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Low-Carbohydrate Diet Review: Shifting the Paradigm

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What does a clinician need to know about low-carbohydrate (LC) diets? This review examines and compares the safety and the effectiveness of a LC approach as an alternative to a low-fat (LF), high-carbohydrate diet, the current standard for weight loss and/or chronic disease prevention. In short-term and long-term comparison studies, ad libitum and isocaloric therapeutic diets with varying degrees of carbohydrate restriction perform as well as or better than comparable LF diets with regard to weight loss, lipid levels, glucose and insulin response, blood pressure, and other important cardiovascular risk markers in both normal subjects and those with metabolic and other health-related disorders. The metabolic, hormonal, and appetite signaling effects of carbohydrate reduction suggest an underlying scientific basis for considering it as an alternative approach to LF, high-carbohydrate recommendations in addressing overweight/obesity and chronic disease in America. It is time to embrace LC diets as a viable option to aid in reversing diabetes mellitus, risk factors for heart disease, and the epidemic of obesity. (*Nutr Clin Pract.* 2011;26:300-308)

Keywords: weight loss; reducing diet; carbohydrate-restricted diet; fat-restricted diet; diabetes mellitus; cardiovascular diseases

A low-carbohydrate (LC) diet is not a new dietary concept. In 1825, Jean Brillat-Savarin published *The Physiology of Taste*, in which he offered a solution to obesity. His solution was to restrict everything that contained starch or flour. Since then, clinicians have adopted a similar approach for their patients. A LC diet limits daily carbohydrate intake to 30-130 g/d. A low-fat (LF) diet restricts daily fat intake to 10%-15% of total calories. Recent short-term and long-term randomized controlled trials—considered the gold standard of research—have shown that LC diets perform as well as or better than LF diets with regard to weight loss, glucose and insulin response, and important cardiovascular risk markers in both normal subjects and those with metabolic and other health-related disorders. These results, and the fact that longitudinal studies have found limited benefit of the LF dietary approach for preventing chronic disease,[1-4] make a LC approach an attractive dietary option.

Given the underlying cause of carbohydrate intolerance, it is frequently surprising to clinicians and patients alike that there is any question that some forms of reduction in dietary carbohydrate is the first line of attack against diabetes and metabolic syndrome. The American Diabetes Association concurs that a LC diet is an acceptable approach for weight loss for up to 1 year. This recommendation also cites evidence that markers of cardiovascular disease (specifically serum levels of triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]) are improved with LC diets compared with LF diets (Figure 1) and acknowledges the benefit of carbohydrate restriction for glycemic control.[5] Taking the 1-year mark at face value, the clinician is confronted with the question, "What diet do I recommend on day 366?" If a patient is doing well on a LC diet for a year, is there a reason to return the patient to his or her previous, presumably less beneficial, diet after a year? It is also important to understand that glycemic control in patients with diabetes[6] and lipid profiles in normal people[7] are improved by carbohydrate restriction even in the absence of weight loss.

The argument may be made that it is not the LF diets that have failed but the will of the American people to follow them. From a clinician's perspective, we prefer not to blame patients but to assist them; in fact, Americans are clearly aware of the purported dangers of fat and have made a substantial attempt to alter the content of their diets.[8,9] That the increase in calories in the American diet over the past 30 years is almost entirely due to an increase in carbohydrate intake should be reason enough to consider carbohydrate reduction a principal target for improving the health of Americans (Figure 2).[9] First demonstrated by LaRosa et al[10] in 1980 and confirmed many times

