Low-Carbohydrate Diets: A Matter of Love or Hate

María-Eugenia Frigolet^a Victoria-Eugenia Ramos Barragán^b
Martha Tamez González^c

^aResearch Department, and ^bNutrition Department, Hospital General 'Dr. Manuel Gea González', and
^cHealth Division, Instituto Tecnológico de Estudios Superiores de Monterrey, Mexico City, Mexico

Key Words

Low-carbohydrate diet • Obesity • Diabetes • Ketosis

Abstract

Low-carbohydrate diets (LChD) have become very popular among the general population. These diets have been used to lose body weight and to ameliorate various abnormalities like diabetes, nonalcoholic fatty liver disease, polycystic ovary syndrome, narcolepsy, epilepsy, and others. Reports suggest that body weight reduction and glycemic control could be attained while following LChD. However, these advantages are more notably found in short periods of time consuming an LChD. Indeed, the safety and efficacy of the latter diets in the long term have not been sufficiently explored. In contrast to what has been proposed, other mentioned pathologies are not improved or are even worsened by carbohydrate restriction. Therefore, the aim of this review is to define the concept of LChD and to explain their clinical effects in the short and long term, their influence on metabolism, and the opinion of nutrition or health authorities. Finally, evincing the research gaps of LChD that are here exposed will later allow us to reach a consensus with regard to their utilization.

Copyright © 2011 S. Karger AG, Basel

Introduction

In the past decades, the prevalence of obesity in the worldwide population has increased dramatically. According to the World Health Organization (WHO) there are more than 1 billion overweight adults and at least 300 million adults with obesity [1]. This disease is associated with a major risk of developing chronic diseases such as type 2 diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, musculoskeletal disorders, and some kinds of cancer such as esophagus, colorectum, breast, endometrium, and kidney [2]. Moreover, childhood obesity and overweight are already epidemic diseases in developing countries. Globally, in 2005 at least 20 million children under 5 years of age were overweight, but in 2010 the number of overweight children rose to 42 million [1].

Because of the comorbidities of obesity and the high prevalence of this disease, at any given time, people attempt to lose weight through numerous diets [3, 4]. Different types of the most popular diets generally used to lose weight modulate macronutrient distribution; therefore, a range of alternatives have evolved offering low-carbohydrate diets (LChD) (e.g. Zone diet), very-LChD (VLChD) (e.g. Atkins), high/low-protein diets, high/low-fat diets, and their combinations [4, 5]. LChD and VLChD

have become a matter of international concern; these are not commonly prescribed by a dietitian and can be acquired through a variety of magazines or books [5, 6]. In addition, controversy exists regarding their safety and whether their adverse or favorable effects could influence the treatment of different pathologies. For these reasons, it is important to define, review, and generate an opinion about the use of LChD and VLChD. Thus, our interest is to show the available information about the beneficial and detrimental effects of such diets to ameliorate obesity and to improve metabolic and other diseases.

History of Carbohydrate Consumption

According to Eaton and Eaton [7], since the Paleolithic era, adaptations that define characteristics of contemporary humans have been selected, i.e. body mass and shape, locomotive capability, masticatory apparatus, growth and developmental schedule, brain size, and resting metabolic rate. Our genome has changed little; thus humans remain adapted for a Paleolithic dietary regimen. At that time, the dietary regimen for Stone Agers was not universal. Their dietary patterns varied depending on the geographic area, climate, and specific ecologic niche [7, 8]. However, it is known that their diet consisted of fish, uncultivated vegetables and fruits, and moderate intakes of nuts and honey. Other products such as grains, oils, and, legumes were occasionally consumed [7, 9, 10]. A recent report explains that starch granules have been retrieved from surfaces of tools utilized in the Middle Stone Age, showing that humans included grass seeds in their diet at least 105,000 years ago [11].

Differences between Paleolithic, Neolithic, and current diets regarding food groups and macronutrient intake have been explored. During the Paleolithic period high quantities of animal products were consumed, but plant-based foods possibly represented a significant proportion of the diet. In this period, hunter-gatherers consumed elevated concentrations of dietary protein (19–35% energy) at the expense of carbohydrates (22–40% energy) [9, 10].

The agricultural revolution during the Neolithic era led to the inclusion of low-glycemic index starchy foods, vegetables, fruits, nuts, vegetable protein, and plant sterols into the human diet [12, 13].

In order to test the effects of the Neolithic diet, starchy foods such as unrefined grains, and legumes, dairy products, olives, dried and fresh fruit, and vegetables were included in the diet of 10 healthy subjects. Although no significant differences in the LDL:HDL ratio were found, the LDL concentration was reduced by over 20% [14].

In particular, food-processing procedures introduced during the industrial periods have fundamentally altered the nutritional characteristics of ancestral diets, i.e. glycemic load, fatty acid and macronutrient consumption, and fiber content. A trial has indicated that the simian diet, which is very high in dietary fiber (55 g/1,000 kcal), reduces risk factors for cardiovascular disease and colon cancer, as previously stated in the fiber hypothesis [15]. Not only has the amount of carbohydrates in the diet changed but also their sources and types have markedly increased since the intake of refined sugar, fructose, and syrups, contributing to the enhanced ingestion of high-glycemic load diets. Consequently, the evolutionary collision of our ancient genome with the nutritional qualities of recently introduced foods may lead to many of the chronic diseases of our era [8].

Defining LChD

LChD have increased in popularity in recent years due to their proposed influence on satiety and weight loss [16]. LChD contain less than 200 g of carbohydrates per day, or less than 30% of the total energy requirement [16, 17]. When the carbohydrate intake is reduced, the fat and protein content in the diet increases, resulting in a low-carbohydrate hyperproteic diet (LChHPD) or nonketogenic low-carbohydrate high-fat diet (NLChHFD) [16]. An example of an LChD is the Zone diet, consisting of a distribution of 30% protein, 40% carbohydrates, and 30% fat [4, 5].

Very-LChHPD (VLChHPD) can have a macronutrient distribution of 25–35% of fat from the total energy intake and 55–65% from proteins [18, 19]. The NLChHFD distribution of fat and protein is varied and is often higher than the daily intake recommendations (range 20–30% and 15–20%, respectively) [20].

On the other hand, VLChD generally have a content of ≤ 20 –50 g/day of carbohydrates and a high fat and/or high protein content [21]. An example of a VLChD is the Atkins diet; its protein content is 35% from the total energy intake, 50% from fat, and only 10% from carbohydrates [4, 5]. A VLChD is generally a ketogenic diet and could contain 60% or more of the total energy as fat [16, 17, 22] (table 1). Although a common response of VLChD is the induction of ketogenesis, this response is not the same in all patients because each individual has a different amount of liver glycogen and their exogenous carbohydrate requirement varies [17].

VLChD alter the metabolism generally in two different manners. First, these diets induce the production of ketone bodies to maintain tissues and organs that are not

Table 1. Distribution of the percent of energy intake for carbohydrates, protein, and lipids in LChD and VLChD

Diet	Energy carbohydrates, %	Energy protein, %	Energy fat, %
LChD	20–40		
LChHPD	20–40	30–60	20–30
NLChHFD	20–40	20–30	30–60
VLChD	0–20		
VLChHPD	0–20	55–65	25–35

receiving sufficient glucose. Second, VLChD promote a slower glycolytic pathway and increased gluconeogenesis in order to maintain glycemia and organ function.

Metabolism of LChD

A low-carbohydrate intake results in a lower circulating insulin/glucagon ratio, which promotes a high level of serum nonesterified fatty acids (NEFAs) used for oxidation and production of ketone bodies. It is assumed that when the carbohydrate availability from liver glycogen and the exogenous carbohydrate supply is reduced during a short-term period to a significant amount, the body will be stimulated to maximize fat oxidation for energy needs [17]. The ketone bodies, mainly produced from the oxidation of NEFAs and ketogenic amino acids such as leucine and lysine, comprise three compounds: acetoacetate (AcAc), 3- β -hydroxybutyrate (3HB), and acetone [23]. Acetone is exhaled, while AcAc and 3HB are the most important ketone bodies synthesized and transported by the blood to extrahepatic tissues such as the brain, kidneys, and heart [23, 24]. In these tissues, AcAc and 3HB are oxidized in the citric acid cycle to meet most of the energy requirements. Ketosis results from serum elevation of ketone bodies; ketoacidosis and ketosis should not be used as synonyms since ketoacidosis is a threatening condition most common in untreated type 1 diabetes. In addition, reduced intake of carbohydrates during a VLChD promotes glycolysis inhibition and acceleration of gluconeogenesis. The latter happens in order to provide glucose to tissues that require it as their sole or major fuel source, such as the renal medulla, central nervous system, gonads, and erythrocytes [25].

