Nutrition 30 (2014) 748–754

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

When and why carbohydrate restriction can be a viable option

Michael Liebman Ph.D. *

Department of Family and Consumer Sciences (Human Nutrition), University of Wyoming, Laramie, WY, USA

ARTICLE INFO

Article history:
Received 6 September 2012
Accepted 7 November 2013

Keywords:
Low carbohydrate diets
Weight loss
Cardiovascular risk factors
Insulin resistance

ABSTRACT

There is a significant amount of controversy related to the optimal amount of dietary carbohydrate. This review summarizes the health-related positives and negatives associated with carbohydrate restriction. On the positive side, there is substantive evidence that for many individuals, low-carbohydrate, high-protein diets can effectively promote weight loss. Low-carbohydrate diets (LCDs) also can lead to favorable changes in blood lipids (i.e., decreased triacylglycerols, increased high-density lipoprotein cholesterol) and decrease the severity of hypertension. These positives should be balanced by consideration of the likelihood that LCDs often lead to decreased intakes of phytochemicals (which could increase predisposition to cardiovascular disease and cancer) and nondigestible carbohydrates (which could increase risk for disorders of the lower gastrointestinal tract). Diets restricted in carbohydrates also are likely to lead to decreased glycogen stores, which could compromise an individual's ability to maintain high levels of physical activity. LCDs that are high in saturated fat appear to raise low-density lipoprotein cholesterol and may exacerbate endothelial dysfunction. However, for the significant percentage of the population with insulin resistance or those classified as having metabolic syndrome or prediabetes, there is much experimental support for consumption of a moderately restricted carbohydrate diet (i.e., one providing approximately 26%–44 % of calories from carbohydrate) that emphasizes high-quality carbohydrate sources. This type of dietary pattern would likely lead to favorable changes in the aforementioned cardiovascular disease risk factors, while minimizing the potential negatives associated with consumption of the more restrictive LCDs.

Introduction

Among the different classes of nutrients, the quantity of carbohydrate consumed is likely to be second only to water in most diets. The major exception would be the recently popularized low-carbohydrate diets (LCDs) that typically provide greater amounts of protein and possibly fat than carbohydrate. The ideal quantity of carbohydrate in a healthy diet has become a controversial issue. Not surprisingly, there are both positives and negatives associated with lowering carbohydrate in the diet. A key question is how low is too low and, conversely, what are the potential drawbacks to consuming too much carbohydrate? This review emphasizes the importance of both carbohydrate quantity and quality, and elucidates why there is a gray area regarding the ideal amount of carbohydrate in the diet. The therapeutic use of low-carbohydrate, ketogenic diets in specialized cases such as in the treatment of epilepsy is considered beyond the scope of this review.

* Corresponding author. Tel.: +1 307 766 5597; fax: +1 307 766 5686.
E-mail address: Liebman@uwyo.edu

0899-9007/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2013.11.021

Low carbohydrate diets: A key to weight loss?

There is a controversy related to the dietary composition that is most effective in promoting a negative energy balance leading to weight loss. In this regard, following an LCD plan has proven to be an effective way for many individuals to lose weight. Many versions of these diet plans exist including the Atkins Diet, the South Beach Diet, and the Zone Diet, each having its proponents. Two relatively recent studies compared four different types of low-calorie diets with respect to their ability to produce weight loss [1,2]. In one of these studies, two of the diets were low-carbohydrate (Atkins and Zone) and two were low-fat, high-carbohydrate (Weight Watchers and Ornish) [1]. In the other study, the four diets were described as low-fat, average-protein; low-fat, high-protein; high-fat, average-protein; and high-fat, high-protein. Carbohydrate ranged from 35% to 65% of total calories [2]. The major finding from both studies was that the amount of weight lost depended on adherence (i.e., how closely the diets could be followed by participants) rather than macronutrient composition. The different diets, when closely followed, were equally effective in producing a negative caloric balance leading to similar weight losses. Thus, these results reiterated what has been considered a basic energy balance-related tenet (i.e., the rate or amount of weight loss primarily depends on the degree of energy restriction rather than on how much carbohydrate, fat, and protein are provided by the weight loss diet).

An appropriate question is whether the effectiveness of LCD plans can be totally attributed to reduced energy intakes or whether there are other contributing factors. For example, there is much experimental support for the assertion that low-carbohydrate, high-protein diets provide a metabolic advantage in terms of increased energy expenditure/thermogenesis. Because of the need to provide glucose to key tissues with an obligatory glucose requirement (including brain and red blood cells), there is a higher rate of gluconeogenesis; this likely leads to an increased protein turnover to supply the amino acids required for glucose synthesis. Increased protein turnover translates to increased energy expenditure, which is clearly advantageous with respect to weight loss [3]. However, compared with the marked reduction in energy intake, which typically occurs with many weight loss diets, it is unclear whether the increased thermogenesis associated with low-carbohydrate, high-protein diets is a major contributor to weight loss. Additional research will be required to provide a definitive answer to this question.