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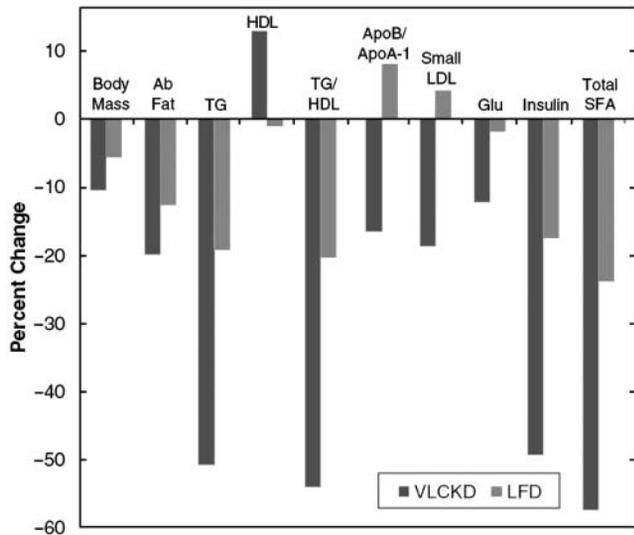
Figure 1. Comparison of low- and high-carbohydrate diets at 12 weeks. Results from trial in which 40 subjects with atherogenic dyslipidemia were randomly assigned to either diet[22]. Ab, abdominal; ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; Glu, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids; TG, triglycerides. LFD, low-fat diet. Adapted from Jakobsen MU, O'Reilly EJ, Heitmann BL et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr*. 2009;89:1425-1432 with permission from the American Society for Nutrition.
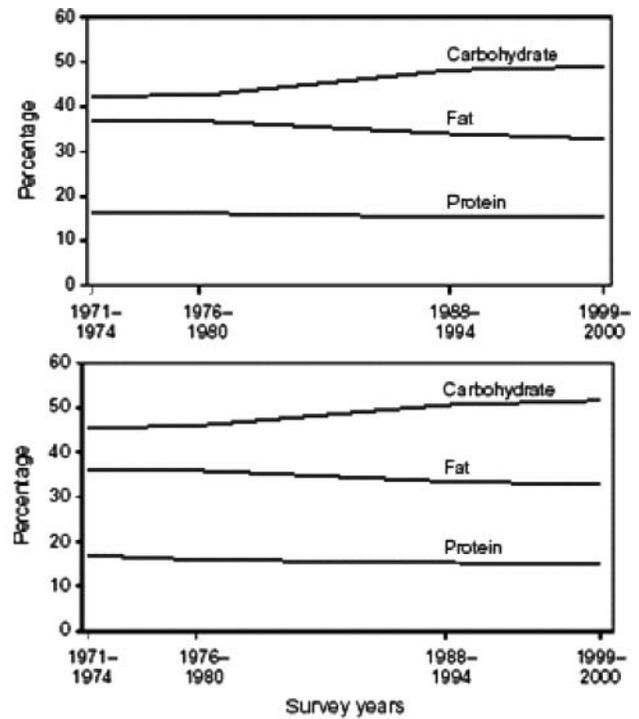

Figure 2. Percentage of kilocalories from macronutrient intake among men (top) and women (bottom) aged 20-74 (age-adjusted), by survey years. Data from National Health and Nutrition Examination (NHANES), United States, 1971-2000.[9]

since,[11] LC diets do not, by necessity, require higher fat or protein intakes, as a spontaneous decrease in overall calorie consumption frequently results in little protein or fat added back in for the carbohydrate that is removed. Although the "one-size-fits-all" approach to diet is universally disavowed, there is nevertheless a tendency for healthcare providers to recommend a single approach even when this approach may not work for many patients.

Definition of Low-Carbohydrate

Diets are frequently characterized by percentage composition, although this method does not address the threshold effects of absolute amount of carbohydrate reduction—reflecting a point at which lowered insulin levels shift the body away from an anabolic state and toward fat oxidation. Although not universally accepted, standardized definitions for discussing carbohydrate reduction have been proposed.[11]

The following definitions are used to quantify fat allowances in various carbohydrate-reduced diets:

1. Reduced-carbohydrate diet: >130 g of carbohydrate per day, up to 45% of total calories

2. LC diet: 30-130 g of carbohydrate per day
3. Very low-carbohydrate ketogenic (VLCK) diet: <30 g of carbohydrate per day; will usually permit ketosis to occur

A low-fat diet contains 10% to 15% of total calories as dietary fat.