Effects of LChD

Obesity and Diabetes

LChD have been widely used for weight control or treatment of obesity. Randomized controlled trials have

shown that LChD are just as effective at controlling body weight as low-fat diets (LFD); nevertheless, blood glucose, HbA1c, and glycemic control are clearly reduced by LChD in comparison with LFD [26, 27]. These beneficial effects are markedly dependent on the duration of the studies. In nutritional studies with obese diabetic subjects, the use of VLChD was shown to reduce body weight, body mass index, blood glucose, triglycerides, and LDL cholesterol [28]. Fat and protein sources may influence whether LChD are associated with type 2 diabetes since animal protein and fat was related to an increased risk of diabetes, but vegetable protein and fat was inversely associated with diabetes risk [29]. VLChD, such as the Atkins diet, are usually high in protein and fat (particularly, saturated fat) to attain successful weight loss. There are several mechanisms by which these diets induce weight loss. This is due to diuresis as a result of glycogen depletion since 1 g of glycogen is usually stored accompanied by 3 g of water [30]. Also, water loss can be associated with ketonuria, which increases renal sodium and water loss. It has been hypothesized that ketogenic diets suppress appetite and have a 'metabolic advantage' by requiring increased gluconeogenesis and upregulating mitochondrial uncoupling protein causing the waste of ATP as heat [25, 31]. Other mechanisms that could induce weight loss are: limitation of food choices, reduction of the palatability of LChD, the satiating effect of high protein intake, an increased thermogenic effect of protein, and increased adipose tissue lipolysis as a result of reduced circulating insulin levels and increased fatty acid oxidation [32–35].

Dietary carbohydrates raise postprandial glucose levels [36]. Different types of carbohydrates exert distinct effects on slow or fast increases in blood glucose concentrations. For instance, low-glycemic foods cause gradual increases in glycemia, while high-glycemic index foods rapidly augment blood glucose [37]. These observations led to the use of LChD for medical nutrition therapy not only for obesity but also to treat diabetes. Clinical studies that have lowered the percentage of dietary carbohydrates and/or the glycemic index of the carbohydrates have consistently shown improvements in glycemic control among individuals with type 2 diabetes [38–42]. However, the best improvements in glycemic control are due to low-glycemic index diets instead of the percentage of carbohydrate content. For example, in the Nurse's Health Study cohort study, low-glycemic index diets were found to be associated with a lower cardiac risk over a 20-year period [43]. A reduced-glycemic index diet without weight loss can also lead to improvement in diabetic control, with enhanced reductions in HgbA1c, when compared with higher-glyce-

mic diets of similar carbohydrate content [38, 44, 45]. The LChD with variation in the glycemic index (low, moderate, and high) have only been found effective for the treatment of obesity and diabetes in the short term [45, 46].

Epilepsy

VLChHF ketogenic diets are commonly used in the treatment of refractory pediatric epilepsy because ketosis induced by diet has been demonstrated to have an anti-convulsant effect [47]. Some authors have reported a neuroprotective effect with the use of these diets and better results in electroencephalograms [48, 49]. Nevertheless, treatment of pediatric epilepsy with VLChD has been associated with stunting and other important complications [50]. In fact, a prospective study that followed 22 children with the same type of refractory epilepsy for 25 months reported a ketotic state, hypoglycemia, refusal to drink fluids, constipation, renal calculi, nausea, and vomiting [51]. Also, long-standing ketosis has been associated with myocardial dysfunction in children after a ketogenic diet to treat intractable seizures [52]. There is evidence as well of relevant relapse of schizophrenia symptoms with LChD, but this conclusion implies the elimination of gluten in addition to the low carbohydrate consumption [53].

Nonalcoholic Fatty Liver Disease

LChD could also represent a dietary treatment for nonalcoholic fatty liver disease (NAFLD), although conclusive evidence is missing [54, 55]. Wanless and Lentz [56] mentioned that 70% of obese patients had liver steatosis, and the degree of steatosis was proportional to the degree of obesity. Thus, a dietary approach for the treatment of obesity and coexistence of NAFLD would be recommended. Tendler et al. [57] conducted a pilot study in 5 individuals with NAFLD that followed a VLChD during 6 months. They found significant weight loss and a decreased systolic blood pressure. Steatosis, necroinflammatory grade, total bilirubin, and the total cholesterol/HDL-C ratio improved in 4 patients. However, the reductions of alanine aminotransferase, insulin, diastolic blood pressure, and state of fibrosis were not statistically significant. The authors discussed that the absence of a comparison group did not allow the determination of whether the effects were a consequence of the ketogenic diet or weight loss [57]. In a randomized trial, hypoenergetic LFD and LChD were equally effective in reducing intrahepatic lipid accumulation in obese or overweight patients [58]. One study described a correlation of breath acetone with liver steatohepatitis, which suggests that humans on a ketogenic diet could have an increased

risk of developing NAFLD [59]. Thus, energy but not necessarily carbohydrate restriction accounts importantly for improvements with NAFLD.

Other Diseases

VLChD and LChD have been described to have a beneficial effect on several conditions such as polycystic ovary syndrome, gastroesophageal reflux, and narcolepsy [30, 60–63]. Despite the popular belief that VLChD are related to the treatment and decreased consequences of polycystic ovary syndrome, not enough studies have investigated this matter. For instance, only one pilot study that included 5 patients concluded that a 6-month diet containing 20 g or less of carbohydrates reduced the serum free testosterone and LH/FSH ratio, with no significant changes in serum insulin, HgA1c, or lipid profile [64].

VLChD have also been evaluated in patients suffering from narcolepsy. Nine patients that adhered to the Atkins diet during 8 weeks reported that their symptoms decreased by 18% [30]. A pilot study suggested amelioration of the symptoms of gastroesophageal reflux when following a LChD and simultaneously reducing fat, caffeine, and acidic food [65]. In addition, esophageal exposure to acid was reduced and improvement of symptoms in 8 subjects was achieved after the consumption of VLChD during 6 days [63]. These are the only studies that affirm a relationship between narcolepsy or gastroesophageal reflux and VLChD; thus, further research comprehending more subjects and different ethnicities is needed.

Furthermore, mild ketosis may be beneficial in certain cancers and neurodegenerative conditions including Alzheimer's and Parkinson's diseases. These effects lack significant data and have not been proven in long-term well-controlled trials [3]. Table 2 summarizes the strength of evidence of LChD effects when used to treat distinct abnormalities.

Mechanisms Regulating the Effects of LChD

It is plausible that the effects of the VLChD or LChD are mainly or partially regulated by ketone production and by modifications in gluconeogenesis velocity. In comparison with a control diet, the AcAc brain uptake is increased 7–8 times in rats following a VLChD or during fasting [82, 83]. As mentioned before, ketosis could have a beneficial or a negative influence on various pathologies [84, 85]. Obese humans and rats have decreased blood ketone bodies because of their impaired capability for β -oxidation and ketogenesis [86]. Ketosis during weight loss in obese subjects maintains the same cholecystokinin concentrations before weight loss, suggesting that ke-

Table 2. Summary of the strength of evidence on LChD that have positive or negative health effects when used in different diseases

LChD in different diseases	Strength of evidence	Positive effects						Negative effects				
		weight loss	glycemic control	lipid control	blood pressure control	improvement on insulin sensitivity	other health benefits	cardio-vascular risk	augment- ed bone resorption	renal calculi	gastro- intestinal symptoms	other consequences
<i>Obesity</i>												
Sacks et al. [66]	A	+	+	+	+	+						increased ratio of urinary microalbumin to creatinine
Foster et al. [67] ^a	B	+	+	+	+	+					+	ketonuria, hair loss, and bad breath
Yancy et al. [68]	A	+		+							+	
Foster et al. [69]	A	+	+	+	+	+		+				poor adherence
Samaha et al. [70]	B	+	+	+	NS	+		+				
Stern et al. [71] ^a	B	+		+		+						
<i>Diabetes</i>												
Gannon and Nuttall [39]	B		+	NS		+						
Haimoto et al. [72]	B	NS	+	+	NS	+					+	
Davis et al. [73]	A	+	NS	+	NS	NS						
Ma et al. [74]	B	NS	NS	NS	NS	NS		+				
Nielsen et al. [75]	A	NS	+			+		+				
<i>NAFLD</i>												
Haufe et al. [58]	A	+	+	+								
de Luis et al. [76]	A	+	+	+	+		ALT, AST improvement					
Shwarz et al. [77]	B	NS	NS	NS								
Browning et al. [78] ^a	B	+	+	+								
<i>PCOS</i>												
Mavropoulos et al. [64] ^a	B	+	NS	NS	+	+	decrease in the LH/FSH ratio					
Moran et al. [79]	B	+	+	+		+						
<i>Epilepsy</i>												
Ríos [51] ^a	B									+	+	metabolic acidosis, anorexia
Neal et al. [80] ^a	A										+	
Groesbeck et al. [81]	B								+	+		slowed growth, hyper-cholesterolemia
<i>GERD</i>												
Austin et al. [63] ^a	B						pH decrease					
Yancy et al. [65]	B											

Information about the results of each study was summarized. Strengths and weaknesses of the studies were recorded. Using an updated rating for levels of evidence, recommendations were graded from A to D based on the level of evidence of the supporting studies, as per the Oxford Centre for Evidence-Based Medicine (OCEBM), March 2009. Only those studies graded with A or B were considered for this table. PCOS = Polycystic ovary syndrome; GERD = gastroesophageal reflux disease; NS = no statistical difference; + = increased.

^a Only these studies administered VLChD.

