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Arguments In Favor Of Ketogenic Diets

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Abstract

Many negative comments have been made about the use of ketogenic diets (KDs) and experts today believe that the best way to lose weight is by cutting back on calories, chiefly in the form of fat. The international consensus is that carbohydrates are the basis of the food pyramid for a healthy diet. However, this review will clarify that low-carbohydrate diets are, from a practical and physiological point of view, a much more effective way of losing weight. It is also argued that such diets provide metabolic advantages, for example: they help to preserve muscle mass, reduce appetite, diminish metabolic efficiency, induce metabolic activation of thermogenesis and favor increased fat loss and even a greater reduction in calories. These diets are also healthier because they promote a non-atherogenic lipid profile, lower blood pressure and decrease resistance to insulin with an improvement in blood levels of glucose and insulin. Low-carbohydrate diets should therefore be used to prevent and treat type II diabetes and cardiovascular problems. Such diets also have neurological and antineoplastic benefits and diet-induced ketosis is not associated with metabolic acidosis, nor do such diets alter kidney, liver or heart functions.

The Evolution Of The Human Diet

Over the course an evolutionary process spanning approximately two million years, human beings have genetically adapted to an isocaloric diet, meaning that energy from food corresponds to equal proportions of proteins, carbohydrates and lipids (30-35%). Traditionally, this was a “hunter-gatherer” diet (based on hunting meat and fish, and gathering vegetables and fruits). Around 6000 years ago, population increases prompted a change in human nomadic lifestyle patterns, which were replaced by a sedentary lifestyle and the “hunter-gatherer” diet gave way to an “agriculture-stockbreeding” diet [[1]]. For these people, the amount of carbohydrate in an average diet increased from very little, to about 30% of their dietary energy intake [[2] , [3] , [4] , [5] , [6]].

Since then, the human diet has changed drastically: protein intake has been reduced to 10-15%; glucid intake has increased to 50-60%; and mono and polyunsaturated fats (MUFA and PUFA) have been replaced by saturated and trans fats. Furthermore, carbohydrates consumed nowadays tend to have a high glycemic index because they are based on grains and refined sugars instead of vegetables and fruits. In such a short evolutionary period of time, human beings have been unable to adapt to this abrupt change in eating habits, and this has been a significant source of

stress for our insulin metabolism [1]. The impossibility of genetically adapting to the new diet, in addition to other factors such as sedentarism and exposure to environmental toxic substances, are partially responsible for chronic diseases like atherosclerosis, essential hypertension, many forms of cancer, diabetes mellitus and obesity [7]. All these factors are very important but overeating is probably a primary factor that would have to be included.

The fact that the nutritional change from a hunter-gatherer diet to a carbohydrate-based diet has affected populations negatively has been revealed by archaeological findings in ancient Egyptian mummies, since tooth decay, cardiovascular disease and obesity were very frequent in those times [8]. More recently, this problem has also been reflected historically by the change in eating habits of Inuit peoples in Alaska. Traditionally, their diet contained 3-5% carbohydrates (since it was based on fish, marine mammals, moose and caribou), obesity was virtually nonexistent and type II diabetes was rare. Since 1961, a growing tendency in type II diabetes and obesity problems has been observed due to a progressive substitution of the traditional protein and fat-based diet by a diet with higher carbohydrate content. This increase has been so dramatic that in 1978, carbohydrates represented 50% of the total calorie contribution in their diet [9]. Another historical fact worth considering when analyzing the nutritional habits of American society is their increased consumption of carbohydrates, either through eating more food in general or by replacing fats with carbohydrates. This leads to an increase in obesity and atherogenic markers such as triglycerides and VLDL [10].

Most hunter–gatherers, for example, are not obese when they live their traditional lifestyle based on a low carbohydrate diet. Many hunter-gatherers consumed a predominantly plant-based diet, which was supplemented with meat when available, and others such as the Inuits consumed a high fat-protein diet. When such people are exposed to high, refined carbohydrate intake, however, they develop truncal obesity and a much higher risk of diabetes, up to 50% in some populations. This high waist-hip ratio and carbohydrate intolerance is shared by all hunter–gatherer populations throughout the world: Canadian Inuits, Native Americans, Mexican Indians, Pima Indians, South American Indians, Middle-Eastern Nomads, African Pygmies, Australian Aborigines, Maoris, South Sea Islanders, etc. [11 , 12 , 13 , 14 , 15 , 16 , 17 , 18 , 19 , 20 , 21 , 22 , 23].

Nevertheless, many factors are responsible for the health and metabolic disturbances currently experienced by modern hunter–gatherers like the Inuits. It is important to remember that millions of people worldwide from different countries have predominantly carbohydrate-based diets and the prevalence of obesity is very low in these countries. Hence other risk factor factors, such as sedentarism and high calorie intake, are clearly relevant in addition to the macronutrient composition of the diet.

Thus, all these data might suggest that it could be wrong to consider carbohydrates as the basis of the human diet.

