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Satellite Symposium: Industry and academic partnerships for developing health-improving products*

Safety and efficacy of high-protein diets for weight loss

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Dietary strategies that can help reduce hunger and promote fullness are beneficial for weight control, since these are major limiting factors for success. High-protein (HP) diets, specifically those that maintain the absolute number of grams ingested, while reducing energy, are a popular strategy for weight loss (WL) due to the effects of protein-induced satiety to control hunger. Nonetheless, both the safety and efficacy of HP WL diets have been questioned, particularly in combination with low-carbohydrate advice. Nonetheless, for short-to-medium-term intervention studies (over several months), increasing the energetic contribution of protein does appear effective. The effects of HP diets on appetite, bone health, renal function, blood pressure, cardiovascular bio-markers, antioxidant status, gut health and psychological function are discussed. Further research is warranted to validate the physiological effects of HP diets over longer periods of time, including studies that modify the quality of macronutrients (i.e. the type of carbohydrate, fat and protein) and the interaction with other interventions (e.g. exercise and dietary supplements).

Weight loss: Body composition: Metabolic profile: High-protein diet: Appetite

What is a high-protein diet?

An important factor to consider is the definition of a 'high-protein (HP) diet', as there are several ways to consider the protein content of a diet. The composition of the diet can be determined as the absolute amount of the protein (grams), the % of total energy as protein or the amount of protein ingested per kg body weight. Normal protein intake in the UK is approximately 16% of energy intake[1] for a sedentary adult, which is approximately 64–88 g/d at energy balance for females and males, respectively. There is no general consensus as to what a 'high'-protein diet is: the food industry use the term 'protein-enriched' for 20% protein from energy. The HP diets reported for weight loss (WL) studies often include 30% of energy intake as protein. There are many variants such as the Zone diet[2] and the CSIRO diet[3]. In general, protein as a percentage of energy is doubled from 15 to 30%. Note, this does not mean that absolute protein intake (g) is doubled, as energy intake is reduced, with only a 20% increase in the actual amount (g) of protein. The guidelines from the Institute of Medicine allow for the inclusion of higher amounts of protein than previously recommended in a healthy diet[4]. This Institute concluded that there is no clear evidence that an HP intake increases the risk of renal stones, osteoporosis, cancer or CVD. Thus, the acceptable protein distribution for maintenance requirements was set to 5–20% of energy for children aged 1–3 years, 10–30% for children aged 3–18 years and 10–35% for adults. It is not clear as to how much protein is required to maximise protein-induced satiety for energy restriction and WL or whether there is a relationship with the energy density of the diet.

Both the safety[5] and efficacy[5] of HP WL diets have been questioned, particularly in combination with low-carbohydrate advice[6]. Low-carbohydrate or very low-carbohydrate diets are described as ketogenic diets when carbohydrate intake is reduced to about 20 g/d to invoke dietary ketosis, the production of the ketone bodies. These

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are β-hydroxybutyrate and acetoacetate (known collectively as ketone bodies), and are produced by the liver as an alternative fuel for the brain. The diet mimics aspects of starvation by forcing the body to burn fats rather than carbohydrates. Normally, the carbohydrates contained in food are converted into glucose, which is then transported around the body and is particularly important in fuelling brain function. However, if there is very little carbohydrate in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood produces a state known as ketosis. One such low-carbohydrate diet example is the 'Atkins dietary revolution'[6]. The authors[7] consider that HP, low-carbohydrate diets (ketogenic diets) do not offer much advantage over HP, moderate-carbohydrate diets in terms of appetite control or metabolic advantage and that their own work on gut health supports the notion of maintaining carbohydrate for a healthy gut microflora[8].

The World Cancer Research Fund UK recommends limiting consumption of red meat and avoiding processed meats to reduce cancer risk when eating for 'healthy eating' at maintenance requirements; specifically, to eat not more than 500 g (cooked weight) per week of red meats, such as beef, pork and lamb, and avoid processed meats such as ham, bacon, salami, hot dogs and some sausages[9]. The World Cancer Research Fund report recommended limiting 'intake of red meat to less than 80 g daily'. The UK Reference Nutrient Intake for adult males (19–50 years) is 55·5 g protein and for females 45·0 g (note not meat intake). The upper recommendation is not to eat more than 1·5 g protein kg per d for the general public not engaged in strenuous physical activity[10]. A WHO consensus document stated that, 'consumption of red meat is probably associated with increased colorectal cancer risk', but also stated that epidemiological studies on meat and colorectal cancer risk are not consistent[11]. Both the Chief Medical Officer's Committee on Medical Aspects of Food[12] and World Cancer Research Fund reports made dietary recommendations based on their qualitative assessments of the epidemiological literature. The Chief Medical Officer's Committee on Medical Aspects of Food[12] report on 'Nutritional aspects of cancer' targeted at the population of the United Kingdom, advised that consumption of red and processed meat for those consuming population average levels (approximately 90 g/d for the United Kingdom population) should not rise for maintenance requirements.