Fig. 1. Metabolic consequences of a VLChD. (1) Serum insulin is decreased by carbohydrate restriction, which leads to lipolysis in adipose tissue and proteolysis in skeletal muscle. (2) Fatty acids from lipolysis are oxidized in the liver, where production of acetyl-CoA induces ketogenesis (synthesis of AcAc and 3HB). Glycerol from lipolysis is used to generate glucose by gluconeogenesis. Amino acids released from muscle are used to produce glucose or ketone bodies according to their glucogenic or ketogenic nature. (3) NEFAs from lipolysis and urea from amino acid utilization are drained into circulation. Also, synthesized glucose and ketone

bodies are delivered into circulation and subsequently used by the central nervous system, kidney, heart, and other organs. In addition, pyruvate and lactate, produced by the heart and kidney, are gluconeogenic substrates for the liver. (4) Organ function can be altered by these metabolic changes since ketosis alters neuron excitability. The kidney is forced to excrete nitrogen, water, and calcium, which affects bone density. Cardiovascular risk, insulin resistance, and liver steatosis could be developed due to the elevated NEFA serum concentration.

tones promote satiety via cholecystokinin [87]. On the other hand, diabetes is an abnormality typically accompanied by increased ketogenesis, sometimes independent of glucose or insulin infusion [88, 89]. Stimulation of adult cardiomyocytes with 3HB induces insulin resistance via the PI3K/Akt pathway [90]. In addition, AcAc-mediated ketoacidosis impairs insulin binding and decreases insulin receptor protein, as well as mRNA and phosphorylation of insulin receptor substrate in adrenal chromaffin cells [91]. In fact, NEFAs are augmented in diabetes and diabetic ketoacidosis, connecting lipolysis, ketogenesis, and diabetes [92]. NEFAs are indeed elevated in serum when liver steatosis develops, and the availability of fatty acids is directly associated with ketogenesis [93].

Proteolytic and lipolytic responses to VLChD or starvation are enhanced in order to generate glucose from amino acids or glycerol as described [94]. Therefore, gluconeogenesis increases in healthy men following a carbo-

hydrate-restricted diet to sustain glycemia [95]. Diabetes also stimulates gluconeogenesis and endogen glucose production despite the presence of hyperinsulinemia and hyperglycemia [96]. Thus, carbohydrate restriction in diabetic patients should be cautioned since the mentioned diet and condition contribute to an exacerbated glucose production. Gluconeogenesis is also upregulated during the development of NAFLD, which could mean enhanced deleterious effects of reduced carbohydrate consumption as exposed before [97]. An integrative model of metabolic modifications induced by VLChD is presented in figure 1.

Another factor that could be involved in the shown effects of LChD is oxidative stress because accelerated lipolysis and increased citric acid cycle flux mediated by carbohydrate restriction promotes reactive oxygen species (ROS) production [98–100]. Free fatty acid release and decreased triglyceride storage leads to adipocyte lipotoxicity and increased oxidative stress [101]. In endo-

thelial cells, palmitate promotes ROS production and endothelial dysfunction [102]. Not only fatty acids promote ROS formation given that high glucose stimulation induces the same effects in various cell types. High glucose mediates ROS formation in adipocytes, human aortic endothelial cells, and pancreatic β cells [103–105]. In postprandial conditions, a meal that causes a higher degree of hyperglycemia increases oxidative stress markers and the susceptibility to oxidize LDL [106]. Therefore, both low and high glucose consumption could contribute to oxidative stress via distinct mechanisms.

The Use of LChD over Short- and Long-Term Periods Short Term

Weight loss is a short-term (3–6 months) consequence of the use of LChD or VLChD without changes in resting energy expenditure or the thermic effect of food in comparison with LFD [107]. Despite rapid augmented weight loss, maintenance of weight loss is not always achieved. Regularly after 1 year, the weight loss induced by LChD or LFD is not different [6, 68–71, 108, 109].

With regard to diabetes, animal models have shown that an 8-week VLChD promotes normal concentrations of blood glucose and insulin in streptozotocin-induced diabetic rats [110, 111]. In humans, HgbA1c and serum glucose are reduced by the short-term use of LChD with no detrimental effects on cardiovascular risk or renal function [112]. A 4-week VLChD versus an LFD could modify the insulin sensitivity since the HOMA index is decreased in overweight women [113]. In overweight and obese subjects with NAFLD the liver triglyceride content is decreased to a greater extent after a 2-week VLChD than after energy restriction [79].

It seems that blood lipids respond differently to the dietary carbohydrate concentration. High-carbohydrate LFD appear to have a more favorable impact on total and LDL cholesterol, whereas LChD have been shown to significantly decrease triglyceride levels and increase HDL cholesterol levels in short-term studies [114]. A recent study in animals showed that a 6-week VLChD versus a Western diet (normal content of carbohydrates) reflected no difference in cardiovascular risk markers when an atherogenesis mouse model (deficient in apolipoprotein E or ApoE^{-/-}) was utilized. However, the VLCh-fed mice had a reduced number of bone marrow and peripheral blood progenitor endothelial cells, which induce vascular regeneration. These results suggest that a VLChD may have adverse effects on neovascularization and vascular health without changes in serum markers [115]. In human studies, a randomized, 8-week trial showed that

LChD may have negative effects on vascular risk by augmenting the overall systemic arterial stiffness in contrast to LFD [116]. Also, following a VLChD versus an LChD during 6 weeks increased the LDL cholesterol, and this was directly related to blood ketone concentrations, meaning that the degree of carbohydrate constraint and consequent ketogenesis as well as the time length influences biochemical parameters [117].

LChD consumption (4–8 weeks) lowers the stool weight and has deleterious effects on the concentration and excretion of fecal short-chain fatty acids and fiber-derived antioxidant phenolic acids compared with a high or moderate carbohydrate intake. The latter suggests that short-term consumption of an LChD may increase the risk of development of gastrointestinal disorders [118, 119].

In summary, short-term carbohydrate restriction could have a negative impact on intestinal homeostasis. However, beneficial metabolic effects have been shown on serum glucose and cholesterol control in healthy, obese, and diabetic patients. Exceeding this time period could bring more detrimental effects as will be exposed.

Long Term

Long-term studies in animals have suggested that body weight, severity of diabetes, plasma NEFA, and insulin secretion are augmented in subjects with 20% of energy as carbohydrates in contrast with normal or high carbohydrate content groups [120]. Also, long-term experiments with rabbits showed that a VLChHFD induces triglyceride production and liver steatosis without changes in plasma glucose or cholesterol [121]. Prodiabetic adipokines and adiponectin have been measured in obese patients after following an LChD or an LFD during 36 months, but only leptin and weight loss were reduced during the first 12 months [122]. However, long-term randomized trials showed that diabetics could benefit from loosely restricting carbohydrates because HbA1c, BMI, and cholesterol profiles were improved staying on a diet of 45 versus 57% of energy as carbohydrates [123]. Other randomized controlled trials have shown that weight loss by carbohydrate restriction improves glucose homeostasis [124]. Additional studies comparing LChD and LFD showed that both are effective in reducing weight and cardiovascular disease risk and improving glycemic control up to 1 year [27, 125]. Thus, long-term duration and the carbohydrate content of the diet determines if the LChD will have beneficial effects in diabetic and obese patients. Table 3 illustrates short and long-term effects of LChD on body weight, insulin sensitivity, blood glucose, and other parameters in humans.

When a VLChD is used for long periods, low intakes of calcium and fiber can occur, causing constipation and alterations in bone function. There has been concern about VLChHFD reducing serotonin concentrations in the brain and causing adverse effects in psychological function, including mood and cognition [142, 143], given the fact that carbohydrates are involved in the synthesis of serotonin (by increasing the plasma ratio of tryptophan to other amino acids) [144–146]. Observational studies have shown that LChD with high protein and fat concentrations are associated with higher levels of anxiety, anger, stress, mood disturbances, fatigue, depression, poor physical exercise performance, and less vigor and imagination [147–150]. Other studies mentioned that VLChD cause symptomatic side effects such as headache, muscle cramps, diarrhea, weakness, and skin rash [68].

The latter symptoms may be associated with the deficiency of thiamine, vitamin C, pyridoxine, niacin, riboflavin, folic acid, phosphorus, iron, copper, manganese, chromium, and/or molybdenum for good natural sources of these vitamins and minerals are carbohydrate sources too. Cereals and breads are usually the most important sources of these micronutrients. Studies that assessed micronutrient deficiencies while following LChD showed a significant lack of several vitamins and minerals even in subjects that were encouraged to take multivitamin supplements [151, 152].

VLChHPD exceed the daily requirements of protein (0.8 g/kg/day) [23, 150]. If the protein intake remains between 25 and 74 g/day, and the calcium intake is 500–1,400 mg/day, the calcium balance is maintained close to equilibrium. However, if the protein intake exceeds 75 g/day, a negative calcium balance tends to be reached. A negative calcium balance is manifested during the first hours (2–4 h) and could be sustained while following a high-protein diet [153]. High protein consumption increases acid excretion mainly as sulphates and phosphates, which leads to an increase in urinary calcium. Calcium is released as a bone cellular response when chronic acid overload in the kidney is present, causing resorption and a decreased bone mass [153–155]. Thus, chronic use of an LChD with increased protein concentrations would reduce the bone mineral content and might play an etiological role in osteoporosis, renal disorders, and other metabolic bone diseases [156]. In fact, an increased intake of fruits and vegetables from 3.6 to 9.5 daily servings is associated with decreased urinary calcium excretion from 157 ± 7 to 110 ± 7 mg/day [151, 152, 157]. The latter is explained because intakes of zinc, magnesium, β -carotene, potassium, fiber, and vitamin C

are associated with a higher bone mass in premenopausal and menopausal women [158, 159]. The β -carotene intake displayed a significantly negative correlation with serum osteocalcin in adults [160]. Furthermore, some studies have demonstrated that consuming the recommended dietary allowance of protein decreases the net renal acid excretion, urinary calcium, and bone mass in young healthy women [161].

