REVIEW

Internist, anesthesiologist and surgeon use of ketogenic diet

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ABSTRACT

Ketogenic diet is being increasingly utilized in recent decades because of its success as an effective tool for short and intermediate-term weight loss. Promoting physiological ketosis from a drastically low carbohydrate diet is the fundamental basis for this diet regime. Though debated, these diets have been demonstrated to be effective, at least in the short- to medium terms, to manage excess weight, hyperlipidemia, and other cardiovascular risk factors. We reviewed the cardiovascular, metabolic, anesthetic, and postsurgical profiles in the literature and summarized technical issues of anesthesia and surgery along with long-term changes from published papers. Doubts with ketogenic diet were raised due to possible renal damage caused by significant excretion of nitrogen found in animal models, the effects of acidosis, and the concerns of increasing triglycerides and cholesterol levels. Though current literature supports the efficacy of very low carbohydrate keto-diets their potential negative effects on renal function and acidosis are debated. An increase in nitrogen excretion during protein metabolism in the postoperative period could lead to renal damage. Research on the value of ketogenic diets is emerging because of its value in weight loss and in managing other pathologies.

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Obesity has become one of the Western world's health crises,[1] and abdominal obesity in particular is one of the main cardiovascular risk factors that, along with dyslipidemia, hypertension and diabetes, constitutes the components of the metabolic syndrome.[2] Although weight loss is a desired objective amongst overweight and obese subjects, and the health benefits of such reductions have been clearly established,[3, 4] there are no definitive data on either the most efficient medium- or long-term dietary protocol.[5, 6] The most widespread and widely accepted dietary strategy is based on a diet with relatively high levels of carbohydrates and low levels of fats but according to some authors this practice is in reality only associated with modest weight loss and poor long-term compliance levels.[7] Indeed, adherence to this type of regime is difficult because patients tend to prefer a fat rich diet. Furthermore, in these dietary protocols, subjects are often led to choose simple carbohydrates and refined sugars rather than the recommended complex carbohydrates and whole grain foods.[8, 9] Thus, the suggestion to follow a low-fat diet could in reality favor the con-

sumption of sugars and refined starches, which can lead to obesity and dyslipidemia, especially in insulin resistant subjects.[10, 11] As a result of the decreased effectiveness of these types of diets, there has been an increased interest in so-called VLCKDs — very low carbohydrate ketogenic diets — in recent years.[12] These diets, albeit debated and at times opposed, have undoubtedly proven to be effective, at least in the short- to medium terms, as weapons to combat excess weight, hyperlipidemia and other cardiovascular risk factors.[13-16] New insights have been communicated recently in favor of keto-Mediterranean diet to lose weight and to reduce cardiovascular risk.[17, 18]

Cardiovascular profile

The positive effects of a VLCKD also seem to apply to cardiovascular risk parameters and respiratory pattern.[19, 20] Despite some authors' doubts regarding their long-term safety [5, 21] and effectiveness compared to "balanced" diets,[22] or even the possible associated increases in triglycerides and blood cholesterol,[23] the majority of recent studies appear to demonstrate how a reduction in carbohydrates, even to the point of reaching a condition of physiological ketosis, can lead to significant improvements in biochemical parameters.[24-31] The effects of a VLCKD appear to be particularly significant in terms of reducing blood triglycerides, lowering total cholesterol and increasing high-density lipoprotein (HDL)-cholesterol.[14, 15, 32-35] Furthermore, VLCKDs appear to be able to increase the volume of HDL-cholesterol micelles,[34] thus contributing to a reduction in cardiovascular risk, unlike the small LDLs which have greater atherogenic potential.[36] The VLCKD effect of reducing total cholesterol can clearly be explained by the reduction in insulinemia, subsequently attenuating the facilitating action on HMGCoA reductase, which is entrusted with the production of cholesterol. Dietary cholesterol introduced would also help the hypocholesterolemic effect of a VLCKD, inhibiting in turn the aforementioned HMGCoA reductase. In other words, insulin increases cholesterol production while exoge-

nous cholesterol has the opposite effect.[37] As a result of these biochemical considerations and experimental and epidemiological data, strong doubts have recently risen regarding the importance of dietary fats, at least as a sole cause, in the rise of cholesterol and triglyceride values. On the other hand, the dyslipidemic role of refined carbohydrates in this area has been strongly reevaluated.[40-48] Recently Paoli et al. demonstrated how a keto-Mediterranean diet works to reduce biochemical patterns linked to cardiovascular risk.[17, 18]