In terms of addressing the overall effectiveness of LCDs, the question of diet adherence also should be discussed. There is some evidence that adherence to these diets is easier for many individuals, at least in the short term. Contributing factors are that LCDs are very well defined in terms of which foods are and are not allowed. A limitation of food choices, the so-called “monotony factor,” also can lead to a spontaneous reduction in food intake, thus contributing to a low-caloric intake. People tend to eat more when a large variety of foods is presented, a classic example being the high-caloric intakes that typically occur at “pot-luck” meals, with the opposite also being true (less variety often equates to lower energy intakes) [4].

Adherence also can be enhanced because LCDs are typically high in protein, thereby rating high in terms of providing satiety/satiation. However, any weight loss diet can take advantage of the protein–satiety connection, by boosting dietary protein, without severely restricting carbohydrates.

Finally, a potentially negative aspect of low- and very LCDs is that they can be difficult to maintain for prolonged periods of time because of the monotony factor. Many of these diets heavily rely on meat, eggs, and cheese and having these foods as the mainstay of most meals can become boring. Thus, providing limited food choices, which can be an advantage in the short term due to the very well-defined nature of these diets, also can be a disadvantage when one considers following such a strict dietary regimen over many months or even years. Other advantages and disadvantages associated with LCDs are addressed in the next sections.

Low carbohydrate diets: Potential positives

There are clearly instances for which replacing a certain amount of dietary carbohydrate with protein is advantageous. Previously mentioned was the argument for a moderate increase in protein, at the expense of carbohydrate, in weight reduction diets. Although high-carbohydrate diets can be just as effective as LCDs in promoting weight loss, there appear to be certain cases for which achieving weight loss with lower carbohydrate intakes will lead to positive metabolic changes.

Many overweight individuals are at increased risk for heart disease, and there is a growing body of evidence that LCDs can lead to favorable changes in certain cardiovascular risk factors. Thus, for these individuals, it may be ideal to institute a diet that effectively leads to weight loss while simultaneously improving risk-factor profiles. This issue was partially addressed by the OmniHeart Randomized Trial [5], which compared the effects of three healthy, weight-maintenance diets on blood pressure and blood lipids. One of the diets was rich in carbohydrates (with an emphasis on unprocessed, healthy carbohydrates), another was rich in protein (with approximately half the protein provided by plant sources), and the third was rich in unsaturated fat (primarily monounsaturated fat). The carbohydrate-rich diet provided 54% of calories from this macronutrient, whereas the remaining two diets provided 44% of the calories from carbohydrate. Study participants were 164 generally healthy adults with higher than optimal blood pressure. Compared with the carbohydrate-rich diet, the other diets led to decreases in blood pressure (with greater reductions in individuals with hypertension) as well as improvements in blood lipids. Both alternative diets led to decreases in blood triacylglycerols (TGs) and the protein-rich diet also led to a reduction in low-density lipoprotein cholesterol (LDL-C). Thus, in this study, although body weights were maintained, consumption of the two diets lower in carbohydrates improved specific markers of cardiovascular health.

Numerous studies have compared the effectiveness of low-carbohydrate, high-protein diets with low-fat low-calorie diets regarding weight loss and changes in cardiovascular risk factors. A recent review of a number of these studies, which were published between 2000 and 2007, concluded that low-carbohydrate, high-protein diets are more effective than low-fat diets at 6 mo, and are at least as effective at 1 y in reducing weight and in improving cardiovascular risk factors [6]. Specifically, the LCDs were associated with more favorable changes in systolic blood pressure (BP) as well as blood TG and high-density lipoprotein cholesterol (HDL-C) levels. Another relatively recent review article summarized the results of five studies that compared the effects of LCDs and low-fat diets on specific cardiovascular risk factors [7]. In contrast to the previously described review article, there were no diet-induced differences in BP. Blood TG and HDL-C changed more favorably in response to LCDs, but total cholesterol and LDL-C changed more favorably in response to low-fat diets.

The blood lipid abnormalities most commonly associated with being overweight are increased TGs and reduced HDL-C, which coincide exactly with those that are most likely to be improved by the adoption of an LCD. Even in the absence of weight loss, studies have documented the ability of LCDs to improve these particular blood lipids [8].

In the United States, a very significant proportion of the adult population has a number of risk factors that tend to cluster together: Obesity (high levels of body fat and/or a high waist circumference), higher than normal fasting blood glucose and insulin levels, high blood TGs and low HDL-C, and high BP (hypertension). This grouping of features, commonly referred to as metabolic syndrome (MetS), is known to increase the risk for developing both type 2 diabetes mellitus (T2 DM) and cardiovascular disease (CVD) [8]. Individuals with MetS are invariably characterized as having insulin resistance (IR), which in turn is thought to be causally related to the abnormal blood parameters, as well as high BP.

