Review Article

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Application and Effectiveness of Dietary Therapies for Pediatric Migraine

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Abstract

Migraine is a representative type of primary headache and a common chronic neurological disease that accounts for a large proportion of headaches in children, adolescents, and adults. Unlike migraine in adulthood, pediatric migraine occurs when brain development is not yet complete. This characteristic may require a new perspective for the treatment and management of pediatric migraine. Dietary therapies, mainly the ketogenic diet and its variants, can have positive effects on pediatric migraine. Several recent studies have revealed that dietary therapies, such as the classic ketogenic diet, modified Atkins diet, and low glycemic index diet, improve various neurological diseases by improving dysbiosis of microbiota, reducing proinflammatory cytokines, and increasing mitochondrial function. Nonetheless, the mechanism through which active dietary therapy affects pediatric migraine requires further research. To achieve this, an important role is played by the neuro-nutritional team, which can develop and manage tolerable diets for pediatric migraine patients through mutual collaboration among pediatric neurologists, nurses, and nutritionists.

Keywords: Diet therapy, Headache, Ketogenic diet, Migraine disorders, Pediatrics

INTRODUCTION

Children and adolescents frequently complain of headaches. Migraine is a common primary headache and a prevalent chronic neurological disease, accounting for a large portion of headaches not only in adults but also in children and adolescents.[1-3] Migraine is commonly perceived as something that occurs primarily in adults. However, beginning with puberty, the prevalence of migraine begins to increase rapidly, and this rapid change is noticeable in female adolescents.[4-6] This rapid increase in migraine prevalence in adolescent girls culminates in a high prevalence of migraine among adult women. Pediatric migraine not only affects daily academic activity, relationships with friends, school, and family life but also is associated with secondary psychological disorders.[3,5] If pediatric migraine is not managed early, it can greatly hinder the normal neurological development of children and adolescents, thus transforming it into a social problem. Therefore, early detection and management of pediatric

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migraine can reduce the prevalence and disease burden of pediatric migraine in adulthood. More attention is now being paid to the diagnosis and treatment of pediatric migraine than was done previously.[6,7]

Pediatric migraine has a slightly higher prevalence in males; however, its prevalence in females increases rapidly after puberty, thus reversing the trend. This suggests that hormonal changes may significantly affect the occurrence of pediatric migraine. Pediatric migraine is thought to have a variety of causes, with various molecular mechanisms, brain networks, genetics, and other factors having complex roles.[2,3] However, the cause of migraine remains unknown. Pediatric migraine differs from adult migraine in that it occurs at a time when brain development is not yet complete. These characteristics suggest that a new perspective is required for the treatment and management of pediatric migraine.[6-8]

TREATMENT OF PEDIATRIC MIGRAINE

Pediatric migraine treatments can be broadly divided into three categories: acute treatment, preventive medication, and non-pharmacological treatment including lifestyle modification and neuromodulation.[3,7] Acute treatment includes drugs such as acetaminophen, ibuprofen, and naproxen, as well as triptans to rapidly alleviate acute headaches in patients. However, the frequent use of acute treatment carries the risk of medication overuse headaches. Triptans are effective migraine-targeted analgesics but may have the side effect of vasoconstriction. Therefore, it is necessary to prevent migraine through appropriate preventive medications and reduce the use of acute treatment. In addition, the ditans, a group of selective 5-HT_{1F} receptor agonists, is an acute treatment that ameliorates the side effects of triptan-induced vasoconstriction. Ditans are currently undergoing a phase III clinical trial in pediatric patients with episodic migraine aged 6–17 years, and not yet widely used in the treatment of pediatric migraine.[2]

Preventive medications include antiseizure medications, antidepressants, beta blockers, calcium channel blockers, and calcitonin gene-related peptide (CGRP) monoclonal antibodies, which have recently received great attention. The CGRP monoclonal antibody is the first migraine-specific preventive medication.[4,8] CGRP is a neuropeptide secreted by the terminal of the trigeminal nerve during a migraine attack. Anti-CGRP monoclonal antibodies are a new medication that achieve migraine prevention by blocking CGRP itself or the CGRP receptor, and its safety has been confirmed. Fremanezumab, galcanezumab, and eptinezumab directly target CGRP (fremanezumab and galcanezumab are available in Republic of Korea), whereas, erenumab is a CGRP receptor antibody. Phase III clinical trials in pediatric patients are in progress.[8] Recently, the American Headache Society's Pediatric and Adolescent Headache special interest group issued an expert opinion suggesting that CGRP monoclonal antibodies could be considered for post-pubertal adolescent patients with chronic migraine who do not respond well to two or more preventive medications.[4,8,9] Additionally, there are GGRP receptor antagonists called gepants, but phase III studies on these are not yet in progress.[8]