Protein intake can be considered not only at an individual dietary requirement level but also at a population level. Although there are still considerable differences between developing and developed countries, increases in income and advances in agriculture have enabled us to enrich and diversify diets over the last 150 years. With higher disposable incomes and urbanisation, people have moved away from mainly plant-based diets of varying nutritional quality (based on indigenous staple grains or starchy roots, locally grown vegetables, other vegetables and fruits and limited foods of animal origin) towards more varied diets that include more processed food, more foods of animal origin, more added sugar and fat, and often more

alcohol. Included in the 'processed foods' is increased meat consumption. In developing countries, meat consumption (estimated from carcass weights) is estimated to have nearly trebled in intake per year from 1962 to 2003, and estimated to rise to 2030[13,14]. At least in the developed world, we currently eat in excess of our energy requirements, contributing to the overweight and obesity problem. Over-eating energy will often mean over consuming protein as an absolute amount (g). This will not improve satiety feedback to curb consumption. In the context of HP diets for WL, this can be considered a diet that contains greater proportion of protein (%) from energy. Increasing protein % will invoke an appetite response to decrease *ad libitum* energy intake. From an environmental point of view, ever-increasing meat and dairy consumption has implications for environmental issues such as greenhouse gas emissions, climate change and land use. These issues of climate change, conservation and sustainability have recently been discussed in a commissioned report for the World Wildlife Fund (Livewell: a balance of healthy and sustainable food choices, 2011)[15].

Relatively little is known about the influence of chronic (excess) oral protein intake on kidney function, since most studies only examine the effect of a short-term change in protein intake. One special interest group in this respect is body builders, because increased muscle size and definition are important as judged by appearance in this competitive sport. Body builders are advised to consume 55–60% carbohydrate, 25–30% protein and 15–20% fat, for both the off-season and pre-contest phases[16]. Apart from the obvious pharmacological con-founders that may influence metabolism, there are a couple of relevant publications that have examined nutritional intake in this unique sports group. Poortmans and Dellalieux[17] investigated body builders and other well-trained athletes using a 7-d nutrition record analysis as well as blood sample and urine collection to determine the potential renal consequences of an HP intake. The data revealed that despite higher plasma concentration of uric acid and Ca, the body builders had renal clearances of creatinine, urea and albumin that were within the normal range. The N balance for both groups became positive when daily protein intake exceeded 1·26 g/kg but there were no correlations between protein intake and creatinine clearance, albumin excretion rate and Ca excretion rate. They concluded that protein intake under 2·8 g/kg does not impair renal function in well-trained athletes as indicated by the measures of renal function utilised. Similarly, Brandle et al.[18] included eighty-eight healthy volunteers with normal renal function (thirty-two vegetarians, twelve body builders with no supplementary protein concentrates, twenty-eight body builders with supplementary protein concentrates and sixteen subjects with no special diet), studied for 4 months. N excretion rates ranged between 2·66 and 33·93 g/d, reflecting a daily protein consumption between 17 and 212 g/d or 0·29 and 2·6 g/kg body weight per d, respectively. Their investigation indicated that chronic oral protein intake of widely varying amounts of protein is a crucial control variable for the glomerular filtration rate in subjects with healthy kidneys. They suggested that these changes reflect in part

structural changes of the glomerulus and tubules due to chronic protein intake, indicating adaptive physiological mechanisms to deal with the HP intake.

Efficacy of high-protein weight loss diets

Short-term body weight and body composition changes

Free-living subjects feeding *ad libitum* from HP diets show a WL of about 1 kg a week[19,20] which is consistent with current dietary advice on rate of WL from health professionals (e.g. British Dietetic Association, http://www.bda.uk.com). As a result of the WL, there are significant improvements in body composition, blood pressure and bio-markers of health. The reduction in body fat mass (kg) and maintenance of lean mass (kg) during energy restriction and WL has been reported previously by other authors and, in part, is related to the protein-enriched composition of the diet[21]. In a recent meta regression, Krieger *et al.*[22] and Clifton *et al.*[23] examined eighty-seven short-term studies and found that protein intakes of >1·05 g/kg of actual (rather than desirable body weight) were associated with 0·6 kg better retention of lean mass, and in studies greater than 12 weeks in duration, this increased to 1·2 kg. In studies that used a carbohydrate intake of less than 35–41 % there was a 2 kg greater loss of fat mass, and this was accompanied by a 0·7 kg greater loss of lean mass. In studies of 12 weeks or more, this increased to 5·6 and 1·7 kg, respectively. Several studies have also looked at body composition to test the hypothesis that HP diets spare the lean body mass of those on energy restricted diets. Most found greater fat loss with the HP diets in comparison with the lower-protein diets, but fewer reported this to be statistically significant, probably a function of body composition techniques, small study sizes, and different applied definitions of 'HP'. In general, it is accepted that a reduced carbohydrate, HP diet is associated with better fat loss and relatively less lean mass loss.

