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VIEWPOINT AND COMMENTARY

Low-Carbohydrate–High-Protein Diets

Is There a Place for Them in Clinical Cardiology?

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Since the last meeting of the American Heart Association, a great deal of media attention has been focused on low-carbohydrate–high-protein diets (LC-HP) and their potential impact on the practice of cardiology. It has been suggested that these diets, which were introduced originally as weight-loss regimens, also have a significantly beneficial effect on a variety of cardiovascular risk factors. It is clear that people who consume such diets have a reduced intake of calories, resulting in a predictable degree of weight loss. These diets induce a moderate level of ketosis and, in some studies, have been shown to improve the lipid profile overall. There is also a reduction in the number of low-density lipoprotein particles. However, these trends also have been observed over periods of 24 weeks or less with low-calorie diets that already have an established record of safety and efficacy. Although there is a public perception that LC-HP diets have a near-perfect "success rate," the attrition rate on these diets varies from 20% to 43%, which is similar to other conventional weight-loss regimens. Additionally, from a nutritional standpoint, these diets are seriously deficient in several micronutrients and dietary fiber, thus creating a need for nutritional supplements. In contrast, the conventional weight-loss regimens have a favorable impact on serum lipids without the accompanying ketosis and have the potential to provide a nutritionally balanced diet without the need for supplements. Because of the nutritional deficiencies inherent in LC-HP diets and the absence of long-term data on their efficacy and safety, they cannot be recommended in place of currently advocated low-fat, low-calorie diets that have an established record of safety and efficacy. (J Am Coll Cardiol 2004;43:725–30) © 2004 by the American College of Cardiology Foundation

Among the more than 3,000 articles presented at the Scientific Sessions of the American Heart Association (AHA) in November of 2002, few captured more public and media attention than the one on low-carbohydrate–high-protein (LC-HP) diets. This study was a two-arm randomized controlled trial that compared the effects of a low-carbohydrate ketogenic diet (<20 g/day; "Atkins type") and nutritional supplements (including fish, borage [a source of linolenic acid], and flaxseed oil) with a low-fat, low-calorie

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diet in overweight/obese, hyperlipidemic (low-density lipoprotein [LDL] >130 mg/dl or triglycerides >200 mg/dl) otherwise-healthy volunteers who were motivated to lose weight for six months. Even though the AHA was not specifically mentioned in the published abstract (1), because the study was funded by the Atkins Center for Complementary Medicine, it swiftly became labeled as a trial of the Atkins diet versus the AHA diet. Media experts ranging from those on major U.S. networks to the more staid British Broadcasting Corporation featured commentaries on the presentation, suggesting that the nutritional theories of the "LC-HP lobby" had been finally vindicated. The public response was no less enthusiastic, and many gained the impression that the AHA itself had made, if not a U-turn, at least a significant change of direction in its advice to the public. In fact, it prompted this august body to issue an immediate clear media advisory distancing itself from any such notion even before the sessions were concluded. The advisory was consistent with the guidelines of the AHA Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism, which states: "High-protein diets are not recommended because they restrict healthful foods that provide essential nutrients and do not provide the variety of foods needed to adequately meet nutritional needs. Individuals who follow these diets are therefore at risk for compromised vitamin and mineral intake, as well as potential cardiac, renal, bone, and liver abnormalities overall" (2).

The public is clearly confused, as indeed are many physicians and health care professionals, about the specific role of LC-HP diets in the management of patients with cardiovascular risk factors, diabetes mellitus, and coronary artery disease. The LC-HP diets engaged the attention of cardiologists initially as a means of inducing weight loss in obese individuals with other common diseases, such as

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Abbreviations and Acronyms

AHA = American Heart Association
BMI = body mass index
GFR = glomerular filtration rate
LC-HP = low-carbohydrate–high-protein
LDL = low-density lipoprotein

hypertension, heart failure, coronary artery disease, and hyperlipidemia. Although many physicians accept the evidence that weight loss occurs on these diets, they are concerned that an LC-HP diet is significantly at odds with the recommendations of the AHA (3) and the National Cholesterol Education Program (Adult Treatment Panel) (4). Because the diets allow unlimited amounts of animal products, the immediate issue is that they are likely to contain excessive quantities of saturated fats and cholesterol.

WHAT IS AN LC-HP DIET?

Usually, LC-HP diets are those that contain significant quantities of animal protein and relatively low amounts of carbohydrates, rendering them ketogenic. Individuals who consume such diets are in a perpetual state of ketosis, which leads to a disproportionate use of fat stores for energy. This is the normal response to caloric deprivation. Table 1 compares two LC-HP diets (5,6) currently in vogue, with conventional recommendations with which physicians are familiar (3,7). It is clear that in the LC-HP diets, the percentage of daily calories provided by protein, total fat, and saturated fat is 2 to 2.5 times higher than in the AHA guidelines. The corresponding value for carbohydrates is typically 30% to 90% lower. Where do these diets, with a surfeit of saturated fat, cholesterol, and practically no carbohydrate and fiber, fit into the management of patients? Are they a weight-loss regimen, or have they other therapeutic benefits for individuals with cardiovascular disease?