There is a very powerful connection between having excess body fat and IR, especially if there is excess adiposity in the intra-abdominal region [9]. Because there is such a high prevalence of overweight and obesity in the United States, it follows that a correspondingly high percentage of the population has some degree of IR. This leads to a compensatory hyperinsulinemia in response to food ingestion. Although hyperinsulinemia can help keep an individual's blood glucose level within the normal range, the metabolic price is the development of elevated blood TGs and lowered HDL-C, and an increased propensity to develop hypertension [10]. These individuals are also at increased risk for developing T2 DM, which typically occurs after a number of years of experiencing hyperinsulinemia. The onset of T2 DM occurs because at some point the pancreas exhibits a diminished capacity to secrete insulin and thus is no longer able to compensate for the worsening insulin resistance [11].

The key point is that there is significant experimental support for the assertion that total carbohydrate intake should be lowered in individuals with IR-induced hyperinsulinemia [12]. In these individuals, a high-carbohydrate diet is likely to put additional stress on the system, resulting in even higher blood levels of glucose and insulin throughout the day. This in turn can exacerbate the blood lipid abnormalities mentioned previously and further increase predisposition to hypertension. In addition to the importance of losing excess body fat, which can significantly improve IR, a lower carbohydrate intake can help minimize the abnormal elevations in blood glucose and insulin that would occur with a higher carbohydrate diet and that ultimately lead to increased risk for CVD.

There are indirect ways to assess whether an individual is likely to have some degree of IR. First of all, as previously stated, having excess body fat in the intra-abdominal region is highly associated with IR [9]. Precise measurements of intra-abdominal, or visceral, fat can be performed using high-tech scanning equipment, but these methods are expensive and generally reserved for the research setting. In lieu of using these sophisticated procedures, an approximation of visceral fat stores can be obtained by measuring waist circumference. Research has established that a waist circumference >40 inches in men, or >35 inches in women, is highly predictive of having excess visceral fat stores [13]. Another way to assess the likelihood of IR is by determining the ratio of blood TGs to HDL-C. A TG-to-HDL-C ratio ≥ 3.0 is suggestive of IR [14].

Finally, there are individuals who are classified as being prediabetic based on a fasting blood glucose level higher than the normal range, but not high enough to fit the diabetes criteria (i.e., a level between 100 and 125 mg/dL). In addition to the cases described here (excess visceral fat, a high TG-to-HDL-C ratio), prediabetic individuals are very likely to exhibit some degree of IR. In all of these cases, replacing some dietary carbohydrate with appropriate sources of either protein or healthy fats will typically lead to favorable alterations in blood TGs and HDL-C. This change in macronutrient distribution, in conjunction with loss of excess body fat and the institution of a sound physical activity program, can contribute to the prevention of T2 DM as well as CVD. In individuals who have already been diagnosed with T2 DM, there is significant experimental support for the use of low-carbohydrate, ketogenic diets to improve glycemic control and insulin sensitivity [15,16]. However, results have been mixed regarding whether LCDs, which are not as severely restricted in carbohydrates as ketogenic diets, are likely to improve glycemic control in individuals with T2 DM [17].

Another potentially positive attribute of LCDs relates to the possibility of an anti-inflammatory effect. It is well established that inflammation is involved in mediating all stages of atherosclerosis [18]. Both animal [19] as well as human studies [20] have suggested an anti-inflammatory effect of LCDs based on favorable changes in the concentrations of specific inflammatory markers.

An additional advantage to the adoption of a LCD is that these diets are typically very low in fructose intake. The primary sources of fructose are table sugar (sucrose) and high fructose corn syrup, which is used as a sweetener in many processed foods including the vast majority of soft drinks manufactured in the United States [21]. Both of these refined products would be severely limited in well-designed LCDs. There is much experimental support for the proposed link between high levels of soft drink consumption and high-caloric intakes and weight gain [22]. However, it is unclear whether this association can be attributed to fructose intake, per se, or whether the relationship is mostly mediated by the lack of energy compensation to the calories provided by soft drinks (i.e., many individuals do not appear to reduce caloric intake from other foods when soft drinks are added to the diet). There is a possibility that excess fructose consumption could exert unique effects on cerebral metabolism that could increase predisposition to overconsumption. For example, a recent study demonstrated that compared with glucose, fructose ingestion resulted in a distinct pattern of cerebral blood flow and a blunted increase in systemic levels of the satiety hormone, glucagon-like polypeptide-1 [23].

Additionally, fructose has a unique metabolic pathway and is more lipogenic than the other monosaccharaides; high intakes have been associated with excess fat synthesis in the liver, and may contribute to the development of MetS, as well as T2 DM [24]. Finally, fructose consumption can lead to an increase in blood uric acid levels, which has been suggested to reduce the availability of nitric oxide (NO); this compound plays a key role in BP regulation as well as maintaining normal function of the blood vessel endothelial layer of cells. It appears that many of the manifestations of MetS can be caused by a fructose-induced rise in uric acid levels [22,24]. A summary of the positive attributes of LCDs is provided in Table 1.

