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POSITION PAPER ON THE APPLICATIONS OF KETOGENIC DIETS IN PATIENTS WITH HEADACHE: CONSENSUS STATEMENT.

Short: Consensus statement on ketogenic diet and Headache.

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Abstract

Headaches are among the most prevalent and disabling disorders and there are several patients' unmet needs in current pharmacological options, while a growing interest is focusing on nutritional approaches as non-pharmacological treatments. Among these, the most promising seems to be the ketogenic diet (KD).

Exactly 100 years ago, KD was used to treat pediatric forms of drug-resistant epilepsy, but progressively applications of this diet also involved adults and other neurological disorders. Evidence of KD effectiveness in migraine comes from 1928, but in the last years different groups of research and clinicians paid attention to this therapeutic option to treat patients with drug resistant migraine and cluster headache, and/or comorbid with metabolic syndrome.

Here we describe all the existing evidence on the potential benefits of KDs in headaches, explore in deep all the potential mechanisms of action involved in the efficacy, and synthesize results of working meetings of an Italian panel of experts on this topic. Aim of the working group is the creation of a consensus on indications and clinical practice to treat with KDs patients with headache. The results here we present are the base for further improvement in the knowledge and application of KDs in the treatment of headaches.

Key words: ketogenic diets, ketosis, ketones, consensus statement, position paper, headache, migraine, cluster headache

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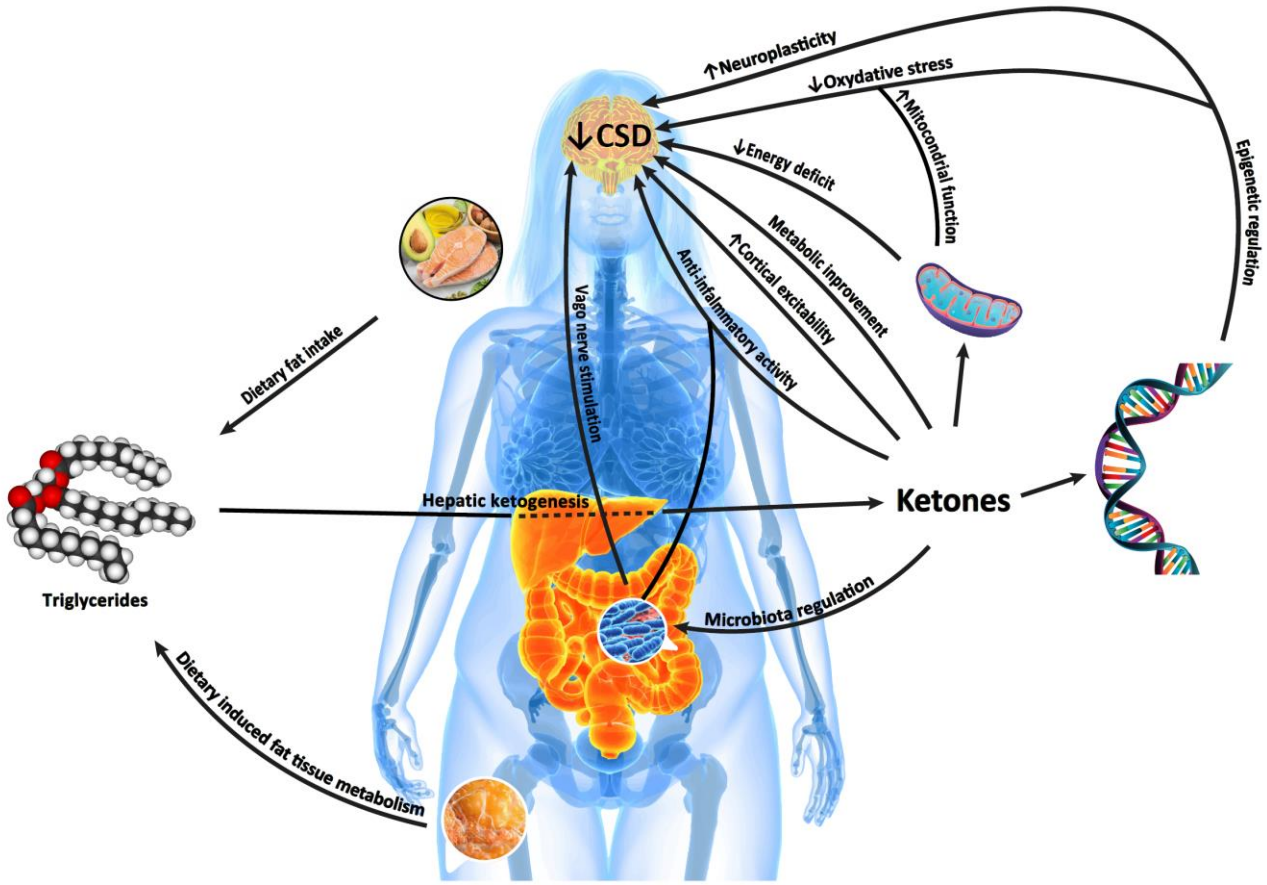

Graphical Abstract

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INTRODUCTION

Headache is one of the most common symptoms reported by people during their life, with an estimated prevalence of 47% [1]. According to the international classification of headache disorders, 3rd edition [2], is possible to classify different primary and secondary forms of headache. The most frequent ones are the tension type headache (22%) and migraine (15%), respectively the second and third most prevalent disorders worldwide, after dental caries [3]. Also in terms of disability, headache is the third most disabling condition, as measured in years of life lived with disability [3]. Despite the global burden of disease, according the World Health Organization, headache disorders are yet worldwide underestimated and undertreated [1]. This undertreatment of headache is particularly actual for patients with migraine who needs to receive a preventive therapy to reduce the number of monthly attacks, and was recently confirmed in large epidemiological and in local real-world studies [4,5]. A preventive treatment should be considered for each patient with at least 4 days of migraine headache per month, or for whom that find symptomatic treatments ineffective or not tolerated [6]. It was estimated that the 38.8% of subjects with migraine are eligible for a preventive treatment, but just the 12.4% undergoes to it [7]. The goal of a pharmacological prophylaxis for migraine is decrease the frequency, severity, and duration of each attack, increase responsiveness to symptomatic treatments and improve patients' quality of life [6]. Unfortunately, all the drugs commonly used to prevent migraine, and other primary headaches, were not ad hoc developed, and their use was adopted for serendipity. Hence, the most of the preventive treatments are characterized by a relatively low responder rate (so, patients will require more preventive medications concomitantly), potentially dangerous drug-drug interactions, and several side effects that induces patients to the discontinuation of treatments [8]. It induces to a little persistence of oral preventive treatments after 6 months, that further decreases at 12 months, also in case of treatments' switch [9]. The most recent biological treatments (OnabotulinumtoxinA and monoclonal antibodies against calcitonin-gene related peptide (CGRP)) showed a better profile of safety, but they are not indicated for all patients and there are some concerns about the cost/effectiveness [10]. Moreover, also these innovative treatments do not warranty efficacy and its persistence in the 100% of patients. In summary, the outcome of preventive

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pharmacological treatments, when started, is unsatisfactory for many patients with migraine, leading to the possible worsening of headache by the development of complications, such as acute medication overuse and headache chronification.

For all that reasons, there is a growing interest about non-pharmacological approaches, such as nutraceuticals [11], lifestyle changes [12,13], and nutritional interventions [14] both intended as foods preferences (in terms of potential trigger foods avoidance and headache induced changes in dietary choices) [15,16], and potential dietary treatment [17,18]. Under the latter point of view, a promising approach could be the ketogenic diet (KD) [19–21] that from one century is used to treat epilepsy and other neurological conditions.

This paper summarizes all the existing evidence on the potential benefits of KD on headache and synthesized results of a working group composed by Italian experts in the treatment of patients with headache by KDs. The purpose of the panelists is to define common indications and practices to address patients to KDs, in order to standardize the treatment, produce stronger evidence about it, and create an instrument useful for other neurologists, professionals of nutrition, clinician of other specialties, general practitioner, and researchers.