Before the emergence of anti-CGRP monoclonal antibodies, migraine was prevented using various antiseizure medications, antidepressants, beta-blockers, and calcium channel blockers. However, these drugs are either have not completed sufficient clinical trials, not approved for use, or have side effects that make them unsuitable for use in children and adolescents. These limitations in addressing pediatric migraine render treatment more difficult and require a different approach than that for adult migraine.[4,8] In addition, the Childhood and Adolescent Migraine Prevention (CHAMP) study, conducted in 2017 targeting patients aged 8 to 17 years, found no significant difference in the headache prevention effect of amitriptyline or topiramate when compared to a placebo. Thus, the need for migraine-targeted preventive medication and other modes of treatment, such as lifestyle modification and cognitive behavior therapy was further requested through the CHAMP study.[7,8,10]

Non-pharmacological treatment, especially lifestyle modification, the third treatment for pediatric migraine, is essential in patients with migraine of all ages. This includes diet therapy, dietary habit correction, and regular, appropriate exercise and is necessary for effective long-term management of pediatric migraine. Lifestyle modifications such as establishing a healthy sleep pattern, sufficient water intake, regular living, regular exercise, and reduction of light stimulation in daily life are important parts in preventing migraine. Among them, eating habits are known to be a very powerful lifestyle modification. Recently, due to

the research on the gut microbiota-brain axis, the relationship between intestinal microorganisms and brain disease has been highlighted. In this context, attempts have been made to prevent and manage pediatric migraine through diet therapy.[11-13] The diet therapies typically implemented in pediatric migraine include ketogenic diets (KDs), the modified Atkins therapy (MAD), and the low glycemic index diet therapy (LGIT), which are currently used in the treatment of intractable epilepsy. This type of dietary therapy is based on good quality, high lipid, and low carbohydrate foods.[13-16]

TYPES OF DIET THERAPY FOR PEDIATRIC MIGRAINE MANAGEMENT

Representative diet therapies for managing pediatric migraine can be considered broad variations of the KD.

1. Classic ketogenic diet (KD) (KD 4:1, KD 3:1)

The KD creates ketone bodies and is based on a weight ratio of lipid and protein+carbohydrate of 4:1, commonly expressed as KD 4:1. KD 4:1 was designed by Dr. Russell Wilder in 1923. KD 3:1, which has a lipid-to-protein +carbohydrate ratio of 3:1, is also widely used, and KD 3:1 shows similar effects as KD 4:1. KD 4:1 and KD 3:1 are considered classic KD.[17,18] Considering the composition of the KD in terms of calories, in KD 4:1, the proportions of lipids is approximately 90% of the calories in the entire diet, carbohydrates are 4%, and proteins are 6%. KD 3:1 indicates that lipids accounted for 87% of total calories. The classic KD stabilizes the brain and exerts antioxidant effects by causing strong ketosis in the body. Additionally, because classic KD restricts overall calories, it aids in weight loss. However, due to considerably high lipid levels, there is a risk of side effects including gastrointestinal problems (nausea, vomiting, diarrhea, constipation, hyperlipidemia, and hypoglycemia), and it is not nutritionally balanced as well. Therefore, classic KD may be difficult to maintain for the long-term management of pediatric migraine. To alleviate the side effects of classic KD, diet therapies such as MAD and LGIT were developed (Figure 1).[19-21]

2. Modified Atkins therapy

Dr. Robert Atkins created the MAD in the 1970s as a diet to treat obesity. Overall, although it inherits the nutrient ratio of the classic KD, approximately 70% to 80% of the calories in the diet consist of lipids, the MAD may or may not restrict caloric intake.[19,21] Although it is not a diet aimed at ketosis, consistent ketosis can be achieved in some patients. MAD has an anti-seizure effect similar to that of classic KD. A recent study reported that the anti-seizure effect of the MAD was not inferior to that of the classic KD.[19] Nevertheless, MAD alleviates the side effects of classic KD and is attracting attention as a treatment for various neurological diseases. MAD has been used not only for epilepsy but also as a dietary therapy for migraine treatment.[18]