Low carbohydrate diets: Potential negatives

There are some specific disadvantages associated with the consumption of LCDs. The initial concern focuses on the dietary regimen, which not only restricts carbohydrate, but protein as well. It should be noted that many LCDs that are promoted for weight loss are actually high in protein, but some are low in both of these macronutrients.

Creating a situation in which body cells are forced to heavily rely on amino acids for energy (as can occur with a diet providing only 20–50 g of carbohydrate/d) can be detrimental because less amino acids will be available for protein synthesis and other critical functions. With LCDs, there will be greater reliance on fat as an energy source by many tissues, with the brain being a notable exception. The central nervous system is unable to use fat for energy purposes and is thus unique in that it has an obligatory requirement for glucose. However, even with severely restricted carbohydrate diets, the brain will never be starved for energy because the body will employ two adaptations to ensure an adequate supply of energy to this tissue. First, the body can respond by breaking down its own protein into amino acids, which then can be used to synthesize glucose in the liver, which is subsequently made available to the brain via the blood. The major downside to this adaptation is the potential loss of skeletal muscle protein to provide the amino acids for glucose synthesis. The second metabolic adaptation to low-carbohydrate, low-calorie

Table 1
Summary of positive attributes of low-carbohydrate diets

Low carbohydrate diets: Pros	Caveats
Low-carbohydrate, high-protein diets can effectively promote weight loss	Long-term adherence may be difficult and it is generally accepted that maintenance of weight loss requires a permanent change in dietary habits
Lead to favorable changes in cardiovascular risk factors, especially in individuals with insulin resistance/metabolic syndrome and individuals with prediabetes; may also exert an anti-inflammatory effect	Additional research is required to determine whether long-term consumption can lead to a decrease in mortality rates
Low-carbohydrate, ketogenic diets can improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus	An unanswered question is to what extent improvements in glycemic control and insulin sensitivity will be maintained in association with a transition to a less carbohydrate-restricted, non-ketogenic diet
Low in fructose intakes due to a decrease in refined carbohydrate intake; excess dietary fructose has been linked to a number of negative health consequences	

diets is one that actually reduces the brain's need for glucose, thereby decreasing the need to use the body's protein stores to provide amino acids for glucose synthesis. With very low-carbohydrate diets, the liver starts to synthesize ketones, which can be used to replace up to about 70% of the brain's requirement for glucose [25].

In summary, the prolonged consumption of low-carbohydrate, low-protein diets can cause some loss of body protein, the majority of which comes from skeletal muscle. However, because the brain switches over to using ketones as a primary fuel source, the rate of this loss of skeletal muscle is considerably slowed. Thus, with respect to sparing body protein, producing a state of ketosis can be considered a positive adaptation. It also should be reiterated that providing adequate dietary protein decreases the likelihood that there is any significant loss of skeletal muscle.

An unanswered question is whether there are other mechanisms by which ketogenic diets could exert a positive effect on weight loss. In a rat model, administration of β-hydroxybutryrate, one of the two major ketones produced by the liver, was demonstrated to have an appetite-suppressing effect [26], however, this contention was not supported in a human study that assessed perceived hunger in response to ketogenic and nonketogenic LCDs [27]. Proponents of the use of ketogenic diets for weight loss also have pointed to the loss of calories via the excretion of urinary ketones; however, it is unclear whether this exerts a clinically significant effect on the energy balance equation.

Some research has suggested that consumption of LCDs is associated with an increase in oxidative stress [28]. At this point, these isolated findings would need to be confirmed by additional research studies before they should be seriously considered.

Other studies have demonstrated that LCDs lower stool weight and decrease the intestinal production of various protective compounds that are derived from nondigestible carbohydrates [29,30]. Key sources of nondigestible carbohydrates are dietary fiber and resistant starch; colonic fermentation of these carbohydrates leads to the production of short-chain fatty acids (acetate, propionate, and butryate), which appears to make an important contribution to colonic function and mucosal health. Both lower stool weight and decreased production of fermentation-derived protective compounds have been associated with an increased risk for developing lower gastrointestinal tract disorders [31].

Many of these LCDs are in fact very high in protein, which, combined with a low intake of potassium-containing fruits and vegetables, can exert a negative effect on the integrity of bone. High-protein diets generate a significant amount of acidic compounds resulting from the breakdown of certain amino acids. This so-called acid load must be neutralized by alkalizing minerals such as potassium. However, if the diet does not provide adequate levels of potassium, bone will release calcium-containing alkalizing salts into the circulation to neutralize the excess acidity. This could lead to excessive bone loss resulting in an increased risk for osteoporosis [32].

