Original Article

Dietary or enteral medium-chain triglyceride usage in a Chinese general hospital

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Objectives: Medium chain triglycerides (MCTs) are of nutritional interest for their unique properties on ingestion, absorption and metabolism. However, dietary and enteral MCTs usage in hospitalized patients in China requires evaluation. **Methods**: A retrospective analysis was conducted on 46 hospitalized patients who were administered MCTs therapy between January, 2012 and December, 2013 in Peking Union Medical College Hospital. The clinical parameters of subjects were evaluated 2 weeks after intervention. All indications and outcomes of MCTs therapy underwent evidence-based evaluation. A survey was conducted on a random sample of 77 doctors to clarify the awareness and knowledge of MCTs therapy among clinicians. **Results**: Among 46 cases undergoing MCTs therapy, there were 21 with gastrointestinal dysfunction (with improvement in 15 cases), 15 with lymphatic anomalies (with improvement in 7 cases), 5 with dyslipidemia (with improvement in 3 cases), 4 with exocrine pancreatic insufficiency (with improvement in 2 cases) and 1 with epilepsy (without improvement). All indications were evidence -based. Although MCTs were being utilized in an increasing number of patients, the survey revealed poor knowledge of their physicochemical properties, medical indications and the therapeutic basis of their use among clinicians. **Conclusions**: MCTs therapy is of benefit in the management of gastrointestinal malabsorption, pancreatic exocrine insufficiency, intestinal lymphangiectasia and dyslipidemia. However, randomized controlled trials with adequate sample size and longer follow-up are required to evaluate further their efficacy, and more educational programs are needed to ensure clinical competence for MCT therapy.

Key Words: medium-chain triglycerides, diet, enteral nutrition, indication, outcome

INTRODUCTION

The medium chain triglycerides (MCTs) are fats with three saturated fatty acids chain containing 6 to 10 carbons each. They can be hydrolyzed rapidly into medium chain fatty acids (MCFAs) and monoglycerides. Compared with long chain triglycerides (LCTs) which serve as most dietary lipid, MCTs have some features of better water miscibility, faster hydrolysis, better absorption into intestinal mucosal cells, and direct transportation of MCFAs into portal circulation. On account of the above advantages, MCTs were first applied to clinical practice in 1950,[1] as a substitute for LCTs in treatment of lipid malabsorption. Then, they were utilized as enteral and parenteral nutritional preparations.

Although previous research has provided sound theoretical grounds for clinical application of MCTs, few clinical studies have been performed on the current application of MCTs therapy. To the best of our knowledge, this preliminary investigation, for the first time, reveals the effects of MCTs-based diet or enteral nutrition on hospitalized patients. We aimed to evaluate the appropriate indications for MCTs administration, clarify the possible effectiveness, and provide effective therapeutic approaches to some specific diseases.

MATERIALS AND METHODS

Data collection

A total of 1152 patients underwent therapeutic nutritional interventions in Peking Union Medical College Hospital (PUMCH) from January, 2012 to December, 2013. Of these, 46 individuals (4.0%) received MCTs therapy. MCTs were prescribed as the main cooking oils, or as enteral preparations. Clinical data of the patients were retrospectively reviewed. Parameters including body weight, albumin, lipid level, uric acid were compared before and after 2 weeks of MCTs therapy.

We conducted a survey on knowledge of MCTs therapy among clinicians. The questionnaires, consisting of 5 questions, were randomly sent to 77 doctors and the responding answers were used for further analysis.

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Statistical analysis

Data were analyzed by SPSS 16.0 statistical software. Continuous variables were expressed as mean±SD. A descriptive analysis was performed on all subjects.

Evidence evaluation

We searched on-line literature on clinical application of MCTs/MCFAs within the past 10 years. The databases included PubMed, Embase, Ovid and Medline. Evidence from literature was evaluated and categorized according to the research type and subject category (Figure 1).

RESULTS

MCTs were utilized in an increasing number of patients (from 11 cases in 2012 to 35 cases in 2013) and clinical specialities (from 4 wards in 2012 to 12 wards in 2013). Wards of gastroenterology (21 cases, 45.7%), pediatrics (5 cases, 10.9%), pneumo-thoracic disease (5 cases, 10.9%), general internal medicine (3 cases, 6.5%), general surgery (2 cases, 4.3%), and oncology (2 cases, 4.3%) were involved more frequently than the other wards. The total of 46 patients comprised 38 adults and 8 children, including a 6-month old infant. The mean age was 39.1 ± 19.9 years (range 6 months ~ 77 years). Male to female ratio was 21/25.