Vascular function has been evaluated in overweight or obese subjects after long-term use of VLChD (52 weeks). A VLChHFD versus an LFD with the same amount of energy impairs flow-mediated dilation, although no differences between diets were found in terms of body weight and endothelial function factors such as adiponectin, E-selectin, and plasminogen activating inhibitor-1 [162]. In healthy subjects, cardiovascular factors tend to remain within reference ranges after 3 years (time according to patients' declarations) of adherence to LChHFD. In most subjects, the ratios of LDL-C/HDL-C and total cholesterol/HDL-C, plasma concentrations of glucose, insulin, glucagon, cortisol, homocysteine, glycerol, and C-reactive protein were normal [163]. Nevertheless, a series of studies have demonstrated that the effects on HDL-C and LDL-C are strongly dependent on the amount of carbohydrate restriction and the intake of saturated fat, and in some cases the LDL-C level may rise despite weight loss [164]. A report that compares the nutrient distribution of 8 popular diets using computer analysis indicates that the cardiovascular risk would increase with the long-term consumption of high-fat diets, which are higher in saturated fat and cholesterol. However, higher-carbohydrate, higher-fiber diets would have the greatest effect in decreasing serum cholesterol and the risk of cardiovascular disease [165]. Thus, conflicting data exists about carbohydrate restriction accompanied by high fat and/or protein concentrations consumed for at least 1 year during weight stability or weight variance.

Long-term survival studies in LCh dieters were conducted in the Greek and Swedish populations. In the Greek study, the mean duration was 4.9 years, and the diet composition was evaluated in the general population without intended weight reduction. Results indicate that lower carbohydrate and higher protein intakes were associated with increased mortality. Similar findings were observed in the Swedish study; in that case only women were included and followed up for a period of 12 years. Both studies concluded that carbohydrate restriction and high protein consumption increase the mortality rate associated with cardiovascular mortality and to a lesser extent or not at all with cancer mortality [166, 167].

Table 3. Body weight, blood glucose, insulin sensitivity, and other parameters measured in humans after reduction of the dietary carbohydrate distribution in the long and short term

Reference	n	Study duration	Diet group	Diagnostic	Body weight	Blood glucose	Insulin sensitivity	Other parameters
<i>Short-term studies (up to 6 months)</i>								
Volek et al. [112]	13	4 weeks	VLChD: 10% Ch, 60% F, 30% P, hypoenergetic standard: 55% Ch, 25% F, 20% P, hypoenergetic	O	⇓ ↓	⇓ ↓	↑↑ ↑	TAG ↓ TC, LDL-C, HDL-C ↑
Bradley et al. [115]	24	8 weeks	LChHFD: 20% Ch, 60% F, 20% P standard: 60% Ch, 20% F, 20% P	O	↓ ↓	↓ ↓	NS NS	systematic arterial stiffness ↑
Johnston et al. [116]	20	6 weeks	VLChD: 5% Ch, 60% F, 35% P LChHPD: 40% Ch, 30% F, 30% P	O	↓ ↓	? ?	↑ ↑	LDL-C ↓ 3HB ↑
Garg et al. [126]	8	21 days	LChD: 35% Ch, hypoenergetic standard: 60% Ch, isoenergetic	D	? ?	NS NS	NS NS	HDL-C ↓ TAG ↑ hyperinsulinemic euglycemic clamp NS
Backes et al. [127]	23	3 months	before and after LChD: 40% Ch, hypoenergetic	O, D	↓	↓	↑	BP, TAG ↓
Boden et al. [128]	10	2 weeks	before and after LChD, hypoenergetic	O, D	↓	↓	↑	TAG, TC ↓
Miyashita et al. [129]	22	4 weeks	LChD: 40% Ch, 35% F, 25% P, hypoenergetic LFD: 65% Ch, 10% F, 25% P, hypoenergetic	O, D	↓ ↓	↓ ↓	↑ NS	visceral fat area ↓ HDL-C ↑
Chen et al. [130]	18	10 days	LChD: 30% Ch HChD: 85% Ch	D	? ?	↓ ↓	↑ NS	–
McLaughlin et al. [131]	57	16 weeks	LChD: 40% Ch, 45% F, 15% P standard: 60% Ch, 25% F, 15% P	O, D	↓ ↓	↓ ↓	↑↑ ↑	TAG, TC, LDL-C, plasma E-selectin ↓ HDL-C ↑
Allick et al. [132]	7	14 days	VLChD: 0% Ch, 89% F, 11% P LFD: 89% Ch, 0% F, 11% P	O, D	NS NS	⇓ ↓	↑↑ ↑	hyperinsulinemic euglycemic clamp NS TAG, LDL-C ↓ FFA, cortisol, HDL-C ↑
Anderson et al. [133]	11	1 week	LChD: 44% Ch, 36% F, 20% P LChHPD: 20% Ch, 36% F, 44% P LFD: 75% Ch, 16% F, 9% P	D	? ? ?	↓ ↓ ⇓	↑ ↑ ↑↑	TAG NS
Gannon et al. [134]	8	10 weeks	LChD: 30% Ch, 40% F, 30% P standard: 55% Ch, 30% F, 15% P	D	NS NS	⇓ ↓	NS NS	NEFA, TAG NS HbA _{1c} ↓
Kirk et al. [135]	22	11 weeks	VLChD: 10% Ch, 75% F, 15% P, hypoenergetic standard: 65% Ch, 20% F, 15% P, hypoenergetic	O	↓ ↓	⇓ ↓	↑ ↑	leptin, HOMA ↓ TAG, ALT, AST NS 3HB ↑
Muzio et al. [136]	100	5 months	LChD: 48% Ch, 33% F, 19% P standard: 65% Ch, 22% F, 13% P	O	↓ ↓	↓ ↓	↑ ↑	HDL-C NS BP ↓
Samaha et al. [137]	79	6 months	LChD: 40% Ch, 37% F, 23% P standard: 55% Ch, 30% F, 15% P	O	⇓ ↓	⇓ ↓	↑↑ ↑	TC, HDL-C, LDL-C, BP NS TAG ↓
Sunehag et al. [138]	36	7 days	LChD: 30% Ch, 55% F, 15% P standard: 60% Ch, 25% F, 15% P	H	? ?	↓ ↓	↑ ↑↑	FFA ↓
Sunehag et al. [139]	13	7 days	LChD: 30% Ch, 55% F, 15% P standard: 60% Ch, 25% F, 15% P	O	? ?	NS NS	↑↑ ↑	adiponectin, CRP, TAG, FFA NS LDL-C, HDL-C, TC, 3HB ↓
Yancy et al. [140]	21	16 weeks	before and after VLChD: 10% Ch, 61% F, 29% P	D	↓	NS	NS	TC, HDL-C, LDL-C NS HbA _{1c} , TAG ↓
Westman et al. [141] ^a	49	24 weeks	VLChD: <30 g/day Ch, isoenergetic standard: 55% Ch, hypoenergetic	O, D	⇓ ↓	↓ ↓	↑ ↑	HbA _{1c} ↓ HDL-C ↑
<i>Long-term studies (1–2 years)</i>								
Wolever et al. [45]	162	1 year	LChHFD: 39% Ch, 40% F, 21% P LChD: 47% Ch, 31% F, 22% P standard: 52% Ch, 27% F, 21% P	D	↓ ↓ ⇓	NS NS NS	↑ ↑↑ ↑↑↑	CRP, HDL-C ↑ BP, FFA, TC NS TAG, HbA _{1c} ↓
Shai et al. [46] ^a	272	2 years	VLChD: 20–100 g/day Ch, isoenergetic HFD: 35% F, hypoenergetic standard: 30% F, hypoenergetic	O	⇓⇓ ⇓⇓ ↓	↓ ⇓ ↓	↑ ↑ ↑	TC:HDL-C ↓ urine ketones ↑
Dashti et al. [53]	64	56 weeks	before and after VLChD: 5% Ch, 60% F, 35% P	O	↓	↓	?	creatinine NS HDL-C ↑ LDL-C, TC, TAG, urea ↓

Table 3 (continued)

Reference	n	Study duration	Diet group	Diag-nostic	Body weight	Blood glucose	Insulin sensitivity	Other parameters
Sacks et al. [66]	811	2 years	LChHPD: 35% Ch, 40% F, 25% P, hypoenergetic NLChHFD: 45% Ch, 40% F, 15% P, hypoenergetic HPD: 55% Ch, 20% F, 25% P, hypoenergetic standard: 65% Ch, 20% F, 15% P, hypoenergetic	O	↓ ↓ ↓ ↓	↓ ↓ ↓↓ ↓	↑ ↑ ↑↑ NS	LDL-C NS HDL-C ↑
Foster et al. [67] ^a	307	2 years	VLChD: 20 g/day Ch standard: 55% Ch, 30% F, 15% P, hypoenergetic	O	↓ ↓	? ?	? ?	adverse symptoms (bad breath, hair loss, constipation, dry mouth), HDL-C ↑ BP, TAG, VLDL-C ↓
Stern et al. [71] ^a	132	1 year	VLChD: <30 g/day Ch, isoenergetic standard: <30% F, hypoenergetic	D	↓ ↓↓	NS NS	NS NS	LDL-C NS TAG ↓ BUN, HDL-C ↑
Brinkworth et al. [117]	118	1 year	VLChD: 4% Ch, 61% F, 35% P LChD: 46% Ch, 30% F, 24% P LChHPD: 40% Ch, 30% F, 30% P standard: 55% Ch, hypoenergetic HFD: 35% F, hypoenergetic standard: 30% F, hypoenergetic	O	NS NS ↓ ↓ ↓↓ ↓	NS NS ? ↓ ↓↓ ↓	NS NS ↑ ↑ ↑↑ ↑	CRP, BP, FRS NS 3HB, LDL-C, Apo B, HDL-C ↑ TAG ↓

The degree of change in parameters increases as the number of arrows is augmented. The number of arrows that note change in body weight, blood glucose and insulin sensitivity indicate a qualitative effectiveness of the various diets used in each study in terms of significantly increasing or decreasing such parameters. The numbers of arrows do not show any quantitative correspondence among results from different studies and only describe whether results were similar or different for every diet used in each study. Same degree changes between groups result from energy restriction and not from dietary carbohydrate concentration. Ch = Carbohydrate; D = diabetic; H = healthy; NS = no statistical difference; TAG = triglyceride;

BUN = blood urea nitrogen; F = fat; P = protein; O = obese; CRP = C-reactive protein; BP = blood pressure; FRS = Framingham Risk Score; TC = total cholesterol; FFA = free fatty acid; HbA_{1c} = glycated hemoglobin; HOMA = homeostatic model assessment; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TC:HDL-C = ratio of total cholesterol to high-density lipoprotein cholesterol.