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KETOGENIC DIET: OVERVIEW AND APPLICATIONS OF KD IN NEUROLOGY

KD could be defined as a "simulated fasting". In fact, it was developed around 1920 as an attempt to prolong the benefits of fasting on epileptic seizures, known since the time of Hippocrates [22], in drug-resistant children.

Fasting therapies were more formally adopted for the treatment of epilepsy in 1911 by the French physicians Guelpa and Marie [23]. In 1921, the endocrinologist H. Rawle Geyelin [24] was the first to report initial data regarding cognitive improvements that occurred in patients adhering to fasting regimens. In the same year, fasting and low-carbohydrate/high-fat diets were proposed to increase ketone levels in normal, healthy subjects and were recommended to promote therapeutic benefits in epileptic children [25]. A subsequent study aimed at evaluating the efficacy of KD on adult epilepsy showed improvement or complete seizure control in 56% of patients [26].

KD was among the therapeutic options in use for epileptic patients until the end of the 1970s, although its use gradually decreased with the progressive advent of more innovative drug therapies, such as diphenylhydantoin, phenobarbital and valproic acid. Only in 1997 KD came back into the limelight following the release of the movie "First Do No Harm", which told the true story of a child treated thanks to this diet, and the birth of the Charlie Foundation, promoter and funder of many advertising and research initiatives related to KD [27].

Over the years, the number of ketosis-related therapies has expanded (from alternative diets to the use of medium-chain fatty acid supplementation and exogenous ketones), while a growing number of reports note the impact of ketotherapy on clinical phenotypes, cellular physiology, and molecular physiology [28].

Currently, ketogenesis finds application in several fields such as the treatment of various neurological conditions both in children [28] and adults [29], gynecology, metabolic syndrome (MetS), and is of recent interest in the field of oncology as well [30].

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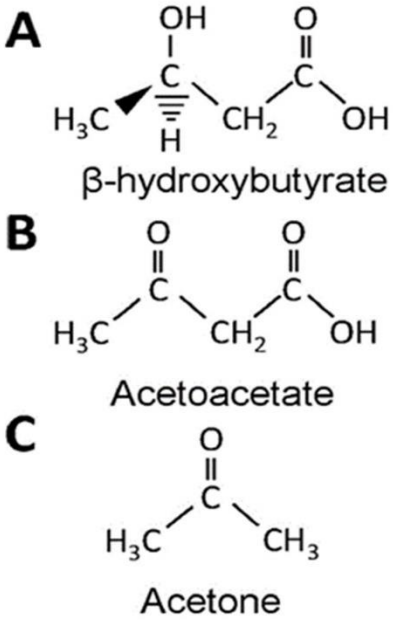
Figure 1



Ketogenic therapies include any intervention that induces the organism to produce ketones: acetoacetate, β-hydroxybutyrate (BHB), and acetone (Figure 1). These are formed from exogenous fatty acids (as in ketogenic high-fat diets commonly used in neurology) or endogenous fatty acids (as in fasting, i.e., the paraphysiological condition in which the human body normally goes into ketosis, and in hypoglucidic-hypolipidic-normoprotein diets). [31]

The common goal of all KD is to induce the production of ketones in the liver through the beta-oxidation of free fatty acids with the aim of mimicking a state of fasting, but without depriving the body of the calories needed to support growth and development [32,33]. The ketones that are generated, acetoacetate and BHB, then enter the bloodstream through which they are transported to metabolically active tissues, i.e., skeletal muscle, heart, and brain, where they are used for energetic purposes [30], whereas acetone, produced by the spontaneous decarboxylation of acetoacetate, is rapidly eliminated through the lungs and urine (Figure 2).

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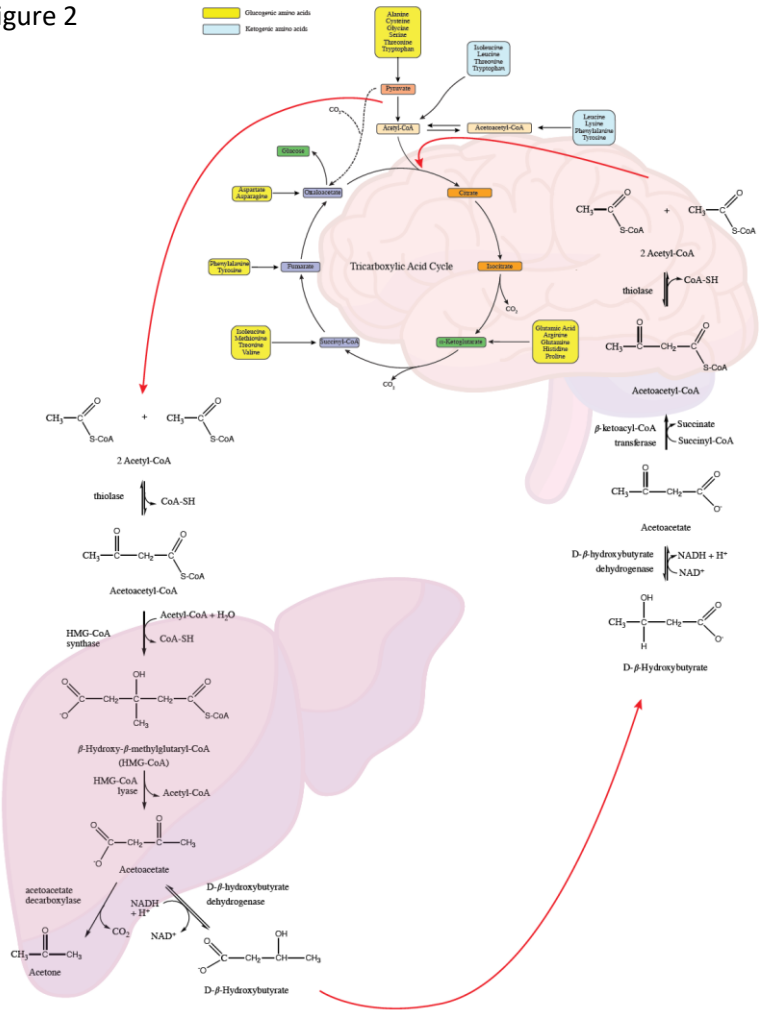
Figure 2



Ketogenic dietary interventions are therefore multiple and, although they have in common the restriction of carbohydrates and adequate protein intake, they differ from each other based on the variation of the lipid quota (Figure 3). The various protocols include:

1. The classic ketogenic diet (CKD), in which the balance between the macronutrients consumed must be calculated. In particular, the ratio between fats and non-fats (carbohydrates+proteins); generally this ratio is 3:1 or 4:1 (i.e., the intake in grams of fats is three or four times that of non-fats). This protocol is characterized by the higher content of fats (main energy source) compared to the protein portion (slightly reduced or normal) and carbohydrates (strongly reduced) [28];
2. The supplementation of medium-chain triglycerides (MCT), in which about 60% of the caloric intake comes from MCT, whose metabolic fate can only be the production of energy, not being able to contribute to the synthesis of adipose tissue; if taken in excess, acetyl-CoA will accumulate, resulting in turn in the biosynthesis of ketones [28];
3. The modified Atkins diet (MAD), also known as the modified ketogenic diet (MKD), the most liberal in terms of protein intake and the least restrictive in terms of the need to weigh each food [28];
4. The Very Low-Calorie Ketogenic Diet (VLCKD), an extreme nutritional protocol (600-800 kcal), limited in time (up to 12 weeks), characterized by a minimum protein content based on the population reference intake for protein adjusted for overweight (≥ 75 g/day), a very limited