LC-HP DIETS AND WEIGHT LOSS

A basic tenet of a dietary approach to weight loss is caloric restriction. In contrast, with LC-HP diets, caloric restriction is not imposed but appears to be an inevitable outcome (8,9). Skov et al. (9) showed that the resulting weight loss on high-protein diets continued for as long as the subject remained on the study protocol (up to six months). These authors concluded that high-protein diets were an effective means of reducing caloric intake and speculated that it was probably due to appetite suppression secondary to ketosis. Regardless of the potential mechanisms involved, there is little doubt that an LC-HP diet results in weight loss. Although similar changes are observed with more conventional low-fat dietary regimens, they have been criticized on the basis that the latter simply "do not work" and do not extend life expectancy (10). Surprisingly, the LC-HP diets have escaped this criticism, presumably because of the widely held but mistaken belief that they are effective invariably. Nevertheless, there is a considerable body of evidence to support the claim that a low-fat diet available ad libitum results in a significant weight loss even when it is the *sole intervention* (11,12). Additionally, when tested in a prospective fashion, the attrition (i.e., failure) rate in healthy individuals on LC-HP diets varies from 20% to 43% in the short term (<6 months) (13–16). These attrition rates are similar to those observed with more conventional weight-loss regimens (14–16). Indeed, when an LC-HP diet is compared directly with other dietary regimens for weight loss, it appears that the weight loss is not a unique consequence of the LC-HP nature of the diet but rather a function of the reduced caloric intake (14–16).

The recent study reported by Westman et al. (1), which compares an Atkins-type diet with a low-fat diet provides

Table 1. Comparison of Macronutrients in Two LC-HP Diets With the ADA Exchange Diet, the AHA Dietary Guidelines, and IOM Recommendations

	Atkins' Diet (5)	Protein Power (6)	ADA Exchange (7)	NCEP III (4)	AHA Guidelines (3)	IOM/NAS (17)
Calories (kcal)	1,600	1,600	1,600	1,600	1,600	1,600
Carbohydrate (g)	22 (5%)	33 (8%)	240 (60%)	220 (55%)	220 (55%+)	220 (50%+)
Protein (g)	146 (35%)	149 (35%)	82 (20%)	60 (15%)	28–72 (12%–18%)	90 (22%)
Fat (g)	104 (59%)	97 (53%)	35 (20%)	53 (30%)	53 (<30%)	40 (27%)
Saturated fat (g)	47 (26%)	33 (19%)	11 (6%)	<7 <12	18 (>10%)	minimize
Cholesterol (mg)	924	657	112	<200	<300	minimize
Dietary fiber (g)	4	11	22	20–30	>25	25 for women, 38 for men

Note only the midpoint of the ranges are quoted for IOM/NAS and NCEP III.

ADA = American Diabetes Association; AHA = American Heart Association; IOM/NAS = Institute of Medicine/National Academy of Science; LC-HP = low-carbohydrate–high-protein; NCEP = National Cholesterol Education Program.

some interesting insights into the relationship between calorie restriction and weight loss. At the time of this writing, the caloric contents of the two diets in the study have not been published. The mean age of subjects was 46 years; the mean baseline body mass index (BMI) was 34.5 kg/m^2. The weight loss over six months was 13.8% for the Atkins-type diet (n = 36) and 8.8% for the low-fat diet (n = 27). However, in a previous publication Westman et al. (13) reported in greater detail the effects of a similar LC-HP diet in a group of 51 free-living individuals motivated to lose weight. Of the individuals, 41 completed 24 weeks on the diet. While participating in the study, they were instructed to eat unrestricted quantities of beef, pork, chicken, fish, shellfish, and eggs. Cheese intake was permitted to 4 oz/day. They were also asked to eat two cups of salad vegetables and one cup of a low-carbohydrate vegetable. At the start of the study, the subjects consumed 25 g of carbohydrates per day until the target weight was attained and thereafter increased carbohydrate consumption to 40 g/day. Their initial BMI ranged from 26 to 33 kg/m^2. After 24 weeks on the diet, there was an average weight loss of 19.8 lbs in the 41 subjects, representing an average reduction in BMI of 3.2 kg/m^2. Reductions in serum cholesterol, LDL, and triglycerides were observed together with a concurrent increase in high-density lipoprotein. In both of these studies, all of the patients were overweight and were motivated to lose weight.

