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ORIGINAL ARTICLE

High-protein diets: are they really safe and effective?

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Abstract: This review summarizes the effects of dietary protein on energy intake and weight loss, as well as its' effects on a variety of health outcomes in adults. Unusual popularity of high-protein induce scientists to analyze its' effectiveness and observe health consequences induced by those diets. Short-term studies indicates that high-protein diets improve weight loss and fat loss, but recently conducted long-term studies negate superiority of high - protein diets to mixed diets. Available data indicate that high-protein diets can promote harmful effects. This review focuses on the impact of high-protein diets on weight loss, body composition, cardiovascular risk, glycemic control, renal function and urinary calcium loss.

Key words: high-protein diet, satiety, weight loss, cardiovascular risk factors, renal function, urinary calcium loss

INTRODUCTION

The prevention of obesity and medical conditions such as hypertension, cardiovascular disease and type 2 diabetes has become a public health priority. As a result, there has been heightened interest in dietary approaches to optimize weight loss and maintain reduced weight. This has led researchers and healthcare professionals to investigate the anthropometric and metabolic effects of diets with varying levels of protein, carbohydrate and fat on food intake and weight control. This review focuses on the impact of high-protein diets on weight loss and body composition, appetite regulation and satiety, cardiovascular risk, glycemic control and potential detrimental consequences of high-protein intake. Numerous studies have shown that diets with high protein content increase satiety which lead to reduced subsequent energy intake and in consequence are associated with greater fat loss and reduced lean mass loss. Although recent evidence supports potential benefit, rigorous longer-term studies are needed to investigate the effects of high protein diets on weight loss and weight maintenance.

ANTHROPOMETRIC EFFECTS

High-protein diets are generally accepted to have beneficial effects on body composition and fat mass reduction [1, 2]. However, since 2000, at least 8 published studies (Table 1) showed no significant difference in weight loss in subjects on low carbohydrate diets matched with controls on low fat diets [3-10]. Long term (12 months) randomized control trials evaluating low carbohydrate diets [7, 11-15] showed greater weight loss at 6 months with reduced carbohydrate intake – a difference no longer seen at 1 year (Table 2). Weight loss from these diets was relatively small, ranging from 2.1% – 7.3% of body weight, and no study showed a significant difference in weight loss between diet groups. Comparable results in meta-analysis of 5 trials including a total of 447 individuals were obtained by Nordmann et al. [16]. After 6 months of dieting, individuals assigned to low-carbohydrate diets lost more weight than those on low-fat diets (weighted mean difference 3.3 kg, p=0.02). However, after 12 months there were no significant differences in weight loss between diet groups. In the next trial, Gardner et al. [17] randomized 311

Table 1 Short–term randomized control trials of high-protein diets on weight loss

Study	Subjects	Duraton	Diet %CHO/ %protein/% fat	Mean weight loss [kg]
Brehm, 2003 [3]	42 obese women	6 months		
Intervention			31/23/46	8.5*
Control			52/17/31	3.9
Farnsworth, 2003 [4]	57 overweight	16 weeks		
Intervention			44/ 27/ 29	7.8
Control			57/ 16/ 27	7.9
Layman, 2003 [5]	24 overweight women	10 weeks		
Intervention			41/ 30/ 29	7.53
Control			58/ 16/ 26	6.96
Luscombe, 2003 [6]	36 obese hyper-insulinemics	16 weeks		
Intervention			45/27/28	7.9
Control			57/16/27	8.0
Luscombe, 2002 [7]	26 obese type 2 diabetics	12 weeks		
Intervention			42/28/ 30	4.9
Control			55/16/ 29	4.3
Parker, 2002 [8]	54 type 2-diabetics	12 weeks		
Intervention			40/30/ 30	5.2
Control			60/15/ 25	5.2
Samaha, 2003 [9]	132 obese	6 months		
Intervention			37/22/41	5.8
Control			51/16/33	1.9*
Yancy, 2004 [10]	119 overweight	6 months		
Intervention			8/26/ 68	12 kg
Control			52/19/29	6.5 kg*

* Statistically significant difference between groups.