A survey, by use of questionnaires, was conducted to assess knowledge of MCTs therapy among clinicians. Seventy seven respondents were enrolled, including 31 surgeons and 46 internists. General knowledge of MCTs treatment was poor in all clinicians (29/77, 37.7%), with only 22.6% (7/31) of surgeons and 47.8% (22/46) of internists familiar with MCT therapy. Only 9.7% (3/31) of surgeons and 17.4% (8/46) of internists knew the main physiochemical properties of MCTs. About 12.9% (4/31) of surgeons and 41.3% (19/46) of internists knew the common indications for MCTs therapy. Only 9.7% (3/31) of surgeons and 26.1% (12/46) of internists knew the therapeutic mechanisms of MCTs treatment in different morbidities.

Gastrointestinal dysfunction (21 cases) and lymphatic anomalies (15 cases) were the most common indications for MCT application. Dyslipidemia (5 cases), exocrine pancreatic insufficiency (4 cases), and epilepsy (1 case) were the other reasons for MCT administration (Table 1).

The patients with gastroenteral dysfunction commonly presented with maldigestion or malabsorption. Low D-xylose absorption occurred in 8/21 (38.1%) patients, hypoalbuminemia (serum albumin <35 g/L) in 13/21 (61.9%) patients, and chronic diarrhea and steatorrhea in 15/21 (71.4%) patients. Ten (47.6%) patients were underweight (BMI <18.5 kg/m^2) and 5 patients (23.8%) were very severely underweight (BMI <15 kg/m^2). After 2 weeks MCTs treatment, an improvement was observed in 61.9% of patients (13 cases): albumine increased in 8 patients; body weight increased in 7 patients; and diarrhea ameliorated in 10 patients (including 5 cases with steatorrhea). One patient had gastrointestinal motility disorder caused by graft-versus-host disease (GVHD) after allo-hematopoietic stem cell transplantation. No improvements were observed after his MCT therapy.

The 15 cases of lymphatic anomalies included lymphatic fistulas (10 cases) and intestinal lymphangiectasia (5 cases). Multiple chylousserositis were the main manifestations of lymphatic fistulas. The effusion fluid became clear and transparent in 2 patients with congenital lymphatic malformation after MCTs therapy, and further laboratory testing confirmed a decreased triglyceride (TG) concentration in serous effusion. No remarkable improvements were observed in the other 8 cases with lymphatic fistulas resulting from malignancy, systemic lupus erythematosus, tuberculosis and iatrogenic injury. As for 5 patients with intestinal lymphangiectasia, the predominant manifestation consisted of steatorrhea, weakness, and hypoalbuminemia. All of them reported decreased frequency of steatorrhea after MCTs administration. Two patients had elevated serum albumin and increased body weight.

Five cases with severe dyslipidemia underwent MCTs therapy. They had an average triglycerides (TG) of 13.6±8.05 mmol/L, and a total cholesterol (TC) of 3.83±1.81 mmol/L. Among them, 4 patients with glycogen storage disease type 1 (GSD 1) presented with hyperuricemia and recurrent hypoglycemia in addition to hyperlipidemia. Decreased TG and uric acid were observed in 2 patients following supplementation of MCTs and uncooked cornstarch. The other patient with nephrotic syndrome also had a decreased TG after initiation of MCTs-based diet.

Moreover, 4 cases of exocrine pancreatic insufficiency were placed on MCTs-rich enteral nutrition in addition to pancreatic enzyme replacement therapy. All had chronic diarrhea, emaciation and anorexia, with 3 of them beingundernourished (BMI <18.5 kg/m^2). Symptoms were alleviated in 2 cases with pancreatic carcinoma and chronic pancreatitis.

In addition, a 26-year old man, who had mitochondrial encephalopathy (Leigh's disease) associated epilepsy, was prescribed a ketogenic diet. Given the patient had concomitant hyperlipidemia (TG 3.26 mmol/L, TC 6.96 mmol/L), MCTs served as the main lipid in the ketogenic diet, providing over 60% of total energy. No improvement was observed and the patient died of pneumonia.