Body Weight

The biochemistry that relates LC nutrition to weight loss and chronic disease rests on the well-known response of the pancreas to dietary carbohydrate. Insulin release is directly related to the amount of glucose in the bloodstream and has a large effect on fatty acid metabolism and storage. Insulin increases fatty acid synthesis via stimulation of acetyl-coA carboxylase and increases triacylglycerol synthesis in the liver through lipoprotein lipase. Cholesterol synthesis increases via activation of hydroxymethylglutaryl-CoA reductase. Storage of fatty acids is favored because insulin inhibits the release of fatty acids from the cell through the activation of the hormone-sensitive lipase. Reducing carbohydrate appears to create a metabolic milieu that can positively affect appetite and reduce fat storage as well as or more effectively than other dietary strategies.[12-15]

Experimental Studies

A recent meta-analysis by Hession et al[16] compared the effects of LC diets with LF diets on weight loss and coronary disease risk factors. A total of 13 studies conducted from 2002 to 2007 that lasted at least 6 months fulfilled the inclusion criteria, with a total of 1,222 participants. The weighted mean difference at 6 months between diets was −4.02 kg in favor of the LC diet group. After 12 months, this difference fell to −1.05 kg. In addition, higher attrition rates were found in the LF group compared with the LC group. Finally, the LC diet demonstrated favorable changes in serum levels of HDL-C and TG as well as systolic blood pressure.

Another study conducted by Gardner et al[12] in 2007 randomized 311 overweight premenopausal women to 1 of 4 popular diets for a 12-month period: Atkins (<20 g CHO/d; no calorie restriction), Zone (40% CHO; calorie-restricted), LEARN (55%-60% CHO, calorie-restricted), and Ornish (<10% fat; no calorie restriction). The mean 12-month weight change was −4.7 kg for those on the Atkins diet, −1.6 kg for those on the Zone diet, −2.2 kg for those on the LEARN diet, and −2.6 kg for those on the Ornish diet. The Atkins group experienced the most improved metabolic effects, with positive changes in HDL-C, TG, and systolic blood pressure.

More recently, a 2-year trial was conducted by Shai et al[13] in which 322 moderately obese individuals were randomized to 1 of 3 diets: a VLC diet with no calorie restrictions; a calorie-restricted Mediterranean diet (MED); or a calorie-restricted LF diet. The mean weight change was −4.7 kg for the VLC group, −4.4 kg for the MED group, and −2.9 kg for the LF group. The ratio of serum total cholesterol to HDL-C decreased in all groups, with the LC group showing the greatest improvement with a relative decrease of 20% compared with the LF group with a decrease of 12%.

These studies show that the LC dietary approach, despite unrestricted caloric intake, is at least as effective as other dietary plans with regard to weight loss. There is some indication that the complexity of human metabolism goes beyond a simple energy balance equation. Some of the most intriguing examples of this are diet studies where calories are held constant and weight loss differs between groups, with greater weight loss observed in the LC group.[17-20] This suggests the possibility that the weight loss may be due to specific metabolic or hormonal advantages of a LC diet. These could include a metabolic advantage with regard to energy expenditure related to increased metabolic rate due to metabolic inefficiencies, increased thermogenesis, and/or increased spontaneous activity. Not mutually exclusive, a spontaneous decrease in calorie consumption is frequently noted in LC diet groups, possibly related to increased satiety effects of protein and/or fat and a restoration of intrinsic appetite control.