Biochemical Rationale

When a diet is based on an excess of carbohydrates, the body uses them as the main source of energy in place of fat. In contrast, the absence of carbohydrates in the diet accelerates the use of fat. This is because insulin blocks lipolysis (by blocking adipocyte lipase) and allows glucose to enter the fat cells. This glucose is turned into triglycerides inside the fat cell through its transformation into acyl-CoA and alpha-glycerophosphate (the acyl-CoA molecules combine to make fatty acids and three of these fatty acids are bound by diglycerol acyltransferase to glycerol, originating from the alpha-glycerophosphate, to form triglycerides). Moreover, the fatty acids originating from dietary fat require the action of the glucose and insulin in order to be transformed

into triglycerides (inside the fat cells), since the insulin allows glucose to enter the fat cells and glucose is necessary for the formation of alpha-glycerophosphate, which is the main source of glycerol for the fatty acids originating from dietary fat to turn them into triglycerides [6]. The last step in the synthesis of the triglycerides is therefore the attachment of glycerol to the fatty acids, a reaction that is catalyzed by diglycerol acyltransferase (DGAT). If for some reason the last stage does not occur, this is due to a deficiency in glucose and insulin to guarantee the supply of glycerol or a failure in the DGAT; hence, it is logical to assume that there will be interruptions in the synthesis of triglycerides. It has been confirmed that mice with a homozygous deficiency of DGAT have less white fat mass and are resistant to the development of dietetic obesity [7]. Hence, low insulin levels in low-carbohydrate diets are likely produce similar effects; this could be one explanation, for the greater success in weight loss of these diets.

The fact that low-carbohydrate diets with an equal number of calories are more effective than low-fat diets [26 , 27 , 28 , 29] can only be explained by the lower metabolic efficiency of low-fat diets. This may be because, from a physiological standpoint, there is a proven link between blood ketone levels and urinary ketones [30] and because acetone is a volatile ketone, part of which is lost through breathing [24]. Thus, energy would be lost through the elimination of urine and breathing ketones. Moreover, if we consider that KDs do not induce hypoglycemia (low glucose levels) despite improvements in the glycemic profile [31 , 32 , 33 , 34], we may assume that gluconeogenesis plays a prominent role. There is a very significant loss of energy in this gluconeogenic process, since 100 grams of average quality protein are necessary to form only 57 grams of glucose [35], thus entailing an energy loss of 43%. Furthermore, during the formation of one mole of glucose from alanine, 6 moles of ATP are lost in the process [36]. This energy loss is significant because one glucose mole gives 38 of ATP [24] and a loss of 6 ATP entails an energy loss of 15.79% in the process of gluconeogenesis from alanine, an amino acid for which gluconeogenesis is metabolically easier than for other amino acids, which is why a global energy loss of around 43% is not surprising.

In addition to being less energy efficient, insulin is necessary for triglyceride formation and high-fat diets increase energy loss through metabolic activation of thermogenesis, since it has been shown that the expression of uncoupling proteins (UCP or thermogenin), which are responsible for thermogenesis, increases in high-fat diets, because monounsaturated fats [37], polyunsaturated fats [38] and saturated fats [39] are all used in their induction.

Low-carbohydrate diets also enhance body composition: body fat is reduced and muscle mass is increased [40]. The conservation of muscle mass associated with these types of diets must involve ketones because it has been shown that ketones can reduce protein catabolism in catabolic situations such as fasting [41].

Metabolic Effects

Weight loss

It should also be remembered that glucose is not the only substance to induce insulin release; this process is also stimulated by certain amino acids, such as arginine and lysine, and gastrointestinal hormones secreted with food consumption such as gastrin, secretin, cholecystokinin (CCK) and gastric inhibitory polypeptide, which are capable of producing a slight increase in insulin secretion. When amino acids are combined with glucose, however, they have a synergistic effect that can double the release of insulin that could produce the same concentration

of glucose [24].

Another important aspect to consider is gastric capacity, which has a satiating effect on the central nervous system, and in which fat and proteins present advantages over carbohydrates because they remain in the stomach for a longer period of time and are therefore capable of prolonging the sensation of satiation for longer than carbohydrates [24]. Nevertheless, high-fiber carbohydrate meals also have high satiating power [42]. The carbohydrates used in KDs should therefore be from high-fiber carbohydrate sources such as vegetables.

Release in CCK, considered to be one of the most powerful appetite suppressants, is also stimulated by the consumption of fat and proteins but not carbohydrates [43]. β-hydroxybutyrate (the major circulating ketone body) has been shown to directly inhibit appetite [44]. The low glycemic nature of a KD may also prevent transient dips in blood glucose, something which can occur with higher carbohydrate diets. Thus, avoidance of hypoglycemic episodes may reduce appetite [45]. Furthermore, protein alone has a greater anorexic effect than carbohydrates that may be mediated by increased central nervous system leptin sensitivity [46] and decreased postprandial ghrelin concentrations [47]. Leptin is produced by adipose tissue and is a circulating signal that reduces appetite. Nevertheless, obese people have unusually high circulating concentrations of leptin. These people are said to be resistant to the effects of leptin. Ghrelin is a hormone produced by cells lining the stomach that stimulate appetite.