A closer examination of the data presented in the foregoing study provides a relatively simple explanation for the observed weight loss. The most important consideration in this study (13) is the daily consumption of calories. Despite the unrestricted nature of the diet, the total energy consumption as assessed from food diaries was only 1,447 calories/day. It is of interest to compare this value with the estimates of energy requirements based on the new guidelines proposed by the Institute of Medicine/National Academy of Science (17). From the data presented in Table 1 of Westman et al. (13), one could estimate the *energy* expenditure to be approximately 2,775 calories for the men and 2,313 calories for the women in the study (17). It is widely recognized that self-reported food diaries underestimate the calorie intake by 10% to 20% if they are used without an appropriate correction term (18,19). Even after applying such a correction, it would appear these subjects endured a significant calorie deficit during the 24 weeks of the study. It is likely that this deficit was at least 400 calories/day. Because it is generally recognized that a cumulative deficit of 3,500 calories would result in a weight loss of 1 lb, one could anticipate a weight loss of approximately 19.2 lbs (i.e., [400 × 7 × 24]/3,500) over 24 weeks. In fact, the subjects lost an average of 19.8 lbs. Thus, simple calorie restriction alone could account for the weight loss observed on this LC-HP diet. There is also evidence to support the suggestion that a significant portion of the initial weight loss is due to loss of body water (20).

LC-HP DIET AND FASTING LIPID PROFILE

In addition to weight loss, another claim made on behalf of the LC-HP diet is its potentially favorable impact upon serum lipid profiles. In the study reported by Westman et al. (13), there was a reduction in total, LDL, and very-LDL cholesterol. It also showed that, in addition to reducing total LDL cholesterol levels, the LC-HP diet was associated with a reduction in the percentage of small LDL particles. Sharman et al. (21) had reported a similar trend in LDL particle size even in the absence of weight loss with a ketogenic diet. Recent studies reported do not confirm these favorable trends (15,16). In these studies, an LC-HP did not result in a significant reduction in either total or LDL cholesterol concentrations after six months. The high-density lipoprotein cholesterol concentration increased in one (15) but not in the other (16). However, there was a significant reduction in triglycerides in individuals who consumed a low-carbohydrate diet in both studies. Nevertheless, it should be noted that many of these favorable changes, including a reduction in serum LDL, could be achieved with conventional weight loss diets either alone (22) or in combination with exercise (23,24). Further, low-fat, high-carbohydrate diets do not consistently decrease LDL particle size (25). An additional issue that merits consideration is the effect of repeated high-fat meals on lipids in the postprandial state.

Postprandial lipemia. Despite the potential benefit in the *fasting* lipid profile, one has to consider the impact of repeated high-fat meals on the "dynamic" changes in the lipid profile during a 24-h period. There is a great deal of evidence suggesting that a high-fat meal creates a state of lipemia (postprandial lipemia) (26). It has been suggested that elevated triglycerides, particularly the remnant very-LDL lipoprotein particles associated with this phenomenon, are atherogenic (27). There are several reports of impairment of endothelium-dependent relaxation during postprandial lipemia (28,29). In addition, postprandial lipemia is associated with increased markers of inflammation and activation of platelets and monocytes (30). Thus, repeated high-fat meals are likely to generate a persistent state of impaired endothelium-dependent relaxation and other atherogenic processes, regardless of any potentially favorable effects on the fasting lipid profile. Although prospective data confirming the association between postprandial lipemia and atherogenesis are still lacking, there are multiple plausible mechanisms by which this phenomenon could contribute to the atherosclerotic process (31).

Potential adverse effects of the LC-HP diet. KETOSIS. Proponents of LC-HP diets suggest that the "unique" weight-loss potential of the diets is due to the state of mild ketosis they generate. However, in studies in which the calorie intake was controlled, weight loss was not a consistent finding, although ketosis was (21,32). Thus, ketosis does not induce weight loss unless it is combined with caloric restriction. The ketogenicity of LC-HP diets appears to be

Table 2. "Adverse" Consequences of LC-HP Diets

Effect	Cause	Reference(s)
Mild dehydration	Water loss and ketosis	(20)
Constipation	Lack of fiber	(13)
Bad breath	Dehydration (?)	(13)
Headaches	Dehydration (?)	(13)
Loss of hair	Nutritional deficiency (?)	(13)
Malnutrition	Caloric deprivation	
Potential long-term health problems, such as cancer	Deficiency of fiber and phytochemicals	(40,42)
Osteoporosis and fractures	Increased rate of bone loss	(36)
Renal insufficiency	Reduction GFR	(43)

GFR = glomerular filtration rate; LC-HP = low-cholesterol–high-protein.

dependent on the degree of carbohydrate deprivation that accompanies the diet. Ketonuria is strongly correlated with the degree of adherence to the diet (13). However, counter-intuitively, hyperinsulinemic obese subjects may in fact benefit from a ketogenic diet in the short term. Over a four-week period, body weight, insulin levels, and blood sugar are lowered by a ketogenic diet (33–35). However, there are no studies examining the effects of such a diet over an extended period of time. It has been argued that many of the side effects stem from the ketosis, which the diet is designed to induce (Table 2). A particular example is the potential for dehydration (20). There is also the suggestion that LC-HP diets contribute to the development of osteoporosis (36).