Lipids

When a patient is advised to lower the fat content of his or her diet for reasons of cardiovascular health, the fat is most often replaced by carbohydrate. For most patients, this leads to elevation in fasting serum TG levels and a concomitant decrease in HDL-C.[21,22] Reducing dietary carbohydrate reliably reduces serum TG, increases HDL-C, and can improve other aspects of the lipid profile. This was true even in studies where there was no change in weight.

Experimental Studies

In 2009, Volek et al[23] compared the effects of 2 hypocaloric diets on 40 subjects with atherogenic dyslipidemia: a carbohydrate-restricted (CR) diet (12% CHO) and a LF diet (56% CHO). After 12 weeks, subjects on the CR diet had more favorable TG (−51%), HDL-C (13%), and total cholesterol/HDL-C ratio (−14%) responses. In addition, the CR group showed more favorable responses in alternative indicators of cardiovascular risk, including low-density lipoprotein (LDL) particle distribution. Despite a 3-fold intake of dietary saturated fat in the CR group, saturated fatty acids in TG and cholesterol esters were significantly decreased compared with the LF group.

These results were similar to those of Yancy et al[14] in 2004, who randomized 120 overweight adults to either a LC diet with no calorie restriction or a calorie-restricted, LF diet. After 24 weeks, the LC diet group had a greater decrease in serum TG levels as well as a greater increase in HDL than the LF group. Changes in the LDL-C levels were not statistically significant. Of note, 76% of LC diet group completed the study versus 57% of the LF diet group.

In another study, Sharman et al[24] compared the effects of 2 calorie-restricted diets on serum lipid levels in 15 overweight men: a VLC diet and a LF diet. Subjects were randomized to 1 of the diets for a 6-week period, after which they crossed over to the other diet for another 6 weeks. Both diets had the same effect on total cholesterol and neither diet changed HDL-C. LDL-C was reduced only by the LF diet (−18%), whereas the fasting serum TG level was only reduced by the VLC diet (−44%). Significant increases in large LDL-1 particles and decreases in smaller, more atherogenic LDL-3 and LDL-4 particles were seen only after the VLC diet was ingested.

Although diets tend to lower serum LDL-C and total cholesterol levels, there is substantial variation. More reliable are the effects of LC diets: improvement in

HDL-C, TG, and, most importantly, LDL particle size. The possibility that it is not LDL-C that is atherogenic but rather the predominance of small, dense LDLs (the so-called pattern B phenotype) is a possible reconciliation of the different risk factors and bears on current questioning of the use of LDL-C as the only focus for predicting cardiovascular disease risk.[25-27]

Blood Glucose and Insulin

Basic biochemistry, agreed-upon knowledge of human physiology, clinical experience, and common sense all concur: high dietary carbohydrate intake will raise blood sugar, and reducing dietary carbohydrate will lower it. Similarly, although also sensitive to other macronutrients, fluctuations in insulin are reduced with LC diets. This is the logical starting point for discussion of hyperglycemia and hyperinsulinemia as seen in diabetes mellitus and other metabolic states. In practice, weight loss improves diabetes mellitus and glucose control, but the mechanism is unknown and may involve de facto reduction in dietary carbohydrate. Emphasis on weight loss as the primary effect of LC diets on glucose control is disingenuous; as noted below and elsewhere,[6] LC diets improve glycemic control in the absence of weight loss.

Experimental Studies

In 2008, Westman et al[28] found significantly greater improvements in hemoglobin A1c (HbA1c) levels, body weight, and HDL-C levels of subjects with obesity and type 2 diabetes following a VLCK diet with no calorie restriction compared with those eating a calorie-restricted, low-glycemic index (LGI) diet. Diabetes medications were reduced or eliminated in 95.2% of participants following the VLCK diet versus 62% of LGI diet participants.

Yancy et al[29] evaluated the effect of a VLCK diet with no calorie restriction on blood glucose and medication use in individuals with type 2 diabetes. After 16 weeks, the 21 individuals who completed the study demonstrated a 16% decrease in mean HbA1c and only 2 subjects requiring diabetes medication did not reduce dosage; 7 subjects discontinued their medications entirely.

