



The role of high-protein diets in body weight management and health

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Abstract

Studies examining the health benefits of high-protein diets typical of most affluent and many developing countries are not consistent. Prospective epidemiological studies relating dietary protein to clinical and metabolic endpoints suggest increased weight gain and increased risk of diabetes amongst those with a high protein intake and an increased risk of cancer with high intakes of red meat, but lower blood pressure and possibly a reduced risk of heart disease with higher protein intakes. The potential for high-protein diets to confer greater benefit than other diets has been examined using *ad libitum* and energy restricted diets. Of greatest interest have been the comparisons between high-protein and high-carbohydrate diets. Many trials have reported greater weight loss especially in the context of *ad libitum* diets over the short-to medium-term, sparing of lean body mass, lowering of triglyceride levels, improved HDL: total cholesterol ratio and improved glycaemic control. Limited data regarding insulin sensitivity are less consistent. A major difficulty in interpreting the results of these studies is that carbohydrate quality has not been taken into account. Furthermore, longer term comparisons of weight reducing diets differing in macronutrient composition have reported similar outcomes, suggesting that compliance is a more important consideration. Nevertheless dietary patterns with high-protein intakes are appropriate for weight reduction and weight maintenance and may be useful for those who have high triglyceride levels and other features of the metabolic syndrome.

Key words: Body weight management: Dietary protein: Obesity: Metabolic syndrome

The traditional hunter-gather diets eaten by our pre-agricultural ancestors were higher in animal protein than contemporary diets⁽¹⁾. However this is of little relevance to current dietary recommendations given that modern protein sources, other dietary attributes, as well as lifestyle patterns, are different from those of traditional hunter-gatherer communities. Studies examining the health benefits of high-protein diets in the modern context have not reported consistent findings, nevertheless examination of the relevant literature suggests that high-protein diets may confer some advantages, particularly for overweight individuals with features of the metabolic syndrome^(2–4).

Epidemiology

Prospective epidemiological studies examining associations between dietary protein and health are relatively sparse and conflicting. Recently several large prospective studies in men and women have shown protein intakes to be associated with increased risk of diabetes^(5–7) corresponding with earlier reports that dietary protein from animal sources was associated with increased insulin resistance in young adults⁽⁸⁾. Although these findings were somewhat attenuated after

adjustment for multiple potential lifestyle and dietary confounders the associations remained statistically significant. Moreover these studies consistently showed that animal protein sources such as red meat explained much of the association. Similarly there is convincing epidemiological evidence linking red meat consumption with increased risk of colorectal cancer^(9,10) but not dietary protein *per se*. In contrast to the increased diabetes risks when comparing extreme intake quartiles, women with the highest protein intakes have previously been shown to be at reduced risk of ischaemic heart disease⁽¹¹⁾, although recent analysis of the same data set and with longer follow-up has shown high red meat intakes were associated with ischaemic heart disease even after adjusting for other risk factors⁽¹²⁾. A similar trend has been shown in men although an association between animal protein and risk of ischaemic heart disease was only shown in men who were initially free of hypertension, hypercholesterolaemia and diabetes⁽¹³⁾. Conversely dietary protein has been shown to be unrelated to risk of stroke in the same group of men⁽¹⁴⁾ but has been shown to be protective in a Japanese population⁽¹⁵⁾. In postmenopausal women total protein and animal protein intakes were not associated with coronary heart disease mortality⁽¹⁶⁾ and cancer mortality⁽¹⁶⁾ when analyses were adjusted

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for potential confounders. However models of isoenergetic substitution of vegetable protein for animal protein suggested reduced risk of coronary heart disease mortality⁽¹⁶⁾. In addition a recent systematic review of the evidence from observational studies and trials examining relationships between protein and blood pressure suggests a modest beneficial effect of protein, especially plant protein⁽¹⁷⁾.

Weight loss

The potential for high-protein diets to confer greater benefits in terms of weight loss than other diets has been examined using *ad libitum* and energy-restricted diets. *Ad libitum* diets are more likely than energy-restricted diets to allow identification of unique properties of protein in facilitating weight loss since strict control of energy intakes will invariably achieve clinically important weight loss that will almost certainly mask any relevant metabolic effects of protein. Interest has particularly centred around comparisons between high-protein and high-carbohydrate diets. In randomized intervention trials *ad-libitum* diets with a relatively high protein content (25–30% of total energy intake) have been shown to facilitate weight and fat loss to a statistically significantly greater extent than high-carbohydrate diets with protein providing 10–20% of total energy^(18–23). A well-designed study by Skov and colleagues compared fat-reduced diets that were either moderately high in protein (protein 25% of energy; carbohydrate 45% of energy) or high in carbohydrate (protein 12% of energy; carbohydrate 58% of energy) in a group of obese adults⁽¹⁸⁾. Energy intakes were not restricted. After 6 months the high-protein group had lost significantly more total body weight (+3.7 kg) and body fat (+3.3 kg) than the high-carbohydrate group and this was accounted for by a spontaneous reduction in energy intake. After 1 year of follow-up the high-protein group had maintained a greater degree of weight loss than the high-carbohydrate group but the difference between the two diets was no longer statistically significant⁽²⁰⁾. However reductions in waist circumference and intra-abdominal adipose tissue remained significantly lower in the high-protein diet group⁽²⁰⁾. Although *ad libitum* intakes were permitted, this study involved intensive dietary counselling and macronutrient composition was tightly controlled by providing the majority of foods consumed through a study-shop. A study undertaken by our group compared two popular diets (the high-protein Zone diet and the high-protein and high fat Atkins diet) with a conventional low-fat, high-carbohydrate diet in overweight, insulin resistant women⁽²¹⁾. As with the Skov *et al* study *ad libitum* energy intakes were permitted for all three diets but foods appropriate to each diet group were not provided. After 6-months individuals on the Zone and Atkins diets had lost significantly more weight and had greater reductions in blood triglyceride concentrations than those on the high-carbohydrate diet. The continuing apparently greater weight and fat loss in the high-protein (Zone) group at 12 months was not statistically significant, but blood triglyceride concentrations remained significantly lower. Furthermore the proportion of individuals who had lost more than 10% of