^a Only these studies administrated different dietary energy contents among groups. In the rest of the studies, the experimental diets were iso-energetically adjusted between groups.

Finally, despite encouragement to explore the long-term consequences of LChD, few studies have described these effects. Controversy still exists regarding safety in terms of cardiovascular risks in humans consuming LChD for a period of 12 months or longer. Professional recommendation of long-term use of LChD is obstructed by the lack of information needed to ensure homeostasis.

The Position of International Organizations

Numerous organizations, including the American Dietetic Association and the American Heart Association, have cautioned against the use of LChD [168, 169]. To lose weight, the American Diabetes Association recommends an LCh or a low-fat energy-restricted diet only for 1 year. In fact, the same organization encourages diabetic patients following an LChD to monitor their lipid profile, renal function, and protein intake (in those with nephropathy) [170].

This is maybe due to the fact that LChD may result in: abnormal metabolism of insulin; salt and water depletion

that may cause postural hypotension, fatigue, constipation, and nephrolithiasis; excessive consumption of animal proteins and fats that may promote hyperlipidemia, and higher dietary protein loads that may impair renal and bone function [31, 171]. Other organizations such as the UK Food Standards Agency, the Canadian Heart and Stroke Foundation, and the US Department of Health and Human Services do not recommend LChD because of the tendency to limit starch and increase saturated and trans fatty acid consumption and because these diets are not a healthy way to lose weight in the long term [172–174]. In Mexico, official guidelines establish that diets that promote rapid weight loss, that risk patients' lives, and that do not have scientific support should not be prescribed [175, 176]. These guidelines also specify that the carbohydrate distribution should be 50–60% of the total energy in subjects with type 2 diabetes. The 50–60% of carbohydrates from the total energy value should focus on complex carbohydrates, sugar should not represent more than 10%, and 35 g of soluble fiber should be included [177].

Conclusions

LChD have become very popular and are currently used to achieve weight loss, to improve metabolic parameters, and to treat and prevent various pathologies. These regimens, which are not individualized plans, are found on the Internet and in books and common media and are often used without medical advice or follow-up. Of course, dietitians could choose these types of diets for certain patients in order to ameliorate a disease or to investigate its effects. As explained before, changes associated with LChD or VLChD consumption are related to the transition from glucocentric to lipocentric metabolism with consequences such as an increased serum NEFA concentration, ketosis, and augmented gluconeolysis and gluconeogenic routes. These changes account for the weight loss seen during the first 6 months following an LChD, although weight loss is similar after 1 year of consuming an LFD or an LChD.

It is true that glycemic control, or serum data regarding insulin, glucose, or HgA1c in diabetics could be improved by a short-term VLChD, although increased insulin sensitivity is not warranted. These beneficial effects suggest that carbohydrate restriction only in short periods could be utilized by obese and diabetic adult patients with no gastrointestinal, bone, renal, cardiovascular, or acid/base alterations, with monitoring of kidney and liver function by health professionals. Of course, patients should be aware and understand the probable adverse effects of consuming these diets. Other possible positive consequences of LChD in humans should be more extensively investigated in short- and long-term trials. In animal models LChD have demonstrated no health advantages; insulin action, triglyceride accumulation, and vascular regeneration of rodents fed a VLChD are worsened in the hippocampus, liver, and vessels, respectively. As explained, LChD could have negative effects not necessarily consistent with serum biochemical indicators. Thus, human studies showing improvements in circulating factors could mask tissue or organ damage, and investigation gaps in this respect should be filled.

If the health benefits of an LChD are only clear in the short term, prescribing this diet for only a couple of months and later changing food habits seems difficult and confounding. Is it not recommended to change the types of nutrients and not their daily concentration or distribution? Nutrition education should promote low-glycemic index food, fiber, plant-derived protein, and lipid intakes and should limit refined sugar, syrup, saturated fat, and high sodium intake. The long-term efficacy may

depend on the education and frequency of follow-up more than on the dietary composition per se. Slow, steady weight loss should be pursued leading to maintenance of a healthy body weight in the long term.

Also, LChD are associated with a decreased consumption of fruits. Sometimes this reduction is so marked that the diet should be complemented with multivitamins. Dietitians know that a healthy diet should be sufficient and complete, in which case multivitamin intake denies that LChD qualify as healthy ones. Also, multivitamin intake makes these diets more expensive. Some groups argue that in ancient times humans consumed less carbohydrates, although a VLChD was never our original diet as suggested. Modifications in the glycemic load and fiber content have maybe had a more important impact than carbohydrate distribution. For instance, the effects of LChD on insulin sensitivity depend mainly on what is used to replace the dietary carbohydrate, and the nature of the subjects studied [178]. Interestingly, ketogenic diets have different effects over insulin sensitivity depending on the fat source. A polyunsaturated fatty acid-enriched diet versus a saturated fatty acid-enriched diet (both ketogenic) rescues insulin sensitivity and decreases LDL-C [179].

The American Diabetes Association recommends an energy-restricted diet (either an LFD or an LChD), which reveals the importance of total energy over nutrient distribution. Other organizations do not even agree to reduce the carbohydrate consumption below 45% of the total energy value to maintain the brain and central nervous system glucose requirements [180]. Besides, alarming long-term results have suggested augmented mortality in subjects consuming a carbohydrate-restricted diet.

Finally, the use of LChD, especially VLChD, should be discussed by professionals and a consensus should be reached regarding whether to use these diets in obese or diabetic patients or patients with other complications, for how long, the extent of carbohydrate restriction, and whether patients should always be supervised by the medical group. Low-carbohydrate diets: definitely a matter of love or hate.

Disclosure Statement

None of the authors has any conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