Longer-term body weight and body composition changes

HP diets provide a potential benefit of improved compliance during WL attempts. HP diets increase WL at 12 months by about 3 kg compared with a high-carbohydrate (HC) diet[23]. HC, low-fat diets have also been shown to reduce weight at 12 months and have additional benefits of high-fibre intake and may reduce the risk of diabetes[24]. However, many people cannot maintain these diets long term, so new solutions have been sought. Surprisingly, trials have only appeared over recent years evaluating the effects of HP diets (including low-carbohydrate versions), and these have shown WL benefits at 6 months, which are lost by 12 months, indicating similar poor compliance at this duration in all regimes[25]. Patient diet choice will depend on dietary preferences and previous experiences with WL regimes. Groups consuming an HP, moderate-carbohydrate diet have an increased likelihood of maintaining WL at 12 months and beyond, with improvements in cardiovascular risk factors and minimal risk of side effects[26,27]. In a 12-month study,

Due *et al.*[25] report substantially greater compliance in subjects consuming a higher-protein diet (25 % protein of energy) with an 8 % drop out rate compared with subjects on a low-protein diet (12 % energy) with a 28 % drop-out. Indeed, the recent extensive EU-wide Diogenes trial[28] examined low-protein and HP diets with low and high glycaemic-index (GI) components. Specifically, of the five popular diet types tested, a HP, low GI diet provided the greatest opportunity for WL maintenance. The dropout rate was lower in the groups that were assigned to HP diets and the groups that were assigned to low-GI diets than in the group that was assigned to the diet that was low in protein and had a high GI (26·4 and 25·6 %, respectively, *v.* 37·4 %; P = 0·02 and P = 0·01 for the HP groups, low-GI groups and LP-low-GI groups, respectively). HP diets have beneficial effects on body fat regulation, but the difference in effect of various types of protein is not known[29]. Animal proteins, especially those from dairy, seem to support better muscle protein synthesis during weight reduction regimes in comparison with plant proteins because they contain all essential amino acids and are generally well digested. This could potentially enhance energy expenditure, but no conclusion can be drawn from the scant evidence[29]. Some studies, but not all, demonstrate a higher satiating effect of whey and fish proteins than other protein sources. The evidence from intervention studies comparing the effects of different protein sources on body weight is inconclusive[29]. However, body composition was not evaluated precisely in these studies and the literature is still incomplete (e.g. comparative data are missing for legumes and nuts). Protein intake enhances energy expenditure, satiety and fat loss, but there is no clear evidence to indicate whether there is a difference in the effect size dependent on the source of the protein, i.e. from animal- or plant-based foods.

Follow-up of weight regain after high-protein weight loss diet

Several groups have examined this question with similar outcomes. Lejeune *et al.*[30] report a 20 % increase in protein intake (through an unmatched supplement) during weight maintenance after a 4-week WL period reduced weight regain by 50 % over the subsequent 3 months. Claessens *et al.*[31] report a similar effect using a matched casein supplement over 12 weeks of weight maintenance, which amounted to a differential of 2·2 kg fat. Layman *et al.*[32] found that a WL diet that had double the amount of protein (1·6 *v.* 0·8 g/kg) led to better body composition at both 4 and 12 months, especially in those participants who lost more than 10 % of their body weight over this period. The recent 'Diogenes' trial provides data on the use of HP, low-GI diets for longer-term weight control. Specifically, weight regain was 0·93 kg less for the 773 participants on a HP diet than for those on a low-protein diet and 0·95 kg less in the groups on a low-GI diet compared with those on a high-GI diet[28]. These data support the use of HP, moderate-carbohydrate diets to achieve weight control.