Gannon and Nuttall[30] examined the effect of 2 isocaloric diets on blood glucose control in 8 men with type 2 diabetes randomized to a 5-week crossover study: either a high-carbohydrate control diet or a LC diet. At the end of the diet intervention period, mean 24-hour serum glucose was 198 mg/dL for the control diet and 126 mg/dL for the LC diet, whereas HbA1c was 9.8 ± 0.5 and 7.6 ± 0.3, respectively. In addition, serum insulin levels were decreased on the LC diet.

Recently, the intensive insulin therapy arm of the ACCORD trial was terminated because of significantly increased mortality, raising concerns about the benefits of tight glucose control. However, the intensive control was entirely drug-based; deaths might have been attributable to the method of targeting glucose rather than the value of the target itself. A LC diet is an alternative to medication (or at least an adjunct to less intensive pharmacology) and can give patients the opportunity to control glucose levels without the risk of hypoglycemic reactions.[31,32]

Blood Pressure

Obesity has been strongly associated with increased blood pressure. The increased size of the vascular bed leads to impaired outflow of blood from the heart and increased pressure in large arteries. In addition, the high circulating levels of insulin that accompany insulin resistance related to obesity have been associated with sodium retention, proliferation of vascular smooth muscle, increased sympathetic nervous system activity, and diminished release of nitric oxide from the endothelium.[33-35] Frequently, the improvements seen in blood pressure with patients eating a LC diet are attributed to the weight loss effects of the diet,[12,14] but recent results demonstrate that improvements in blood pressure may be independent of weight loss and related to other mechanisms, as noted below.

Experimental Studies

Yancy et al[36] evaluated changes in blood pressure in their 2010 comparison study of 146 overweight males randomized to either a VLC diet with no calorie restrictions or a calorie-restricted, diet plus orlistat, a weight-loss medication (LF+O). After 48 weeks, the VLC diet group had greater improvement in both systolic and diastolic blood pressure despite similar weight loss in both groups. Systolic blood pressure decreased by 5.9 mm Hg in the VLC group and increased by 1.5 mm Hg in the LF+O group. Diastolic blood pressure decreased by 4.5 mm Hg in the VLC group and increased by 0.4 mm Hg in the LF+O group.

In a study by Frisch et al,[37] 165 subjects were assigned to either a LC diet or a LF diet, both of which were calorie-restricted. Although both diets resulted in similar weight loss, systolic blood pressure was significantly lower in the LC group (–5 mm Hg) compared with the LF group (–1 mm Hg) at 12 months.

In the studies evaluated, compared with a LF diet, a LC diet was found to produce greater improvements in blood pressure independent of weight loss.

Other Therapeutic Benefits

It has been proposed[11,23,38] that carbohydrate restriction creates a unique metabolic environment from which multiple effects may radiate. In preliminary studies, the range of health effects for which there is evidence of benefit of carbohydrate restriction includes polycystic ovarian syndrome,[39] gestational diabetes,[40] cancer,[41-44] gastroesophageal reflux disease,[45,46] schizophrenia,[47] nonalcoholic fatty liver disease,[48] epilepsy,[49-51] and age-related macular degeneration.[52]

Carbohydrate Reduction for Life

Carbohydrate reduction has advantages that go beyond VLC therapeutic diets. For patients who are being treated successfully on a LC diet, this way of eating can be extended in a more flexible form to a long-term dietary pattern. Studies support the use of LC diets for weight loss, diabetes, and cardiovascular health for periods of more than a year.[13,53,54] Members of the general population who have not yet reached clinically significant levels of metabolic dysregulation may need guidance in preventing deterioration in health; for some, a LC diet may be a more effective approach than a LF one.