their initial body weight remained significantly higher after one year on the high-protein diets in our study⁽²⁰⁾ as was the case with the study by Skov and colleagues^(20,22). It is also relevant to note that in both studies the high-carbohydrate diets were not high in dietary fibre with participants on average achieving less than 25 g dietary fibre per day, even though a high dietary fibre intake was intended (at least in our study⁽²⁴⁾).

When comparing energy-restricted diets the evidence relating to weight loss is less consistent. The majority of studies comparing high-protein diets with low-fat, high-carbohydrate diets have not found differences in weight loss either over the medium term (8–16-weeks)^(25–30,23) or the long term (12-months)^(31,32). Two studies have compared the effectiveness of four popular diets for weight loss over 12-months and reported no particular benefit of the high-protein Zone diet^(33,34). In these studies subjects were given relatively intensive counselling support in the early months of the study after which time the level of support was reduced. One of the studies found that weight loss was associated with measures of adherence to the dietary advice but there were no differences between the four dietary approaches⁽³³⁾. In the other study although weight loss on the Zone diet (high-protein) was not different to that on the two high-carbohydrate diets, it was significantly lower than that achieved by the high fat Atkins diet⁽³⁴⁾. Long-term studies such as these are not surprisingly associated with poor compliance and high dropout rates making it difficult to draw definitive conclusions regarding the effects of macronutrient composition on weight loss^(31,35,33,34). One study that reported greater weight and fat loss with an energy-restricted high-protein diet compared with a high-carbohydrate diet involved very high protein intakes (45% of energy)⁽³⁶⁾. Subjects lost 8.8 kg on the high-protein diet compared with 6.1 kg on the high-carbohydrate diet over four weeks. To achieve this all meals were provided and it is unlikely that this level of protein intake could have been sustained in a more free-living context. Lasker and colleagues found greater fat loss and weight loss in their 4-month study comparing a high-protein diet with a high-carbohydrate diet but the study appeared to be underpowered and the results just bordered statistical significance⁽³⁰⁾. Somewhat more convincing evidence for a benefit of high-protein diets during weight loss was provided in a 12-month study by Clifton and colleagues⁽³²⁾. Although weight loss was not statistically significantly different between subjects assigned to high-protein or high-carbohydrate diets, a post-hoc analysis showed that in subjects in the highest tertile of self-reported protein intake (>88 g/d of protein) weight loss was twice that observed in the lower two tertiles of intake⁽³²⁾.

A particularly important limitation of the studies which have concluded that high protein intakes confer benefits in terms of weight loss when compared with high-carbohydrate diets relates to the nature of carbohydrate consumed by those randomized to the various high-carbohydrate comparison groups. High-carbohydrate diets which consist predominantly of foods high in rapidly digested starches and sugars and are low in dietary fibre would be unlikely to promote weight loss⁽³⁷⁾. None of the studies involving energy restriction thus far

mentioned have specifically addressed the nature of carbohydrate in the comparison diets. Of those that have reported dietary fibre intakes, in only a few studies have subjects assigned to the high-carbohydrate diets achieved intakes of more than 25 g of fibre per day^(25,27,28), generally assumed to be the lower level of intake that may confer benefit⁽³⁸⁾. However insufficient information was provided to determine whether the carbohydrate consumed was of appropriate quality. None of these studies, whether or not dietary fibre intakes were adequate, reported differences in weight change between the high-protein and high-carbohydrate diets. Recent research conducted by our group has addressed this issue⁽³⁹⁾. We compared a relatively high-protein diet with a low-fat, high-carbohydrate diet that was rich in dietary fibre derived principally from minimally processed grains, cereals and legumes. The 8-week trial was designed as a proof of concept study aiming to achieve weight loss. A total dietary protein intake of 28% of energy, of which 75% was derived from animal sources (including dairy), was achieved on the high-protein diet compared with 22% of energy in the high-carbohydrate, high-fibre diet. Dietary fibre intakes were 24 g/d and 39 g/d respectively. Participants on both diets lost weight (4.5 kg on the high-protein diet and 3.3 kg on the high-carbohydrate, high-fibre diet), and reduced waist circumference, truncal fat, systolic blood pressure, fasting plasma glucose, total and LDL-cholesterol and triglyceride, insulin and an increase in insulin sensitivity, and without any loss of lean body mass. However participants on HP lost 1.3 kg more weight and 1.3 kg more total body fat and achieved a greater reduction in diastolic blood pressure (3.7 mm Hg). Although improvements in most other risk factors were more marked on the high-protein diet than the high-carbohydrate, high-fibre diet the differences between diets did not achieve conventional levels of statistical significance.