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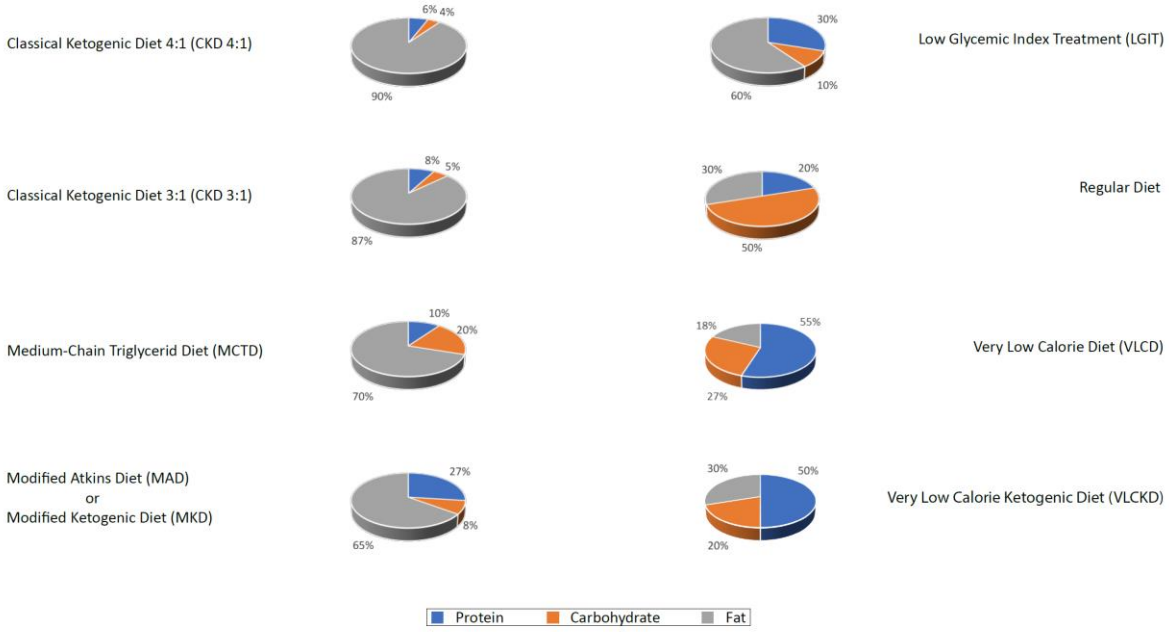
carbohydrate content (30-50 g/day), a fixed amount of fat (20 g/day, derived mainly from olive oil and omega-3), and micronutrients to meet the Dietary Reference Intake (DRI), in accordance with the European Food Safety Authority (EFSA) [31,34].

Figure 3



CKD and MKD protocols are sometimes referred to as Low-Carb High-Fat (LCHF) because of the peculiar distribution of macronutrients. It should be emphasized that ketogenic protocols produce a ketonemia never high, up to about 5 mM, therefore not comparable to the harmful levels found in ketoacidosis, typical of type I Diabetes Mellitus, in which blood ketones reach a range between 10 and 25 mM [35,36].

In addition to the above-mentioned protocols, it is worth mentioning the Low Glycemic Index Diet (LGIT), characterized by the intake of a higher quantity of carbohydrates (60-80 g/day) distributed over several meals, all coming from low glycemic index sources. This diet, although not strictly ketogenic, has been shown to be effective in some forms of epilepsy.[28]

SPECIFIC EVIDENCE OF THE EFFECTIVENESS OF KD IN HEADACHES

Clinical Evidence in Migraine

The first evidence of a potential benefit of the KD diet as a prophylaxis of migraine dates back to 1928 [37], starting from the erroneous assumption that migraine was an attenuated form of epilepsy, and that the

ketonuria sometimes found at the end of an attack in patients with cyclic vomiting and migraine was consequent to a physiological state of ketosis established to lead to the cessation of the attack itself.

A further study in 1930 [38] on 50 migraine patients showed an improvement of headache in 39 patients, with a total remission of headache in 50% of treated cases and a reduction of at least 50% of headache in 75% of patients.

The next mention in the Literature of the possible benefit of KD in migraine is from 2006 [39] and describes a single clinical case in which a chronic migraine (≥ 15 days/month) associated to medication overuse headache (MOH) had regressed during a prolonged period of treatment with VLCKD.

Furthermore, two additional cases [40] of obese patients with episodic migraine (< 15 days/month) improved with a VLCKD approach have been reported. To confirm this fortuitous observation, the same authors performed a proof-of-concept study [41] comparing on 95 patients with episodic migraine two weight-loss diet regimens: one VLCKD, the other hypocaloric nonketogenic. The study design foresaw for the group of patients undergoing KD a single month of ketosis, followed by another 5 months of non-ketogenic diet: one month of progressive reintroduction of carbohydrates in which patients continued to take nutraceutical supplements used also during the diet; one month of reintroduction of carbohydrates in the absence of these supplements; 3 months of "standard" slimming diet, similar to the one followed by the other group that had not undergone KD. At the end of the study, a slight improvement in migraine parameters was observed in both groups of patients compared to baseline. However, in the group that followed VLCKD there was a dramatic improvement of all migraine parameters during the ketosis state, which promptly regressed once KD was discontinued.

In light of these premises, in order to clarify definitively the real effect of KD on episodic migraine, a controlled, randomized crossover, double-blind study was conducted comparing 2 isocaloric diets of 800 Kcal per day: one VLCKD, the other Very Low Calorie non-Ketogenic Diet (VLCnKD) in a population of 35 obese migraineurs. At the end of the trial, the response rate (the number of patients with ≥50% reduction in headache frequency) was 74.28% of patients during VLCKD, compared with 5.7% during VLCnKD [42].

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Latterly, a group of 14 subjects with episodic migraine underwent to a one-month MCT supplementation without any dietary limitation. At the end of the study patients self-reported an improvement in terms of frequency, duration, and symptom severity of migraine [43].

More recently, the efficacy of a 3-month normo-caloric KD was also tested in a group of 23 patients with MOH [44]. Starting from a frequency of 30 days per month they decreased to 7.5; median headache duration tapered from 24 to 5.5 hours, and symptomatic drugs consumption from 30 to 6 doses per month.

Clinical Evidence in Cluster Headache.

In cluster headache (CH), reports of the efficacy of the ketogenic diet are limited to a single article in the scientific literature [45], although this is a much-discussed topic in various online patient discussion forums [46–49].

In a case series conducted prospectively for 3 months on 18 patients with drug-resistant chronic cluster headache (CCH) who were asked to follow a MAD diet, 15 patients were considered responsive to the diet: 11 had complete resolution of headache and 4 had an average reduction in attacks of ≥ 50% during the diet. At baseline, the mean monthly number of attacks for each patient was 108.71 (SD = 81.71); at the end of the third month of the diet, it decreased to 31.44 (SD = 84.61) [45]. Although preliminary and inconclusive, these results seem promising and suggest that CH patients may also benefit from KD.