The lower metabolic efficiency and anorexic effect of protein may contribute to weight loss. In fact protein intake is inversely associated with abdominal obesity in multi-ethnic populations [48].

Bearing in mind all these physiological concepts, a logical hypothesis might be that carbohydrates alone and in large quantities could induce obesity; when consumed together with fat, carbohydrates allow fat to build up; when consumed together with proteins, carbohydrates multiply their obesity-inducing effect; and finally, carbohydrates have a lower satiating effect than lipids and proteins. Therefore, the best combination for many people to lose weight would be a diet containing fat and proteins, as this would achieve blood levels of insulin that would allow a metabolic change to take place to combat fat accumulation and favor the use of accumulated fat. Glycolytic metabolism would therefore make way for lipolytic or oxidative metabolism. The activation of this lipolytic metabolic route triggers the appearance of ketones in the blood, which is a natural response to fasting, prolonged exercise and high fat content diets [49]. For this reason, from a physiological standpoint, weight loss strategies that are based on the reduction of fat intake and the maintenance of carbohydrate intake as a main source of energy may be incorrect and would only be effective through simple calorie restriction and not through metabolic change. Metabolic change is achieved when the content of carbohydrates in the diet is low enough to cause Ketosis (hence the name “ketogenic” or “low-carbohydrate” diets). The question is what level of ketosis is necessary to define a ketogenic diet (KD)? This will depend on the purpose of such diet. When used for weight loss, a carbohydrate intake of less than 0.2-0.4 grams per kilogram of weight per day must be achieved and you can eat limitless amounts of fat and protein. However, KDs used to treat intractable pediatric epilepsy are the most restrictive for obtaining stronger ketosis, since although they are very low in carbohydrates (less than approximately 10g/day), they are also low in proteins and very high in fat: the lipid to non-lipid (protein+carbohydrates) ratio is about 4:1 [50 , 51 , 52 , 53].

The cardiovascular system and glucose metabolism

Compared with low-fat diets, low-carbohydrate diets foster an improvement in blood glucose

levels, insulin and insulin resistance [34]. Moreover, insulin resistance is believed to play a central role in the pathogenesis of cardiovascular dysmetabolic syndrome, which is characterized by a constellation of hypertension, dyslipidemia, glucose intolerance and hyperuricemia [54]. Insulin resistance promotes dyslipidemia (high triglycerides, total cholesterol and lower high-density lipoprotein) [55] regardless of obesity [56] and carotid intima-medial thickness (which is an early indicator of atherosclerosis), regardless of blood pressure, weight and whether or not the individual is a smoker or diabetic [57].

Insulin levels are the main cause of hypertension associated with obesity [58]. This is due to the fact that hyperinsulinemia causes antinatriuresis, antikaliuresis, and antiuricosuria [59]. It is therefore not surprising that insulin resistance is associated with hypertension [60]. Another benefit is that there is an inverse association between higher dietary protein intake and blood pressure [61 , 62], which may be linked to liquid loss through increased urea production/elimination as urea comes from protein metabolism and kidneys need to eliminate urea with a large quantity of water [63].

The nervous system

Ketosis has been shown to protect against cerebral damage produced by hypoxia [64] and toxic substances such as free radical MPP deriving from meperidine [65], which produces an instant neurological form of Parkinsonism [66].

The KD is an effective and well-tolerated medical therapy for intractable epilepsy. Although ketosis is believed to produce the anticonvulsant effects of KDs, the mechanisms involved are still unknown [67].

Anti-tumor activity

KDs have shown to be efficient in reducing tumor size. Specifically, it has been confirmed that in astrocytomas they can reduce tumor mass by 80% through the inhibition of angiogenesis [68]. Another factor that may be involved in this tumor inhibition is the reduced availability of glucose to the tumor [69].

Anti- inflammatory activity

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine secreted by several types of immune defense cells including lymphocytes, eosinophils, neutrophils and monocyte/macrophages [70]. It is also secreted along with ACTH by the pituitary gland in response to stressors such as endotoxinemia [71]. New functions have been reported recently for MIF in several processes, such as cell proliferation, angiogenesis, atherosclerosis and wound healing [72 , 73]. Ketone bodies reportedly counteract certain inflammatory processes [74 , 75] by blocking the ketonase activity of MIF[76] .