Another potentially negative effect of LCDs is the depletion of the body's glycogen stores. Because glucose is a primary energy source for exercising muscle, low glycogen stores can compromise an individual's ability to perform any sort of prolonged exercise. A recent study demonstrated that LCDs can enhance feelings of fatigue during exercise and can reduce an individual's desire to exercise [33]. Increased physical activity is an important component of any well-designed weight loss program, and exercise has been shown to be critical in terms of successful maintenance of weight loss. Thus, individuals who are physically active, or plan to increase their levels of physical activity, may wish to avoid diets that are most severely restricted in carbohydrates.

LCDs restrict foods that provide high-quality carbohydrates (i.e., those found in whole grains, legumes, fruits, and vegetables). High-quality carbohydrate sources tend to be rich in various health-promoting compounds (vitamins, minerals, dietary fiber, phytochemicals), whereas the opposite is generally true for poor quality (highly processed) carbohydrate sources. Phytochemicals are plant-derived compounds that are not formally classified as nutrients but nonetheless are major contributors to human health via the protection they provide against a number of age-related diseases, including CVD and cancer. Many specific compounds are classified as phytochemicals, and they are most heavily concentrated in the previously mentioned sources of high-quality carbohydrates. For example, flavonoids (which represent a large and diverse set of compounds) are present in many fruits, vegetables, nuts, grains, and legumes and appear to act as general antioxidants [34]. Some have been demonstrated to prevent the oxidation of LDL and to inhibit platelet aggregation, two actions that decrease risk for CVD. Other flavonoids exert anti-inflammatory and antitumor actions [35]. In summary, limiting the intake of high-quality carbohydrate sources is likely to lead to low-fiber, low-phytochemical–containing diets, a dietary pattern that could increase risk for various chronic diseases and overall mortality.

LCDs that are high in saturated fat may lead to an increase in LDL-C [36] or a lower reduction in this lipoprotein compared with that which occurs with low-fat diets [37]. However, even if LDL-C is increased, the clinical significance of this alteration is unclear because there is evidence that the increase is largely confined to the larger-sized LDL particles, which are known to be less atherogenic than small, dense LDL particles [38].

Finally, it is important to consider the effect of LCDs on endothelial tissue because endothelial dysfunction is considered to be an independent risk factor for atherosclerosis [39]. A key

Table 2
Summary of potentially negative attributes of low carbohydrate diets

Low carbohydrate diets: Cons	Caveats
Prolonged consumption of low-carbohydrate, low-protein diets can cause some loss of body protein/skeletal muscle	This is minimized or totally negated if the diet provides adequate protein
May lead to an increase in oxidative stress	Additional research is required to confirm these preliminary findings
Decreased nondigestible carbohydrate intakes may increase risk for lower gastrointestinal tract disorders	Although potential mechanisms are clearly established, studies using gastrointestinal tract disorders as the endpoint are primarily epidemiologic
Prolonged consumption of low-carbohydrate, high-protein diets could create an acid load in the body that could lead to excessive bone loss	Inclusion of potassium-rich foods in the diet can minimize the use of calcium-containing bone material to neutralize the excess acid
Lead to decreased glycogen stores which could compromise ability to maintain high levels of physical activity	
Can lead to increased LDL-cholesterol if diet is high in saturated fat	Increase appears to be primarily confined to the larger sized LDL particles, which are known to be less atherogenic than small, dense LDL particles
Can lead to a decrease in flow mediated dilation, suggestive of a decrease in endothelial function	Appears to be primarily related to the high total fat/saturated fat content of many low-carbohydrate diets

feature of endothelial dysfunction appears to be impaired NO bioavailability. The production and release of NO by endothelial cells has a number of cardioprotective effects including relaxing smooth muscle cells and preventing leukocyte adhesion and migration into the arterial wall, platelet adhesion and aggregation, and adhesion molecule expression [40]. Bioavailability of NO in humans is typically determined by assessing the degree of vasodilation induced by local stimulation of its production by specific stimuli, which have been referred to as vascular reactivity tests. The most commonly used test of this nature is the assessment of flow-mediated dilation (FMD) of the brachial artery, which involves ultrasound analysis of brachial artery diameter after a short period of investigator-induced forearm ischemia. Another method, which is relatively new, focuses on small artery endothelial function and involves the determination of the small artery reactive hyperemia index. This latter method has been referred to as peripheral arterial tonometry and provides information about vascular function of the peripheral small arteries of the finger [41]. It remains to be established whether vascular responses in the brachial artery and the small arteries of the finger are always related and whether these two measures are equally effective in predicting endothelial dysfunction.