In a second six month study we compared in indigenous Māori adults at risk of diabetes, the standard dietary prescription emphasizing benefits of fibre-rich carbohydrate foods, and a diet compatible with food choices of indigenous people including more protein-rich foods and less carbohydrate with a control diet (unpublished data). We found that a high-protein diet (30% of energy) based on traditional and western high protein foods achieved a meaningful and highly statistically significant reduction in body weight (2.6 kg), waist circumference (3 cm) and body fat (1.6 kg) compared with the control diet. This was maintained even after cessation of intensive, prescriptive advice. The conventional high-carbohydrate high-fibre advice, although associated with small statistically significant losses in total body weight (1.9 kg) when compared with the control diet, did not produce changes in waist circumference or body fat. Wholegrain cereals and breads which are staple foods in a fibre-rich high-carbohydrate diet were not favoured by the Māori participants who did not appreciably increase their intake of dietary fibre despite intensive advice to do so. Given that advice to increase fibre-rich carbohydrate foods and decrease fat, the cornerstones of current recommendations, are unacceptable for New Zealand Māori, a diet relatively high in protein would

seem to be an appropriate alternative for them and possibly other indigenous populations.

Several of the studies which did not show an effect of diet on body weight loss have shown that compared with high-carbohydrate diets high-protein diets appear to preserve lean body mass and/or lead to reduced fat mass during weight loss which is of particular relevance with regard to the metabolic syndrome^(40,18,25,41,2,42,30,23,43). A meta-regression of 87 dietary intervention studies involving energy restriction and lasting for four or more weeks showed that while diets involving carbohydrate restriction were associated with increased weight and fat loss, protein intake was not⁽²⁾. It is important to note that the nature of the carbohydrate was not considered in the meta-regression. Nevertheless higher protein intakes (>1.05 g protein kg⁽⁻¹⁾) were associated with greater retention of lean muscle mass during weight loss and there was a trend towards enhanced fat loss. The research carried out by our group did not find superior retention of lean body mass during weight loss on high-protein diets in comparison with high-carbohydrate diets. However the protein intakes achieved on our high-carbohydrate diets were 20-22% of total energy which is relatively high compared to the high-carbohydrate diets reported in the meta-regression⁽²⁾. This reflects the nature of diets typically consumed by New Zealanders.

Uncontrolled intervention studies assessing the effectiveness of high-protein diets without a comparative group provide further limited evidence of benefits of a high-protein diet. In one such study Weigle and colleagues increased protein intake without carbohydrate restriction (i.e. at the expense of dietary fat). This appeared to facilitate weight loss despite *ad-libitum* intake of energy⁽⁴¹⁾. Healthy non-obese subjects consumed a weight-maintaining standard protein diet (15% of energy) for 2 weeks, followed by a weight-maintaining high-protein diet (30% of energy) and then an *ad-libitum* high-protein diet for 12 weeks. Carbohydrate content was maintained at 50% of energy during all 3 dietary phases. Subjects reported a decrease in appetite and a reduction in energy intake of approximately 2000 kJ/d during the *ad libitum* phase. This resulted in a constant rate of weight loss during the 12-week period. Fat loss accounted for 76% of the weight loss. However in a separate but parallel study by this group similar effects on satiety, energy intake and weight loss were observed in subjects following an *ad-libitum* low-fat, high-carbohydrate diet for 12 weeks⁽⁴⁴⁾. Thus while the high-protein approach was beneficial the evidence suggested no particular advantage over a low-fat, high-carbohydrate diet. In another study overweight subjects with metabolic syndrome also successfully lost weight and fat following a carbohydrate-restricted diet that was relatively high in protein and MUFA (the South Beach Diet)⁽⁴⁵⁾. A high-protein diet (Zone Diet) has been reported to be beneficial in men with gout and risk factors for the metabolic syndrome, resulting in weight loss and corresponding improvement in metabolic syndrome risk factors as well as a significant reduction in gout attacks⁽⁴⁶⁾. These results are of interest because the high-protein diet was rich in purines (derived principally from protein-rich flesh foods) whereas dietary



recommendations for gout generally include a restriction of dietary purines⁽⁴⁷⁾. Thus while uncontrolled studies do not generate definitive conclusions these studies suggest that high-protein diets may be an effective treatment option for individuals with metabolic syndrome.

Insulin sensitivity

Reducing adiposity is generally associated with increased insulin sensitivity⁽⁴⁸⁾. However relatively few studies have compared the effects of high-protein diets varying in macronutrient composition on insulin sensitivity. Limited data suggest that moderately high-protein weight-loss diets (25–30% of energy) improve glucose metabolism and insulin sensitivity in comparison with low-fat, high-carbohydrate diets. Piatti and colleagues compared the effect of high-protein and high-carbohydrate weight loss diets on insulin sensitivity in obese women⁽⁴⁰⁾. After 3 weeks, insulin sensitivity measured with the euglycaemic clamp was maintained on the high-protein diet but had declined by approximately 30% on the high-carbohydrate diet. While there were no statistically significant differences in weight loss, there was a greater retention of fat-free mass in the high-protein group which may account for the difference in insulin sensitivity. In men and women with type two diabetes Parker and colleagues also showed that compared with a high-carbohydrate diet a moderately high-protein diet was associated with improved insulin sensitivity, measured by a 150 min low-dose glucose and insulin infusion test. Again both groups lost a similar amount of weight although women lost more abdominal fat on the high-protein diet⁽⁴⁹⁾. In contrast Sargrad and colleagues conducted a small, parallel-design, eight-week weight-loss trial in 12 individuals with type two diabetes comparing high-protein and high-carbohydrate diets. While weight loss was equivalent on the two diets there was a 25% increase in total body glucose uptake (euglycaemic clamp) on the high-carbohydrate diet, but no change on the high-protein diet⁽⁵⁰⁾. Differences in extent of impairment in carbohydrate metabolism, variation in methods of assessing insulin sensitivity and limited power of the studies due to small sample sizes may well explain these inconsistencies. However further studies are required to elucidate the effect of protein on insulin sensitivity in overweight and obese individuals and those with type two diabetes or impaired glucose tolerance.