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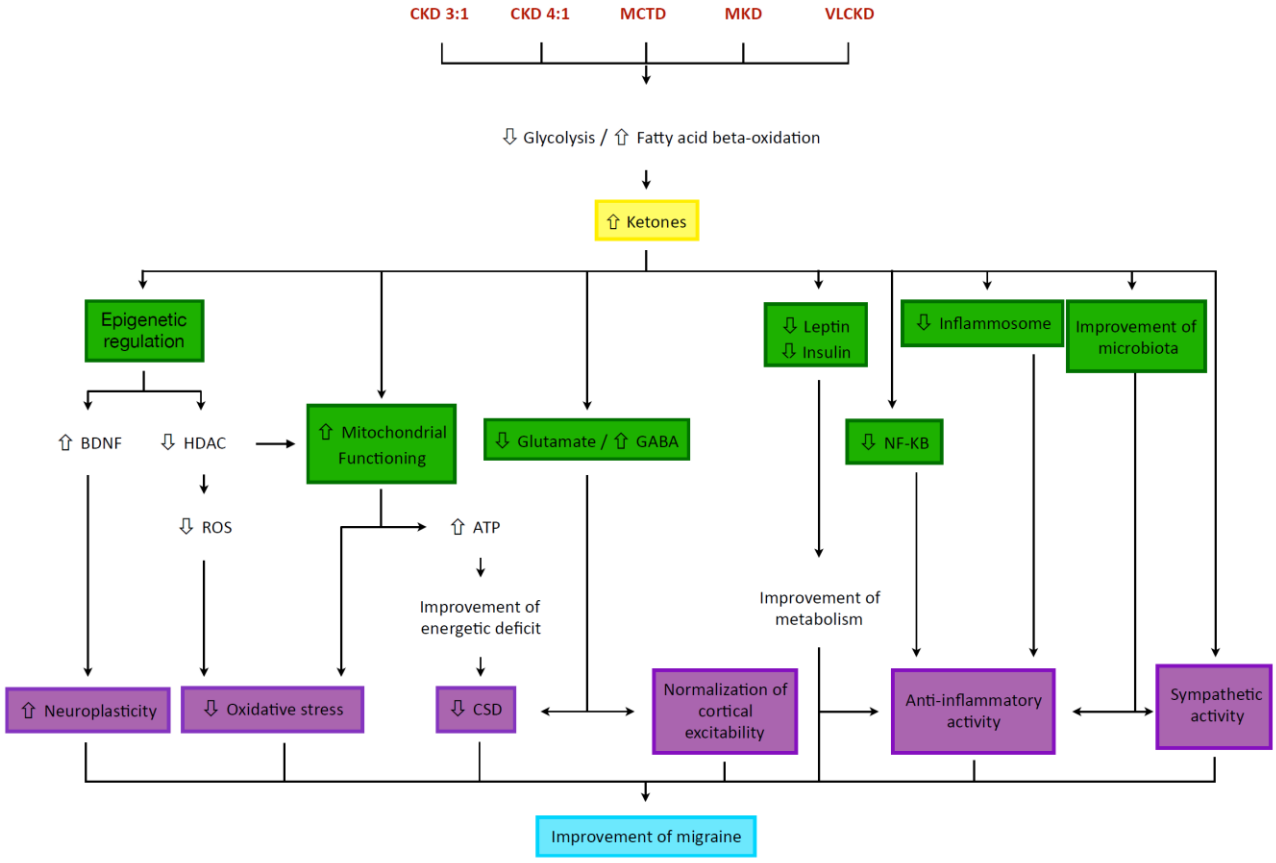
MECHANISMS OF ACTION

The mechanisms of action by which the ketogenic and non-ketogenic nutritherapeutic approaches may act are multiple (Figure 4), summarized as follows.

Figure 4



Neurophysiology

Through the study of evoked potentials (EPs) and brainstem/spinal reflexes, it is possible to study the functioning of different brain structures, like the cortex and the trigeminal nucleus caudalis. Through these methods it is possible to identify and monitor some pathophysiological markers of migraine, including habituation that is a decremental response to repeated non-salient stimuli, common to many biological systems. In most of the migraine patients, this phenomenon is absent in the intercritical period, whereas it normalizes during an attack. This has been widely demonstrated, both at the cortical and subcortical levels [50].

Thus, by the study of EPs (which analyze cortical activity) and of the blink reflex (which analyzes brainstem activity) it has been observed that regardless of the mode of stimulus received (visual, somatosensory and trigeminal nociceptive), during ketogenesis the interictal lack of habituation normalizes in migraine, while the deficit of habituation at the brainstem level persists [51,52]. This has led the authors to conclude that the action of ketones is exerted at the cortical level, not at the brainstem level, where the so-called "migraine generator" could be localized [53]. Therefore, the effect of KD could be exerted downstream of the triggering of the crisis.

Cerebral energy metabolism

Several magnetic resonance spectroscopy studies highlight that the brains of migraine subjects are consistently in energy deficit compared with those of healthy subjects[54,55].

The greater energy efficiency of ketones compared with glucose (100 g glucose generates 8.7 kg ATP, 100 g BHB can produce 10.5 kg ATP, and 100 g acetoacetate 9.4 kg ATP) [56] will alleviate the energy deficit described in the migraine brain.

From a molecular point of view, BHB is metabolized directly in the mitochondria to acetyl-CoA, which in turn is directed to oxidative metabolism in the Krebs cycle to produce ATP. At sufficiently high blood concentrations of ketones, under normal glycemic conditions, BHB can meet the entire basal neuronal requirement and approximately half of the activity-dependent neuronal requirement [57]. In general, ketones can cover up to 60-70% of energy requirements during a state of physiological ketosis [58] and are used by synaptic terminals and all brain cells as an energy substrate, especially by neurons and oligodendrocytes, which use them three times more efficiently than astrocytes [59,60].

Mitochondrial Functioning

In addition to improving energy metabolism, KD also improves mitochondrial biogenesis, as has been documented in animal model studies. Specifically, KD has been shown to promote the conversion of adipose tissue to brown fat, with an increase in median adipose tissue size and cAMP values of approximately 60%, a 2.5-fold increase in cAMP-binding proteins (suggestive of increased sympathetic

activity that would cause increased lipolysis), and an increase in mitochondrial oxidative phosphorylation proteins [61]. All of this would result in increased mitochondrial size and increased efficiency of lipolytic mechanisms. At the same time, this is associated with a halving of plasma levels of insulin and leptin [61], which by inducing insulin resistance contribute to the genesis of headache [62].

In addition, KD improves mitochondrial membrane permeability. This allows for greater exchanges, facilitating the supply of energy substrate and the release of waste and oxidative products that could damage mitochondria [63,64].

Oxidative stress

Migraine patients (in both chronic and episodic forms) exhibit increased oxidative stress [65].

The synthesis of 2 molecules of acetyl-CoA to be used for energy purposes by glucose involves the conversion of 4 molecules of NAD+ to NADH: 2 molecules of NAD+ are reduced at the cytoplasmic level, 2 at the mitochondrial level. On the contrary, the biosynthesis of the same 2 molecules of acetyl-CoA from BHB involves only the reduction of 2 molecules of NAD+ to NADH, both in the mitochondrion, preserving the cytoplasmic NAD+ pool (7) and thus preventing cellular aging by an epigenetic mechanism (inhibition of histone deacetylase) [66].

BHB reduces the production of reactive oxygen species [67] through its action on mitochondrial complex II [68,69]; furthermore, due to the increased heat of combustion of BHB relative to that of pyruvate, BHB also increases the efficiency of ATP production from the mitochondrial proton gradient and reduces free radical production [70].

BHB has also been shown to reduce lipoperoxidation caused by three days of intrastriatal glutamate injections in mice [71].

Anti-inflammatory mechanisms

Inflammatory phenomena related to nitric oxide (NO) pathways and involving nuclear factor-kappaB (NF-KB) are among the central drivers in migraine pathophysiology [72] by the activation of that transcription

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factor in the nucleus trigeminalis caudalis [73]. This inflammatory process is inhibited by the agonism of the hydroxy-carboxylic acid receptor 2 (HCA2) [74] that is, inter alia, expressed in dendritic cells and neuroglia, and has as endogenous ligand the BHB.[75,76]. Hence, BHB could lead to an inhibition of neuroinflammatory phenomena by the activation of HCA2 receptors that in turn reduces the proinflammatory stimulation of NF-KB induced by NO signaling.

Moreover, it is possible to hypothesize that also the inflammosome is involved in the inflammatory mechanisms typical of migraine; in fact, this protein complex, involved in the intracellular genesis of inflammation, has been related to headache manifestations having the characteristics of migraine [77,78]. BHB in immune cells has an inhibitory effect on the inflammosome, reducing the production of inflammatory cytokines and consequently inflammation [79].