Literature concerning the clinical application of MCTs-based diet or enteral nutrition within the recent ten years was collected from on-line databases. A total of 118 references were retrieved and evaluated. Case reports and case series were the most common research type (39.8%, 47 papers), followed by animal tests (28.0%, 33 papers) and reviews (19.5%, 23 papers). Whereas randomized controlled trials (RCTs) and evidence-based clinical guidelines accounted for only 9.3% (11 papers) and 3.4% (4 papers), respectively. (Figure 1)

DISCUSSION

MCT, a special type of dietary fat, can be found naturally in coconut oil, palm kernel oil and milk lipids. MCTs are of increasingly nutritional interest on account of its unique properties on ingestion, absorption and metabolism. However, our results showed that MCTs are not broadly and sufficiently utilized in all specialities as a dietary or enteral intervention, despite of a gradual growth during the last 2 years. There are some reasons for the phenomenon. First, poor knowledge of MCTs therapy among clinicians is the dominant cause. Our survey result

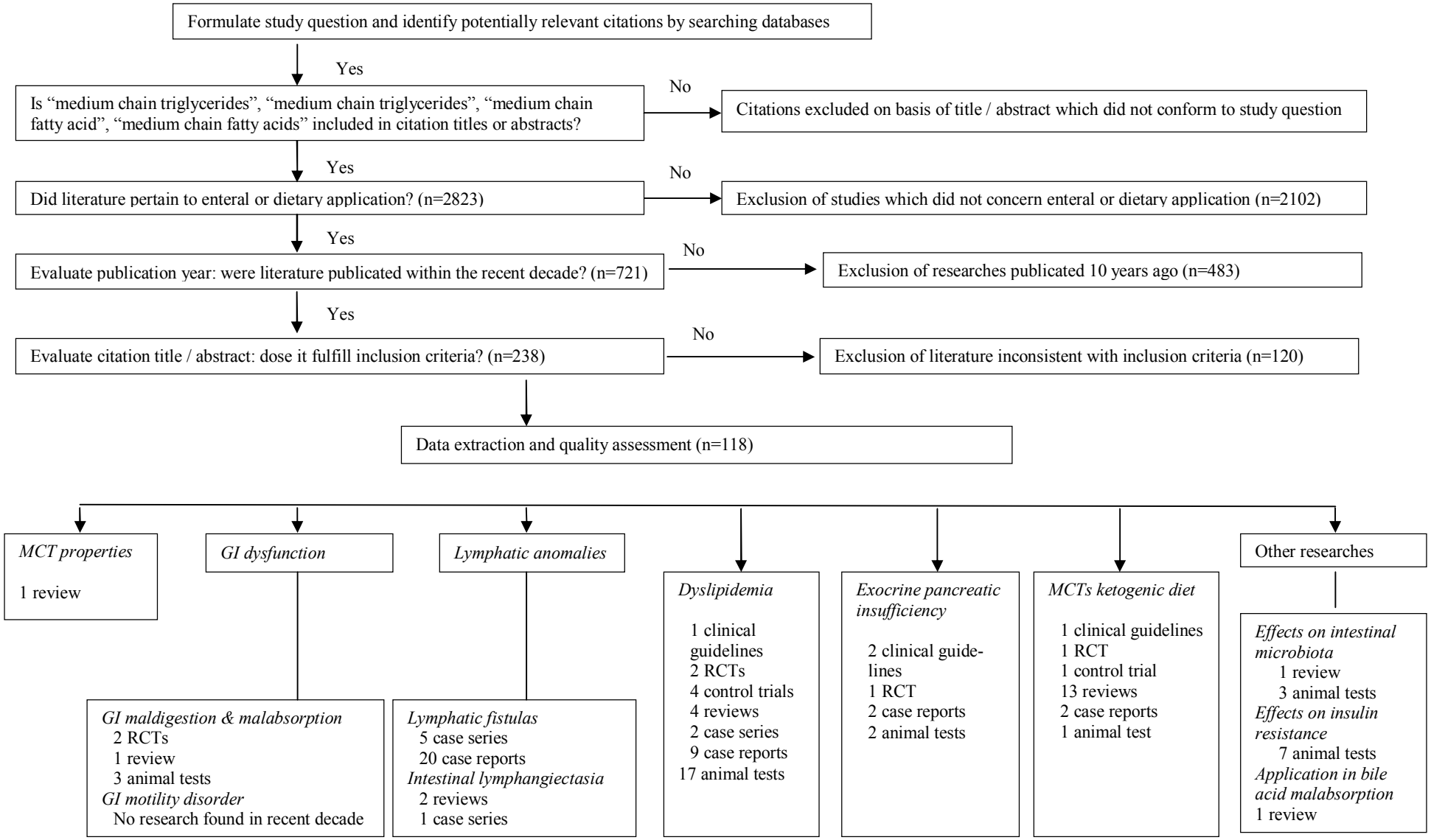

Figure 1. Summary of search methodology, literature assessment and an overview of publications categorized by different indications of MCTs therapy. GI: gastrointestinal; RCT: randomized controlled trial.

Table 1. Clinical data of patients prescribed with MCTs therapy and outcomes after 2 weeks.