In the context of weight maintenance limited data suggest that increased dietary protein intakes may be associated with reduced insulin sensitivity and alterations in glucose metabolism that are considered unfavourable⁽⁵¹⁾. Adults who habitually consume high-protein diets (>0.8 g protein/kg/d) have been shown to have lower insulin sensitivity and increased endogenous glucose production than those consuming low protein diets (<0.8 g/kg/d)⁽⁵²⁾. We recently reported on the effect on body composition and metabolic risk factors of a diet moderately high in both protein and dietary fibre and without advice to restrict energy intake in women at risk of developing diabetes⁽⁵³⁾. This study also examined the effect of the diet on insulin sensitivity measured with the dynamic

insulin sensitivity and secretion test (DISST)⁽⁵⁴⁾. We found that individuals following the high-protein and high-fibre diet had a significant reduction in insulin sensitivity in comparison with individuals following standard dietary advice even though body composition and blood lipids were significantly improved (unpublished data). These apparently conflicting findings about the effect of high-protein diets on insulin sensitivity are currently being examined further in large controlled trials.

Animal studies shed some light on the action of protein but do not explain the apparently conflicting findings. A study in normal adult rats showed that high-protein, reduced-carbohydrate diets led to reduced insulin-mediated glucose disposal, raised fasting glucose concentrations and increased hepatic glucose production⁽⁵⁵⁾. When carbohydrate was added back into the low-carbohydrate diets insulin sensitivity was restored suggesting that it was the lack of carbohydrate rather than an excess of protein that caused the insulin resistance. Long-term high-protein feeding has also been shown to improve hyperglycaemia and glycosuria in severely diabetic rats⁽⁵⁶⁾.

Other metabolic syndrome abnormalities

Although the effect of high-protein diets on insulin sensitivity is unclear, especially in weight stable individuals, this dietary approach has consistently been shown to improve a range of abnormalities associated with the metabolic syndrome in comparison with standard high-carbohydrate diets. A consistent finding in intervention studies has been a reduction in plasma triglyceride concentrations in conjunction with weight loss with moderately high-protein diets in comparison with high-carbohydrate diets^(18,57,26,19,21,28,29,22,43). Several studies have also found a relative improvement in HDL-cholesterol on high-protein diets^(58,43). There is some evidence that high-protein diets may be particularly beneficial in individuals with features of the metabolic syndrome. Noakes and colleagues reported that subjects with elevated triglyceride concentrations lost more weight on a high-protein diet compared with a high-carbohydrate diet whereas individuals with lower triglyceride concentrations lost a similar amount of weight on both diets⁽²⁸⁾. Other groups have reported inverse relationships between protein intake and blood pressure, particularly in hypertensive individuals^(59–62,4). Moreover high-protein, reduced-carbohydrate diets have been shown to improve measures of glycaemic control in subjects with T2DM^(49,63,64). It should be noted, once again, that the nature of the carbohydrate in the comparison high-carbohydrate diets was not considered in these studies.

Protein and body weight epidemiology

In contrast with the findings of controlled trials of high-protein diets a number of epidemiological studies have found a positive association between red meat consumption (a major contributor to protein intakes in Western diets^(65–67)) and weight gain^(68–74). In an analysis of the Oxford cohort of the large European Prospective Investigation into Cancer (EPIC) study

Rosell and colleagues found that meat eaters gained more weight than vegans over 5.3 years and this was strongly associated with a higher percentage of energy from protein and a lower intake of dietary fibre⁽⁷⁴⁾. Very recently an analysis of the EPIC population including 103,455 men and 270,348 women showed that total meat intake as well as intakes of red meat, poultry and processed meat was positively associated with weight gain in all subjects, irrespective of sex, degree of adiposity and smoking status, during 5 years of follow-up⁽⁷⁵⁾. However Vergnaud and colleagues showed that meat intake was associated with weight gain even after adjusting for dietary pattern scores suggesting the possibility that residual confounding might fully explain the observed associations⁽⁶⁸⁾. The findings of these cohort studies would seem to be sufficient to negate the findings that a relatively high-protein diet may be an effective strategy for promoting weight loss and improving the metabolic derangements in those who are overweight, obese or have factors of the metabolic syndrome or diabetes.

Mechanisms for the effect of protein on weight loss

High-protein diets may influence energy balance by increasing post-meal satiety and increasing basal energy expenditures⁽⁷⁶⁾. These factors may largely explain the effects of protein on weight and fat loss. Acute meal studies have shown that subjects report greater satiety after consuming higher protein meals compared with standard high-carbohydrate meals^(77,78), in some cases resulting in increased post-meal energy expenditure⁽⁷⁹⁾ or reduced energy intake at a subsequent meal^(80,81). Controlled metabolic studies conducted in respiration chambers show that over the duration of one to several days, high-protein diets (providing protein in excess of requirements) continue to be more satiating than diets higher in both fat and carbohydrate although energy intake is not reduced^(82,83). Higher protein intakes may increase energy expenditure by increasing diet induced thermogenesis (DIT)⁽⁷⁶⁾. DIT relates to the amount of energy required for absorbing and metabolising the nutrients (including increased body protein turnover in the case of amino acids) and storing that which is not immediately oxidised for energy. DIT values have been shown to be substantially greater (17%) for protein-rich meals than for fat-rich and carbohydrate-rich meals^(82,84,76). A relative inefficiency in protein metabolism may contribute to the higher DIT and thus the weight loss benefits reported with higher protein diets. Amino acids in comparison with fatty acids and glucose are catabolised less efficiently, yielding lower net amounts of ATP⁽⁷⁶⁾. On the basis of acute studies in respiration chambers it has been proposed that the greater diet-induced energy expenditure with high-protein meals also contributes to increased feelings of satiety as a result of increased oxygen consumption and body-temperature⁽⁸²⁾ but the evidence is not consistent⁽⁸⁴⁾.