A key question relates to the effect of LCDs on endothelial dysfunction. A number of studies have suggested that LCDs that are high in fat, particularly saturated fat, are associated with a decrease in FMD [42–45] or in the small artery reactive hyperemia index [41]. Additionally, a recently published letter to the editor, which summarized the results of a systematic review and meta-analysis of six trials, indicated that LCDs were associated with reductions in FMD when compared with low-fat diets [46]. Other researchers, however, have reported either no effect of LCDs on FMD [47,48] or an improvement in FMD with this type of dietary pattern [49]. Despite the overall lack of consistency in results, it appears reasonable to conclude that any adverse effects of LCDs on endothelial function can be attributed to the high total fat/saturated fat content of many of these diets rather than the relative lack of carbohydrate. Thus, an unanswered question is whether LCDs that are very high in protein and provide only moderate levels of saturated fat have the potential to exert a negative effect on endothelial function.

A unique aspect of a previous study [49] was that FMD was assessed both before and after ingestion of a high-fat meal. In the postprandial test condition, consumption of an LCD for the previous 12 wk was associated with an improvement in FMD compared with baseline at the 3 h point. The researchers asserted that prior diet history has a significant effect on the metabolic response to meals. Relevant to this study, prior adaptation to an LCD had been demonstrated to lead to a marked reduction in the postprandial lipemic response to a standardized high-fat meal, which may have contributed to the improvement in FMD observed in the postprandial state. Another possibility is that an improvement in IR associated with consumption of the LCD might be related to a greater synthesis of NO, a key marker of normal endothelial function. Regardless of the specific mechanism, improvement in FMD postmeal ingestion is a potentially important finding because, as was suggested by these investigators, it may be more clinically relevant to assess vascular function in the postprandial rather than the postabsorptive state. An inconsistency in the results of this study was that there was little change in FMD in response to the LCD at the 1.5- and 4.5-h postmeal ingestion points. This weakens the overall assertion of an improvement in endothelial function in response to the 12-wk period of low-carbohydrate feeding. However, based on the results of this study, this type of dietary regimen does not appear to lead to endothelial dysfunction in response to a high-fat meal. An overview of the potentially negative attributes of LCDs is provided in Table 2.

Energy nutrient intakes: General points

It is clear that there are distinct advantages and disadvantages to lowering the carbohydrate content of the diet. So what is the optimal level of carbohydrate in the human diet? The classic thinking as reflected in the dietary recommendations by various governmental and nongovernmental agencies is that diets should be highest in carbohydrate (>50% of total calories), relatively low in fat ($\sim$30% of total calories), with the remainder of the calories provided by protein ($\sim$15% of total calories). However, the recommendation regarding carbohydrate lacks specificity (e.g., how high is too high?) and is also problematic for other reasons. First and foremost, a critical stipulation related to the high-carbohydrate recommendation is that there should be a heavy reliance on naturally occurring, fiber-containing, high-quality carbohydrates (i.e., those found in whole grains, legumes, fruits, and vegetables) whereas highly processed, fiber-depleted carbohydrate foods (e.g., refined grains, soft drinks, and other high sugar-containing foods) should be limited. As previously stated, high-quality carbohydrate sources tend to be rich in various health-promoting compounds (vitamins, minerals, dietary fiber, phytochemicals), whereas the opposite is generally true for poor-quality (highly processed) carbohydrate sources.

The various categories related to the quantity of carbohydrate provided in the diet are summarized in Table 3. It is apparent that all three categories representing various levels of carbohydrate

Table 3
Classification of diets based on carbohydrate content

Carbohydrate diet classification	Amount of carbohydrate
High-carbohydrate diets	>65% of total calories
Typical carbohydrate diets	45%–65% of total calories
Moderately restricted carbohydrate diets	26%–44% of total calories
Low-carbohydrate diets	<130 g/d (which represents 26% of calories of a 2000 calorie diet)
Very low-carbohydrate diets	Typically provide 20–50 g of carbohydrate; depending on total caloric intake, carbohydrates are likely to provide 5%–15% of total calories

restriction (moderate, low, very low) conflict with the general recommendation that diets should be highest in carbohydrate.

An additional consideration relates to the ideal distribution of calories between protein and fat in association with LCDs. Advantages of high protein over high fat include those related to weight loss and weight maintenance (i.e., higher satiety and thermogenesis, lower caloric density of the diet, greater retention of lean body mass with weight loss) and there is a decreased likelihood of negative effects on LDL-C and endothelial function. Unlike low-carbohydrate, high-fat diets, low-carbohydrate, high-protein diets are generally not ketogenic because of the excess of gluconeogenic substrates (amino acids) supplied to the liver. Increased glucose synthesis by hepatic tissue negates the need to synthesize ketones to be used as an alternate fuel source. Because of the lack of research support for greater efficacy of ketogenic over nonketogenic diets for weight loss [27], it does not appear ketogenic diets should be promoted for this purpose. Additionally, low, carbohydrate, high-fat diets can cause an elevation in plasma free fatty acids potentially leading to intramyocellular lipid accumulation and IR. In contrast, this does not occur with low-carbohydrate, high-protein diets, most likely attributed to the up-regulation in hepatic gluconeogenesis [50]. Although high-protein diets are typically contraindicated for individuals with kidney disease, a recent 2-y study did not find any negative effects of this type of diet on kidney function in healthy individuals [51].