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Table 2 Long-term randomized control trials of low-carbohydrate diet on weight loss

Study	Subjects	Duration	Diet	Mean weight loss [%]	Dropout rate [%]
Foster, 2003 [14]	63 obese	12 months			
intervention			20g CHO/day × 2 weeks then gradual increase in CHO until weight stable	7.3	41
control			60 % CHO, 15 % protein, 25 % fat	4.5	
Due, 2004 [13]	50 overweight or obese	24 months			
intervention			25 % protein, <30 % fat	7.1 at 12 months	18 at 12 months
control			12% protein, < 30% fat	4.9 at 12 months	
Dansinger, 2005 [12]	160 obese and overweight with insulin resistance or type 2 diabetes	12 months			
intervention 1			<20 g CHO with gradual increase to 50 g CHO/day	2.1	42
intervention 2			40% CHO, 30% protein, 30% fat	3.2	
intervention 3			Point system calorie control	3.0	
intervention 4			Vegetarian with 10% fat	3.3	
Brinkworth, 2004 [11]	66 overweight or obese with insulin resistance	17 months			
Intervention			40% CHO, 30% protein, 30% fat	4.1	35
control			55% CHO, 15% protein, 30% fat	2.9	
McAuley, 2005 [7]	96 overweight women with insulin resistance	12 months			
intervention 1			< 20g CHO/day *2 weeks then gradual increase to 50 g/day	5.5	18
intervention 2			40% CHO, 30% protein, 30% fat	7.0	
control			55% CHO, 15% protein, 30% fat <8% saturated fats	4.5	
Stern, 2004 [15]	32 obese with insulin resistance or type 2 diabetes	12 months			34
intervention			<30 g CHO/day	3.9	
control			<30% kcal from Fat -500 kcal/day	2.3	

* Statistically significant difference between groups.

overweight/obese premenopausal women to the Atkins, Zone, LEARN or Ornish diets in a 12-month prospective study. At the beginning (2 month) and in the middle (6 month) of the study the authors reported significantly greater weight loss with the Atkins diet. The mean 12-month weight change was 4.7 kg for Atkins, 1.6 kg for Zone, 2.2 kg for LEARN, and 2.6 kg for Ornish. Weight change among the Zone, LEARN, and Ornish groups did not differ significantly at any time point. Although the Atkins group lost more weight, the magnitude of weight loss was modest. To answer the question of whether ketosis has a metabolic advantage, the effect of a ketogenic low-carbohydrate (KLC) diet compared with a nonketogenic low-carbohydrate (NLC) diet on weight loss was conducted by Johnston et al. [18]. Twenty obese individuals were randomized to a 1,500 kcal diet and to limit carbohydrate to 9% (KLC) or 42% (NLC) of total energy. At the end of the 6-week trial, mean total weight loss and fat loss did not differ significantly between diet groups (-6.3 versus -7.2 kg, respectively). In that case, the severity of carbohydrate restriction may have been a more important factor than protein content in the weight–loss diet. Considering the duration of weight loss programmes, Sacks et al. [19] proved that reduced-calorie diets in the long term result in clinically meaningful weight loss regardless of which macronutrients they emphasize. In this study, 811 overweight adults were randomly assigned to one of 4 diets; distinguishable in the amount of energy derived from fat, protein, and carbohydrates. The amount of weight loss after ars was similar in participants assigned to a diet with lower or higher protein, fat and carbohydrates content.