There is some evidence from acute meal studies that different proteins appear to influence appetite, satiety and energy expenditure to a greater or lesser extent. Whey protein (derived from milk) has been shown in some studies to be

more satiating than casein or soya but results are inconsistent, possibly due to widely varying amounts of protein provided in the test meals⁽⁸⁵⁾. Animal proteins may increase protein oxidation and energy expenditure more than plant-derived proteins such as soya⁽⁸⁶⁾. The effects of different proteins appear to be related to the composition of amino acids in the protein source and the digestibility of the protein, which may have varying effects on the concentrations of hormones associated with appetite regulation (i.e. anorexigenic hormones) including cholecystokinin (CCK), glucagon-like-peptide-1 (GLP-1) and peptide tyrosin-tyrosin (PYY)^(85,76).

It has also been proposed that specific amino acids consumed in the diet may be directly channelled into the synthesis of neurotransmitters involved in appetite regulation⁽⁷⁶⁾. For example there has been some interest in the amino acid tryptophan because it may be a precursor for the synthesis of the anorexigenic neurotransmitter serotonin. However, while it is possible to increase serotonin activity through increased tryptophan intake, tryptophan supplementation in a single meal did not appear to influence satiety⁽⁸⁷⁾. Moreover an *ad-libitum* high-protein diet which led to spontaneous energy reduction and weight-loss found no evidence of dietary-induced changes in tryptophan or serotonin to explain this⁽⁸⁸⁾.

Elevated concentrations of specific amino acids in high-protein diets may explain the effect of protein in sparing lean muscle mass during weight loss. In a review of the role of leucine in weight loss Layman and Walker hypothesize that the branched chain amino acids (BCAA), in particular leucine, have a key metabolic role in muscle sparing by acting as both a regulator and a substrate for muscle protein synthesis⁽⁸⁹⁾. Supplementation with leucine has been shown to stimulate muscle synthesis during catabolic conditions such as exercise or overnight fasting in acute studies. In weight-loss trials high-protein diets (125 g/d protein) designed to provide twice the leucine concentration found in standard low-fat, high-carbohydrate diets resulted in a greater loss of fat mass without any greater loss of lean muscle mass compared with high-carbohydrate diets^(26,43). The metabolic pathways that are dependent on leucine appear to be optimised with a high-protein diet (approximately 25-30% of energy) based on high quality proteins such as those found in eggs, dairy products and meat. However experimental evidence to support a specific role of leucine in sparing lean mass during weight loss is limited.

Leucine may also play an important role in regulating glucose homeostasis. Leucine (and the other BCAAs) provide amino nitrogen for the synthesis of the amino acid alanine. Alanine is required for hepatic gluconeogenesis which is important for maintaining stable blood glucose concentrations particularly in the fasting condition^(90,89). Feeding subjects a high-protein breakfast has been shown to increase plasma levels of leucine and alanine whereas a high-carbohydrate diet had no effect on plasma amino acid concentrations⁽⁹⁰⁾. However whether or not a leucine-rich high-protein diet will improve glucose homeostasis remains to be shown.

Two amino acids found in red meat, taurine and arginine, could explain the positive associations observed between



high-protein diets and blood pressure lowering. Taurine has been shown to improve blood pressure in hypertensive humans and rats⁽⁹¹⁾, while arginine has been shown to improve vasodilation, endothelial function and blood pressure in subjects with hypertension^(92,93). However other factors associated with higher protein diets, such as reductions in carbohydrate or sodium intakes, may also improve blood pressure⁽⁶²⁾.

Conclusion

In short term studies, when compared with high-carbohydrate diets, diets relatively high in protein promote a greater reduction in body fat and blood pressure and an improved lipid profile. Several plausible mechanisms have been proposed for the effects of a high-protein diet on body weight loss but differences are most striking when *ad libitum* energy intakes are permitted suggesting that weight loss is mediated via a reduction in energy intake rather than unique thermic properties of protein. Most studies have paid little attention to the nature of dietary carbohydrate in the comparison diet but two recent studies suggest that even when wholegrains, vegetables and fruits predominate and dietary fibre is appreciably raised, the high-protein diets still confer some benefits. Comparison studies continuing for a year or longer suggest that these benefits are not sustained in the long term. While this may be due to reducing compliance over time, failure to demonstrate convincing benefit in the long term is a major limitation in drawing conclusions and making definitive recommendations regarding the use of high-protein diets. However it seems reasonable to suggest that relatively high-protein diets are an appropriate option for the treatment and avoidance of excess body fat, especially for those who have clinical and metabolic features which characterise the metabolic syndrome and for indigenous people who generally find high-fibre carbohydrate foods unappealing or unacceptable. Prospective epidemiological data have generated conflicting results. This and the failure to demonstrate benefit in long term trials preclude more general advice to increase the proportion of protein in the diet.