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Potential side effects of high-protein weight loss diets

Physiological and metabolic effects of high-protein weight loss diets

Appetite. Protein is more satiating than carbohydrate and fat in the short term, over 24 h and in the long term[33]. In the short-term 'fast' proteins are more satiating than 'slow' proteins, and animal protein induces a higher thermogenesis than vegetable protein. In the longer term, the higher post-absorptive satiety and thermogenesis are sustained irrespective of the protein source[34]. A variety of investigations have examined the effect of HP diets on satiety. Typically, these studies presented one of several preloads with varying protein content to each subject on separate occasions in a cross-over design. For several hours following the consumption of the preload, subjective satiety ratings were measured repeatedly. Halton and Hu[34] summarised the main findings that of the fourteen studies that compared HP to at least one other macronutrient, eleven found that the protein preload significantly increased subjective ratings of satiety. Other studies that have used nose-clips (to reduce the impact of cephalic digestive cues involved in early satiation) and liquid format[35,36] have not found effects of HP meals suggesting a role in sensory characteristics in promoting satiety. The Maastricht lab has published many preloading studies that suggest that HP diets are more satiating in comparison with normal protein meals, when fed at iso-energetic amounts[37–39].

In summary, the evidence supports the conclusion that meals higher in protein tend to increase satiety when compared with meals lower in protein, at least in the short term. Overall, the weight of evidence suggests that higher-protein intakes cause a decreased subsequent energy intake, although the results are not entirely consistent. It appears that the closer the methodology is to real-life situations (real food *v.* liquid, sense of taste unaltered, free living *v.* whole body calorimeter), the more likely it is for protein to exert a significant decrease in subsequent energy intake. The majority of preload studies do find a decreased subsequent energy intake with a higher-protein preload. There are, however, some methodological issues concerning this type of research. Satiety appears to be influenced by a wide variety of factors including palatability, food mass, energy density, fibre and GI. When using real foods, it is difficult if not impossible to control for all of these influences at the same time while still delivering different amounts of protein[34].

The mechanisms promoting protein-induced satiety are not clear, but are likely to involve elevated amino acid concentrations, responses of anorexigenic hormones and protein-induced energy expenditure[38]. Hunger, or at least motivation to eat, is influenced by the palatability of the diet and this is an important determinant of intake[40] in both short-term[41] and longer-term[42] studies. Indeed, it has been suggested that lower energy intakes during dieting are due to a lower palatability, or monotony, of the diet[43]. In real life dieters may, by default, adopt more limited diet choice because their nutritional knowledge is less. Were studies conducted over longer periods, palatability ratings may gradually decrease, as desire for even a favourite food will wane if offered repeatedly[44].

Bone health including osteoporosis. Millions of people are affected by osteoporosis, and women are four times more likely to suffer from this disease than men. Nutrition plays an important role in both the prevention and the pathogenesis of this chronic disease. Numerous studies have established that dietary Ca and vitamin D are critical nutrients for both accruing and maintaining skeletal mass. In contrast, our understanding of how other dietary components, such as protein, affect Ca homoeostasis and skeletal metabolism is limited[45]. Our ability to accurately measure changes in mineral homoeostasis has improved considerably in the last two decades. We now have better ways to non-invasively assess rates of skeletal formation and resorption, to quantify bone mass and to measure parathyroid activity. Using these tools, a more complex picture of the effects of protein on Ca metabolism and skeletal homoeostasis, particularly during low-dietary-protein conditions, is beginning to emerge. Protein is known to be essential to bone collagen synthesis, but it is the Ca-wasting effect of a HP intake that remains at the focal point of the debate. It has long been suggested that 'too much' protein (with no set definition of 'too much' given in the research literature) can have a negative effect on bone health via increased calciuria. Research has shown that higher-protein diets do promote increased excretion of Ca in the urine[46], which is taken to suggest adverse effects on bone or to support the impact of bone loss. The underlying premise is that an HP (especially animal protein) diet creates a higher acid load due to the high S amino acid content, which cannot be neutralised by the kidneys. To compensate, the body pulls Ca from the skeleton to balance the pH at the expense of the bone structure, and Ca is excreted in the urine. However, few studies have supported this theory. The effect of dietary protein in the skeleton appears to be favourable to a small extent or, at least, is not detrimental[47]. A meta-analysis of randomised placebo-controlled trials indicated a positive influence of all protein supplementation on lumbar spine bone mineral density. No significant effects were identified for soya protein or milk basic protein on lumbar spine bone mineral density[48]. The positive effect(s) seems to come from meat protein. For example, HP diets (particularly those high in meat) have been shown to reduce the risk of fractures in post-menopausal women[49]. The effect of high-animal protein intakes on Ca utilisation and bone health has been recently reviewed[50]. Increased potential renal acid load resulting from an HP intake (intake above the current RDA of 0·8 g protein/kg body weight) has been closely associated with increased urinary Ca excretion. However, more recent findings do not support this assumption. Neither whole body Ca balance, nor bone status indicators, are negatively affected by the increased acid load. Indeed, beneficial effects of protein such as increasing intestinal Ca absorption and circulating insulin-like growth factor-I while also lowering serum parathyroid hormone sufficiently offset any negative effects of the acid load of protein on bone health. On the basis of recent findings[50], consuming protein (including that from meat) higher than current RDA for protein is beneficial to Ca utilisation and bone health, especially in the elderly. A HP diet with adequate Ca and fruits and vegetables is