One Diet Does Not Fit All

Various genetic and metabolic profiles may predispose certain patients to adverse risks of an LF diet or, conversely, to improved response to a LC one. Although reducing dietary fat can reduce LDL-C, for portions of the population it can also result in increases in reduced LDL particle size, a more atherogenic lipid profile.[55] This effect is heritable and suggests that caution should be used in suggesting population-wide dietary fat reductions.[56] When dietary fat is reduced, it is often replaced by carbohydrate. Individuals who may be more susceptible to dyslipidemia related to this dietary change include those with a higher fasting insulin concentrations and higher body weight.[21] Low serum HDL-C, accompanied by elevated TG levels, is often the predominant lipid abnormality in obese or diabetic patients hospitalized with cardiovascular disease.[57] This population may benefit from the lipid profile improvements related to a LC diet.

LC diets have a positive impact on obesity, elevated serum TG levels, reduced serum HDL-C levels, impaired glucose metabolism, and hypertension, a cluster of medical disorders used to define the clinical criteria for metabolic syndrome (MetS).[58] Insulin resistance is thought to be the common denominator underlying the expression of each of these markers.[59] Carbohydrate restriction addresses all of the features of MetS and is the logical therapy for those diagnosed with the syndrome.[23,60,61]

Most studies demonstrate that the incidence of MetS is lower in African American adults than in Caucasians, despite the fact that the individual clinical outcomes predicted by MetS—stroke, myocardial infarction, and type 2 diabetes—are more frequent in African Americans, a fact that cannot be adequately explained by social and economic differences in these populations.[62,63] Recent developments in understanding reduced expression of several genes and transcription factors related to carbohydrate metabolism in African Americans may explain this disconnect.[64] In this light, a diet that reduces carbohydrate impact on metabolism may be especially appropriate for this population.

Appetite and Satiety

Certain food types may stimulate feeding whereas others produce satiety. These influences should be taken into account when recommending a long-term dietary approach. LC, high-fat diet studies frequently demonstrate a spontaneous reduction in caloric intake on an ad libitum diet.[12-15] Although this effect has been attributed to boredom with the diet,[65] the appetite-driving and/or satiety effects of various macronutrients may be below conscious awareness and should be considered in light of our current food environment.[66]