- World Health Organization: Preventing chronic diseases: a vital investment. WHO global report. 2005. http://www.who.int/chp/chronic_disease_report/contents/en/index.html.
- World Health Organization: Diet, nutrition and the prevention of chronic diseases. Joint WHO/FAO expert consultation. WHO Technical Report Series 916. Geneva, WHO, 2003.
- Nordmann AJ, Nordmann A, Briel M, et al: Effects of low-carbohydrate vs. low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:285–293.
- Gardner CD, Kiazand A, Alhassan S, et al: Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study – a randomized trial. *JAMA* 2007;297:969–977.
- Dansinger ML, Gleason JA, 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;293:43–54.
- Bravata DM, Sanders L, Huang J, et al: Efficacy and safety of low-carbohydrate diets: a systematic review. *JAMA* 2003;289:1837–1850.
- Eaton SB, Eaton SB 3rd: Paleolithic vs. modern diets-selected pathophysiological implications. *Eur J Nutr* 2000;39:67–70.
- Cordain L, Eaton SB, Sebastian A, et al: Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 2005;81:341–354.
- Cordain L, Eaton SB, Miller JB, et al: The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. *Eur J Clin Nutr* 2002;56(suppl):42–52.
- Cordain L, Miller JB, Eaton SB, et al: Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am J Clin Nutr* 2000;71:682–692.
- Mercader J: Mozambican grass seed consumption during the Middle Stone Age. *Science* 2009;326:1680–1683.
- Kendall CW, Jenkins DJ: A dietary portfolio: maximal reduction of low-density lipoprotein cholesterol with diet. *Curr Atheroscler Rep* 2004;6:492–498.
- Keys A: Mediterranean diet and public health: personal reflections. *Am J Clin Nutr* 1995;61:S321–S323.
- Jenkins DJ, Kendall CW, Popovich DG, et al: Effect of a very-high-fiber vegetable, fruit, and nut diet on serum lipids and colonic function. *Metabolism* 2001;50:494–503.
- Trowell H, Painter N, Burkitt D: Aspects of the epidemiology of diverticular disease and ischemic heart disease. *Am J Dig Dis* 1974;19:864–873.
- Stock AL, Yudkin J: Nutrient intake of subject of low carbohydrate diet used in treatment of obesity. *Am J Clin Nutr* 1970;23:948–952.
- Adam-Perrot A, Clifton P, Brouns F: Low-carbohydrate diets: nutritional and physiological aspects. *Obes Rev* 2006;7:49–58.
- Kerksick CM, Wismann-Bunn J, Fogt D, et al: Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutr J* 2010;22:9–59.
- Crowe TC: Safety of low-carbohydrate diets. *Obes Rev* 2005;6:235–245.
- Mahan LK, Escott-Stump S: Guidelines for dietary planning; in Mahan KL, Escott-Stump S: *Krause's Food and Nutrition Therapy*, ed 12. Barcelona, Elsevier, 2009.
- Westman EC, Feinman RD, Mavropoulos JC, et al: Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr* 2007;86:276–284.
- Johnston CS, Tjonn SL, Swan PD, et al: Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. *Am J Clin Nutr* 2006;83:1055–1061.
- Sumithran P, Proietto J: Ketogenic diets for weight loss: a review of their principles, safety and efficacy. *Obes Res Clin Pract* 2008;2:1–13.
- Lehninger AL, Nelson DL, Cox MM: *Bioenergetics and metabolism*; in Lehninger AL, Nelson DL, Cox MM: *Principles of Biochemistry*, ed 3. New York, Worth, 2005.
- DeVivo DC, Leckie MP, Ferrendelli JS, et al: Chronic ketosis and cerebral metabolism. *Ann Neurol* 1978;3:331–337.
- Ben-Avraham S, Harman-Boehm I, Schwarzfuchs D, et al: Dietary strategies for patients with type 2 diabetes in the era of multi-approaches: review and results from the Dietary Intervention Randomized Controlled Trial (DIRECT). *Diabetes Res Clin Pract* 2009;86 (suppl 1):S41–S48.
- Hession M, Rolland C, Kulkarni U, et al: 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.
- Best TH, Franz DN, Gilbert DL, et al: Cardiac complications in pediatric patients on the ketogenic diet. *Neurology* 2000;54:2328–2330.
- De Koning L, Fung TT, Liao X, et al: Low-carbohydrate diet scores and risk of type 2 diabetes in men. *Am J Clin Nutr* 2011;93:844–850.
- Husain AM, Yancy WS Jr, Carwile ST, et al: Diet therapy for narcolepsy. *Neurology* 2004;62:2300–2302.
- Erlanson-Albertsson C, Mei J: The effect of low carbohydrate on energy metabolism. *Int J Obes* 2005;2:26–30.
- Acheson KJ, Blondel-Lubrano A, Oguey-Araymon S, et al: Protein choices targeting thermogenesis and metabolism. *Am J Clin Nutr* 2011;93:525–534.
- Kather H, Wieland E, Scheurer A, et al: Influences of variation in total energy intake and dietary composition on regulation of fat cell lipolysis in ideal-weight subjects. *J Clin Invest* 1987;80:566–572.
- Halyburton AK, Brinkworth GD, Wilson CJ, et al: Low-and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr* 2007;86:580–587.
- Veldhorst MA, Westerterp KR, van Vught AJ, et al: Presence or absence of carbohydrates and the proportion of fat in a high/protein diet affect appetite suppression but not energy expenditure in normal/weight human subjects fed in energy balance. *Br J Nutr* 2010;104:1395–1405.
- Buse JB, Polonsky KS, Burant CF: Type 2 Diabetes Mellitus; in Larsen PR, Kronenberg HM, Melmed S, et al (eds): *Williams Textbook of Endocrinology*, ed 10. Philadelphia, Saunders, 2003.
- Jenkins DJ, Wolever TM, Taylor RH, et al: Glycemic index foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 1981;34:362–366.
- Brand-Miller J, Hayne S, Petocz P, et al: Low-glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care* 2003;26:2261–2267.
- Gannon MC, Nuttall FQ: Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. *Diabetes* 2004;53:2375–2382.
- Garg A, Bantle JP, Henry RR, et al: Effects of varying carbohydrate content of diet in patients with non-insulin dependent diabetes mellitus. *JAMA* 1994;271:1421–1428.
- Coulston AM, Hollenbeck CB, Swislocki AL, et al: Persistence of hypertriglyceridemic effect of low-fat high-carbohydrate diets in NIDDM patients. *Diabetes Care* 1989;12:94–101.
- Garg A, Bonanome A, Grundy SM, et al: Comparison of a high-carbohydrate diet with a high-monounsaturated fat diet in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1988;319:829–834.
- Halton TL, Willett WC, Liu S, et al: Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med* 2006;355:1991–2002.
- Jebb SA, Lovegrove JA, Griffin BA: Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISK (Reading, Imperial, Surrey, Cambridge, and Kings) trial. *Am J Clin Nutr* 2010;92:748–758.
- Wolever TM, Gibbs AL, Mehling C, et al: The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr* 2008;87:114–125.
- Shai I, Schwarzfuchs D, Henkin Y, et al: Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241.
- Uttenlocher PR: Ketonemia and seizures: metabolic and anti-convulsant effects of two ketogenic diets in childhood epilepsy. *Pediatr Res* 1976;10:536–540.

- 48 Kossoff EH: The ketogenic diet: it's about 'time'. *Dev Med Child Neurol* 2009;51:252–253.
- 49 Joshi CN, Greenberg CR, Mhanni AA, Salman MS: Ketogenic diet in Alpers-Huttenlocher syndrome. *Pediatr Neurol* 2009;40:314–316.
- 50 Vining EP: Long-term health consequences of epilepsy diet treatments. *Epilepsia* 2008;49:27–29.
- 51 Ríos VG: Complications of treatment of epilepsy by a ketogenic diet. *Rev Neurol* 2001;33:909–915.
- 52 Kraft BD, Westman EC: Schizophrenia, gluten, and low-carbohydrate, ketogenic diets: a case report and review of the literature. *Nutr Metab (Lond)* 2009;6:10–13.
- 53 Dashti HM, Mathew TC, Khadada M, et al: Beneficial effects of ketogenic diet in obese diabetic subjects. *Mol Cell Biochem* 2007;302:249–256.
- 54 Gill HK, Wu GY: Non-alcoholic fatty liver disease and the metabolic syndrome: effects of weight loss and a review of popular diets – are low carbohydrate diets the answer? *World J Gastroenterol* 2006;12:345–353.
- 55 York LW, Puthalapattu S, Wu GY: Nonalcoholic fatty liver disease and low-carbohydrate diets. *Annu Rev Nutr* 2009;29:365–379.
- 56 Wanless IR, Lentz JS: Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology* 1990;12:1106–1110.
- 57 Tendler D, Lin S, Yancy WS Jr, et al: The effect of a low-carbohydrate ketogenic diet on non alcoholic fatty liver disease: a pilot study. *Dig Dis Sci* 2007;52:589–593.
- 58 Haufe S, Engeli S, Kast P, et al: Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology* 2011;53:1504–1514.
- 59 Solga FS, Alkhuraishe KC, Cope K, et al: Breath biomarkers and non-alcoholic fatty liver disease: preliminary observations. *Biomarkers* 2006;11:174–183.
- 60 Douglas CC, Gower BA, Darnell BE, et al: Role of diet in the treatment of polycystic ovary syndrome. *Fertil Steril* 2006;85:679–688.
- 61 O'Neil DF, Westman EC, Bernstein RK: The effects of a low-carbohydrate regimen on glycemic control and serum lipids in diabetes mellitus. *Metab Syndr Relat Disord* 2003;1:291–298.
- 62 Lim SS, Clifton PM, Noakes M, et al: Obesity management in women with polycystic ovary syndrome. *Womens Health (Lond Engl)* 2007;3:72–86.
- 63 Austin GL, Thiny MT, Westman EC, et al: A very low-carbohydrate diet improves gastroesophageal reflux and its symptoms. *Dig Dis Sci* 2006;51:1307–1312.
- 64 Mavropoulos JC, Yancy WS, Hepburn J, et al: The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab (Lond)* 2005;2:35.
- 65 Yancy WS Jr, Provenza D, Westman EC: Improvement of gastroesophageal reflux disease after initiation of a low-carbohydrate diet: five brief case reports. *Altern Ther Health Med* 2001;7:116–119.
- 66 Sacks FM, Bray GA, Carey VJ, et al: Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859–873.
- 67 Foster GD, Wyatt HR, Hill JO, et al: Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010;153:147–157.
- 68 Yancy WS Jr, Olsen MK, Guyton JR, et al: A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 2004;140:769–777.
- 69 Foster GD, Wyatt HR, Hill JO, et al: A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348:2082–2090.
- 70 Samaha FF, Iqbal N, Seshadri P, et al: A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003;348:2074–2081.
- 71 Stern L, Iqbal N, Seshadri P, et al: The effects of a low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004;140:778–785.
- 72 Haimoto H, Sasakabe T, Wakai K, et al: Effects of a low-carbohydrate diet on glycemic control in outpatients with severe type 2 diabetes. *Nutr Metab (Lond)* 2009;6:6–21.
- 73 Davis NJ, Tomuta N, Schechter C, et al: Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes Care* 2009;32:1147–1152.
- 74 Ma Y, Olendzki BC, Hafner AR, et al: Low-carbohydrate and high-fat intake among adult patients with poorly controlled type 2 diabetes mellitus. *Nutrition* 2006;22:1129–1136.
- 75 Nielsen JV, Joensson EA: Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutr Metab (Lond)* 2008;5:14.
- 76 de Luis DA, Aller R, Izaola O, Gonzalez Sagrado M, et al: Effect of two different hypocaloric diets in transaminases and insulin resistance in nonalcoholic fatty liver disease and obese patients. *Nutr Hosp* 2010;25:730–735.
- 77 Schwarz JM, Linfoot P, Dare D, et al: Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenenergetic diets. *Am J Clin Nutr* 2003;77:43–50.
- 78 Browning JD, Bajer JA, Rogers T, et al: Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr* 2011;93:1048–1052.
- 79 Moran LJ, Noakes M, Clifton PM, et al: Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:812–819.
- 80 Neal EG, Chaffe H, Schwartz RH, et al: The ketogenic diet for the treatment of childhood epilepsy: a randomized controlled trial. *Lancet Neurol* 2008;7:500–506.
- 81 Groesbeck DK, Bluml RM, Kossoff EH: Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol* 2006;48:978–981.
- 82 Bentourkia M, Tremblay S, Pifferi F, et al: PET study of 11C-acetoacetate kinetics in rat brain during dietary treatments affecting ketosis. *Am J Physiol Endocrinol Metab* 2009;296:E796–E801.
- 83 Amiel SA, Archibald HR, Chusney G, et al: Ketone infusion lowers hormonal responses to hypoglycemia: evidence for acute cerebral utilization of a non-glucose fuel. *Clin Sci (Lond)* 1991;81:189–194.
- 84 Veech RL: The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins Leukot Essent Fatty Acids* 2004;70:309–319.
- 85 Malewiak MI, Griglio S, Le Liepvre X: Relationship between lipogenesis, ketogenesis, and malonyl-CoA content in isolated hepatocytes from the obese Zucker rat adapted to a high-fat diet. *Metabolism* 1985;34:604–611.
- 86 Chearskul S, Delbridge E, Shulkes A: Effect of weight loss and ketosis on postprandial cholecystokinin and free fatty acid concentrations. *Am J Clin Nutr* 2008;87:1238–1246.
- 87 Dreschfeld J: The Bradshaw Lecture on diabetic coma. *Br Med J* 1886;2:358–363.
- 88 Barrena HC, Gazola VA, Furlan MM, et al: Ketogenesis evaluation in perfused liver of diabetic rats submitted to short-term insulin-induced hypoglycemia. *Cell Biochem Funct* 2009;26:383–387.
- 89 Pelletier A, Tardif A, Gingras MH, et al: Chronic exposure to ketone bodies impairs glucose uptake in adult cardiomyocytes in response to insulin but not vanadate: the role of PI3-K. *Mol Cell Biochem* 2007;296:97–108.
- 90 Yokoo H, Saitoh T, Shiraishi S, et al: Distinct effects of ketone bodies on down-regulation of cell surface insulin receptor and insulin receptor substrate-1 phosphorylation in adrenal chromaffin cells. *J Pharmacol Exp Ther* 2003;304:994–1002.
- 91 Binimelis J, Webb SM, Serrano J, et al: Plasma immunoreactive somatostatin is elevated in diabetic ketoacidosis and correlates with plasma non-esterified fatty acid concentration. *Diabet Med* 1987;4:221–224.
- 92 Beylot M: Regulation of in vivo ketogenesis: role of free fatty acids and control by epinephrine, thyroid hormones, insulin and glucagon. *Diabetes Metab* 1996;22:299–304.
- 93 Finn PF, Dice JF: Proteolytic and lipolytic responses to starvation. *Nutrition* 2006;22:830–844.
- 94 Bisschop PH, Pereira Arias AM, Ackermans MT, et al: The effects of carbohydrate variation in isocaloric diets on glycogenolysis and gluconeogenesis in healthy men. *J Clin Endocrinol Metab* 2000;85:1963–1967.