3. Low glycemic index diet therapy

LGIT also called as the liberalized KD, was first introduced in 2005. This is also a high-lipid diet in terms of the overall nutrient ratio, but the ratio of fat to total calories is set at 50% to 60%.[22] For reference, in a typical diet, fat accounts for about 20% to 30% of the total calories. Therefore, LGIT is still a high-lipid diet in comparison. Carbohydrates comprise approximately 10% to 15% of the total daily calories and the diet focuses on carbohydrates that are considered to have a low glycemic index (GI). Low GI ingredients raise blood glucose levels slowly. The LGIT uses ingredients with a GI of 50 or less, including most vegetables, garlic, mushrooms, tomatoes, strawberries, oatmeal, apples, oranges, cherries, dark chocolate, milk, and yogurt.[22,23] Foods classified as high GI, such as rice, bread, bagels, potatoes, and watermelons, are excluded or significantly restricted from the LGIT diet. LGIT also has a significant anti-seizure effect and contributes to brain stabilization. A recent study reported that LGIT was not inferior to the classic KD and MAD in reducing seizures by >50% in patients with drug-resistant epilepsy.[19] In addition, it is nutritionally balanced and can be included in various diets, making it suitable for long-term maintenance. Due to LGIT's tolerability, it has recently replaced the classic KD and MAD in various neurological diseases including pediatric migraine.[21-23]

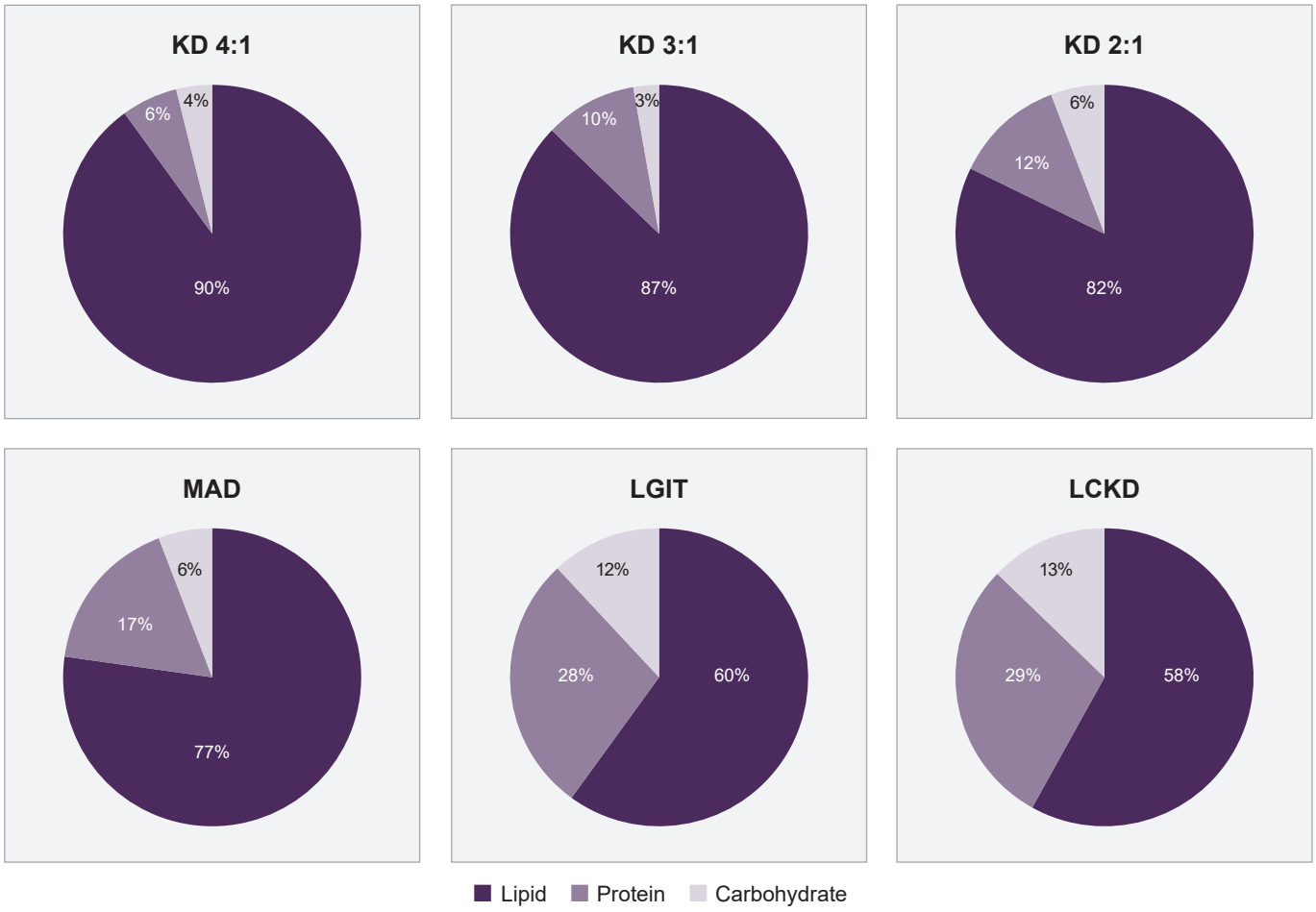

Figure 1. Types of dietary therapies and ratio of calories by nutrient for pediatric migraine.
KD, ketogenic diet; MAD, modified Atkins diet; LGIT, low glycemic index diet; LCKD, low-calorie ketogenic diet.