METABOLIC EFFECTS

Recent studies have focused on the physiological adaptations that occur during low-carbohydrate, high-protein diets [8]. Reduced hunger through alterations in gut hormones, delayed gastric emptying and improved insulin resistance are suggested mechanisms through low-carbohydrate diets exert their effects [2, 8, 20-22]. In a 12-week study by Hayes and Miller [21], men and women with the metabolic syndrome were instructed to follow a low-carbohydrate diet with 2 phases similar to the South Beach diet. Phase I was very low carbohydrate (10% carbohydrate, 60% fat, 30% protein) and phase II was more moderate in carbohydrates (40% carbohydrate, 30% protein, 30% fat). Both diets were isocaloric. Fasting and postprandial levels of serum leptin, insulin, ghrelin and cholecystokinin were measured at baseline and after the completion of phase I and phase II. Dietary intake and hunger were also assessed following each phase. Plasma fasting insulin decreased overall and was significantly associated with increased dietary protein ($p<0.02$) but not with reduced carbohydrate intake. Both fasting leptin and ghrelin increased and were not associated with any changes in macronutrient composition. Postprandial cholecystokinin levels rose compared with baseline and were associated with higher consumption of dietary protein, but not reduced intake of carbohydrates. Patients reported increased hunger throughout the intervention but significantly reduced energy intake overall from baseline. The authors suggest that these findings demonstrate the role of high-protein, low-carbohydrate diets in altering measures of adiposity as well as gut peptides that influence satiety and intake. Other research confirm the theory that higher protein diets enhance weight loss due to increased energy expenditure, satiety and a decreased subsequent energy intake [15, 21, 23]. To investigate the impact of dietary protein on metabolism and satiety in 30 healthy subjects with a body mass index (BMI; in kg/m^2) of 20-30 and aged 18-60, years Smeets et al. [15] measured the effects of a high-protein lunch on energy expenditure, substrate oxidation and satiety related hormones (GLP-1, ghrelin, and PYY). In this single-blind, randomized crossover the study subjects received a standard breakfast and lunch with adequate or high protein content. The macronutrient composition of the lunch was either 10/60/30% of energy from protein/carbohydrate/fat (adequate protein, AP) or 25/45/30% of energy from protein/carbohydrate/fat (high protein, HP). Both lunches provided 35% of each subject's individual daily energy requirements, were equal in energy content (kJ), weight (g) and energy density (kJ/g). After the high protein lunch, satiety and meal induced thermogenesis was significantly higher than after the normal protein lunch (p=0.02), but the effects of a single high protein meal in the postprandial state were not mediated by increased plasma GLP-1 or PYY concentrations and decreased plasma ghrelin concentration. Over the longer term (meals or days), plasma GLP-1, PYY, and ghrelin responses most probably augment and may contribute to the increased satiety observed for high protein foods and diets. For example, in a controlled environment of a respiration chamber, satiety and metabolic rate were assessed over 4 days, comparing high versus normal protein diets (protein/carbohydrate/ fat: 30/40/30% of energy vs. 10/60/30% of energy) implying ~60 g or ~180 g of protein, respectively. Results showed that the high protein diet increased 24-hour satiety over the 4 days and decreased hunger compared with the adequate protein diet, while there was no difference in energy intake between these 2 regimens (subjects were fed in energy balance). The authors concluded that adequate dietary protein improves satiety, decreases hunger, and does so without changes in energy intake by influencing metabolism and appetite hormones directly. Increasing dietary protein versus simply restricting dietary carbohydrate may be essential to reduce cravings and improve satiety. This is consistent with the observation that restrained eaters who limit dietary carbohydrate alone experience greater carbohydrate cravings and diminished satiety more than protein restrictors [24-26].

BLOOD LIPIDS AND CARDIOVASCULAR RISK

The impact of high protein diets on metabolic parameters should be estimated before establishing optimal protein intake. However, assessing the independent effects of a specific macronutrient on the lipoprotein profile is challenging in connection with changes in the dietary macronutrients and weight reduction. Variations of these factors may have equivalent, but not additive benefits for dyslipidemia [27]; furthermore, there is much variability in metabolic responses among individuals [24]. The meta-analysis by Nordmann et al. [16] concluded that low-carbohydrate, high-protein diets are associated with more favourable changes in levels of triglycerides and HDL cholesterol, but less favorable changes in total cholesterol and LDL cholesterol than conventional, lower protein diets. More recent trials have also reported beneficial lipoprotein changes, as well as improvement in additional cardiovascular risk factors with high-protein diets. Noakes et al. [28] reported superior short-term benefits of an isocaloric very low-carbohydrate, highprotein diet on fasting HDL-cholesterol, triglycerides, and insulin levels, and similar improvement in weight, fasting glucose, blood pressure and C-reactive protein, compared with higher carbohydrate, lower protein diets over 12 weeks. The next 6-month trial of 88 abdominally obese adults showed similar weight loss and comparable improvement in risk factors, such as blood pressure, C-reactive protein, fasting insulin and glucose with low-carbohydrate and high-carbohydrate diets, but differential diet effects on plasma lipids were again noted [29]. To examine dietary effects in a high-risk population, 100 adults with metabolic syndrome were randomly assigned to energy-restricted diets with moderate variations in macronutrient content (48% of energy as carbohydrate, 19% as protein, 33% as fat vs. 65% of energy as carbohydrate, 13% as protein, 22% as fat) [7]. Over 5 months, weight loss and resolution of the metabolic syndrome between these 2 diet groups was comparable. Specific dietary effects beyond weight loss were evident with greater reduction in blood pressure and triglycerides in the lower carbohydrate, higher protein diet group, and increased reduction in LDL-cholesterol in the higher carbohydrate, lower protein diet group. A similar effect was achieved by Samaha et al. [9], who compared the low carbohydrate, high protein Atkins diet (22% protein) to a low fat diet (16%) on severely obese subjects. The authors suggested that matching the macronutrient composition of the diet to patients' specific metabolic profiles may be advantageous for optimal reduction in cardiovascular risk factors in at-risk populations. While more research is still needed in this area, it appears that higher protein diets are not harmful to blood lipids in the short term, and the exchange of protein for carbohydrate may actually be beneficial for blood lipids [30-32].