Epigenetics

Histone hyperacetylation is generally associated with activation of gene expression; therefore, class I histone deacetylase (HDAC) activity suppresses such expression. BHB is structurally similar to butyrate, the canonical HDAC inhibitor [80]. Fasting, which increases plasma levels of BHB, is associated with increased histone acetylation in a number of tissues [66], including nerve tissue [81]. BHB has been shown to be an inhibitor of HDAC (HDAC1, HDAC3, and HDAC4 class I and II types) by a dose-dependent mechanism, resulting in upregulation of genes involved in the FOXO3A network, including catalase, mitochondrial superoxide dismutase (Mn-SOD), and metallothionein 2. This results in a gene expression mediated protection against oxidative stress and by regulating metabolism [66].

BHB also regulates BDNF (brain-derived neurotrophic factor) expression in the brain, particularly in the hippocampus. In addition to KD, exercise also increases BHB levels and BDNF expression in the hippocampus [81].

Another mechanism of epigenetic control is exerted by the so-called micro RNA (miRNA). It was recently observed that KD can modulate miRNAs in sense of the promotion of antioxidant and anti-inflammatory biochemical pathways [82] that could in turn lead to protection from migraine.

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Finally, also DNA methylation, the most known epigenetic mechanism, has shown to be involved in regulation of migraine pathophysiology by the modulation of gene expression of CGRP [83]. KD is able to modify the methylation state of genes and this mechanism of action was called in cause to explain its activity on epilepsy [84]. A similar mechanism of action could be called in cause for the proposed efficacy of KD on migraine.

Cortical Spreading Depression (CSD)

It is well known how important CSD is in the pathophysiology of migraine (at least in migraine with aura).

The gap between low ATP levels and excessive neuronal activation during the interictal phase [85,86] could lead to a metabolic imbalance capable of promoting CSD and activating the trigeminovascular system, thus triggering a migraine attack [87–89].

KD also has a protective effect on CSD because ketones reduce its propagation rate [90,91], as well as making its initiation less likely by correcting the energy deficit (see above).

Glutamate/GABA balance

BHB and KD induce increased biosynthesis of gamma-amino hydroxybutyric acid (GABA, the most important inhibitory neurotransmitter) via a decarboxylation process that irreversibly converts glutamate (GLU). In addition, further depletion of the brain concentration of GLU may be due to its use for energy purposes during KD [91]. All of this should lead to less GLU being available intracerebrally. This is important because GLU in addition to being an amino acid is the most important excitatory neurotransmitter, and is known to be a trigger for migraine [92–94]. Moreover, the cerebral cortex of migraine patients has a higher concentration of GLU [95]. Because of the above, it can be assumed that KD reduces both absolute GLU concentration and glutamatergic excitatory activity due to the increased concentration of GABA, which exerts an opposite neurotransmitter action.

Gut-brain axis

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Migraine very frequently may be associated with gastrointestinal disorders (nausea, dyspepsia). A gastric dysfunction causes the transit towards the intestine of not properly digested food, which may promote alterations of the microbiota with the development of putrefactive processes and consequent local inflammatory reaction [96,97]. This phlogistic state could induce an activation of vagal afferents towards the hypothalamus [98,99] leading to a worsening of migraine [100]. In support of this hypothesis, vagal inhibitory modulation presents a beneficial effect on migraine [101–104], cluster headache [105], and epilepsy [106].

KD, besides having a sympathomimetic activity [107] (thus counterbalancing vagal parasympathetic hyperactivity), also acts positively on the regulation of the intestinal microbiota [108], which is in turn involved in the pathogenesis of migraine, as suggested by two double-blind studies on the efficacy of probiotic supplementation [109,110].

Intracerebral Glucose Metabolism

A further possible mechanism of action involved in the efficacy of KD in migraine is related to a potential improvement of patients' intracerebral glucose metabolism. In particular, we speculate about a role for the SLC2A1 gene, accounting for GLUT1 deficiency syndrome, an autosomal recessive disorder in which the type 1 glucose transporter (responsible for crossing the blood-brain barrier of this sugar) has reduced or absent function. Several cases have been reported in the literature in which migraine was part of the symptom spectrum of GLUT1 deficiency syndrome [111] and regressed following the establishment of a KD. It could be supposed that the presence in heterozygosity of polymorphisms or mutations in this gene may lead to intermediate phenotypes due to decreased sugar supply to the brain, leading to the development of a clinical parade of neuropsychiatric symptoms, including migraine. The only existing therapy in GLUT1 deficiency syndrome is KD, because ketones do not require the activity of this transporter to cross the blood-brain barrier, bypassing the metabolic blockade and restoring proper energy metabolism [112,113]. Like this pathology, it is possible to hypothesize a protective role of KD from any abnormality of glucose metabolism in migraine subjects.

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Migraine and Metabolic Syndrome

MetS is characterized by the presence of a group of criteria defined in a consensus document published in 2009 by the IDF, NHLBI, AHA, WHF, and IASO [114].

Harmonized criteria for diagnosis:

- obesity, defined as abdominal circumference (≥95 cm man and ≥80 cm woman) plus at least 2 of the criteria below;

- hypertension (blood pressure ≥130/85 mmHg or patient on antihypertensive therapy);

- fasting blood glucose (≥110 mg/dl);

- triglyceridemia (≥150 mg/dl);

- low plasma HDL levels (< 40 mg/dl man and < 50 mg/dl woman).

The MetS predisposes to the possibility of developing cerebrovascular and cardiovascular diseases, diabetes, cancer, polycystic ovary syndrome, etc.

In addition, MetS is more prevalent in migraineurs (21.8% with aura, 16.8% without aura) than in controls (14.5%), [115] and is related to the development of its chronicity, especially of MOH [116]. Among the characteristics of MetS, those most correlated with migraine with and without aura are low HDL cholesterol levels, hyperglycemia, and excess visceral fat [117].

Migraineurs exhibit a tendency toward hyperinsulinism compared with healthy subjects and those with other forms of headache [118,119], and they have more cerebrocardiovascular events (which is the expected outcome of MetS) and more risk factors for such events [120].

Obesity and underweight are two risk factors for the development of migraine and its chronicity [121]. In general, there is a correlation between the frequency of migraine attacks and two weight measures, BMI and waist; this association is stronger in patients on prophylactic therapy, who are also more frequently found to be overweight [122]. In contrast, in obese subjects a high total fat free mass (lean mass) would

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seem to be a protective factor against the development of migraine [123]. In addition, it has been reported that weight loss may lead to an improvement in the frequency of migraine attacks [41,124,125]. Therefore, it is conceivable that a body recomposition aimed at reducing fat mass and preserving/increasing lean mass may be protective against migraine. Typically, such recomposition is observed precisely with VLCKD-type slimming protocols [126].

Interestingly, weight gain is a common side effect of most migraine prophylaxis treatments. In particular, flunarizine, valproic acid, and amitriptyline induce weight gain related to higher levels of insulin, leptin, and peptide C [127], along with changes in hypothalamic orexinergic peptide levels [128–130]. The above mentioned changes induced by the use of preventive treatments for migraine, in particular weight gain [121], alterations of insulin and leptin levels [62], and the development of leptin resistance (which in turn is potentially responsible for worsening headaches regardless of weight gain [131]), could counteract the efficacy of therapies, leading in the long term to a worsening of the pre-existing migraine (in a sort of "prophylactic paradox") and therefore to the discontinuation of therapy for ineffectiveness and/or weight gain. Actually, it has been reported that patients on preventive therapy for migraine tend to develop a worsening of metabolic parameters related to the worsening of headache [122].

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STUDY GROUP RECOMMENDATIONS ON THE MANAGEMENT OF HEADACHE PATIENTS USING A KETOGENIC DIET.