Results Of Clinical Trials

The effectiveness of ketogenic diets in weight loss

In addition to the fact that an equal number of calories are ingested, KDs are more effective for achieving fat loss than conventional high-carbohydrate/low-fat diets. Low-carbohydrate diets have

even proved to be more effective than conventional diets for more selective fat loss and conserving muscle mass [[26] , [77]]. Benoit et al. reported that when a 1000 kcal KD (10 g of carbohydrates/day) was consumed for 10 days, seven male subjects lost an average of 600 g/day, of which 97% was fat [[77]]. Young et al. [[26]] compared three diets, each consisting of 1800 kcal, but containing different proportions of carbohydrates (104 grams, 60 grams and 30 grams, respectively) and observed a negative correlation between the proportion of carbohydrates in the diet and weight loss and a positive correlation with lean weight loss. Thus, the lowest carbohydrate diet proved to be most effective way of losing weight and conserving muscle mass. Willi et al. [[78]] also concluded that the use of a low-carbohydrate diet in adolescents with morbid obesity was effective for weight loss and conserving muscle mass. Sondike et al. [[28]] found that the use of a low-carbohydrate diet in adolescents without calorie restrictions in fats and proteins was a more effective way of losing weight than a low-fat diet and significantly improved triglyceride and cholesterol levels. The aforementioned authors also affirmed that in adolescents on a low-carbohydrate diet with no calorie restriction in terms of fats and proteins, despite consuming an average of 700 Kcal more per day than the group on the low-fat diet, weight loss was more than double and the improvement in the level of triglycerides was more pronounced [[79]]. These findings were also confirmed by Greene et al. [[27]], who showed that with an equal number of calories and even increasing the number of calories by 300 or more, low-carbohydrate diets foster greater weight loss than low-fat diets. Samaha et al. performed a six-month study and found that severely obese subjects with a high prevalence of diabetes or metabolic syndrome lost more weight over the course of six months on a carbohydrate-restricted diet than on a calorie-fat-restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustment for the amount of weight lost [[80]]. Yancy et al. [[81]] also conducted a six month study and concluded that a low-carbohydrate diet program achieved better participant adherence and greater weight loss than a low-fat diet program. All these studies have one important limitation: the study period in each case was never longer than 6 months. However, Foster et al. and Stern et al. [[82] , [83]] compared low carbohydrate diets to traditional diets (low calorie-high carbohydrate diets in clinical trials) for weight loss over the course of one year. In both clinical trials, low carbohydrate diets produced greater weight loss than the conventional diet for the first six months, but the differences were not significant at 1 year. In both diets, adherence was poor but, the participants on the low-carbohydrate diet displayed more favorable overall outcomes at 1 year than those on a conventional diet. Dansinger et al. [[84]], in another one-year clinical trial, compared the effectiveness of 4 popular diets (Atkins, Zone, Weight Watchers, and Ornish) for weight loss and reported that overall dietary adherence rates were low, although increased adherence was associated with greater weight loss for each diet group. All 4 diets resulted in modest statistically significant weight loss at 1 year, with no statistically significant differences between diets. Brinkworth et al. [[85]] performed a clinical intervention study on two groups of subjects randomly assigned to either a standard protein or high-protein diet. These authors also reported poor long-term dietary adherence behavior for both dietary patterns at month 17. Taking into account all these long-term studies, the real problem associated with long-term diets is poor adherence. People get bored following the same food patterns. Therefore strong willpower is needed to achieve better adherence.

Another advantage of low-carbohydrate diets is the full feeling they provide and the suppression of hunger, unlike high-carbohydrate diets since carbohydrates do not satisfy the appetite and may even increase it [[86]].

Cardiovascular benefits

Contrary to past opinions, KDs also lead to improvements in cardiovascular health. When analyzing the nutritional habits of American society, carbohydrate consumption has risen, resulting in an increase in obesity and atherogenic markers such as triglycerides and VLD [10]. For Dasthi et al. [32], the use of a KD with obese patients over a period of 12 weeks, in addition to being effective and safe for weight loss, also modified cardiovascular risk factors favorably in these patients. Specifically, there is a significant decrease in fasting and postprandial (in response to high-fat meals) blood triglyceride levels [87] and both blood levels are considered independently as risk factors for cardiovascular disease [88 , 89]. Furthermore, the phenomenon of carbohydrate-induced hypertriglyceridemia is long established [10 , 90 , 91 , 92]. The serum triglyceride levels decreased more and high-density lipoprotein cholesterol level increased more with the low-carbohydrate diet than with the low-fat diet: at 6 months [81] and at 12 months [82]. Bearing in mind that the atherogenic lipoprotein phenotype is characterized by an increase in liver production of VLDL, low levels of HDL and a predominance of small LDL particles [93], it is surprising that low-fat and high-carbohydrate diets favor this atherogenic profile in patients who previously did not have this problem [94]. Low-carbohydrate high-fat diets, on the other hand, improve all aspects of atherogenic dyslipidemia, decreasing fasting and postprandial triglyceride levels and increasing HDL and LDL particle size. These diets prompt an increase in larger LDL particles, a drop in smaller LDL particles and a decrease in the cholesterol/HDL ratio [87 , 95 , 96], which lowers glucose levels and favors weight loss [87 , 96]. KDs based around proteins also have cardiovascular benefits, such as decreasing total cholesterol, LDL and triglyceride levels and increasing HDL levels [32]. When comparing low-carbohydrate/high-protein diets and low-carbohydrate/high-fat diets, it seems that the difference between both diets in relation to blood lipid levels lies in the LDL, which are significantly lower in high-protein diets [97].
Low-carbohydrate diets clearly have short-term cardiovascular benefits, but such benefits can also be observed over longer periods of time: 6 months, since improvements in blood pressure and blood levels of total cholesterol, LDL, HDL and triglycerides are noted in the 6 month period [98 , 99]; 12 months, since the low-carbohydrate diet was associated with a greater improvement in certain risk factors for coronary heart disease (higher HDL and lower triglyceride levels) [82 , 83].

