vegetarian diet did not change any outcome variable compared with an omnivorous weight loss diet. Offering choice of diet had no effect nor was there any interaction with diet type [38].

Conclusions

In virtually all studies, vegetable protein is superior to animal protein with lower rates of heart disease and T2DM and lower blood pressure than animal protein. Dairy protein seems to be superior to meat protein but a large intervention with increased dairy intake showed no effects. Soy appears to have very little effect on LDL cholesterol in more recent studies.

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