Disease status	n	Clinical data		
		Characteristic presentation	Outcome of MCTs therapy after 2 weeks	
			Cases with improvement	Cases without improvement
Gastroenteral dysfunction	21		15	6
Inflammatory bowel disease	9	Abdominal pain and chronic diarrhea	7	2
Protein losing enteropathy	2	Chronic diarrhea	2	
Celiac disease	5	Chronic diarrhea	4	1
Short bowel syndrome	3	Chronic diarrhea	1	2
Steatorrhea with unkown etiology	1	Chronic diarrhea	1	
Gastrointestinal GVHD[§]	1	Motility disorder (vomiting, nausea and acid regurgitation)		1
Lymphatic anomalies	15		7	8
Lymphatic fistulas (etiologies)	10	Chylousserositis (chylous ascites, chylothorax or chyloushydropericardium)	2	8
Malignancy	4			4
SLE[※]	1			1
Tuberculosis	2			2
Congenital lymphatic malformation	2		2	
Iatrogenic injury caused by thoracic surgeries	1			1
Intestinal lymphangiectasia	5	Steatorrhea	5	0
Lymphangiomyomatosis	1		1	
Lymphatic malformations	3		3	
Constrictive pericarditis	1		1	
Dyslipidemia	5		3	2
Glycogen storage disease	4	Hepatomegaly, hypoglycemia and hyperlipidemia	2	2
Nephrotic syndrome	1	Edema, proteinuria and hypolipidemia	1	
Exocrine pancreatic insufficiency	4		2	2
Cystic fibrosis	2	Bronchiectasia, pneumonitis and loss of weight		2
Pancreatic carcinoma	1	Abdominal pain and anorexia	1	
Chronic pancreatitis	1	Chronic diarrhea	1	
Epilepsy	1		0	1
Leigh's disease	1	Epileptic seizures		1

[§]GVHD: graft-vesus host disease; [※]SLE: systemic lupus erythematosus.

support this explanation. Most clinicians, especially for surgeons, were lacking knowledge of physiochemical properties, medical indications, therapeutic mechanisms of MCTs therapy. More education programmes are needed to expand and improve the knowledge of MCTs therapy amongst clinicians. Second, clinical trials in the literature did not provide adequate evidence for indications of MCTs therapy. Collection of literature on MCTs (Figure 1) reveals that most publications are case reports, case series, animal tests, in vitro research studies and reviews. Comparatively, much less evidence is derived from RCTs or evidence-based clinical guidelines. Therefore, more prospective and randomized studies with larger sample sizes are required to provide convincing evidence of efficacy of MCTs interventions.

In our patients, enteral or dietary MCTs were prescribed for 5 main indications: gastrointestinal dysfunction, lymphatic anomalies, dyslipidemia, exocrine pancreatic insufficiency as well as epilepsy. These indications are in line with the previous reports.

Evidence-based evaluation of current clinical application of MCTs

Gastrointestinal dysfunction

With rapid and complete hydrolysis, MCTs are digested faster and more completely than LCTs.[2] A randomized controlled trial (RCT) with a small sample size demonstrated that MCTs intervention reduced diarrhea frequency, improved malnutrition and shortened the length of hospitalization for children with acute diarrhea.[3] Another multicenter RCT also revealed that MCTs and protein-enriched enteral nutrition significantly improved the outcomes of patients with major abdominal operations for gastrointestinal malignancies.[4] Furthermore, evidence from several case reports and animal experiments showed that dietary MCTs may exert beneficial effects on many diseases with gastrointestinal dysfunction, such as short bowel syndrome, celiac disease, Whipple's disease, inflammatory bowel diseases, enteritis, gluten enteropathy, tropical or idiopathic sprues, and neonatal malabsorption.[1,5,6]

Consistent with the recommendation from the previous literature, gastrointestinal dysfunction served as the primary indication for MCTs therapy in our patients. Symptoms of maldigestion and malabsortion were alleviated in most patients (15/21) during 2-weeks of treatment. Nevertheless, MCTs therapy was ineffective to relieve symptoms of gastrointestinal reflux in 1 patient with GVHD. Although previous research[7] proposed that MCTs could accelerate duodeno-cecal transit time and improve antro-

duodenal motility, no more data have been updated or supplemented within the last decade. The effects of MCTs on gastrointestinal motility still need to be proven.