In relation to cardiovascular health, these diets have also proven to be effective for hypertension [100 , 101].

Low-carbohydrate/high-protein diets are more effective than high-carbohydrate diets for decreasing blood pressure (both diastolic and systolic) [100].

Benefits in the prevention and treatment of type II diabetes

Low-carbohydrate diets also have beneficial effects in the prevention and treatment of type II diabetes, since they improve the glycemic profile [32 , 102 , 103 , 104], insulin sensitivity, hemoglobin A_{1c} [102 , 103 , 104] and reduce plasma triglyceride and cholesterol levels. KDs may also result in spontaneous reductions in energy intake [106]. These diets should therefore be recommended in the prevention of not just cardiovascular problems but also type II diabetes [99]. Volek et al. [34] observed that in comparison with a low-fat diet, a low-carbohydrate diet improved blood glucose levels, insulin and insulin resistance, and was also more effective for weight loss in obese and overweight women. Nobels et al. [31] and Brehm et al. [61], also reported that a low-carbohydrate diet, besides reducing weight and blood pressure, corrected glucose metabolism, as revealed by a decrease in glucose and insulin circulating in the blood. Furthermore, Bisschop et al. [33]

compared the effects of three diets (A: 85% carbohydrates and 0% fat; B: 4% carbohydrates and 41% fat; C: 83% fat and 2% carbohydrates) and observed that diet C was able to turn a glycolytic metabolism into a lipolytic metabolism, with fat becoming the main source of energy. In type II diabetes, insulin resistance gives rise to an inability to decrease glucose blood levels due to an impaired capacity to use glucose for energy and to store glucose as glycogen. According to the results obtained in the study, a high-fat low-carbohydrate diet does not suppress the removal of glucose from the blood as a result of the body's ability to increase the storage of glucose as glycogen and avoid hypoglycemia with improved gluconeogenesis. Bisschop et al. [33] also emphasize that although a lipolytic metabolism is present in low-carbohydrate high-fat diets and in fasting, important differences exist between them because the former do not cause insulin resistance and cause glucose to be stored as glycogen, whereas the latter causes insulin resistance and does not increase glucose storage.

Yancy et al. [105] examined the safety and effectiveness of a KD for improving glycemic control in patients with type II diabetes. After 16 weeks, the 19 men and women completing the study displayed significant improvements in glycemic control (HbA1c decreased 15%) and triglyceride levels, significant weight loss of 7%, and improvements in fasting serum glucose. Diabetes medications were discontinued or reduced in 13 of the participants. Results indicated that type II diabetics may benefit from a KD, since body weight and triglycerides were reduced and improved glycemic control enabled participants to use less medication.

Over the course of one year, comparing a low-carbohydrate diet and a low-fat/ low-calorie/ high-carbohydrate diet, the low-carbohydrate was associated with a greater improvement in glycemic control [83].

As regards insulin resistance, polycystic ovary syndrome, an endocrine disorder characterized by insulin resistance, central obesity, and abnormal blood lipid levels, is common in women of reproductive age. Westman et al. [106] and Mavropoulos et al. [107] studied the effects of a KD on polycystic ovary syndrome. After 24 weeks, the KD led to significant improvement in weight, percent free testosterone [99 , 100], LH/FSH ratio, and fasting insulin in women with obesity and polycystic ovary syndrome over a 24 week period [100]. These results indicated that a KD may be beneficial for women with polycystic ovary syndrome.

Neurological benefits

The development of Alzheimer's disease and the accumulation of amyloid-β have been linked to dietary factors. Engelhart et al. [108] found that a high intake of cholesterol, saturated fat, trans and total fat, and a low intake of MUFA, PUFA, n-6 PUFA, and n-3 PUFA were not associated with an increased risk of dementia or its subtypes. Nevertheless, diets rich in saturated fat have been repeatedly associated with dementia in epidemiological studies [107 , 108 , 109 , 110 , 111 , 112], although they have been difficult to reproduce [113]. Moreover, several experiments in mouse models seem to confirm the link between lipid rich diets and Alzheimer's disease. Using transgenic mouse models of Alzheimer's disease, several groups have reported that high-fat diets or diets with added cholesterol increased levels and deposition of the amyloid-β peptide [114 , 115 , 116 , 117 , 118]. However, these studies did not examine the effects of lipid rich diets in combination with low carbohydrate intake. Van der Auwera et al. [119] showed that a diet high in saturated fats and low in carbohydrates can actually reduce levels of amyloid-β peptide in a mouse model of Alzheimer's disease. They concluded that dietary strategies aimed at reducing amyloid-β peptide levels should take into account interactions of dietary components and metabolic outcomes, paying particular attention to carbohydrate levels, total calories and the presence of ketone bodies.