important for bone health and osteoporosis prevention[50]. More research is required to resolve the protein debate. The protein intakes and balance of different protein sources with a variety of different foods as indicated by the dietary guidelines represent appropriate dietary advice.

Renal function. Valid concerns exist that HP diets may induce clinically important alterations in renal function and health. HP consumption has been found, under various conditions, to lead to glomerular hyperfiltration and hyperaemia, acceleration of chronic kidney disease, increased proteinuria, diuresis, natriuresis and kaliuresis with associated blood pressure changes, increased risk for nephrolithiasis and various metabolic alterations[51–53]. Unfortunately, a comprehensive understanding of the implications of HP diets is limited by the lack of a universally accepted definition for HP intake, a paucity of rigorous long-term human interventional studies that lead to reliance on short-term or fairly circumstantial evidence, and sparse data on the effects of HP consumption in obese individuals. In addition, matters are further complicated because the renal impact of HP diets for limited periods is most likely different than that for more chronic consumption (see later). Nevertheless, although there are no clear renal-related contraindications to HP diets in individuals with healthy kidney function, the theoretical risks should be reviewed carefully with the patient and clinician. In contrast, HP diets have the potential for significant harm in individuals with chronic kidney disease and should be avoided if possible. Because chronic kidney disease is often a silent disease, all individuals should undergo a screening for serum creatinine and a urinary dipstick test for proteinuria before the initiation of such a diet.

There has been some debate as to the safety of HP WL diets with regard to kidney function. In populations with established renal disease, it has been shown that limiting protein to the RDA level may slow down the progression of disease[54]. Whether or not HP (WL) diets adversely affect kidney function in healthy populations is not so clear. An often-cited review paper, Eisenstein *et al.*[55] assessed the evidence and came to the conclusion that there is little evidence for adverse effects of HP diets on renal function in individuals without established renal disease. Several studies have reported that HP diets cause hyperfiltration up to a saturation point of approximately 125 g/d[18,56–59] although net hyperfiltration (filtration expressed as a function of renal mass) did not occur when protein intake varied in the range of 70–108 g/d. These higher-protein intakes are related to an increase in renal mass[60]. Other measures of renal function are similarly inconsistent. In evaluating the clearance of creatinine, urea and albumin, one study compared the very HP diet of body builders to that of athletes consuming moderate protein diets. No adverse effects in the parameters measured were found with protein intake up to 2·8 g/kg[17]. There is evidence that higher-protein intakes can significantly increase the risk of kidney stones[61], uric acid stones[62] and Ca stones[63]. However, one study found a decrease in Ca oxalate stones with a higher compared with a lower-protein group[64].

A randomised control trial comparing HP, low-carbohydrate and HP, very-low-carbohydrate diets for 1 year[65] indicated that there were no changes in either group in serum creatinine levels or estimated glomerular filtration rate (eGFR), and urinary albumin excretion values remained in the normoalbuminuria range. This study provides preliminary evidence that long-term WL with a very-low-carbohydrate diet does not adversely affect renal function compared with a HC diet in obese individuals with normal renal function. Similarly, intervention studies by Li *et al.*[66] and Skov *et al.*[60] also indicate that protein-enriched meal replacements or an HP diet have no adverse outcomes on routine measures of kidney function, up to 1 year. It may be that 12 months is not long enough to reveal adverse effects and further work may be necessary to examine this area.