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References

- Konner M & Eaton SB (2010) Paleolithic nutrition: twenty-five years later. *Nutr Clin Pract* **25**, 594–602.
- Krieger JW, Sitren HS, Daniels MJ, *et al.* (2006) Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. *Am J Clin Nutr* **83**, 260–274.
- Nordmann AJ, Nordmann A, Briel M, *et al.* (2006) Effects of Low-Carbohydrate vs Low-Fat Diets on Weight Loss and Cardiovascular Risk Factors: A Meta-analysis of Randomized Controlled Trials. *Arch Intern Med* **166**, 285–293.
- Hession M, Rolland C, Kulkarni U, *et al.* (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev* **10**, 36–50.
- Song Y, Manson JE, Buring JE, *et al.* (2004) A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. *Diabetes Care* **27**, 2108–2115.
- Schulze MB, Schulz M, Heidemann C, *et al.* (2008) Carbohydrate intake and incidence of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr* **99**, 1107–1116.
- Sluijs I, Beulens JW, van der AD, *et al.* (2010) Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care* **33**, 43–48.
- Pereira MA, Jacobs DR Jr, Van Horn L, *et al.* (2002) Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA* **287**, 2081–2089.
- Larsson SC & Wolk A (2006) Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* **119**, 2657–2664.
- World Cancer Research Fund/American Institute for Cancer Research (2007) *Food, Nutrition, and Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; available at <http://www.dietandcancerreport.org/>
- Hu FB, Stampfer MJ, Manson JE, *et al.* (1999) Dietary protein and risk of ischemic heart disease in women. *Am J Clin Nutr* **70**, 221–227.
- Bernstein AM, Sun Q, Hu FB, *et al.* (2010) Major dietary protein sources and risk of coronary heart disease in women. *Circulation* **122**, 876–883.
- Preis SR, Stampfer MJ, Spiegelman D, *et al.* (2010) Dietary protein and risk of ischemic heart disease in middle-aged men. *Am J Clin Nutr* **92**, 1265–1272.
- Preis SR, Stampfer MJ, Spiegelman D, *et al.* (2009) Lack of association between dietary protein intake and risk of stroke among middle-aged men. *Am J Clin Nutr* **91**, 39–45.
- Sauvaget C, Nagano J, Allen N, *et al.* (2003) Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Int J Epidemiol* **32**, 536–543.
- Kelemen LE, Kushi LH, Jacobs DR Jr, *et al.* (2005) Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol* **161**, 239–249.
- Altorf-van der Kuil W, Engberink MF, Brink EJ, *et al.* (2010) Dietary protein and blood pressure: a systematic review. *PLoS One* **5**, e12102.
- Skov AR, Toubro S, Ronn B, *et al.* (1999) Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. *Int J Obes Relat Metab Disord* **23**, 528–536.
- Samaha FF, Iqbal N, Seshadri P, *et al.* (2003) A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* **348**, 2074–2081.
- Due A, Toubro S, Skov AR, *et al.* (2004) Effect of normal-fat diets, either medium or high in protein, on body weight in overweight subjects: a randomised 1-year trial. *Int J Obes Relat Metab Disord* **28**, 1283–1290.
- McAuley KA, Hopkins CM, Smith KJ, *et al.* (2005) Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia* **48**, 8–16.