Creation of the study group

A group of experts in the field of headache with a specific interest in KD was identified by Drs Cherubino Di Lorenzo and Giulio Sirianni, based on scientific publications, congress proceedings, and direct knowledge of the prescription of KD to treat headache. Through this selection, specialists from eight Headache Centers have been identified and have agreed to participate in our board (Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, IRCCS - Ospedale Bellaria Carlo Alberto Pizzardi of Bologna, Piero Palagi Hospital of Florence, Headache Center of the Polo Pontino of the Sapienza University of Rome, San Carlo Borromeo Hospital of Milan, IRCCS - San Raffaele Pisana of Rome, Humanitas Gradenigo Hospital of Turin, Azienda Ospedaliera Santa Maria della Misericordia of Udine). All centers have been treating headache patients with KD for a period ranging from one to ten years. In four cases the Centers have a Keto-Team, or in-house medical consultants and/or dietitians experienced in the use of KD.

Participants were asked to complete a questionnaire about their direct experience with the specific topic. Responses and comments were collected by Dr Grazia Semeraro and incorporated into a document that was discussed in two roundtables by the group of experts. At the end of this work, a draft concluding report was produced and shared, revised by 3 external experts, one in the field of migraine (Gianluca Coppola), another one in the field of adults' neurological indications (Mackenzie C Cervenka), and the last in the field of MetS (Gianni Spera), the final version of which is this document.

Recommendations

Patient Selection

The expert panel agreed that patients to be referred to KD are predominantly migraine subjects with and without aura, both in the episodic form [(≥4 days/month, <15 days/month), analogous to other prophylaxis as reported by SISC and ANIRCEF (the 2 Italian scientific societies dealing with headache) guidelines [132,133] and chronic (≥15 days/month), subjects with MOH and subjects with CH, episodic in active phase

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or chronic. Within these diagnostic groups, the indication to KD is considered for overweight, obese or with MetS subjects, and for those whit resistance, non-tolerability, or contraindications (evidenced by history or medical records) to prophylactic drug therapies and for patients who have expressly asked the specialist to start this diet therapy, not wanting to undergo a pharmacological prophylaxis. In addition, the indication for a KD should also be reconsidered in cases in which a previous dietary failure was attributable to the inadequacy of the dietary protocol, which was not developed in light of the specificities imposed by the therapeutic indication for headache (see below). In the selection phase, patients should be made aware of the goals to be achieved: reduction of headache days by at least 50% of analgesic consumption and of any prophylactic drugs. The patient must be informed and fully aware of the commitment he/she must make in following the diet therapy treatment.

Multidisciplinary evaluation and diet therapy

All participants in the working group agreed that the patient would only receive by the headache specialist, after the clinical evaluation, the proposal to perform KD, which would then have to be screened and possibly approved by the nutrition professional (dietologist, nutritionist, and dietitian) who would develop and personalize the diet.

Hence, in all the headache centers involved in the board, once the patient has been selected for evaluation by the nutrition professional, the diet is started only after an outpatient visit by the latter to confirm suitability for KD, and to elaborate and explain the diet therapy scheme. The choice of the type of diet to be followed by the patient is also determined according to the patient's preferences, in order to increase his/her ability to adhere to the new dietary plan, so as not to create excessive discomfort in home and work life. It is not necessary to hospitalize the patient or undergo a preventive fast.

One of the most delicate moments of the diet therapy course for the patient is certainly the beginning of the diet. Different approaches have been proposed, from the sudden change of the diet to a more gradual start with a LGIT or MKD with an initial ratio of about 1:1, and then increase the fat intake and reduce the glucidic and protein intake. In cases where there is a transient worsening of the clinical picture in the first

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days of the diet, additional meals can be provided, in addition to any pharmacological therapy to control headaches. If there is no response to the diet within 3 months, the ketogenic ratio can be increased further. If ineffectiveness persists, the diet can be discontinued by month 6.

KD requires specific integrations of minerals (cations) and vitamins. In particular, the subject with headache presents specificities with respect to other neurological indications of KD. It is necessary to pay attention to a correct integration of magnesium and folic acid, whose deficiency may be associated with a worsening of headache [134]. In KD, especially for LCHF diets, Omega-3 supplementation may be useful to improve the lipid profile and possibly benefit from an additive protective effect on headache (a finding proposed by several authors but not yet consolidated) [135].

By a review of each center practice, it resulted that the types of diet used in the treatment of headache were similar to those used in the field of epilepsy, with some specificities.

1. Unlike other neurological diseases, migraine can in some cases recognize specific trigger foods for each patient; in general, excessive use of foods containing biogenic amines (aged cheeses and sausages), especially histamine (nuts), monosodium glutamate and processed foods should be discouraged [136]. In addition, some patients have reported worsening headache by consuming foods with gluten additives, excess fermentable oligo- and mono-saccharides and polyols (FODMAP), or using seed oil.
2. In Italy, the VLCKD protocols are widely used for weight loss, generally not used in the neurological field as ketogenic therapies. However, these protocols have been used on several obese patients by all centers of our working group and their efficacy on migraine has been repeatedly reported in the literature [39–42]. The use of these diets should be limited to no more than 12 consecutive weeks [34], at the end of which the patient either exits the state of ketosis (even receiving the indication to follow a maintenance diet of LGIT or Mediterranean type without added sugars), or transit to a normo-caloric KD of longer duration.
3. In the field of epilepsy, the use of 3:1 CKD is common, as can be seen in literature. On the contrary, since the centers involved in this board are mainly active in the treatment of adult subjects, few of

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their patients have been assigned to follow a CKD with a high ketogenic ratio (≥3:1) because of the difficulty of matching the caloric requirement to the protein one (for instance, in case of a protein need of 70 gr and considering a daily intake of 30 gr of carbohydrates, to fulfill the 3:1 ratio should be assumed 300 gr of fats, for a total daily amount of 3100 kcal). Therefore, most used diets were MKD (maintaining a ketogenic ratio around 2:1), MCTD, and VLCKD (for obese patients).

4. Although exogenous ketone sources (salts or esters) are already commercially available and regarded as a promising therapy in both epilepsy [137] and migraine [20], no center of those involved in the working group has developed its own clinical experience in this regard. While waiting for data on clinical trials [138], some remarks are however raised about their use as it would determine a partial effect compared to that of a KD. In fact, the therapeutic action of the diet is not only due to the role played by ketones, but also to the change in the macronutrients consumed (see LGIT diet) and the correction of insulin resistance typical of migraine sufferers. Therefore, while suspending judgment on this approach, the board expresses some caution towards it, especially from a metabolic point of view.

Contraindications

Absolute and relative contraindications to treatment should be ruled out before having patients start the diet (Table 1). If there is a contraindication to KD, a nutritherapy approach may still be pursued by addressing patients to an LGIT protocol. Some contraindications may arise after starting the diet, as is the case of pregnancy. In the absence of data on the safety of a KD approach for the mother and fetus [139], when the event of pregnancy occurred during KD, the patient should be immediately transitioned to an LGIT diet.

Socioeconomic aspects and the presence of a family support network should also be taken into account before proposing the diet to the patient.

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Table 1.

ABSOLUTE CONTRAINDICATION	RELATIVE CONTRAINDICATION
Porphyria Pyruvate carboxylase deficiency Fat metabolism disorders	Pregnancy and breastfeeding Renal failure Severe nephrolithiasis Hepatic failure Pancreatitis Type 1 Diabetes Mellitus Arrhythmias Angina Recent myocardial infarction Severe osteoporosis Alcoholism Eating disorder Poor compliance

Patient monitoring

Before starting the diet, the patient should undergo an electrocardiogram and a complex laboratory evaluation (Table 2). These examinations should be repeated every six months, while in the case of diets of longer duration (>12 months) the board proposes to perform also Bone Densitometry and Echo Abdomen.

It is also recommended that nutrition professionals to whom patients will be referred, in addition to height and weight, take note of anthropometric measurements (including waist circumference and plicometry) and possibly perform an examination of body composition (eg, Bioimpedance).

The working group agrees that patients undergoing KD should keep a headache diary during treatment to monitor headache parameters and a food diary in which to note each food ingested and monitor body weight. It is also recommended, in case of lack of response to nutritive therapy, to measure the production of ketones, mainly through urine (cheapest and most common method), but also through the exhaled or capillary blood. It is recommended that blood glucose be re-evaluated extemporaneously in case of asthenia, dizziness, sweating, or other physical symptoms.