Conclusions

A strong case can be made that minimally processed, carbohydrate-rich foods provide an ideal source of energy for human metabolism. A heavy reliance on these foods, including whole grains, legumes, fruits, and vegetables, leads to the added benefits associated with the consumption of a phytochemical-rich diet. This provides a strong rationale for the assertion that for the majority of the population, long-term consumption of diets that would generally be considered to be highly restrictive in terms of carbohydrate (i.e., those that provide < 130 g carbohydrate/d, which represents the fourth and fifth categories depicted previously) is not likely to promote optimal health.

On the other hand, there are well-established advantages associated with some degree of carbohydrate restriction, particularly with respect to both weight loss diets and inducing favorable changes in cardiovascular risk factors. For individuals with IR or classified as having MetS or prediabetes, a number of cardiovascular risk factors (i.e., hypertriacylglycerolemia, low HDL-C, hypertension, hyperglycemia) can be significantly improved by the consumption of a diet that is at least moderately restricted in carbohydrate. Thus, for these individuals, a diet that provides 26% to 44% of calories from carbohydrate may be an ideal range in terms of facilitating improvements in cardiovascular risk factors, while at the same time allowing for enough emphasis on high-quality carbohydrate sources to ensure that it also provides a sufficient level of dietary fiber as well as phytochemicals.

A final point is whether there are instances for which the most restrictive LCDs should be recommended for the general population. In support of this contention is the evidence that the greater the restriction of carbohydrates, the greater the improvement in the combination of cardiovascular risk factors that constitute MetS [8]. However, research studies have not addressed whether these highly restrictive LCDs promote optimal health in terms of overall quality of life and increased longevity. Additionally, many individuals would likely find these types of diets very difficult to adhere to over long periods of time. Thus, until the long-term beneficial effects of these most restrictive LCDs have been documented, I believe the potential negatives argue against their adoption by the general population.

References

[1] Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. JAMA 2005;293:43–53.
[2] Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–73.
[3] Feinman R, Fine EJ. Thermodynamics and metabolic advantage of weight loss diets. Metab Syndr Relat Disord 2003;1:209–19.
[4] McCrory MA, Suen VMM, Roberts SB. Biobehavioral influences on energy intake and adult weight gain. J Nutr 2002;132:3830S–4S.
[5] Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. JAMA 2005;294:2455–64.
[6] Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low fat/low-calorie diets in the management of obesity and its comorbidities. Obes Rev 2009;10:36–50.
[7] Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Brehm BJ, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors. Arch Int Med 2006;166:285–93.
[8] Volek JS, Feinman RD. Carbohydrate restriction improves the features of metabolic syndrome. Metabolic syndrome may be defined by the response to carbohydrate restriction. Nutr Metab 2005;2:31–47.
[9] Despres J, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.
[10] Reaven GM. The insulin resistance syndrome: Definition and dietary approaches to treatment. Annual Rev Nutr 2005;25:391–406.
[11] Olefsky JM, Nolan JJ. Insulin resistance and NIDDM: Cellular and molecular mechanisms. Am J Clin Nutr 1995;61(Suppl):980S–6S.
[12] Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) of syndrome X? A viewpoint strongly against. Curr Opin Lipidol 1997;8:23–7.
[13] The National Heart, Lung, and Blood Institute expert panel on the identification, evaluation, and treatment of overweight and obesity in adults. J Am Dietet Assoc 1998;98:1178–91.
[14] McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Int Med 2003;139:802–9.
[15] Hussain TA, Mathew TC, Path FRC, Dashti AA, Asfar S, Al-Zaid N, et al. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition 2012;28:1016–21.
[16] Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr 2013;67:789–96.
[17] Castaneda-Gonzalez LM, Gascon MB, Cruz AJ. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: A systemic review of RCT greater than 12 weeks. Nutr Hosp 2011;26:1270–6.
[18] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
[19] Leite JO, DeOgburn R, Ratliff J, Su R, Smyth JA, Volek JS, et al. Low-carbohydrate diets reduce lipid accumulation and arterial inflammation in guinea pigs fed a high-cholesterol diet. Atherosclerosis 2010;209:442–8.
[20] Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, et al. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids 2008;43:65–77.