The satiety effects of protein are well-documented,[60,67] although carbohydrate reduction does not always result in significantly increased protein consumption. Carbohydrate restriction may also work through changes in interaction of gastrointestinal sensory signals that are only now being elucidated. In practice, a comparison between a breakfast of eggs (22% CHO) and a breakfast of bagels (72% CHO) resulted in reduced energy intake over 24 hours for subjects who had eggs for breakfast.[68] In addition, subjects reported increased hunger 3 hours after the bagel breakfast. In a 6-week weight loss intervention, 28 overweight premenopausal women were randomized to either a LC diet with no calorie restriction or a calorie-restricted, LF diet. Despite having no calorie restrictions, the LC group spontaneously reduced energy intake to a level similar to that of the calorie-restricted group. At the same time, self-rated hunger scores decreased in the LC diet group compared with the LF group.[69] Controlling calorie intake without hunger is an important part of weight management and health maintenance. A diet that assists people in doing so can be part of a preventive care approach.
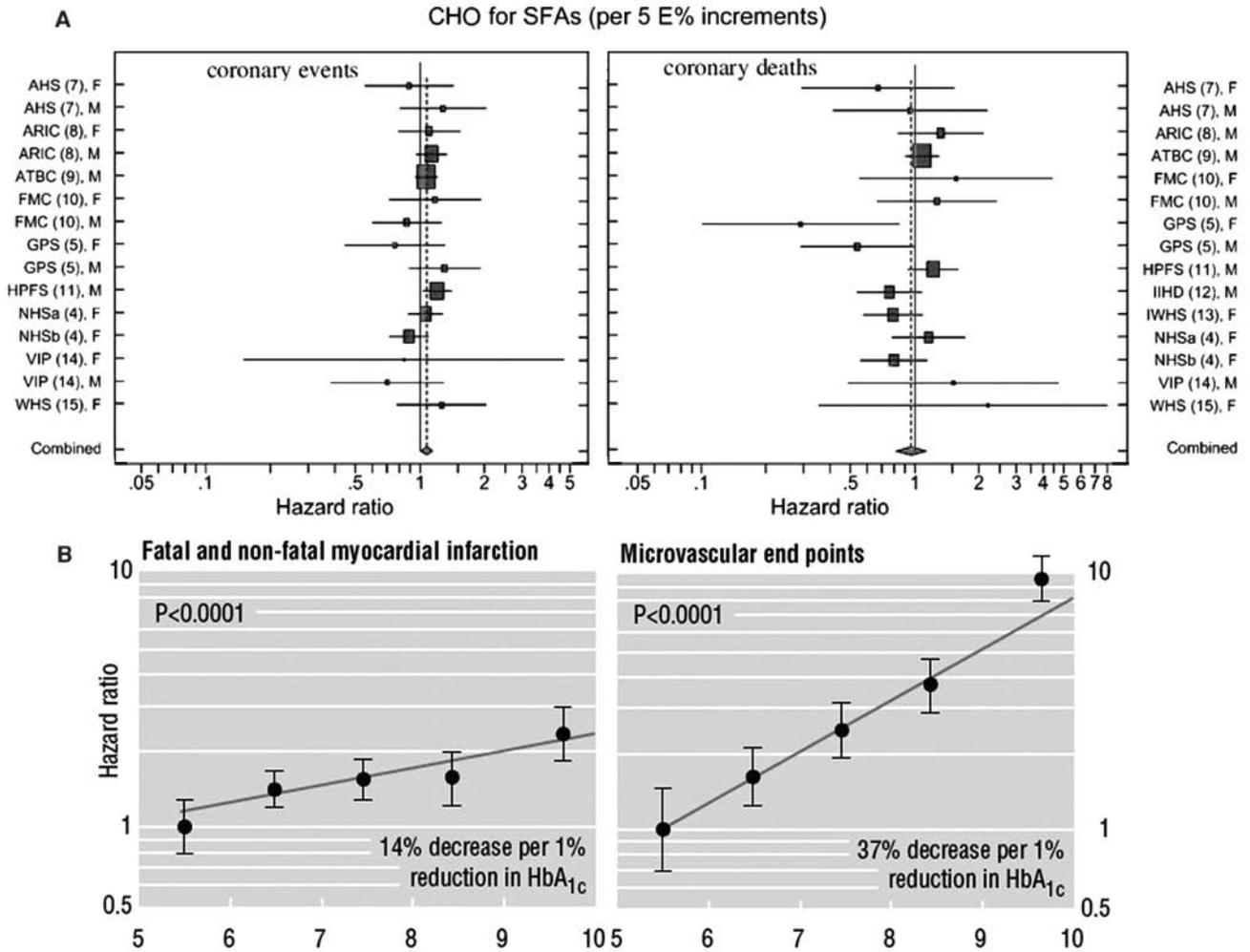
Figure 3. Effect of change in dietary saturated fatty acid (SFA) intake and hemoglobin A1c levels on cardiovascular events. (A) Hazard ratio for coronary events or deaths for increments of replacement of SFA with CHO. Figure redrawn from Jakobsen et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr*. 2009;89:1425-1432. (B) Hazard ratio for macro- or microvascular end points as a function of HbA1C (%). Figure redrawn from Stratton et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412. Error bars show 95% confidence intervals. Note: Hazard ratios <1.5 (>0.66) are considered weak, and data for which confidence intervals cross 1 are considered to show no effect. Reproduced from Stratton IM, Adler AI, Neil AW, et al. Association of glycaemia with macrovascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *Brit Med J*. 2000;321:405-412 with permission from BMJ Publishing Group Ltd.