Taken together, there is little evidence that HP diets pose a serious risk to kidney function in healthy populations. More susceptible groups such as diabetics and those with existing renal disease should exercise more caution with higher-protein intakes. This approach is supported by data from large-scale US studies. The Nurses' Health Study suggests that women with mild renal insufficiency had a greater decline in renal function with a higher-protein intake[67]. Those with normal renal function had no such decline. Recent work on an aging population[68], where renal function tends to decline (as indicated by reduced glomerular filtration rate), has investigated whether dietary protein is associated with impaired renal function. Data from two nested case–control studies within the Women's Health Initiative Observational Study (*n* 2419) were examined. Protein intake was estimated using an FFQ and eGFR from cystatin C. To account for the original study designs, inverse probability weights were applied. Self-reported energy and protein were calibrated using bio-markers of energy and protein intake. Associations between protein intake and renal function were estimated by weighted linear and logistic regression models. Average calibrated protein intake was 1·1 (SD 0·2) g/kg body weight per d). Twelve per cent (*n* 292) of women had impaired renal function. The odds of impaired renal function, defined as eGFR <60 ml/min per 1·73 m^2, was not associated with calibrated protein intake. When eGFR was modelled continuously, there was no association with calibrated protein whether protein was expressed in absolute (g/d) or relative to energy (protein % energy/d), but protein relative to body weight (g/kg body weight per d) was associated with higher eGFR. There was no evidence for effect modification by age, BMI or general health status. These data suggest higher-protein intake is not associated with impaired renal function among post-menopausal women without a diagnosis of chronic kidney disease.

Studies that measure renal function often monitor liver function. For example, protein-enriched meal replacements as part of a weight management programme were studied in a placebo-controlled clinical trial utilising two iso-energetic meal plans utilising either an HP-enriched or a standard protein meal replacement in an outpatient WL programme[66]. There was no significant change noted in liver function at 1 year. Since obesity is often linked to fatty liver, WL *per se* is associated with beneficial changes in markers of liver function[69].

CVD risk factors including lipaemia

Foods and diets high in protein may vary in saturated fat and nutritional composition, and concerns have been raised regarding the effect of HP diets on serum lipids and subsequent CVD risk. There are limited epidemiological data on HP intake and cardiovascular risk. A prospective cohort study by Hu et al.[70] found that a higher protein intake (24% of energy v. 15% of energy) was associated with a decreased risk of CHD during 14 years of follow-up. Both animal and plant protein contributed to the lower risk. Risk was increased in the lowest quintiles of animal protein intake in women even after controlling for energy intake and traditional cardiovascular risk factors (median animal protein intake: lowest quintile 42·7 g/d, highest quintile 81·6 g/d). Iso et al.[71] found that very low levels of animal protein intake were associated with an increased risk of haemorrhagic stroke. This is consistent with ecological data from Japan that suggests a low intake of protein increases the risk of intraparenchymal haemorrhagic stroke[72]. Furthermore, in a meta-analysis of cross-sectional investigations, Liu et al. found an inverse association between dietary protein and blood pressure in both sexes[73], although further studies will be needed to confirm this association.

Another area of controversy is the effect of HP diets on blood lipids. Farnsworth et al.[74] and Skov et al.[60] found a decrease in TAG with higher-protein diets, whereas Parker et al.[75] found a lower LDL cholesterol level with a higher-protein diet. Finally, Wolfe found that the isoenergetic substitution of animal protein for carbohydrate raises HDL cholesterol and lowers TAG levels in hypercolesterolaemic subjects[76] and normolipaemic subjects[77]. Jenkins et al.[78] conducted a 1 month study of a high wheat protein diet (27%) compared with a control diet (16%) in hyperlipaemic subjects and found decreases in TAG and oxidised LDL cholesterol on the higher-protein diet. However, other investigators studying dietary protein and WL[79] found no significant differences in lipid profile between subjects consuming higher- v. lower-protein diets. Although more research is still needed in this area, it appears that higher-protein diets at the very least are not detrimental to blood lipids in the short term and the exchange of protein for carbohydrate may actually be beneficial for blood lipids[80].

The GI is a well-described property of carbohydrate-containing foods that predicts the body's blood glucose response[81]. GI may be important in weight control efforts because it modulates hunger and satiety. Because protein has a minimal short-term effect on blood glucose in comparison with carbohydrate, it can be used in metabolic studies and WL efforts that strive to lower the GI of any particular diet. Although protein produces a lower blood glucose level than carbohydrate, it is known to produce an insulin response.

HP foods such as meat, poultry, seafood, eggs, seeds and nuts are high in purines. Purines are broken down into uric acid, so excess consumption of these foods increases uric acid levels and may cause gout in susceptible individuals[82].