Metabolic profile

Insulin resistance is the condition underlying type 2 diabetes (T2D), but it also exists in the wider population of non-diabetics and it interrupts — to varying degrees — the action of insulin on cells, leading to a wide range of signs and symptoms. The main feature of insulin resistance is the reduced capacity of muscle cells to take on circulating glucose. An insulin resistant person will divert the largest proportion of diet-introduced carbohydrates to the liver where most of it will be converted into fats (de novo lipogenesis) instead of being oxidized by skeletal muscle in order to gain energy.[38-41] Hellerstein [42] reports that de novo lipogenesis accounts for approximately 20% of new triglycerides, and this higher conversion rate of diet-introduced carbohydrates into fats (the majority of which enter into circulation as saturated fats), significantly increases the risk of diabetes and heart disease. Thus, insulin resistance functionally manifests itself as "carbohydrate intolerance". When the quantity of carbohydrates in a diet is limited to such a low level that there is no significant conversion into fats (a level that varies from person to person), then the signs and symptoms of insulin resistance improve and often disappear completely. Bistran et al.[43] reported that the reduction in insulinemia is more significant, in a short time span, in individuals with T2D who followed a VLCKD compared with those who followed a low-calorie or low-carbohydrate diet. Gumbiner et al.[44] followed T2D obese individuals for three weeks on two types of low-calorie (650

kcal) diets where one of the two had a much lower carbohydrate content (24 *vs.* 94 g /day). As expected, the low carbohydrate content diet led to significantly higher levels of ketones in circulation (approximately 3 mmol/L), which is associated with a fall in hepatic glucose production. It is interesting to note that there was a strong inverse correlation between ketones in circulation and hepatic glucose production, suggesting that higher ketone levels are associated with more favorable effects in glycemic control in diabetic patients. More recently, Boden *et al.*[45] carried out a study on T2D obese patients following a low carbohydrate regime (<20 g/day) for two weeks, which reported a reduction in glycaemia (7.5-6.3 mmol/L) and glycated hemoglobin (7.3-6.8%). When ketogenic diet was prescribed to T2D obese patients for 56 weeks, significant improvements were recorded regarding both weight and metabolic parameters. Indeed, the level of blood glucose, total cholesterol, LDL-cholesterol, triglycerides, and urea showed a significant decrease from week 1 to week 56.[46] It is interesting to note that in a recent study on non-diabetic overweight subjects it was reported that during the ketosis period, levels of glycaemia on an empty stomach did not vary significantly but there was an increase in postprandial glycaemia. This suggests ketosis has different effects on glucose homeostasis in diabetic and non-diabetic individuals. Other studies support the long-term effectiveness of a ketogenic diet in the management of T2D complications [47, 48] leading to significant reductions in body fat, improvements in glycemic control, glycated hemoglobin, insulinemia and, in some cases, a reduction in or suspension of insulin requirements.

Anesthesiological and postsurgical profile

The American Society of Anesthesiologists (ASA) deems obesity to be responsible for "a series of alterations in states of health" and considers carriers of this pathology to be at ASA level 3 out of the 5 classes that make up the scale. This is because obesity, especially in its severe forms, is accompanied by a series of comorbidities, most commonly including diabetes mellitus, hypertension, respiratory insufficiency, chronic pulmonary heart disease. Organ diseases are not uncommon and neither are gallstones, hepatic steatosis and changes in coagulation functions that lead to a predisposition to deep vein thrombosis (DVT). It has been established that an obese person's heart, in response to the growth in intravascular volume, pumps a greater volume of blood in any given unit of time and is subject to chronic overload. Cardiac output has to increase by approximately 0.1 L/min to perfuse each kilogram of adipose tissue.[49] Hypervolemia, which is often observable in these patients, facilitates the emergence of systemic arterial hypertension, which if overlooked contributes to the development of cardiomegaly and consequent cardiac insufficiency. Severely obese subjects' respiratory apparatus is often burdened with latent forms of respiratory insufficiency with a prevalence of obstructive deficits. Polycythemia, alterations in the VA/Q ratio and a frequent but shallow breathing pattern produce, over time, a state of hypoxia and hypercapnia. The latter, along with hypervolemia, favors the emergence of hypertension in the pulmonary circulation with a trend in the most severe cases to chronic cardiopulmonary disease. It follows that some severely obese patients with systemic arterial and pulmonary hypertension can easily develop the clinical picture of biventricular failure.[50] Moreover, other anesthetic considerations in obese patients include the following:

— technical issues: these include difficulties in venipuncture of both peripheral and, especially, central vessels due to uncertainty regarding anatomical points of reference. The placement of a venous catheter in a subclavian or internal jugular vein could become complicated and lead to the accidental puncturing of an artery or to pneumothorax. The latter could lead to serious complications for obese patients with latent respiratory insufficiency. The risk of gastric reflux during induction of anesthesia, especially in obese diabetics, is a dangerous complication which suggests, in addition to the precautionary administration of

antacids or gastrokinetics, the role of prophylactically placing a gastric tube.[51] Finally, the difficulties in maintaining airway patency during induction of anesthesia can lead to varying degrees of difficulties during endotracheal intubation. The presence of macroglossia and frequent limitations to neck motility due to a retronuchal protuberance need to be carefully examined. In cases of difficulty securing the airway, it might be prudent to carry out the maneuver under local anesthetic with the aid of a fiber optic bronchoscope;

— pharmacodynamic issues: excessive increases in adipose mass causes changes to distribution volumes. Obesity independently affects the filtering capacity of the kidney. Therefore, better assessment of kidney function and dosage adjustment of drugs eliminated by the kidney is needed in obese patients. Renal clearance determines the plasma concentration of some drugs, such as opiates and benzodiazepines by affecting their half-life and duration;[52]

— pathophysiological problems: in the event of a laparotomy, prolonged increases in intra-abdominal pressure can significantly reduce cardiac output. Venous return, an indicator of preload, is effectively impeded both by compression of the inferior vena cava and by an increase in average endothoracic pressure, which is associated with the rise of the diaphragm. Excessive intra-abdominal pressure also exerts a parallel significant influence on respiratory functions: progressive cephalic displacement of the diaphragm compresses the lungs, a restrictive change that mimics the pre-existing obstructive pathology. This leads to a reduction in the remaining functional capacity, an increase in peak alveolar pressure and a reduction in pulmonary compliance.[53] In some patients, respiratory complications such as V/Q mismatch, fall in PaO_2, increase in $PaCO_2$ and respiratory acidosis.[20] However, a selectively planned anti-Trendelemburg position at approximately 45° and the versatility of modern automatic ventilators are solutions to the problems expressed thus far. Choosing a favorable inhale-exhale ratio, increasing the oxygen inhalation proportion (FiO_2) and, finally,

adopting a moderate positive end-expiratory pressure (PEEP), all improve respiratory functions with minimum hemodynamic repercussions, allowing for safer anesthesia.

In addition to these primarily anesthetic elements, certain surgery related issues should not be forgotten:

— abdominal: postoperative complications, especially in obese patients, include incisional hernias and stoma complications. The former is a possible complication arising from laparotomies but rarely occur after laparoscopies. They have a variable incidence rate from 0.5 to 14.5%. Treatment is clearly of a surgical nature using plastic, more commonly with (and only rarely without) the insertion of a mesh. Stoma complications, which can be divided into early (28%) and late (6%), have a 25-35% incidence rate. Early complications include hemorrhages, ischemia with subsequent necrosis, dehiscence of the mucocutaneous membrane and abscesses; late ones include retraction, peristomal dermatitis, peristomal hernias and fistulas;

— orthopedics: venous thromboembolisms is a particularly concerning postoperative complication (75% in hip replacements) for patients who have undergone major orthopedic surgery (hip and knee replacements) occurring between the fifth and seventh day. 20% of these develop pulmonary embolisms and 3% die as a result of it.

In light of the above, preoperative weight reduction emerges as fundamental to (peri and post) operative success and as such, should become a fundamental and integral part of preparation for major surgery. Weight loss, carried in the short to medium term (30-40 days) with personalized dietary plans, ensures a reduction in the convalescence period and at the same time allows anesthesiologists and surgeons to limit the risk of operative complications.

Long-term changes

One of the most common criticisms raised against the use of VLCKDs is the so-called "yo-yo effect", namely the regaining of weight once the dietary regime is no longer being followed.[54, 55] In other words, some skeptics and