- 95 Boden G: Gluconeogenesis and glycogenolysis in health and diabetes. *J Investig Med* 2004;52:375–378.
- 96 Haque M, Sanyal AJ: The metabolic abnormalities associated with non-alcoholic fatty liver disease. *Best Pract Res Clin Gastroenterol* 2002;16:709–731.
- 97 Delarue J, Magnan C: Free fatty acids and insulin resistance. *Curr Opin Clin Nutr Metab Care* 2007;10:142–148.
- 98 Curtis JM, Grimsrud PA, Wright WS, et al: Downregulation of adipose glutathione S-transferase A4 leads to increased protein carbonylation, oxidative stress, and mitochondrial dysfunction. *Diabetes* 2010;59:1132–1142.
- 99 Tretter L, Adam-Vizi V: Alpha-ketoglutarate dehydrogenase: a target and generator of oxidative stress. *Philos Trans R Soc Lond B Biol Sci* 2005;360:2335–2345.
- 100 Vigouroux C, Caron-Debarle M, Le Dor C, et al: Molecular mechanisms of human lipodystrophies: from adipocyte lipid droplet to oxidative stress and lipotoxicity. *Int J Biochem Cell Biol* 2011;43:862–876.
- 101 Chinen I, Shimabukuro M, Yamakawa K, et al: Vascular lipotoxicity: endothelial dysfunction via fatty-acid-induced reactive oxygen species overproduction in obese Zucker diabetic fatty rats. *Endocrinology* 2007;148:160–165.
- 102 Lin Y, Berg AH, Iyengar P, et al: The hyperglycemia-induced inflammatory response in adipocytes: the role of reactive oxygen species. *J Biol Chem* 2005;280:4617–4626.
- 103 Srinivasan S, Hatley ME, Bolick DT, et al: Hyperglycaemia-induced superoxide production decrease eNOS expression via AP-1 activation in aortic endothelial cells. *Diabetologia* 2004;47:1727–1734.
- 104 Sakai K, Matsumoto K, Nishikawa T, et al: Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells. *Biochem Biophys Commun* 2003;300:216–222.
- 105 Ceriello A, Bortolotti N, Motz E, et al: Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia. *Metabolism* 1999;48:1503–1508.
- 106 Brehm BJ, Spang SE, Lattin BL, et al: The role of energy expenditure in the differential weight loss in obese women on low-fat and low-carbohydrate diets. *J Clin Endocrinol Metab* 2005;90:1475–1482.
- 107 Brehm BJ, Seeley RJ, Daniels SR, et al: A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab* 2003;88:1617–1623.
- 108 Shils ME: *Modern Nutrition in Health and Disease*, ed 9. Baltimore, Williams & Wilkins, 1999.
- 109 Al-Khalifa A, Mathew TC, Al-Zaid NS, et al: Therapeutic role of low-carbohydrate ketogenic diet in diabetes. *Nutrition* 2009;25:1177–1185.
- 110 Karabatas LM, Lombardo YB, Basabe JC, et al: High-protein diet: effect on insulin secretion patterns from streptozotocin-diabetic rats and mice. *Acta Physiol Pharmacol Ther Latinoam* 1992;42:239–254.
- 111 Dyson PA: A review of low and reduced carbohydrate diets and weight loss in type 2 diabetes. *J Hum Nutr Diet* 2008;21:530–538.
- 112 Volek JS, Sharman MJ, Gómez AL, et al: Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J Am Coll Nutr* 2004;23:177–184.
- 113 Noble CA, Kushner RF: An update on low-carbohydrate, high-protein diets. *Curr Opin Gastroenterol* 2006;22:153–159.
- 114 Foo SY, Heller ER, Wykrzykowska J, et al: Vascular effects of a low-carbohydrate high-protein diet. *Proc Natl Acad Sci USA* 2009;106:15418–15423.
- 115 Bradley U, Spence M, Courtney CH, et al: Low-fat versus low-carbohydrate weight reduction diets: effects on weight loss, insulin resistance, and cardiovascular risk – a randomized control trial. *Diabetes* 2009;58:2741–2748.
- 116 Johnston CS, Tjinn SL, Swann PD, et al: Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. *Am J Clin Nutr* 2006;83:1055–1061.
- 117 Brinkworth GD, Noakes M, Clifton PM, et al: 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;101:1493–1502.
- 118 Russell WR, Gratz SW, Duncan SH, et al: High-protein, reduced-carbohydrate weight-loss diets promotes metabolite profiles likely to be detrimental to colonic health. *Am J Clin Nutr* 2011;93:1062–1072.
- 119 Kaneko T, Wang PY, Wang Y, et al: The long-term effect of low-carbohydrate/high-fat diet on the development of diabetes mellitus in spontaneously diabetic rats. *Diabetes Metab* 2000;26:459–464.
- 120 Birkner E, Kasperczyk S, Kasperczyk A, et al: Metabolic and antioxidative changes in liver steatosis induced by high-fat, low-carbohydrate diet in rabbits. *J Physiol Pharmacol* 2005;56:45–58.
- 121 Cardillo S, Seshadri P, Iqbal N: The effects of a low-carbohydrate versus low-fat diet on adipocytokines in severely obese adults: three-year follow-up of a randomized trial. *Eur Rev Med Pharmacol Sci* 2006;10:99–106.
- 122 Haimoto H, Iwata M, Wakai K, et al: Long-term effects of a diet loosely restricting carbohydrates on HbA1c levels, BMI and tapering of sulfonylureas in type 2 diabetes: a 2-year follow-up study. *Diabetes Res Clin Pract* 2008;79:350–356.
- 123 Boiling CL, Westman EC, Yancy WS Jr: Carbohydrate-restricted diets for obesity and related diseases: an update. *Curr Atheroscler Rep* 2009;11:462–469.
- 124 Larsen RN, Mann NJ, Maclean E, et al: The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomized controlled trial. *Diabetologia* 2011;54:731–740.
- 125 Brinkworth GD, Noakes M, Buckley JD, et al: Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 months. *Am J Clin Nutr* 2009;90:23–32.
- 126 Garg A, Grundy SM, Unger RH: Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. *Diabetes* 1992;41:1278–1285.
- 127 Backes AC, Abbasi F, Lamendola C, et al: Clinical experience with a relatively low carbohydrate, calorie-restricted diet improves insulin sensitivity and associated metabolic abnormalities in overweight, insulin resistant South Asian Indian women. *Asia Pac J Clin Nutr* 2008;17:669–671.
- 128 Boden G, Sargrad K, Homko C, et al: Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med* 2005;142:403–411.
- 129 Miyashita Y, Koide N, Othusuka M, et al: Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. *Diabetes Res Clin Pract* 2004;65:235–241.
- 130 Chen M, Bergman RN, Porte D Jr: Insulin resistance and beta-cell dysfunction in aging: the importance of dietary carbohydrate. *J Clin Endocrinol Metab* 1988;67:951–957.
- 131 McLaughlin T, Carter S, Lamendola C, et al: Effects of dietary macronutrient intake on insulin sensitivity and secretion and glucose and lipid metabolism in healthy, obese adolescents. *J Clin Endocrinol Metab* 2005;90:4496–4502.
- 132 Allick G, Bisschop PH, Ackermans MT, et al: Beneficial effect of low carbohydrate in low calorie diets on visceral fat reduction in type 2 diabetic patients with obesity. *Diabetes Res Clin Pract* 2004;65:235–241.
- 133 Anderson JW: Effect of carbohydrate restriction and high carbohydrates diets on men with chemical diabetes. *Am J Clin Nutr* 1977;30:402–408.
- 134 Gannon MC, Hoover H, Nuttal FQ: Further decrease in glycated hemoglobin following ingestion of a LoBAG30 diet for 10 weeks compared to 5 weeks in people with untreated type 2 diabetes. *Nutr Metab (Lond)* 2010;7:64–81.
- 135 Kirk E, Reeds DN, Finck BN, et al: Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology* 2009;136:1552–1560.
- 136 Muzio F, Mondazzi L, Harris W, et al: Effects of moderate variations in the macronutrient content of the diet on cardiovascular disease risk factors in obese patients with the metabolic syndrome. *Am J Clin Nutr* 2007;86:946–951.
- 137 Samaha FF, Iqbal N, Seshadri P, et al: A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003;348:2074–2081.