Gut health

There is epidemiological evidence for a protective effect of fruits, vegetables and whole grains in almost all major cancers afflicting western society today including colorectal, breast, pancreatic, lung, stomach, oesophageal and bladder cancer[83–86]. Fruits and vegetables contain a large variety of compounds such as dietary fibres, isothiocyanates and polyphenols that possess antioxidant and anti-inflammatory activities and are implicated in providing protection against cancer. Dietary fibres have a myriad of benefits in the colon such as diluting carcinogenic compounds, accelerating stool transit time, increasing production of beneficial fermentation products such as butyric acid and decreasing detrimental metabolites such as N-nitrosamines, in addition to lowering colonic pH. All of these effects have been proposed as being helpful in reducing colon cancer risks. The current scientific evidence strongly suggests that it is not the consumption of one or two varieties of vegetables and fruit that confer a benefit, but rather the intake of a wide variety of plant foods[87–89]. HP diets tend to have reduced carbohydrate content, in the form of fruits, vegetables (if starchy foods are not adequately replaced by other types of low-carbohydrate-containing vegetables) and grains. This may theoretically place an individual at an increased disease risk if such a diet is followed long term, and fruit and vegetable intakes remain low[90].

HP dieting is associated with increased consumption of meat, and red meat consumption has been linked to colorectal cancer[91], but the evidence is not straightforward. Increased intakes of meat and increased incidence of colorectal cancers have been observed in some epidemiological studies[92–94]; however, this is specific to processed meat. It has been shown that a daily increase of 100 g of all meat or red meat is associated with a 12–17% increased risk of colorectal cancer[95]. However, the WL induced by dieting may counteract the observed epidemiological risks of increased meat consumption. Thus, the relationship between meat consumption and colorectal cancer risk remains controversial[96]. Subsequent to the report of the National Academy of Sciences, 'Diet and Health'[97], which implicated red meat as a causative factor in the aetiology of colorectal cancer, two subsequent reports have reviewed the epidemiological evidence on meat and colorectal cancer risk[9,12]. The report of the World Cancer Research Fund report concluded: 'The evidence shows that red meat probably increases risk and processed meat possibly increases risk of colorectal cancer'[9]. The report from Chief Medical Officer's Committee on Medical Aspects of Food judged that 'there is moderately consistent evidence from cohort studies of a positive association between the consumption of red or processed meat and risk of colorectal cancer'[12]. A WHO consensus statement reached a similar conclusion, stating that, 'consumption of red meat is probably associated with increased colorectal cancer risk', but also stated that epidemiological studies on meat and colorectal cancer risk are not consistent[11]. One US epidemiological study is often quoted, and reported high intake of red and processed meat in 1982 and again in 1992/1993 to be associated with higher risk of colon cancer

after adjusting for age and energy intake but not after further adjustment for BMI, cigarette smoking and other covariates[91]. This suggests that obesity *per se* (excess body fat) is also a factor. When long-term consumption was considered, persons in the highest tertile of consumption had higher risk of distal colon cancer associated with processed meat and ratio of red meat to poultry and fish relative to those persons in the lowest tertile. Long-term consumption of poultry and fish was inversely associated with risk of both proximal and distal colon cancer. High consumption of red meat was associated with higher risk of rectal cancer. The authors concluded that prolonged high consumption of red and processed meat may increase the risk of cancer in the distal portion of the large intestine. The European Prospective Investigation into Cancer and Nutrition study, the largest study undertaken, also found this was true only for processed meats[92]. The risk of colorectal cancer can be reduced substantially by eating chicken and fish, undertaking regular exercise and by WL itself. In addition, eating more than 28 g fibre/d removes the effect of meat altogether. So in terms of HP diets, replacing processed meat with fish or chicken and/or ensuring fibre intake is high is the best strategy.

Fibre has been promoted for a long time as necessary and healthy. Consuming complex dietary fibre is beneficial for gut health because it feeds gut bacteria and produces SCFA which serve as a fuel for colonocytes (butyrate) and controls cell metabolism and renewal, as well as expression and synthesis of some important biomolecules. Current UK guidelines recommend, at a population level, daily intake of NSP of 18 g (individual range 12–24 g)[10]. The US guidelines advise intakes of up to 24 g/d, for an adult[98,99]. Since fibre-rich foods tend to be high in starch (cereals/grains/legumes) or sugar (some fruits), they are often limited when energy counting. In the context of energy counting, most vegetables are viewed as acceptable by most standards, and overall tend to contain just water plus fibre, rather than being starch/sugar rich. Duncan *et al.*[100] found that when obese subjects switched to a low-carbohydrate diet (24 g/d), butyrate production (estimated from faecal samples) fell linearly with carbohydrate intake. Changes in bacterial species included a reduction in *Roseburia* spp. and *Eubacterium rectale*, both of which produce butyrate from carbohydrates *in vitro*. Brinkworth *et al.*[101] and Polivy & Herman[102] found that faecal butyrate excretion was 30–60 % lower in subjects eating a high-fat low-carbohydrate diet compared with an HC diet. The level of *Bifidobacterium* spp., which are frequently used as probiotics, also decreased. The results of these studies show a clear trend: carbohydrate intake and levels of butyrate correlate directly. Ergo, it is assumed that a healthy diet must have a good amount of starch and non-digestible polysaccharides to produce butyrate and promote colon health.