opponents of VLCKDs suggest that the beneficial effects are only transient. There is no universally accepted definition of "maintaining weight loss" following a diet but a reasonable parameter would be that proposed by Wing and Hill in 2001, who define it as "individuals who have intentionally lost at least 10% of their body weight and maintained the result for at least a year".[56] The "10%" criteria were chosen due to its well documented effects, such as an improvement in risk factors for diabetes and cardiovascular disease, while the "one year" criterion was proposed with the agreement of USA Institute of Medicine.[57] The mechanisms underlying weight loss in VLCKDs are still subject to debate. One hypothesis is that using energy from protein is a 'costly' process for the body and could thus lead to a "loss of calories" and thus to greater weight loss than other less energy costly diets.[58] During the first phase of a VLCKD 60-65g of glucose per day are needed to satisfy "glucose requirements": 16% of these are obtained from glycerol while the majority is derived from gluconeogenesis, so from exogenous or endogenous protein.[59] Gluconeogenesis is a process that takes up 400-600 Kcal/day.[58] However, there is no direct evidence to support this hypothesis and a recent study reported that there were no changes in resting energy expenditure after a VLCKD.[60] Some authors maintain that the results obtained from a ketogenic diet could be attributed to a loss of appetite caused by a greater sense of satiety caused by the intake of protein [58] or due to some effect on appetite controlling hormones.[61] Other authors suggest that this may be due to the anorectic effect of ketone bodies.[62] Nonetheless, independent of the weight loss mechanisms involved in VLCKDs, there is substantial agreement on its medium-term effectiveness. However, as previously affirmed, one of the main problems is weight control and preventing weight regain. The data from research by Paoli et al.[63] demonstrate that a Mediterranean variety of VLCKD (defined as KEMEPHY) is able to cause significant weight and body fat losses which are maintained for at least a year. VLCKD does not appear to influence base-line energy expenditure (either positively or a negatively) but recent data have shown that it could improve the oxidization of fats and thus lower the respiratory quotient.[60] Regarding the influence of hormones on weight regain, one possible explanation is linked to a long-term increase in orexigenic signals. Sumithran et al. have shown that very low calorie diets lead to a long-term increase in appetite mediators in circulation, which encourages weight regain after even a year of initial weight loss.[64] It has also been demonstrated that a ketogenic diet has only a marginal effect on ghrelin levels and that subjective appetite ratings were lower than when subjects were in a state of physiological ketosis.[61] Furthermore, we must consider that doctors and nutritionists have some concerns regarding some elements of VLCKDs.[21, 23] The main concern is the possibility of renal damage caused by significant excretion of nitrogen during protein metabolism, which can cause an increase in glomerular filtration.[58] But there are conflicting results: some authors indicate the possibility of kidney damage [65, 66] based on the results of animal studies, whilst others, using animal models. Meta-analysis and research on humans, in contrast, suggest that even a high protein intake does not alter renal function. In particular, subjects whose renal function is within acceptable range, an above average protein intake can lead to some functional and morphological changes without negative effects.[67] A prudent approach is justified in subjects with renal insufficiency, even at a subclinical level, and in patients undergoing kidney transplants. It is also worth considering that a VLCKD is not necessarily a "protein rich diet" (as it can have a greater overall proportion without having a large actual content).

New applications: neurodegenerative diseases

It has been noted that single nutrients can have a positive effect on the health of skeletal muscle and that a combination of nutrients can reduce the signs and symptoms of certain neuromuscular diseases.[68] On the other hand, it has also been noted that the effects of diet

on health are linked to the general relationship between various macro and micro nutrients rather the single elements themselves. In the third decade of the 20th century VLCKDs were used to treat patients who had pharmacological resistance to epilepsy [69] whilst more recently VLCKDs have been applied to a variety of illnesses including obesity, Polycystic ovary syndrome (PCOS), cancer,[70, 71] diabetes [30] and other pathological conditions.[72, 73] Others have investigated the relationship between VLCKDs and neuromuscular diseases, during which interesting prospects have emerged [74] especially regarding amyotrophic lateral sclerosis (ALS), Alzheimer's (AD) and Parkinson's disease (PD):

— ALS is a progressive neurodegenerative disease that affects spinal and cortical motor neurons, causing progressive weakening and loss of skeletal muscle. The affected person dies within five years of the first symptoms, normally due to respiratory paralysis. At the moment, there are no effective treatments of ALS. Its causes are complex and multifactorial, involving both genetic and environmental factors: excessive oxidative damage, accumulation of neurofilaments and mitochondrial dysfunction have all been suspected underlying hypotheses. As with other neurodegenerative diseases, mitochondrial involvement makes a VLCKD a promising probable synergetic instrument in the treatment of ALS.[75, 76] In approximately 10% of ALS patients, mitochondrial damage is a result of a mutation in the gene that codifies the enzyme Cu/Zn superoxide dismutase 1 (SOD1).[77] This mutation causes a reduction in the activity of mitochondrial complex 1, as measured in the skeletal muscle and spinal cords of ALS patients.[78] Results show that ketone bodies can act on mitochondrial function favoring, for example, the recovery of the complex after a pharmacological blockade.[79] Other studies of note report that the integration of a ketone body precursor (caprylic acid) improved mitochondrial and motor neuron functions and in an ASL mouse group;[80]