4. Other diet therapies for pediatric migraine management

In addition to representative KDs such as the classic KD, MAD, and LGIT and their variants, the KD 2:1, the low-calorie ketogenic diet (LCKD), the very-low-calorie ketogenic diet (VLCKD), the polyunsaturated fatty acid (PUFA)-enriched diet, and the gluten-free diet can be implemented for the management of pediatric migraine.[24,25] In KD 2:1, lipids account for 82% of total calories, and it is a KD variant that falls between KD 3:1 and MAD.[26] The LCKD sets total calories to 800–1,200 kcal/day and the proportion of lipids to approximately 58% of total calories. The VLCKD sets the total calories to 600–800 kcal/day and the lipid ratio to approximately 43% of the total calories. Both the LCKD and VLCKD are characterized by low calories, low carbohydrates, and normal protein content, and are diets that can be used for migraine patients with obesity or obstructive sleep apnea. However, in LCKD and VLCKD, electrolyte imbalance may arise from excessive calorie restriction, which may actually worsen headaches; therefore, it is necessary to implement it according to individual circumstances. The introduction of the PUFA-enriched diet was a response to the high levels of saturated or mono-unsaturated fatty acids in the KD. PUFAs are classified as omega-3 (alpha-linoleic acid and docosahexaenoic acid) and omega-6 fatty acids (linoleic acid and gamma-linolenic acid). Diet therapy using PUFA is known to have positive effects on neuronal and cardiovascular functions, and can improve the side effects associated with KD. For those

with migraine and celiac disease, a gluten-free diet can reduce the frequency of migraine.[23,27]

MECHANISM OF DIET THERAPY FOR PEDIATRIC MIGRAINE

The term 'gut-brain axis,' frequently mentioned in recent research papers, emphasizes the interaction between the brain and gastrointestinal tract. Nutrients absorbed from the gastrointestinal tract not only provide energy to operate the brain but also provide materials for organizing the brain network, and may point to the possible mechanism between migraine and diet therapy.[26] These mechanisms involve inflammation and gut microbiota profiles. Dysbiosis of microbiota can increase gut permeability and proinflammatory cytokines.[16,28] Inflammatory mediators such as interleukin (IL)-1 beta, IL-6, IL-8, tumor necrosis factor alpha, and interferon-gamma are known to induce visceral pain, and most are related to migraine attacks. CGRP may increase due to dysbiosis of the microbiota, which may disturb gastric acid secretion, causing migraine and abdominal disturbances simultaneously. The gut microbiota is involved in the production of tryptophan metabolites via the tryptophan-kynurenine pathway in the intestine. Tryptophan is the precursor of serotonin which plays a significant role in the pathophysiology of migraine in the brain.[16] In addition, studies have reported on the relationship between inflammatory cytokines and dysbiosis of microbiota in diseases including irritable bowel syndrome, celiac disease, and migraine.[29]

Several recent studies have revealed that diet therapies, such as KD, MAD, and LGIT, improve neurological diseases by alleviating the dysbiosis of microbiota, reducing proinflammatory cytokines, and increasing mitochondrial function.[26-28,30] Additionally, there is evidence that mitochondrial dysfunction plays a role in the pathophysiology of migraine, and that the KD and its variants can improve mitochondrial function by increasing adenosine triphosphate (ATP) production.[31-33] This increase in ATP production can ameliorate secondary chronic fatigue caused by migraine. Anticipated advancements in future research are expected to substantiate and augment the diverse neuroprotective functions of KD and its variants. These functions include the inhibition of neuroinflammation, reduction of CGRP levels, and improvement of serotoninergic dysfunction.[31]