POOR LONG-TERM NUTRITION. One of the main concerns regarding the uncritical use of LC-HP diets is the relative absence of many micronutrients and fiber. When these deficiencies are considered in conjunction with the hypocaloric nature of the diet, there is a real danger of malnutrition in the long term. It is self-evident that humans cannot endure a daily deficit of 400 to 500 calories on an ongoing basis unless strict goals are set regarding weight loss. If such precautions are not taken, it is indeed possible to generate a malnutrition-modulated type of diabetes mellitus that is associated with insulin resistance (37,38). However, it has to be recognized that these issues can only be resolved by undertaking long-term studies of the effects of ketogenic diets with caloric restriction in normal subjects and patients with a variety of clinical syndromes affecting the cardiovascular system. A fruitful area of inquiry would be the examination of how an individual could be weaned off a LC-HP diet without a rebound increase in weight. Some proponents of these diets have suggested that when the weight target has been reached one could introduce more carbohydrates with reversion to the initial low-carbohydrate state if weight gain recurs, a perpetual "dietary yo-yo state" that has little relation to healthy eating (5). This "weight cycling," which is not unique to LC-HP diets, has been well described and may be associated with adverse effects on health (39).

As many have advocated, LC-HP diets should be accompanied by a variety of dietary supplements to avoid deficiency disorders. Indeed, in the study reported by Westman et al. (13) the subjects were given significant quantities of an extensive list of supplements (totaling 65!), which included 1,200 mg of flax seed oil, 1,200 mg of borage seed oil, 1,200 mg of fish oil, and 15 IU of vitamin E. The costs of these items are not negligible, and they are unlikely to forestall the long-term consequences of energy deprivation. Another related aspect that merits serious consideration is that LC-HP diets seriously diminish the consumption of several food groups, such as fruit, bread, grain and cereals, and vegetables. The amount of fiber is derisory despite its value in preventing certain forms of cancer (40) and lowering serum lipids (41). The recommendations released by the Institute of Medicine indicate that the daily allowance for men and women should be 25 and 38 g, respectively. Finally, the emerging field of phytochemicals suggests that there is a strong likelihood that these substances that are present in abundance in fruits and vegetables may in fact prevent the occurrence of certain forms of cancer (42).

RENAL DYSFUNCTION. An analysis of women enrolled in the Nurses Health Study provides an interesting insight into the long-term consequences of a high-protein diet. Knight et al. (43) analyzed changes in renal function in 1,624 women who provided blood samples in the year 1989 and again in 2000. Protein intake, which was estimated in the years 1990 and 1994 using food frequency questionnaires, was found to be 76.7 g/day. *This value is approximately 50% of the recommended protein intake in the LC-HP diets shown in Table 1.* Renal function was evaluated in terms of serum creatinine and glomerular filtration rate (GFR). The latter was calculated from conventional formulae (44,45). The authors concluded that a high-protein intake was associated with a decline in GFR in women with mild renal insufficiency. It is of interest to note that those designated as having mild renal insufficiency had a serum creatinine of 0.88 mg/dl (range 0.77 to 1.09 mg/dl) and a GFR of 71.0 ml/min/1.73 m^2. The serum creatinine in this range would rarely signal an alert to potential renal insufficiency.

WHAT PRACTICAL ADVICE SHOULD BE GIVEN TO INDIVIDUALS WHO SEEK INFORMATION ABOUT THE LC-HP DIETS?

Given the media focus of LC-HP diets, it is inevitable that physicians will encounter patients who insist on embarking on this type of diet. It is important that these patients understand that the long-term (beyond six months) consequences of an LC-HP, hypocaloric diet are unknown and that they have a clear appreciation of the adverse effects that could be expected while on the diet (Table 2).

In conclusion, use of LC-HP diets run counter to all the current evidence-based dietary recommendations for

healthy populations (3,17). These diets do not meet the nutritional requirements of healthy people based on the current dietary reference intakes for many vitamins and minerals and recommendations for dietary fiber. When used for weight loss, these diets are associated with several potential adverse effects and nutrient deficits, and the long-term consequences of their continued use are unknown. On the basis of evidence currently available, LC-HP diets cannot be recommended as a part of a long-term care plan for weight management in patients who smoke or have common diseases that affect the cardiovascular system, such as hypertension, hyperlipidemia, diabetes mellitus, and coronary atherosclerotic vascular disease, where endothelial dysfunction is a feature.

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