Barriers to Acceptance

As clinicians, we must evaluate all possible solutions to improvement in patient care, recognizing that the majority of our population is overweight or obese. We must at times step back from academic research and focus on basic physiology, common sense, and—most importantly—the patient. Observational studies are no substitute for a patient with a glucometer. Conventional scientific and medical thinking has been wrong before;

consider the response to Semmelweis's call for hygiene in birthing wards, and, more recently, the effects of hormone replacement therapy to reduce heart disease in women. Although Americans have changed their eating habits toward the recommended lower fat and higher carbohydrate intake, the current epidemic of obesity and diabetes would suggest that these recommendations have had little impact on improving health.[70] It is time to move beyond outdated notions that persist far beyond any scientific evidence to support

them, the clinical versions of "urban myths," and put the patient first.

Clinical Myths

Concerns that reducing carbohydrate intake will have an adverse effect on kidney function have been answered many times. It should be noted that LC intake does not imply high protein intake. The Dietary Reference Intakes support a wide range of protein intake, from 10% to 35% of calories; only diets above this range can accurately termed "high protein." In any case, it is established that higher protein diets do not have an adverse effect on healthy kidneys.[71-75] In fact, improvements in hypertension that can be achieved by carbohydrate reduction may assist in protecting kidney function.

Another concern is that fiber intake will fall below recommended levels. The major sources of dietary fiber in the American diet are white flour and potatoes,[76] foods with a high blood sugar impact and little nutritive value. Information from the Active Low-Carbers Forum, an on-line support group for people who have chosen a low-carbohydrate eating pattern, shows that one of the primary dietary changes that takes place when switching to a LC diet is a large increase in consumption of leafy green vegetables.[77] A diet that shifts eating patterns away from white flour and potatoes toward leafy green vegetables is considered beneficial to overall health.

A persistent concern regarding carbohydrate diets is that carbohydrate removed from the diet will be replaced with saturated fat. The effect of saturated fat on heart disease is dependent on the overall characteristics of the diet and, in particular, the effects of carbohydrate on insulin that shift the metabolism toward fatty acid synthesis and storage.[11] Recent meta-analyses and epidemiologic studies show that replacement of carbohydrate with saturated fat is, if anything, beneficial for risk reduction; these results must be added to the failure of numerous large-scale population studies to show a correlation between dietary saturated fat and cardiovascular disease.[78-82] At the same time, clinicians are acutely aware of the health risks, including cardiovascular disease, which arise when HbA1c becomes elevated (Figure 3).[83]

Research supports the safety of VLCK diets for humans.[32,84-86] There are, however, certain populations in which reducing carbohydrate intake to very low levels may not be appropriate: patients with insulin-dependent diabetes, thyroid defects, inborn errors of metabolism, ketotic hypoglycemia of childhood, corticosteroid, or growth hormone deficiency, certain elderly populations, and individuals who consume excess amounts of alcohol or aspirin.[86] Although these people should avoid VLC diets, patient who are not responding to LF diets and those with genetic and metabolic risk factors, including

high serum levels of insulin, TG, and glucose, may benefit from carbohydrate restriction.

Conclusion

The shift in metabolism that occurs on a LC diet heralds a shift in our current dietary paradigm. Changing the macronutrient content of the diet changes the metabolic profile. Although increasing fiber and decreasing saturated fat intake may be of concern to those whose diets are high in carbohydrates, they may be of less concern to those whose diets are not. Increasing vegetable consumption and decreasing consumption of foods low in nutritional value is a dietary goal cited numerous times in the 2010 Dietary Guidelines recommendations.[87] Reducing dietary carbohydrate can accomplish this goal while improving glucose control, insulin response, atherogenic dyslipidemia, and other cardiovascular risk factors, in addition to reducing caloric intake without hunger. This makes carbohydrate reduction a sensible dietary approach to achieving and maintaining health.

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