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Table 2

MONITORING				
Before starting	**Every day**	**Every 6 months**	**Every 12 months**	**In case of non-response to KD**
Complete blood count Glycemia* Basal insulin OGTT (Glycemic level, Insulin level) Total cholesterol LDL, HDL, Tg Direct bilirubin Indirect bilirubin GOT e GPT Uricemia/Azotemia Creatininemia Homocysteinemia Protein electrophoresis Na, K, Cl, Ca, P, Mg Folates Vitamin B12 Vitamin D Urinalysis EKG Blood pressure Weight	Headache diaries Eating diaries	Complete blood count Glycemia* Basal insulin Total cholesterol LDL, HDL, Tg Direct bilirubin Indirect bilirubin GOT e GPT Uricemia/Azotemia Creatininemia Homocysteinemia Protein electrophoresis Na, K, Cl, Ca, P, Mg Folates Vitamin B12 Vitamin D Urinalysis EKG Blood pressure Weight	BMD/DEXA Abdominal ultrasonography	Evaluation of ketones (blood, urine or breath)

Side effects

In general, the centers involved in the board have rarely found the onset of side effects in patients who scrupulously follow the assigned indications. Among the most frequent are muscle cramps, asthenia, hypotension, constipation, and unintended weight loss. To correct the first four, it is almost always sufficient to adjust the supplementation of specific minerals and hydration. In case of unintended weight loss, if it is not possible to correct it, it may be necessary for the patient to abandon the diet, but he/she can be directed towards an LGIT diet. The side effects rarely encountered were hyperlipidemia (generally transitory and well controlled by the assumption of Omega-3 or hypolipidemic drugs),

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gallstones (especially in case of heavy weight loss, treatable with ursodeoxycholic acid), menstrual irregularity (mainly in VLCKD protocols), and alopecia and nail fragility (usually after long periods of diet, treatable with specific supplements). Gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and diarrhea were more rarely reported. On the other hand, however reported in literature, neither prurigo pigmentosa (the so called keto rash) [140], nor mood alterations [141] due to the prolonged duration of the weight loss diet were observed by members of the bord in their practice (Table 3).

Table 3

SIDE EFFECTS		
COMMON	**INFREQUENT**	**VERY INFREQUENT**
Muscle cramps Fatigue Hypotension Constipation Undesired weight loss	Hiperlipidaemia Gallbladder stones Menstrual irregularity Alopecia Nail fragility	Nausea Vomiting Abdominal pain Diarrhoea Prurigo pigmentosa (keto rash)* Mood disorders*

Causes for reduced compliance

The reasons that most frequently lead patients to reduce compliance with the diet were found to be, in order: inadequate response to treatment, intolerance to carbohydrate restriction or craving for carbohydrates, deviating too much from dietary preferences, monotony and poor dietary variability, disruption of family harmony (eating the same meal together / having to cook different dishes), the creation of problems at work (embarrassment in eating differently from colleagues / impossibility to respect meal times / impossibility to be able to consume ketogenic meals at work), costs, difficulty in managing social life and continuing the diet during the vacations, the impossibility of having a dedicated care-giver, the excessive loss of time to organize shopping and meal preparation, the persistence of some residual attacks despite the diet.

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Some of these issues should be deeply analyzed with the patient to improve adherence to the diet. Inadequate response to treatment may depend on peculiarities specific to the patient with headache, which must be known to the nutrition professional. It is common experience in several centers that patients did not initially respond to KD until a protocol was formulated that avoided certain potentially trigger foods. The nutrition specialist should help the patient with the finding of raw materials, explaining which foods to choose to avoid mistakes, and providing with a variety of recipes or substitutes so that all the eating preferences could be satisfied; in this way, phenomena such as cravings for sweet foods, detachment too much from one's dietary preferences, and dietary monotony could be avoided. Thanks to an adequate training of the patient, it is possible to teach him/her what to eat when he/she is away from home and in social contexts, thus eliminating these factors that hinder the success of the diet (holidays / social contexts). In fact, the time needed to dedicate to the diet is almost always a false problem, since by adequate training the patient will not need more time than he/she needs to eat a free diet; furthermore, the existence of ready-to-eat meal replacement products on the market could even save time and make it more practical to follow the diet, even for those who do not have the support of a dedicated caregiver. The last element that could contribute to reduce the patient's compliance is the high costs to be sustained. Certainly, the lack of a dedicated keto-team and therefore the need to carry out examinations and consultations externally can greatly increase the costs for the patient. On the other hand, even prophylactic drug therapies would need monitoring, an aspect that is often underestimated by headache specialists. Concerning the direct costs of the diet, a diet based on good quality food (possibly organic) comparable to the costs of a KD.

Duration of the diet

There is no optimal duration for the diet that can be generalized to all patients. In case of efficacy, the minimum duration of the diet should not be less than 3 months (as for all prophylactic therapies), so when the target weight is reached in overweight/obese subjects, the caloric intake should be modified to allow the continuation of the KD, if starting with a weight-loss diet. In patients with episodic CH in active phase, the diet can be suspended at least one month after the presumed end of the cluster and

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not before one month after the last attack. In episodic and/or chronic migraineurs and in those with chronic CH resistant to other prophylactic therapies, the duration of treatment should be agreed with the patient according to their preferences. The experience of Headache Centers suggests that at the end of therapy there may be a transient persistence of benefit directly proportional to the kg lost (in the case of obese patients, for diets of shorter duration), to the duration of the diet (in the case of normal weight subjects), and to the effectiveness of KD as a detoxification treatment in MOH. Thanks to the experience of centers that have been applying this treatment for a longer period of time, we can roughly say that by suspending the diet after three months the persistence of the benefit tends to occur in about 20% of patients, after six months in about 30% of patients (in both cases these benefits persist more in subjects who have lost a lot of kg), after 12 months in about 50% of patients (regardless of weight loss). For longer durations of KD no clearly greater after-effects have been observed and in general after one/two years from the suspension of the diet the headache tends to worsen again. Therefore, it is advisable to invite patients to discontinue treatment after 12 months in order to take advantage of the possible transitory persistence of the benefit even by suspending treatment. If desired, KD can be cycled just like other prophylactic headache therapies. In case of headache recurrence upon discontinuation, especially for chronic patients, the diet can be restarted. To date, there are some patients who have been on the diet continuously for more than six consecutive years without discontinuation.

There is no unique protocol for discontinuing the diet. In the case of LCHF protocols, fats must be progressively reduced; in the case of VLCKD, fats must be increased. In both cases, there is a tendency to have a 1:1 ketogenic ratio reached and then transition to an LGIT for a variable period of time to allow the progressive increase of the carbohydrate amount. Although the majority of patients were advised a Mediterranean-type maintenance diet, preferring low-glycemic index carbohydrate sources, many patients subsequently returned to a free diet, sometimes re-adopting bad eating habits, although others preferred to continue to eat following an "Atkins" or "Paleo" style or following a "Zone Diet".

Pharmacological management

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KD should be seen as an add-on therapy to any existing pharmacological prophylaxis, which could be subsequently reduced up to the possible suspension in case of headache improvement. In fact, there are no absolute contraindications to the use of symptomatic and prophylactic headache medications during KD protocols, but attention must always be paid to the carbohydrate content of the single dose, especially in liquid and sachet formulations; intramuscular vials and suppositories do not contain carbohydrates, while tablets have small amounts.