GLYCEMIC CONTROL

The impact of high-protein, low-carbohydrate diets on glycemic control has been evaluated in many of the above-mentioned studies. There is a growing body of evidence to suggest that such diets [19, 33, 34] may improve insulin sensitivity or lower fasting insulin concentrations in those with type 2 diabetes [1, 11, 15, 33, 35-39] following dietary intervention. It seems that improvement in glucose metabolism or insulin sensitivity in response to high-protein diets involves a beneficial effect of weight loss; however, it is unclear whether these outcomes are a direct result of dietary macronutrients or reduced body weight (Table 3). The impact of low carbohydrate diets on glycemic control and weight loss efficiency remains a topic of controversy because study results do not clearly confirm the efficacy of dietary interventions. A review of 6 studies on low glycemic index or glycemic load diets for overweight and obesity conducted by the Cochrane Collaboration [40] confirmed beneficial effects of intervention diets, but study results appear modest in the analysed group; McMillan-Price et al. [1] and Das et al. [41] received similar results. In the first study [1], 129 overweight or obese adults received one of four 12 week reduced fat, high-fibre diets with a defined glycemic load. Diets 1 and 2 were high carbohydrate (55% total energy), while diets 3 and 4 were high protein (25% of total energy); all diets aimed for the same fat content (30% total energy). The diets were further defined as containing high and low glycemic index carbohydrate, respectively. All 4 diets resulted in significant reductions in body weight but there were no significant differences between groups. In a subanalysis of women, the glycemic index had a significant

Table 3 Low-carbohydrate studies and glycemic control in type 2 diabetes

study	subjects	design	duration [weeks]	diet	differences in weight loss	HgbA1C	fasting glucose	dropout rate [%]
Meckling, 2004 [1]	32 obese/overweight insulin resistance, type 2 diabetes	RCT	10		no			29
intervention				50-70 g CHO/Day		NM	↔	
control				62% CHO, 20 % FAT, 18% protein		NM	↔	
Boden, 2005 [33]	10 obese; type 2 diabetes	pre-post	3		yes	↓	↓	0
intervention				<21 g CHO/day		NM	NM	
control				43% CHO, 19% protein, 38% fat				
Sargrad, 2005 [38]	12 obese; type 2 diabetes	RCT	8		no			0
intervention				40% CHO, 30% protein, 30% FAT		↔	↔	
control				55% CHO, 15 % protein, 30% fat		↓	↓	
Gannon, 2004 [35]	11 overweight/obese type 2 diabetes	Randomized cross-over with 5 week washout	10		no			27
intervention				20% CHO, 30% protein, 50% fat		↓	↓	
control				55% CHO, 15% protein, 30% fat		↔	↔	
Stern, 2004 [15]	132 obese with/without type 2 diabetes; insulin resistance	RCT	52		no			34
intervention				< 30gCHO/Day		↓[1]	↓	
control				<30% kcal from fat; -500 kcal/day		↓	↓	
Brinkworth, 2004 [11]	66 obese/overweight type 2 diabetes	RCT	64		no			42
intervention				40% CHO, 30% protein, 30% fat		↔	↔	
control				55% CHO, 15 % protein, 30% fat		↔	↔	
Gannon, 2003 [36]	12 normal weight/overweight/ obese;type 2 diabetes	Randomized cross-over with 2-5 weeks washout	10		no	↓	↔	0
intervention				40% CHO, 30% protein, 30% fat				
control				55% CHO, 15 % protein, 30% fat		↔	↔	
Gerhard, 2004 [37]	11 normal weight/overweight/ obese; type 2 diabetes	Randomized cross-over with 6-12 weeks washout	6		yes			0
intervention				45% CHO, 15% protein, 40% fat		↔	↔	
control				65% CHO,15% protein, 20% fat		↔	↔	