22. McAuley KA, Smith KJ, Taylor RW, *et al.* (2006) Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. *Int J Obes (Lond)* **30**, 342–349.
23. Claessens M, Van Baak MA, Monsheimer S, *et al.* (2009) The effect of a low-fat, high-protein or high-carbohydrate ad libitum diet on weight loss maintenance and metabolic risk factors. *Int J Obes* **33**, 296–304.
24. McAuley KA, Williams SM, Mann JI, *et al.* (2002) Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomized controlled trial. *Diabetes Care* **25**, 445–452.
25. Farnsworth E, Luscombe ND, Noakes M, *et al.* (2003) Effect of a high-protein, energy-restricted diet on body composition, glycemic control, and lipid concentrations in overweight and obese hyperinsulinemic men and women. *Am J Clin Nutr* **78**, 31–39.
26. Layman DK, Boileau RA, Erickson DJ, *et al.* (2003) A Reduced Ratio of Dietary Carbohydrate to Protein Improves Body Composition and Blood Lipid Profiles during Weight Loss in Adult Women. *J. Nutr* **133**, 411–417.
27. Johnston CS, Tjonn SL & Swan PD (2004) High-Protein, Low-Fat Diets Are Effective for Weight Loss and Favorably Alter Biomarkers in Healthy Adults. *J. Nutr* **134**, 586–591.
28. Noakes M, Keogh JB, Foster PR, *et al.* (2005) Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. *Am J Clin Nutr* **81**, 1298–1306.
29. Krauss RM, Blanche PJ, Rawlings RS, *et al.* (2006) Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am J Clin Nutr* **83**, 1025–1031.
30. Lasker DA, Evans EM & Layman DK (2008) Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: A randomized clinical trial. *Nutr Metab (Lond)* **5**, 30.
31. Brinkworth GD, Noakes M, Keogh JB, *et al.* (2004) Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *Int J Obes Relat Metab Disord* **28**, 661–670.
32. Clifton PM, Keogh JB & Noakes M (2008) Long-term effects of a high-protein weight-loss diet. *Am J Clin Nutr* **87**, 23–29.
33. Dansinger ML, Gleason JA, Griffith JL, *et al.* (2005) Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* **293**, 43–53.
34. Gardner CD, Kiazand A, Alhassan S, *et al.* (2007) Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA* **297**, 969–977.
35. Brinkworth GD, Noakes M, Parker B, *et al.* (2004) Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: one-year follow-up of a randomised trial. *Diabetologia* **47**, 1677–1686.
36. Baba NH, Sawaya S, Torbay N, *et al.* (1999) High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. *Int J Obes Relat Metab Disord* **23**, 1202–1206.
37. Poppitt SD, Keogh GF, Prentice AM, *et al.* (2002) Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. *Am J Clin Nutr* **75**, 11–20.
38. Mann J (2007) Dietary carbohydrate: relationship to cardiovascular disease and disorders of carbohydrate metabolism. *Eur J Clin Nutr* **61**, Suppl. 1, S100–S111.
39. Te Morenga LA, Levers MT, Williams SM, *et al.* (2011) Comparison of high protein and high fiber weight-loss diets in women with risk factors for the metabolic syndrome: a randomized trial. *Nutr J* **10**, 40.
40. Piatti PM, Monti F, Fermo I, *et al.* (1994) Hypocaloric high-protein diet improves glucose oxidation and spares lean body mass: comparison to hypocaloric high-carbohydrate diet. *Metabolism* **43**, 1481–1487.
41. Weigle DS, Breen PA, Matthys CC, *et al.* (2005) 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* **82**, 41–48.
42. Leidy HJ, Carnell NS, Mattes RD, *et al.* (2007) Higher Protein Intake Preserves Lean Mass and Satiety with Weight Loss in Pre-obese and Obese Women. *Obesity* **15**, 421–429.
43. Layman DK, Evans EM, Erickson D, *et al.* (2009) A moderate-protein diet produces sustained weight loss and long-term changes in body composition and blood lipids in obese adults. *J Nutr* **139**, 514–521.
44. Weigle DS, Cummings DE, Newby PD, *et al.* (2003) Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. *J Clin Endocrinol Metab* **88**, 1577–1586.
45. Hayes MR, Miller CK, Ullbrecht JS, *et al.* (2007) A carbohydrate-restricted diet alters gut peptides and adiposity signals in men and women with metabolic syndrome. *J Nutr* **137**, 1944–1950.
46. Dessein PH, Shipton EA, Stanwix AE, *et al.* (2000) Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis* **59**, 539–543.
47. Emmerson BT (1996) The management of gout. *N Engl J Med* **334**, 445–451.
48. Mann JI (2006) Nutrition recommendations for the treatment and prevention of type 2 diabetes and the metabolic syndrome: an evidenced-based review. *Nutr Rev* **64**, 422–427.
49. Parker B, Noakes M, Luscombe N, *et al.* (2002) Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. *Diabetes Care* **25**, 425–430.
50. Sargrad KR, Homko C, Mozzoli M, *et al.* (2005) Effect of high protein vs high carbohydrate intake on insulin sensitivity, body weight, hemoglobin A1c, and blood pressure in patients with type 2 diabetes mellitus. *J Am Diet Assoc* **105**, 573–580.
51. Tremblay F, Lavigne C, Jacques H, *et al.* (2007) Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. *Annu Rev Nutr* **27**, 293–310.
52. Linn T, Santosa B, Gronemeyer D, *et al.* (2000) Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia* **43**, 1257–1265.
53. Te Morenga L, Williams S, Brown R, *et al.* (2010) Effect of a relatively high-protein, high-fiber diet on body composition and metabolic risk factors in overweight women. *Eur J Clin Nutr* **64**, 1323–1331.
54. Lotz TF, Chase JG, McAuley KA, *et al.* (2006) Transient and steady-state euglycemic clamp validation of a model for glycemic control and insulin sensitivity testing. *Diabetes Technol Ther* **8**, 338–346.