Ketogenic diets for intractable seizures

The KD is an effective and well-tolerated medical therapy for intractable childhood epilepsy [[52] , [53] , [120] , [121] , [122] , [123] , [124] , [125]], adolescent epilepsy [[126]] and very probably adult epilepsy [[127]].

It has been shown that the state of ketosis induced by the consumption of a KD that is high in fat and low in carbohydrates has a protective effect against epileptic attacks in children since it allows better control of these attacks [[128]] and can be potentially more effective than new anticonvulsant drugs in cases of intractable epilepsy [[120]], working synergistically or complementarily to anticonvulsant drugs such as valproic acid and phenytoin, respectively, elevating seizure thresholds and reducing seizure severity [[129]]. Specifically, in a study of 58 patients with histories of approximately 20 seizures per day, refractory to over 6 drugs, a KD was effective in two thirds of the cases. In one third, it produced the cessation of seizures and in another third a significant reduction in frequency [[130]]. Kossof et al. [[53]] examined 20 children (aged 3 to 18) who were having between 4 and 470 seizures a week and who did not respond to drug therapy. The children were put on a diet that included fewer carbohydrates than the standard Atkins diet, for six months. Of the 16 who completed the study, 13 (65%) displayed a greater than 50 percent improvement in seizures, seven (35%) achieved a greater than 90 percent improvement and four were seizure-free. The overall side effects were low, with one child developing a complication that did not warrant stopping the diet, despite a brief period of hospitalization. Finally, the authors concluded that a modified Atkins diet is an effective and well-tolerated therapy for intractable pediatric epilepsy.

Severe myoclonic epilepsy in infants or Dravet syndrome is one of the most malignant epileptic syndromes. Caraballo et al. [[131]] studied the severity and intractability of seizures in patients with Dravet syndrome, and reported a significant reduction in the number of seizures in 10 of the 13 children who remained on the diet, showing that the KD is an interesting therapeutic alternative. Even when seizure reduction was not dramatic, the patient's quality of life improved, and the number of antiepileptic drugs administered to all the children was reduced to one or two. These authors stated that children with Dravet syndrome should be offered the KD immediately after three adequate trials of antiepileptic drugs have failed.

Carbohydrate neoplastic effects versus ketogenic diet antineoplastic effects

Many scientists believe that the healthiest diets contain 55-70% carbohydrates and that KDs may be potentially cancerous since many epidemiological studies have linked a high intake of animal products with the genesis of cancer. However, when collecting and analyzing data, these studies fail to take into account the possible effects of dietary carbohydrates and glucose metabolism abnormalities, which are important confounding variables. Factors related to the carbohydrate and glucose metabolism, such as the energetic contribution of carbohydrates, glycemic index and glycemic load, fasting glycemia and insulinemia, as well as glucose and insulin levels after oral glucose load, are associated with the risk of developing many types of cancer. Therefore, these factors should be borne in mind when collecting and interpreting epidemiologic information. Moreover, many studies have reported tumor-inhibitory effects in KDs [[132]].

A direct link has been identified between the risk of endometrial cancer and the glycemic index [[133]] or glycemic load [[133] , [134]]. Augustin et al. [[135]] found a connection between carbohydrate intake and the risk of gastric cancer. Augustin et al [[136]] also found a direct link between glycemic index and glycemic load and the risk of ovarian cancer and, consequently, a possible role of hyperinsulinemia/insulin resistance in the development of ovarian cancer. Borugian et al. [[137]]

reported that increased non-fiber ("effective") carbohydrate and total carbohydrate consumption are both associated with the increased risk of colorectal cancer in both sexes. In women, relative risk is higher for the right colon, whereas in men the relative risk is higher for the rectum. Franceschi et al. [138] found a positive link between the glycemic index and glycemic load and colorectal cancer. It has been suggested that this association is caused by insulin resistance; insulin resistance therefore leads to colorectal cancer [139 , 140] through the lesion-promoting effect of elevated levels of insulin, glucose or triglycerides [139]. The most important carbohydrates associated with the risk of colorectal cancer are bread, cereal dishes, potatoes, cakes and desserts, and refined sugar intake. In contrast, fish, raw and cooked vegetables and fruit displayed a negative association with the risk. Consumption of eggs and meat (white, red or processed meats) appeared to be non-influential [141]. In relation to the risk of developing breast cancer, Holmes et al. [142] discovered no evidence linking meat or fish intake during mid-life and later with the risk of breast cancer. Nevertheless, carbohydrates provided by starch were the most frequently found component contributing to the positive association with breast cancer. Starch food sources included food such as white bread, pasta, rice, crackers and cookies were particularly linked [143]; this is due to the proven association between the glycemic index or glycemic load and the risk of breast cancer, possibly due to the role of hyperinsulinemia/insulin resistance in breast cancer development [144]. Franceschi et al. [143] found that high intakes of polyunsaturated and unsaturated fatty acids were associated with a lower risk of breast cancer and that saturated fatty acids, protein and fiber were not significantly associated with breast-cancer risks. Romieu et al. [145] also found a positive connection between carbohydrate intake and breast cancer risk but not with fat intake.