different effect in the high-carbohydrate diets (lowering the glycemic index doubled the fat loss from 2.8 kg to 4.5 kg) than in the high-protein diet. Overall, women instructed to follow the low glycemic index, high-carbohydrate diet produced the best clinical outcome, reducing both fat mass and LDL cholesterol levels. The authors concluded that glycemic load, and not just overall macronutrient content, influences weight loss, particularly in women. Das et al. [41] conducted a 1-year study randomizing 34 overweight men and women to either a high glycemic load diet (60% carbohydrate, 20% fat, 20% protein) or a low glycemic load diet (40% carbohydrate, 30% fat, 30% protein), both reduced by 30% total calories for weight loss. There was no statistically significant difference between groups in mean energy intake, percentage weight loss (-7.81 for low glycemic load and -8.04 for high glycemic load), body fat loss, or resting metabolic rate throughout the 12-month trial. Thus, the authors concluded that diets differing substantially in glycemic load induce comparable long-term weight loss.

SAFETY AND LONG-TERM OUTCOMES

The debate about the safety of high protein diets with regard to kidney function is still extant. Populations with established renal disease may slow the progression of disease when the amount of dietary protein is limited to the RDA level [42], but the influence of high protein diets on kidney functions in healthy populations is not clear. In a recent review paper, Eisenstein and Roberts [43] assessed the results and came to the conclusion that there is little evidence for adverse effects of high protein diets on renal function in individuals without established renal disease. Several studies have reported that high protein diets cause hyperfiltration up to a saturation point of approximately 125 g/day [44-46], although net hyperfiltration did not occur when protein intake varied in the range of 70-108 grams a day [47] because higher protein intakes were associated with increased renal mass. Other measures of renal function are similarly inconsistent. In evaluating renal clearance of creatinine, urea, and albumin, one study compared these parameters in body builders consuming high protein diets with well-trained athletes consuming medium-protein diets and found no adverse consequences of protein intakes up to 2.8 g/kg [48]. There is evidence that higher protein intakes can significantly increase the risk of kidney stones [49], uric acid stones, and calcium stones [50]. However, one study found a significant decrease in calcium oxalate stones with a higher compared to a lower protein group [51]. Taken together, there is little evidence that high protein diets determine a serious risk to kidney function in healthy populations; however, further long term studies are needed. More susceptible groups, such as diabetics and those with existing renal disease, should address more caution to higher protein intakes. Defining the absolute amount of protein in high-protein weight loss diets is important before assessing the diets' potential harmful effects on bone kinetics. Recently published short-term [52] and long-term [53] studies have not demonstrated detrimental effects of high-protein weight loss diets, but further investigations of the long-term impact of those diets on renal and bone health are warranted. The lack of evidence about the effects of long-term protein intake should be caution for practitioners using high-protein diets with patients at risk for renal disease (i.e., patients with diabetes, kidney stones, and gout) [54]. The American Diabetes Association recommends that protein should comprise 20% or less of total energy intake until the long-term effects of higher protein intake on diabetes management and kidney function are known [55]. Thus, until more data are available regarding the safety of excessive protein intake, it may be prudent to recommend a moderate amount of protein for weight loss which is also considered feasible, safe, and effective for improvement in body composition [56].

CONCLUSIONS

Randomized, controlled trials continue to indicate comparable, if not superior, effects of high-protein low-carbohydrate diets on weight loss, preservation of lean body mass, and improvement in several cardiovascular risk factors for up to 12 months. Although increases in dietary protein can be effective in helping people to lose weight over the short-term, there appears to be no metabolic advantage on long-lasting weight control and health outcomes, particularly in high-risk populations with dyslipidemia, diabetes and metabolic syndrome. Long term data are still needed because heterogeneity between studies makes it difficult to draw firm conclusions. Due to the lack of long-term studies, the safety of these diets is also uncertain. Mounting evidence suggests that excess protein intake (popular weight loss diets may double the percentage of total energy as protein) may exert harmful influence on calcium homeostasis and possibly bone mass. Additional adverse effects of high-protein intake on kidneys have been suggested but available data remain inconclusive. Current recommendations referring to high-protein diets should emphasize the need for further research, particularly considering potential harmful effects for individuals at risk groups.

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