- 138 Suneag AL, Toffolo G, Treuth MS, et al: Effects of dietary macronutrient content on glucose metabolism in children. *J Clin Endocrinol Metab* 2002;87:5168–5178.
- 139 Suneag AL, Toffolo G, Campioni M, et al: Effects of dietary macronutrient intake on insulin sensitivity and secretion and glucose and lipid metabolism in healthy, obese adolescents. *J Clin Endocrinol Metab* 2005;90:4496–4502.
- 140 Yancy WS Jr, Foy M, Chalecki AM, et al: A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab (Lond)* 2005;2:34.
- 141 Westman EC, Yancy WS Jr, Mavropoulos JC, et al: The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab (Lond)* 2008;5:36.
- 142 Brinkworth GD, Buckley JD, Noakes M, et al: Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Arch Intern Med* 2009;169:1873–1880.
- 143 Halyburton AK, Brinkworth GD, Wilson CJ, et al: Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr* 2007;86:580–587.
- 144 Fernstrom HM, Fernstrom JD: Brain tryptophan concentrations and serotonin synthesis remain responsive to food consumption after the ingestion of sequential meals. *Am J Clin Nutr* 1995;61:312–319.
- 145 Fernstrom JD: Tryptophan, serotonin and carbohydrate appetite: will the real carbohydrate craver please stand up! *J Nutr* 1998;118:1417–1419.
- 146 Leathwood PD: Tryptophan availability and serotonin synthesis. *Proc Nutr Soc* 1987;46:143–156.
- 147 Ince BA, Anderson EJ, Neer RM: Lowering dietary protein to US recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. *J Clin Endocrinol Metab* 2004;89:3801–3807.
- 148 Butki BD, Baumstark J, Driver S: Effects of a carbohydrate-restricted diet on affective responses to acute exercise among physically active participants. *Percept Mot Skills* 2003;96:607–615.
- 149 Keith RE, O'Keeffe KA, Blessing DL, Wilson GD: Alterations in dietary carbohydrate, protein, and fat intake and mood state in trained female cyclists. *Med Sci Sports Exerc* 1991;23:212–216.
- 150 Evans WJ, Hughes VA: Dietary carbohydrates and endurance exercise. *Am J Clin Nutr* 1985;41:1146–1154.
- 151 Gardner CD, Kim S, Bersamin A, Dopler-Nelson M, et al: Micronutrient quality of weight-loss diets that focus on macronutrients: results from the A TO Z study. *Am J Clin Nutr* 2010;92:304–312.
- 152 Bourges H, Casanueva E, Rosado J: Recomendaciones de Ingestión de Nutrientes para la Población Mexicana: Base Fisiológica, ed 1. Mexico City, Editorial Panamericana, 2009, vol 1.
- 153 Kerstetter JE, Allen LH: Dietary protein increases urinary calcium. *J Nutr* 1989;20:134–136.
- 154 Crowe TC: Safety of low-carbohydrate diets. *Obes Rev* 2005;6:235–245.
- 155 Green J, Kleeman CR: Role of bone in regulation of systemic acid-base balance. *Kidney Int* 1991;39:9–26.
- 156 Wurtman RJ: Nutrients that modify brain function. *Sci Am* 2000;246:50–59.
- 157 Chen YM, Ho SC, Woo JL: Greater fruit and vegetable intake is associated with increased bone mass among postmenopausal Chinese women. *Br J Nutr* 2006;96:745–751.
- 158 New SA, Robins SP, Campbell MK, et al: Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? *Am J Clin Nutr* 2000;71:142–151.
- 159 New SA, Bolton-Smith C, Grubb DA, et al: Nutritional influences on bone mineral density: a cross-sectional study in premenopausal women. *Am J Clin Nutr* 1997;65:1831–1839.
- 160 Kang MH, Kim MH, Bae YJ, et al: Vegetable and fruit intake and its relevance with serum osteocalcin and urinary deoxypyridinoline in Korean adults. *Nutr Res Pract* 2010;4:421–427.
- 161 Stein K: High-protein, low-carbohydrate diets: do they work? *J Am Diet Assoc* 2000;100:760–761.
- 162 Wycherley TP, Brinkworth GD, Keogh JB, et al: 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* 2009;267:452–461.
- 163 Grieb P, Kłapcińska B, Smol E, et al: Long-term consumption of a carbohydrate-restricted diet does not induce deleterious metabolic effects. *Nutr Res* 2008;28:825–833.
- 164 Clifton PM, Keogh J: Metabolic effects of high-protein diets. *Curr Atheroscler Rep* 2007;9:472–478.
- 165 Anderson JW, Konz EC, Jenkins DJ: Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J Am Coll Nutr* 2000;19:578–590.
- 166 Lagiou P, Sandin S, Weiderpass E, et al: Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J Intern Med* 2007;261:366–374.
- 167 Trichopoulou A, Psaltopoulou T, Orfanos P, et al: Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur J Clin Nutr* 2007;61:575–581.
- 168 American Heart Association: High-protein diets: AHA recommendation. 2003. http://www.heart.org/HEARTORG/Getting-Healthy/NutritionCenter/High-Protein-Diets_UCM_305989_Article.jsp.
- 169 American Dietetic Association: Position of the American Dietetic Association: weight management. *J Am Diet Assoc* 2009;109:330–346.
- 170 Bantle JP, Wylie-Rosett J, Albright AL, et al: Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2008;31:61–78.
- 171 Kossoff EH, Pyzik PL, Furth SL, et al: Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. *Epilepsia* 2002;43:1168–1171.
- 172 Food Standards Agency: Starchy food. 2009. <http://www.eatwell.gov.uk/healthy-diet/nutritionessentials/starchfoods/>.
- 173 Heart and Stroke Foundation of Canada: Position statement: low carbohydrate diets and heart disease and stroke. 2004. [http://www.heartandstroke.com/atf/cf/%7B99452D8B-E7F1-4BD6-A57D-B136CE6C95BF%7D/LowCarbDiets_PS\(04\)-English.pdf](http://www.heartandstroke.com/atf/cf/%7B99452D8B-E7F1-4BD6-A57D-B136CE6C95BF%7D/LowCarbDiets_PS(04)-English.pdf).
- 174 US Department of Health and Human Services: Your guide to a healthy heart. 2005. http://www.nhlbi.nih.gov/health/public/heart/other/your_guide/healthyheart.pdf.
- 175 Secretaría de Salud: México sano. 2008. http://portal.salud.gob.mx/descargas/pdf/period_mexsano/mexicosano_dic08.pdf.
- 176 Secretaría de Salud: Norma Oficial Mexicana NOM-174-SSA1-1998, para el manejo integral de la obesidad. 1998. <http://www.salud.gob.mx/unidades/cdi/nom/174ssa18.html>.
- 177 Secretaría de Salud: Norma Oficial Mexicana NOM-015-SSA2-1994, para la prevención, tratamiento y control de la diabetes mellitus en la atención primaria. 1994. <http://www.salud.gob.mx/unidades/cdi/nom/015ssa24.html>.
- 178 Wolever TM: Dietary carbohydrates and insulin action in humans. *Br J Nutr* 2000;83(suppl 1):97–102.
- 179 Fuehrlein BS, Rutenberg MS, Silver JN, et al: Differential metabolic effects of saturated versus polyunsaturated fats in ketogenic diets. *J Clin Endocrinol Metab* 2004;89:1641–1645.
- 180 Sheard NF, Clark NG, Brand-Miller JC, et al: Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. *Diabetes Care* 2004;27:2266–2271.