KDs have shown to be efficient in reducing the size of tumors and avoiding the loss of muscle mass associated with disease in humans [146 , 69] and mice [147].

Adverse Effects

A higher intake of total and saturated fat is widely believed to contribute to the development of coronary heart disease. This belief is largely based on ecological studies relating dietary intake of saturated fat and the incidence of coronary heart disease. The principle of carbohydrate restriction says that by keeping insulin low, the metabolism is biased towards lipid oxidation rather than storage or the effects of fatty acids on peripheral tissues. Most studies that have reported deleterious effects of saturated fat have been carried out in the presence of high carbohydrate, which begs the question as to whether such effects carry over into hypocaloric conditions or those where insulin is better controlled [148 , 149 , 150 , 151]. In the Seven Countries Study [152], intake of saturated fat as a percentage of calories was strongly correlated with coronary death rates across 16 defined populations in seven countries (r=0.84). Interestingly, the correlation between the percentage of energy from total fat and coronary heart disease incidence was much weaker (r=0.39). Indeed, the regions with the highest (Finland) and lowest (Crete) coronary heart disease rate had the same amount of total fat intake, about 40% of energy, which was the highest among the 16 populations. In a more recent analysis of the Seven Countries Study [153], Kromhout et al. found a strong positive correlation between 25-year death rates from coronary heart disease and intakes of four major long-chain saturated fatty acids (all r > 0.80) and *trans* fatty acids (r=0.78).

Data from international comparisons as well as migration studies, although they provide evidence for the importance of diet and environmental factors in the cause of coronary heart disease, are inadequate for testing specific hypotheses regarding the role of individual dietary components due to the confounding effect of other aspects of diet, physical activity, smoking, obesity and economic

development. Prospective cohort studies of individuals, in which diet is assessed prior to the occurrence of disease, are typically considered to be the strongest non-randomized design. Despite the long-standing interest in the diet-heart hypothesis, the number of cohort studies that have directly addressed associations between dietary fat intake and risk of coronary heart disease is surprisingly low and the results are not consistent. A significant positive association between saturated fat intake and the risk of coronary heart disease was found in two studies [[154] , [155]] but not in others [[156] , [157] , [158] , [159] , [160] , [161] , [162]]. A significant inverse association between polyunsaturated fat intake and coronary heart disease was found in only one study [[160]], but not in others [[156] , [159] , [161] , [162]]. The interpretation of these findings is complicated by the small study size, inadequate dietary assessment, incomplete adjustment for intake of total energy, failure to account for *trans* isomers of unsaturated fats and lack of control for intakes of other types of fat and other components of diet.

As for the serious concerns regarding the possible negative effects of KDs on the heart, kidney and liver functions and situations of acidosis, it must be emphasized that low-carbohydrate diets do not produce harmful alterations in kidney [[69] , [156] , [157] , [158]] or liver functions [[79] , [163] , [164]]. This is because high-protein diets are not associated with harmful alterations of kidney functions in patients with normal kidney functions [[166] , [167]] and also because ketosis, which is linked to the use of KDs, is not associated with acidosis and does not alter heart function [[68]]. This is demonstrated by Inuit peoples, who can live on a diet based almost exclusively on fat; they do not suffer acidosis as a result of ketones, and therefore do not suffer from Ketoacidosis. This is due to the physiological situations in which the body is capable of adapting to the change from a carbohydrate-based diet to a very low-carbohydrate diet, in such a way that even the brain cells that obtain almost all their energy from glucose are able to adapt and obtain between 50% and 75% of their energy from fat [[24]], specifically ketone bodies, a brain metabolic change that also occurs with fasting [[168]]. This would explain why ketoacidosis appears fundamentally in pathological situations such as diabetes mellitus and starvation [[24]], in other words situations in which there is no insulin or this is ineffective. This does not occur with KDs since, as explained previously, the amino acids and gastrointestinal hormones produced with food ingestion are able to stimulate the release of low doses of insulin which, in accordance with the findings of the authors cited, are sufficient to avoid pathological situations deriving from the total absence of the insulin effect and are necessary to avoid fat accumulation, thus promoting fat loss and improving insulin sensitivity. Nevertheless, the KD may produce a state of ketoacidosis, as in the case reported by Chen et al. [[169]] in a 40-year-old obese white woman. She had morbid obesity, known to be a pathological situation that can be associated with many metabolic problems. This may be the explanation in the case reported because it is the only case of ketoacidosis reported in the entire bibliography consulted in relation to KDs and weight loss.

In connection with acidosis, since ketosis from KDs is not linked to acidosis, it would clearly not affect the activities that can increase acidosis such as physical activity. Indeed, some studies indicate that the use of KDs does not imply a limitation in physical activity, the only exception being reduced performance in anaerobic activities such as weight lifting or sprints, and should therefore be borne in mind by certain sports competitors [[170]]. Some authors go even further, showing that KDs increase performance in aerobic physical activities such as cycling, due to the fact that the organism is better prepared to use fat as a source of energy [[171]] since a metabolic adaptation occurs in which fat becomes the main source of energy without affecting blood glucose levels [[172]], thus a glycolytic metabolism becomes a lipolytic metabolism.