55. Rossetti L, Rothman DL, DeFronzo RA, *et al.* (1989) Effect of dietary protein on in vivo insulin action and liver glycogen repletion. *Am J Physiol* **257**, E212–E219.
56. Siegel EG, Trapp VE, Wollheim CB, *et al.* (1980) Beneficial effects of low-carbohydrate–high-protein diets in long-term diabetic rats. *Metabolism* **29**, 421–428.
57. Jenkins DJ, Kendall CW, Vidgen E, *et al.* (2001) High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. *Am J Clin Nutr* **74**, 57–63.
58. Wolfe BM & Piche LA (1999) Replacement of carbohydrate by protein in a conventional-fat diet reduces cholesterol and triglyceride concentrations in healthy normolipidemic subjects. *Clin Invest Med* **22**, 140–148.
59. Stamler J, Elliott P, Kesteloot H, *et al.* (1996) Inverse relation of dietary protein markers with blood pressure. Findings for 10,020 men and women in the INTERSALT Study. INTERSALT Cooperative Research Group. INTERNATIONAL study of SALT and blood pressure. *Circulation* **94**, 1629–1634.
60. Appel LJ, Sacks FM, Carey VJ, *et al.* (2005) Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* **294**, 2455–2464.
61. Hu FB (2005) Protein, body weight, and cardiovascular health. *Am J Clin Nutr* **82**, 242S–247S.
62. Hodgson JM, Burke V, Beilin LJ, *et al.* (2006) Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr* **83**, 780–787.
63. Gannon MC, Nuttall FQ, Saeed A, *et al.* (2003) An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. *Am J Clin Nutr* **78**, 734–741.
64. Layman DK, Clifton P, Gannon MC, *et al.* (2008) Protein in optimal health: heart disease and type 2 diabetes. *Am J Clin Nutr* **87**, 1571S–1575S.
65. Witteman JC, Willett WC, Stampfer MJ, *et al.* (1989) A prospective study of nutritional factors and hypertension among US women. *Circulation* **80**, 1320–1327.
66. Slimani N, Fahey M, Welch AA, *et al.* (2002) Diversity of dietary patterns observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. *Public Health Nutr* **5**, 1311–1328.
67. Ministry of Health (2003) *Food and Nutrition Guidelines for Healthy Adults: A background paper*. no. 0-478-25839-9. Wellington, NZ: Ministry of Health.
68. Vergnaud AC, Norat T, Romaguera D, *et al.* Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. *Am J Clin Nutr* **92**, 398–407.
69. French SA, Jeffery RW, Forster JL, *et al.* (1994) Predictors of weight change over two years among a population of working adults: the Healthy Worker Project. *Int J Obes Relat Metab Disord* **18**, 145–154.
70. Kahn HS, Tatham LM & Heath CW Jr (1997) Contrasting factors associated with abdominal and peripheral weight gain among adult women. *Int J Obes Relat Metab Disord* **21**, 903–911.
71. Kahn HS, Tatham LM, Rodriguez C, *et al.* (1997) Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. *Am J Public Health* **87**, 747–754.
72. Schulz M, Kroke A, Liese AD, *et al.* (2002) Food groups as predictors for short-term weight changes in men and women of the EPIC-Potsdam cohort. *J Nutr* **132**, 1335–1340.
73. Bes-Rastrollo M, Sanchez-Villegas A, Gomez-Gracia E, *et al.* (2006) Predictors of weight gain in a Mediterranean cohort: the Seguimiento Universidad de Navarra Study 1. *Am J Clin Nutr* **83**, 362–370, quiz 394–365.
74. Rosell M, Appleby P, Spencer E, *et al.* (2006) Weight gain over 5 years in 21,966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond)* **30**, 1389–1396.
75. Vergnaud AC, Norat T, Romaguera D, *et al.* (2010) Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. *Am J Clin Nutr* **92**, 398–407.
76. Westerterp-Plantenga MS, Nieuwenhuizen A, Tome D, *et al.* (2009) Dietary protein, weight loss, and weight maintenance. *Annu Rev Nutr* **29**, 21–41.
77. Veldhorst MA, Nieuwenhuizen AG, Hochstenbach-Waelen A, *et al.* (2009) Effects of high and normal soyprotein breakfasts on satiety and subsequent energy intake, including amino acid and 'satiety' hormone responses. *Eur J Nutr* **48**, 92–100.
78. Veldhorst MA, Nieuwenhuizen AG, Hochstenbach-Waelen A, *et al.* (2009) Comparison of the effects of a high- and normal-casein breakfast on satiety, 'satiety' hormones, plasma amino acids and subsequent energy intake. *Br J Nutr* **101**, 295–303.
79. Smeets AJ, Soenen S, Luscombe-Marsh ND, *et al.* (2008) Energy expenditure, satiety, and plasma ghrelin, glucagon-like peptide 1, and peptide tyrosine-tyrosine concentrations following a single high-protein lunch. *J Nutr* **138**, 698–702.
80. Barkeling B, Rossner S & Bjorvell H (1990) Effects of a high-protein meal (meat) and a high-carbohydrate meal (vegetarian) on satiety measured by automated computerized monitoring of subsequent food intake, motivation to eat and food preferences. *Int J Obes* **14**, 743–751.
81. Bowen J, Noakes M, Trenerry C, *et al.* (2006) Energy Intake, Ghrelin, and Cholecystokinin after Different Carbohydrate and Protein Preloads in Overweight Men. *J Clin Endocrinol Metab* **91**, 1477–1483.
82. Westerterp-Plantenga MS, Rolland V, Wilson SA, *et al.* (1999) Satiety related to 24 h diet-induced thermogenesis during high protein/carbohydrate vs high fat diets measured in a respiration chamber. *Eur J Clin Nutr* **53**, 495–502.
83. Lejeune MP, Westerterp KR, Adam TC, *et al.* (2006) Ghrelin and glucagon-like peptide 1 concentrations, 24-h satiety, and energy and substrate metabolism during a high-protein diet and measured in a respiration chamber. *Am J Clin Nutr* **83**, 89–94.
84. Raben A, Agerholm-Larsen L, Flint A, *et al.* (2003) Meals with similar energy densities but rich in protein, fat, carbohydrate, or alcohol have different effects on energy expenditure and substrate metabolism but not on appetite and energy intake. *Am J Clin Nutr* **77**, 91–100.
85. Veldhorst M, Smeets A, Soenen S, *et al.* (2008) Protein-induced satiety: effects and mechanisms of different proteins. *Physiol Behav* **94**, 300–307.
86. Mikkelsen PB, Toubro S & Astrup A (2000) Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. *Am J Clin Nutr* **72**, 1135–1141.
87. Nieuwenhuizen AG, Hochstenbach-Waelen A, Veldhorst MA, *et al.* (2009) Acute effects of breakfasts containing alpha-lactalbumin, or gelatin with or without added tryptophan, on hunger, 'satiety' hormones and amino acid profiles. *Br J Nutr* **101**, 1859–1866.
88. Koren MS, Purnell JQ, Breen PA, *et al.* (2007) Changes in plasma amino Acid levels do not predict satiety and weight loss on diets with modified macronutrient composition. *Ann Nutr Metab* **51**, 182–187.



89. Layman DK & Walker DA (2006) Potential importance of leucine in treatment of obesity and the metabolic syndrome. *J Nutr* **136**, 319S–323S.
90. Layman DK, Shiue H, Sather C, *et al.* (2003) Increased dietary protein modifies glucose and insulin homeostasis in adult women during weight loss. *J. Nutr* **133**, 405–410.
91. Militante JD & Lombardini JB (2002) Treatment of hypertension with oral taurine: experimental and clinical studies. *Amino Acids* **23**, 381–393.
92. Lekakis JP, Papathanassiou S, Papaioannou TG, *et al.* (2002) Oral L-arginine improves endothelial dysfunction in patients with essential hypertension. *Int J Cardiol* **86**, 317–323.
93. Ast J, Jablecka A, Bogdanski P, *et al.* (2010) Evaluation of the antihypertensive effect of L-arginine supplementation in patients with mild hypertension assessed with ambulatory blood pressure monitoring. *Med Sci Monit* **16**, CR266–CR271.