Antioxidant status

There are concerns that restrictive WL diets may have a negative impact on antioxidant status because of the reduced fruit and vegetable component. There has only been one published study examining the effect of HP diets on antioxidant status[20]. These data suggest that an HP WL diet does not impair plasma indices of antioxidant status and bio-markers of cardiovascular and metabolic health, at least within 4 weeks, in otherwise healthy obese subjects. The study compared HP low-carbohydrate and HP, moderate-carbohydrate diets. In general, improvements in bio-markers of health associated with WL were similar between the low-carbohydrate and moderate-carbohydrate diets. None of the subjects were deficient in vitamins, and although the diets were associated with a small reduction in plasma concentrations of retinol, vitamin E (α-tocopherol) and β-cryptoxanthin ($P<0·005$), these were still above values indicative of deficiency. Antioxidant supplements may be warranted if HP low-carbohydrate WL diets are consumed for a prolonged period. Alternatively, recommended daily allowance of vitamins and micronutrients may be met by judicious inclusion of mixed fruits and vegetables, even when low-carbohydrate intake is adopted.

Psychology

Dieting and stress and cognitive function. It has been proposed previously that dieting may be harmful to psychological well-being[102], because dieters have reported increased anxiety and irritability[103] during WL therapy. However, studies have suggested that depression, body image perception and mood can be improved during substantial WL[104]. These concerns involve the following logic: (i) dieting promotes weight cycling, which is hazardous to health[105], (ii) dieting contributes to the development of eating disorders[102,106] and (iii) dieting rarely produces successful WL, therefore the associated stress is without purpose[107,108]. French and Jeffery[104] reviewed all these issues and concluded that (i) the term 'dieting' can refer to chronic dieting, desire to lose weight or weight control behaviours and these conditions may have different effects on health and therefore need to be distinguished, (ii) dieting is not usually associated with nutritional deficiencies, adverse psychological adaptation/reaction or the development of eating disorders and (iii) recommendations for WL involving changes in eating and exercise habits are therefore warranted. Negative effects on mood are therefore mainly associated with either a failure to lose or maintain body weight. It may be, however, that mode of WL can cause transient changes in psychological health. Consumption of meals with different macronutrient content may influence the stress-induced physiological and psychological response during dieting. There are limited data on this topic. One study investigated the effects of consumption of a HP v. HC meal on the physiological cortisol response and psychological mood response[109]. Subjects participated in four treatments with and without exercise and two diet meals (HP and HC) as a randomised cross-over design: rest-protein, stress-protein, rest-carbohydrate and stress-carbohydrate. Stress was induced by means of a psychological computer-test. The test-meal was either a HP meal (En % protein:carbohydrat:fat, 65:5:30) or a HC meal (En % protein:carbohydrate:fat, 6:64:30), and both meals were matched for energy density (4 kJ/g) and daily energy requirements (30 %). Salivary cortisol levels, appetite

profile, mood state and level of anxiety were measured in each test session. Consumption of the HP v. HC meal did not affect feelings of depression, tension, anger or anxiety. Cortisol levels did not differ between the four test-sessions in men and women. Consumption of the test-meals increased cortisol levels in men in all conditions, and in women only in the rest-protein and stress-protein condition. Men showed higher cortisol levels than women. Consumption of meals with different macronutrient contents, i.e. HP v. HC, does not influence the physiological and psychological response differentially. Men show a higher meal-induced salivary cortisol response compared with women. Future research may focus on personalised nutrition and the role of diet composition and eating patterns to enhance mood or compliance to WL strategies.

Conclusions

With the ever-increasing obesity problem comes the search for effective dietary strategies to (i) prevent weight gain, (ii) promote WL, (iii) maintain a lower body weight. Surgical and pharmacological approaches for weight management are only accessible for a small percentage of the obese population. Human subjects have a plentiful supply of appealing, cheap, energy-dense foods and beverages that promote overconsumption and the challenge for public health sectors is how to encourage the population to make sensible food choices for safe and healthy eating. There is no one dietary approach that will fix this complex problem, but HP diets seem to provide a tool to promote WL, in healthy subjects. The benefits of WL need to be weighed against the consequences of excess adiposity on health. With larger EU-funded studies being published and more work underway, the limitations and applications of HP diets for weight control will undoubtedly become clearer.

Acknowledgements

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