[21] Johnson RJ, Murray R. Fructose, exercise, and health. Curr Sports Med Rep 2010;9:253–8.
[22] Bray GA. Fructose: Should we worry? Int J Obes 2008;32:S127–31.
[23] Page KA, Chan O, Arora J, Belfort-DeAguiar R, Dzuira J, Roehmholdt B, et al. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 2013;309:63–70.
[24] Angelopoulos TJ, Lowndes J, Zukley L, Melanson KJ, Nguyen V, Huffman A, et al. The effect of high-fructose corn syrup consumption on triglycerides and uric acid. J Nutr 2009;139:1242S–5S.
[25] Mullins G, Hallam CL, Broom I. Ketosis, ketoacidosis and very-low-calorie diets: Putting the record straight. Nutr Bull 2011;36:397–402.
[26] Honors MA, Hargrave SL, Kinzig KP. Acute and chronic effects of β-hydroxybutryate on food intake and body weight. Appetite 2007;49:298 (abstract).
[27] Johnson CS, Tjonn SL, Swan PD, White A, Hutchins H, Sears B. Ketogenic, low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. Am J Clin Nutr 2006;83:1055–61.
[28] Frigolet M, Barragan VR, Gonzalez MT. Low-carbohydrate diets: A matter of love or hate. Ann Nutr Metab 2011;58:320–34.
[29] Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high fat and high carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. Br J Nutr 2009;101:1493–502.
[30] Russell WR, Gratz SW, Duncan SH, Holtrop G, Ince J, Scobbie L, et al. High-protein, reduced-carbohydrate weight-loss diets promote metabolic profiles likely to be detrimental to colonic health. Am J Clin Nutr 2011;93:1062–72.
[31] O'Keefe SJ. Nutrition and colonic health: The critical role of the microbiota. Curr Opin Gastroenterol 2008;24:51–8.
[32] Johnston CS, Tjonn SL, Swan PD, White A, Sears B. Low-carbohydrate, high-protein diets that restrict potassium-rich fruits and vegetables promote calciuria. Osteoporosis Int 2006;17:1820–1.
[33] White AM, Johnston CS, Swan PD, Tjonn SL, Sears B. Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: A pilot study. J Am Dietet Assoc 2007;107:1792–6.
[34] Bodewes TCF, Luttikhold J, van Stijn MFM, Visser M, van Norren K, Vermeulen MAR, et al. Antioxidant properties of flavonoids. Curr Org Chem 2011;15:2616–26.
[35] Craig WJ. Phytochemicals: Guardians of our health. J Am Dietet Assoc 1997;97(Suppl 2):S199–204.
[36] Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomized controlled trials. Br J Nutr 2013;110:1178–87.
[37] Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy WS, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: A meta-analysis of randomized controlled clinical trials. Am J Epidemiol 2012;176(Suppl):S44–54.
[38] Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr 2006;83:1025–31.
[39] Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: A meta-analysis. Int J Cardiovasc Imaging 2010;26:631–40.
[40] Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelial dysfunction as a target for prevention of cardiovascular disease. Diabetes Care 2009;32:S314–21.
[41] Merino J, Kones R, Ferre R, Plana N, Girona J, Aragones G, et al. Negative effect of a low-carbohydrate, high protein, high-fat diet on small peripheral artery reactivity in patients with increased cardiovascular risk. Br J Nutr 2013;109:1241–7.
[42] Wycherley TP, Brinkworth GD, Keogh JB, Noakes M, Cuckley JD, Clifton PM. Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. J Intern Med 2010;267:452–61.
[43] Varady KA, Bhutani S, Klempel MC, Phillips SA. Improvements in vascular health by a low-fat diet, but not a high-fat diet, are mediated by changes in adipocyte biology. Nutr J 2001;10:8.
[44] Miller M, Beach V, Sorkin JD, Mangano C, Dobmeier C, Novacic D, et al. Comparative effects of three popular diets on lipids, endothelial function, and C-reactive protein during weight maintenance. J Am Diet Assoc 2009;109:713–7.
[45] Phillips SA, Jurva JW, Syed AQ, Syed AQ, Kulinski JP, Pleuss J, et al. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. Hypertension 2008;51:376–82.
[46] Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: Evidence from a systematic review and meta-analysis. Br J Nutr 2013;110:969–70.
[47] Keogh JB, Brinkworth GD, Clifton PM. Effects of weight loss on a low-carbohydrate diet on flow-mediated dilatation, adhesion molecules and adiponectin. Br J Nutr 2007;98:852–9.
[48] Keogh JB, Brinkworth GD, Noakes M, Belobrajdic DP, Buckley JD, Clifton PM. Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. Am J Clin Nutr 2008;87:567–76.
[49] Volek JS, Ballard KD, Silvestre R, Judelson DA, Quann EE, Forsythe CE, et al. Effects of dietary carbohydrate restriction versus low-fat diet on flow-mediated dilation. Metabolism 2009;58:1769–77.
[50] Green JG, Johnson NA, Sachinwalla T, Cunningham CW, Thompson MW, Stannard SR. Low-carbohydrate diet does not affect intramyocellular lipid concentration or insulin sensitivity in lean, physically fit men when protein intake is elevated. Metabolism 2010;59:1633–41.
[51] Friedman AN, Ogden LG, Foster GD, Klein S, Stein R, Miller B, et al. Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. Clin J Am Soc Nephrol 2012;7:1103–11.