— AD is the most widespread neurodegenerative disease and the main cause of dementia amongst the elderly. AD symptoms include general cognitive impairment with memory deficits and personality changes. The causes of this cognitive decline can be attributed to progressive synaptic dysfunction and successive neuron loss, mainly in the cortex, the limbic system and in subcortical regions.[81] As with other chronic diseases, AD treatments can be divided into two categories: 1) symptomatic treatments (which offer temporary improvements in the symptoms without changing the progression of the disease itself); and 2) treatments that are potentially able to change the natural history of the disease (slowing or stopping the decline of cognitive functions over the years). Although there are some FDA approved drugs, such as acetylcholinesterase inhibitors and memantine (an antagonist to the glutamate used to improve behavioral symptoms), there is currently no effective treatment to prevent, change or interrupt AD, and the majority of drugs approved for treatment only offer moderate symptomatic effects.[81-83] Considering the close link between the aging process and AD, the positive effects of a VLCKD on the central nervous system and the multifaceted nature of the disease (mitochondrial and metabolic changes), it would not be wrong to hypothesize that there might be a rationale for using a VLCKD on these patients.[84] For example, an *in-vitro* study demonstrated that the addition of a ketone body (beta-hydroxybutyrate) protects hippocampal neurons from toxicity.[85] It was also shown that a long-term diet (8 months) that included a keto ester improved the levels of amyloid plaque and tau protein accumulation in middle-age mice (8.5 months).[86] As previously stated, mitochondrial dysfunction has been implicated in the etiology of AD.[84] A reduction in glial and neuronal mitochondrial metabolism has been demonstrated in the elderly compared to healthy young subjects.[87] This dysfunction, which is related to decreased energy production from reduced pyruvate mitochondrial oxidation, could be involved in the production of pathological proteins responsible for AD;

— although the pathogenesis of sporadic Parkinson's disease (PD) remains unresolved,

there is substantial evidence that the primary cause is the degeneration of dopaminergic neurons in the *substantia nigra*, leading to movement anomalies and other disturbances in cortical function. It has been suggested that a change in mitochondrial function that involves the substantia nigra plays an important role in the start and progression of PD.[88] For example, Kashiwaya *et al*. used 1-methyl-4-phenylpyridinium, MPP(+), which leads to the death of dopaminergic neurons in the *substantia nigra* by inhibiting mitochondrial NADH dehydrogenase, to produce a syndrome that is similar to Parkinson's in neurons from midbrain cultures. ß-hydroxybutyrate protects these neurons from MPP(+) associated toxicity.[85]

Conclusions

Despite the available literature supporting the efficacy of VLCKDs, some doubts remain regarding their safety, in particular in relation to two elements, namely renal function and acidosis. Renal damage would be caused by the increase in nitrogen excretion during protein metabolism, an increase of which would lead to an increase in glomerular pressure and hyperfiltration.[59] However, in reality the data in literature are contradictory, with some authors maintaining the possibility of renal damage above all on the basis of experimental models on rats and pigs [89, 90] while others — supported by other animal models and meta-analysis on humans — advocate that maintaining high protein intake does not affect the renal function.[91] In fact, in subjects whose renal system is intact changes in protein intake lead to functional and morphological renal changes without negative effects.[97] Renal effects are not actually to be excluded but if there were any they would be limited to the subject's blood pressure; the amino acids involved in the processes of gluconeogenesis and/or ureagenesis generally have an effect of lowering of blood pressure while acidifying amino acids can cause increases in blood pressure.[92-94] Subjects with renal insufficiencies, even subclinical ones, or who have undertaken kidney transplants or have metabolic syndromes and/

or obesity related conditions are more susceptible to the hypotensive effect of amino acids, particularly sulphur containing amino acids (Tau, Met, Cis-Cis, Cys).[93] The correlation between obesity and a reduced number of nephrons on raising pressure generally puts type 2 diabetics and metabolic syndrome subjects at risk [94] even if the effects in patients with renal pathologies and diabetes are not always consistent with the hypotheses.[95-97] Nonetheless, some authors have demonstrated the positive influence of reducing protein intake, at least in the short-term, on the albuminuria of type 2 diabetics.[96] The same authors later noted that a restriction in protein intake seemed neither necessary nor useful in the long term.[97] It should furthermore be underlined that ketoy relatively high in protein [18] and thus renal risks are virtually insignificant.[91] Regarding the possible risk of acidosis, it is worth remembering that the concentration of ketone bodies during a VLCKD does not exceed 8 mM/L.[20, 98] VLCKDs are commonly noted as a useful tool in weight reduction but their wider therapeutic effects are becoming ever more noticeable. Further research on the value of ketogenic diets is emerging not only for its value in weight loss, but also in other pathologies.

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