Another drawback that has been attributed to high-protein diets is that they have a negative effect

on the calcium metabolism and are therefore damaging in relation to bone density. There are conflicting studies that state that the consumption of high levels of protein does not affect bone density negatively [[173] , [174]], that the consumption of low levels of protein has a negative impact on older people's bone density [[173]] and that an increase in animal protein intake to 1.55 grams per kilogram of body weight per day has a beneficial effect on the bone mass of older people [[175]]. Moreover, no link has been found between the consumption of proteins/phosphorus and calcium absorption efficiency [[176]], and also the negative effect on bone mass can be avoided when proteins levels are very high, by consuming 20 mg of calcium per gram of protein consumed [[177]].

Nevertheless, KDs have side effects and most of them have been reported in KDs used to treat intractable pediatric epilepsy. This is very likely due to the fact that these KDs are the most restrictive since they are very low in carbohydrates (less than about 10g/day), low in proteins and very high in fat. The lipid to non-lipid (protein+carbohydrates) ratio is about 4:1 [[50] , [51] , [52] , [53]] for strong ketosis.

Another problem possibly associated with epilepsy KDs is that Hopkins protocol has a fasting phase and fluid restriction [[178] , [179]]. In fact, Kim et al. [[180]] concluded in their study that initial fasting and fluid restriction are not essential for the KD and that the tolerability of this treatment may be improved. Ballaban et al. [[50]] found that only 10% (5 patients) of children (total: 52) in their study experienced serious adverse effects events after initiation of the diet: two patients developed severe hypoproteinemia within 4 weeks of starting the diet, and 1 of them also developed lipemia and hemolytic anemia; 1 child developed Fanconi's renal tubular acidosis within 1 month of starting the diet and two other children manifested marked increases in liver function tests, one during the initiation phase and the other 13 months later. Bergvist et al. [[51]] found an association between selenium deficiency in KDs and cardiomyopathy. Selenium deficiency was found in 20% of the patients evaluated and only one of them had cardiomyopathy, with normal cardiac physical examination and ECG, but abnormal echocardiogram. They found that selenium supplementation improved levels in all children. Kang et al. [[52]] found dehydration as the most common early-onset complication (46.5% patients), especially in patients who started the KD with initial fasting. Gastrointestinal disturbances, such as nausea/vomiting, diarrhea and constipation, were the second most common early-onset complication noted (38.8% patients), sometimes associated with gastritis and fat intolerance. Other early-onset complications detected in patients, in order of frequency, were hypertriglyceridemia (27.1% of patients), transient hyperuricemia (26.4%), hypercholesterolemia (14.7%), various infectious diseases (9.3%), symptomatic hypoglycemia (7%), hypoproteinemia (5.4%), hypomagnesemia (4.7%), repetitive hyponatremia (4.7%), low concentrations of high-density lipoprotein (3.9%), lipoid pneumonia due to aspiration (2.3%), hepatitis (2.3%), acute pancreatitis (0.77%), and persistent metabolic acidosis (0.77%). Late-onset complications also included osteopenia (14.7%), kidney stones (3.1%), cardiomyopathy (0.77%), secondary hypocarnitinemia (1.6%), and iron-deficiency anemia (1.6%). They concluded that most KD complications are transient and can be easily remedied with various conservative treatments. As regards KDs and kidney stones, the high risk of both uric acid and calcium stone formation is due to the conjunction of hypercalciuria, acid urine and low urinary citrate excretion with low fluid intake [[181]]. Fluid intake should therefore be optimum in KDs to prevent kidney stone formation.

Summary

In the opinion of most physicians and nutrition experts, carbohydrates should be a major component of daily energy intake for a healthy lifestyle. For that reason, this paper presents a

one-sided review of the literature (the other is already well-known), giving scientific arguments in favor of ketogenic diets and proving that these diets are safe and may be very useful for weight loss, glucose intolerance, type II diabetes, neurological disorders or epilepsy and cancer.

Conclusions

Low-carbohydrate diets are a safe, effective way of losing weight, promoting non-atherogenic lipid profiles, lowering blood pressure, diminishing resistance to insulin with an improvement in blood levels of glucose and insulin and they also have neurological and antineoplastic benefits.

Explanations And Suggestions For Future Research

No study has shown that this type of diet is good for everyone or that such diets are safe or effective for long-term use. Carnivorous animals are known to follow this diet throughout their lives but can it be demonstrated that a carnivorous diet with a few vegetables is the best option for humans?

Perhaps the answer lies in the evolution of human diet, for example in Inuit peoples: traditionally, their diet contained 3-5% carbohydrates (since it was based on fish, marine mammals, moose and caribou), obesity was virtually nonexistent and type II diabetes was rare.

Further research is needed on the safety and effectiveness of this diet, and for that reason a low-carbohydrate diet under medical supervision would be the most suitable option.

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