However, although the co-occurrence of a KD with common drug therapies is generally judged to be safe, some additional aspects should be kept in mind:

1. Topiramate may interfere with renal function by promoting stone formation and modifying the proper excretion of ketones through the urine, facilitating metabolic acidosis. In addition, it can cause hyposthenia and determine cardiac alterations that could be added to those potentially due to possible electrolyte alterations related to diet. Its use should be carefully monitored, possibly limited and, where feasible, the dosage should be scaled back in subjects who were already taking it before starting a KD.
2. Valproic acid can alter hepatic metabolism, creating problems in the genesis of ketones. The use of this drug should also be monitored or limited during KD.
3. Beta-blockers and verapamil may result in bradycardia and hyposthenia that would add to those due to KD, in which case drug dosages should be revised.
4. Corticosteroids, often used as salvage therapy in status migrainosus (a debilitating migraine attack lasting for more than 72 hours), as a strategy to interrupt the medication overuse in MOH, and as prevention in CH, may interfere with ketogenesis because of its impact on hepatic functioning and because of its hyperglycemic power. Therefore, use of steroids should be carefully evaluated, severely limited, and monitored during a KD.
5. Flunarizine and amitriptyline, in addition to also being able to result in ECG alterations, may, along with valproic acid, result in increased appetite and ponderal status. This could contrast with the

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compliance to the diet and with the possible desire to lose weight. These aspects should be considered in case of co-treatment.

6. Although symptomatic drugs (non-steroidal anti-inflammatory drugs (NSAIDs), Triptans, Ergot-derivatives, combination drugs) are not contraindicated in KD, sometimes their overuse can nullify the diet preventive effect on migraine. From the experience of centers that have treated many MOH with KD, even when patients do not interrupt medication overuse, it appears that in more than 50% of cases the diet is effective in blocking overuse of analgesics and headache chronicity. If this does not happen, a discontinuing therapy without corticosteroids can be combined without interrupting the diet, often with excellent results even in patients in whom previous attempts at medication overuse ending have failed. In general, however, caution should be exercised with the overuse of NSAIDs and acetaminophen because of the impact these drugs may have on renal and hepatic metabolism.

Future perspectives

Possible future developments emerged from the discussion of the working group on KD in headache. The first thing highlighted by the board participants is the poverty of studies compared to epilepsy, for which there are many publications and clinical trials. Therefore, it is hoped that this type of scientific research development can also be carried out in the field of headaches, in order to consolidate more and more evidence on the topic. In particular, it would be interesting to evaluate the impact of an MKD in migraine and CH in double-blind studies.

Additional topic to be studied in these KD responsive headaches would be the effect of supplementation of MCTs with a more palatable and liberal diet, such as LGIT, to see if there could be a benefit for such headaches as well with this approach. Still to be evaluated is the role of KD in other rarer forms of trigeminal autonomic headaches, such as paroxysmal hemicrania and continuous hemicrania. Similarly, the effect of KD in tension-type headache should be evaluated: it is the common opinion of the panel participants that this form of headache does not benefit from this approach, but there is a lack of studies ratifying its ineffectiveness.

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Another aspect stigmatized by the members of our board is the current difficulty for a Headache Center to have a Keto-Team, which is essential in the dietary management of patients. In particular, a physician dedicated to the metabolic/nutritional aspects (internist, endocrinologist, or specialist in nutritional sciences) and a dietician (a key element to be able to formulate the KD in patients with migraine) or a nutritionist, in addition to any other professional figures such as a dedicated nurse and psychologist, are identified as necessary for the creation of the Keto-Team.

In order to facilitate patient access to this type of care, it would be appropriate to create specific complex care pathways to automate, after the proposal of the headache specialist to begin nutritherapy, the intake and all the subsequent diagnostic-therapeutic process. It could be the task of the dedicated nurse to set the schedule of appointments with the various professionals involved: the physician who assesses the patient's suitability for the diet, periodic meetings with the nutrition professional, and follow-up visits with the headache specialist. The realization of these pathways within public or affiliated healthcare facilities could, in addition to simplifying the process for the patient, reduce costs.

In order to increase the diffusion of these nutritherapies and improve patient compliance, it would be appropriate to involve the world of associations and organize with them courses of ketogenic cooking and information material, both printed and digital. The group of experts hopes that in the future it will be possible to organize specific training for patients and their families within the centers and provide them with dedicated brochures.

Author Contributions: CDL ad Giulio Sirianni (GS) made substantial contribution to the project and implementation of the panel of experts' creation. CDL and Grazia Semeraro (GrS) performed the literature review and created the preliminary material for the board meetings. CDL, GB, PB, AB,GDA, GE, FF, RG, GP, MPP, NR, GS and MV participated to the work as discussants into the board. GrS took

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minutes of the meetings and prepared drafts of the report. GC, MCC and Gianni Spera (GiS) revised the report and the final version of manuscript.

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Informed consent: Not applicable.

Abbreviations:

ATP	Adenosine Triphosphate
BDNF	Brain-Derived Neurotrophic Factor
BHB	β-Hydroxybutyrate
CCH	Chronic Cluster Headache
CGRP	Calcitonin-Gene Related Peptide
CH	Cluster Headache
CKD	Classic Ketogenic Diet

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CoA-SH	Coenzyme A
CSD	Cortical Spreading Depression
EP	Evoked Potentials
DRI	Dietary Reference Intake
EFSA	European Food Safety Authority
GABA	Gamma-Amino Hydroxybutyric Acid
GLU	Glutamate
HCA2	Hydroxy-Carboxylic Acid Receptor 2
HDAC	Histone Deacetylase
KD	Ketogenic Diet
LCHF	Low-Carb High-Fat
LGIT	Low Glycemic Index Diet
MAD	Modified Atkins Diet
MCT	Medium-Chain Triglycerides
MetS	Metabolic Syndrome
miRNA	Micro RNA
MKD	Modified Ketogenic Diet
MOH	Medication Overuse Headache
Mn-SOD	Mitochondrial Superoxide Dismutase
NAD^+	Nicotinamide adenine dinucleotide (oxidized form)
NADH	Nicotinamide adenine dinucleotide (reduced form)

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NF-KB	Nuclear Factor kappaB
NO	Nitric Oxide
ROS	Reactive Oxygen Species
OGTT	Oral glucose Tolerance Test
VLCKD	Very Low-Calorie Ketogenic Diet
VLCnKD	Very Low Calorie non-Ketogenic Diet

Figure legends:

Figure 1. Ketones

Figure 2. Biochemistry of intrahepatic ketogenesis and energy metabolism of ketones. CoA-SH = Coenzyme A; NAD^+ = Nicotinamide adenine dinucleotide (oxidized form); NADH = Nicotinamide adenine dinucleotide (reduced form).

Figure 3. Macronutrient composition of dietary interventions

Figure 4. Potential mechanisms of action of the ketogenic diet. ATP = Adenosine triphosphate; BDNF = Brain Derived Neurotrophic Factor; CKD 3:1 = Classic ketogenic diet with ketogenic ratio 3:1; CKD 4:1 = Classic ketogenic diet with ketogenic ratio 4: 1; CSD = Cortical Spreading Depression; GABA = Gamma-aminobutyric acid; HDAC = Histone deacetylase; LGIT = Low glycemic index diet; MCTD = Medium chain triglyceride diet; MKD = Modified ketogenic diet; ROS = Reactive oxygen species; VLCKD = Very low-calorie ketogenic diet.

Table legends:

Table 1. Absolute and relative contraindications to ketogenic diet

Table 2. Patient monitoring. *Extemporaneous assessment in case of asthenia, dizziness, sweating, or other physical symptoms. LDL = Low-density lipoprotein; HDL = High-density lipoprotein; Tg = Triglycerides; GOT = Glutamic-oxalacetic transaminase; GPT = Glutamic-pyruvic transaminase; Na =

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Sodium ; K = Potassium; Ca = Calcium; P = Phosphorus; Mg = Magnesium; Vit B12 = Vitamin B12; Vit D = Vitamin D; ECG = Electrocardiogram; MOC = Computerized Bone Mineralometry; DEXA = Dual Energy X-ray Absorptiometry.

Table 3. Side effects of ketogenic diet. *Not directly observed by the authors in the patients they followed on the ketogenic diet.

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