CURRENT STUDIES ON DIET THERAPY FOR PEDIATRIC MIGRAINE

Existing studies on diet therapy in pediatric migraine are very rare and limited. Patients are highly resistant to strong diet therapy in the pediatric age group, so consideration is needed regarding the appropriate intensity of diet therapy.[34] However, studies of diet therapy in adults are useful as a reference for the application of diet therapy in pediatric migraine. Research on KD and its variants as therapies for neurological diseases has increased rapidly since 1995. A randomized controlled study published by Di Lorenzo et al.,[35] reported that VLCKD significantly reduced the mean number of days with migraine in overweight patients. A retrospective observational study by Valente et al.,[15] reported that monthly headache days, acute medication intake, and body mass index were all significantly reduced 3 months after starting KD. In a retrospective single-center pilot study by Tereshko et al.,[27] three diet therapies, KD 2:1, LGIT, and VLCKD implemented in 76 migraine patients significantly reduced migraine frequency and intensity. In addition, the results on Migraine Disability Questionnaire, Headache Impact Test, and fatigue severity scale were significantly reduced.[27] In a systematic review recently reported by Caminha et al.,[36] KD and its variants were summarized as migraine prevention therapy with fewer side effects in both adolescents and adults. Lelleck et al.[24] presented the possibility of individually managing LGIT using digital methods. In addition, a recent study targeting pediatric age is attracting attention. Pasca et al.[37] reported that sleep stabilization was achieved in a patient with chronic pediatric migraine through KD, and this result was confirmed by polysomnography (Table 1). Likewise, interest in the effectiveness and safety of KD and its variants as a preventive treatment for migraine is increasing, and research on their application to pediatric migraine increasing.

CONCLUSION

Although the treatment of pediatric migraine follows that for adult migraine, the available acute and preventive medications are limited when compared with those for adults. Additionally, because brain and gastrointestinal tract development is not yet complete in adolescents, active nutritional interventions such as diet therapy may be

Table 1. Current studies on dietary therapies for migraine

Study	Target patient (n)	Age (yr)	Study design	Type of diet therapy	Duration of study	Outcome
Di Lorenzo et al.[35]	35	18–65	Prospective	VLCKD	4 wk	VLCKD patients experienced −3.73 (95% CI, −5.31 to −2.15) migraine days. The 50% responder rate for migraine days was 74.28% (26/35 patients) during the VLCKD period.
Valente et al.[15]	23	47.22±15.21	Retrospective	VLCKD, KD 2:1, MAD, LGIT	3 mo	Reduction in monthly headache days (12.5±9.5 vs. 6.7±8.6; p<0.001) Reduction in days of acute medication intake (11.06±9.37 vs. 4.93±7.99; p=0.008) Reduction in patients' weight (73.8±15.2 vs. 68.4±14.6; p<0.001) and BMI (26.9±6.2 vs. 23.7±8.1; p<0.001)
Tereshko et al.[27]	76	45.90±14.77	Prospective	KD 2:1, LGIT, VLCKD	3 mo	The 50% responder rate for migraine days was 74.28% (26/35 patients) during the VLCKD period. KD protocols effectively improved migraine intensity, frequency, MIDAS, and HIT-6.
Lelleck et al.[24]	First study=49 Second study=71	First study=41±9.2 Second study=40±12.3	Prospective	LGIT	16 wk	Reduction of headache and migraine days, as well as reductions in HIT-6 and MIDAS scores. Migraine days decreased by 2.40 days (95% CI, −3.37 to −1.42), HIT-6 improved by 3.17 points (95% CI, −4.63 to −1.70), and MIDAS by 13.45 points (95% CI, −22.01 to −4.89).
Pasca et al.[37]	7	14–18	Prospective	Classic KD	3 mo	5/7 patients reported an improvement in migraine symptoms in terms of duration of the attacks, frequency, and intensity.

VLCKD, very-low-calorie ketogenic diet; CI, confidence interval; KD, ketogenic diet; MAD, modified Atkins diet; LGIT, low glycemic index diet; BMI, body mass index; MIDAS, Migraine Disability Assessment Test; HIT-6, Headache Impact Test 6.

effective. Lifestyle modification is essential for the fundamental treatment of primary headaches such as migraine. However, as with most migraine prevention medicines that have been released thus far, the mechanism by which active diet therapy affects pediatric migraine requires further research.[37,38] To achieve this, a neuro-nutritional team composed of pediatric neurologists, nurses, and nutritionists who can develop and regularly manage a tolerable diet for pediatric migraine patients is key. In the future, the importance of diet therapy will be highlighted not only as a preventive treatment for pediatric migraine but also as a lifestyle modification. Advancements in methodologies for basic research and clinical applications are expected.[39]

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Formal analysis, Funding acquisition, Resources, Validation, Writing–original draft, Writing–review & editing: JHN.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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