Pancreatic exocrine insufficiency

The smaller molecular size of MCTs or medium chain fatty acids (MCFAs), facilitates the action of pancreatic lipase. And even in cases without pancreatic lipase or bile salts or both, MCTs can be directly absorbed.[1] However, there is no consensus on MCTs supplementation in patients with pancreatic exocrine insufficiency. A RCT, attempting to evaluate the difference between MCT-enriched commercial dietary supplements and homemade food for patients with chronic pancreatitis, found no significant advantage of MCTs.[8] A consensus in Italy also disapproved MCTs therapy for patients with chronic pancreatitis (grade B).[9] However, the International Consensus Guideline Committee (ICGC) recommended enteral nutrition with a small peptide-based and MCTs oil formula to improve the tolerance (Grade B), after carefully reviewing of the available clinical trials on acute/chronic pancreatitis.[10]

In our study, MCTs-based enteral nutrition was conducive to improve undernourishment in patients with exocrine pancreatic insufficiency caused by pancreatic carcinoma and chronic pancreatitis. However, 2 cases of cystic fibrosis with severe undernutrition did not have a good response to MCTs therapy. The co-morbidities of bronchiectasia, recurrent pneumonitis, aggravation of malnutrition and increased energy consumption, might account for poor outcome of MCTs intervention.

Lymphatic anomalies

Transportation of middle chain fatty acids (MCFAs) is different from long-chain fatty acids (LCFAs), which are predominantly absorbed in the form of chylomicrons into the lymphatic system. The MCFAs are bound to serum albumin and transported directly into the portal circulation, bypassing the intestinal lymphatic system.[1] Case reports and case series show that MCTs therapy reduced the lymphoid flow in the lymphatic vessels, and thereby decreased protein and fat loss from intestinal tract in patients with intestinal lymphangiectasia,[11] and amelioratedchylous effusion in patients with lymphatic fistulas.[12]

Our study confirmed the efficacy of MCTs therapy in all patients with intestinal lymphangiectasia. Whereas, lymphatic fistulas caused by malignancies, systemic lupus erythematosus, tuberculosis infection and severe trauma had poor response to MCTs therapy.

Dyslipidemia

MCTs undergo more rapid β-oxidation in liver and are less stored in adipocytes than LCTs.[13] Previous studies including RCTs have demonstrated that dietary MCFAs/MCTs can suppress lipogenesis and increase lipolysis in adipose tissue, decrease cholesterol levels in blood and liver, and improve lipid profile in patients with dyslipidemia, obesity and metabolic syndrome.[1,14,15]

Besides, MCFAs can directly enter mitochondrial matrix for fatty acid β-oxidation, without depending on carnitine transport system which serves as a necessary shuttle system for LCFAs.[16] Glycogen storage disease type 1 (GSD 1) usually presents with severe dyslipidemia due to blockade of LCFAs oxidation by inhibition of carnitine palmitoyltransferaseI (CPT I).[17] MCFAs can be directly transferred into mitochondria in absence of CPT I. Therefore, they can lower serum triglyceride and lead to more efficient energy utilization by bypassing the blockade of LCFAs oxidation. The EFNS guidelines also recommends MCTs-based diet in the management of fatty acid mitochondrial disorders, such as carnitine and carnitine palmitoyltransferase deficiency, as well as LCFAs β-oxidation defects.[18]

In accordance with the above mentioned evidence, 1 patient with nephrotic syndrome and 2 patients with GSD 1 showed significant improvements in lipid profile after 2 weeks of MCT therapy. But for children, metabolic parameters involving growth and development, should be regularly evaluated, and essential fatty acids (EFA) should be supplemented where necessary.

MCT ketogenic diet

MCTs serve as a significant constituent in MCT ketogenic diet. Ketogenic diets are characterized by high fat and restricted intake of carbohydrate and protein, with anticonvulsant effect on patients with intractable epilepsy.[19] MCTs have been introduced as alternative fat source in ketogenic diet since 1970.[19] Results of a RCT suggested that MCT ketogenic diet was as efficacious and tolerable as the classic ketogenic diet,[20] and allowed more carbohydrate and protein intake. The 2011 guidelines for epilepsy approved the antiepileptic effect of MCT ketogenic diet and recommended MCT ketogenic diet for epileptic patients with concomitant carnitine deficiency or dyslipidemia.[21] However, among all the literature (661 articles, 1990-2013) on dietary therapy for epilepsy, MCT ketogenic diet associated studies only accounted for 6.4%.[22] Therefore, more studies are needed to testify its advantage over other dietary management.

In our study, MCT ketogenic diet was administrated for one patient with intractable epilepsy (due to mitochondrial encephalomyopathy) and concomitant hyperlipidemia. Application of ketogenic diet on such cases is based on isolated case reports[23] and the efficacy of treatment remains to be proven.

In addition, some studies provide clues for MCTs application in other diseases. A review, based on case reports and case series, indicated that a low-fat diet with MCTs may ameliorate symptoms of bile acid malabsorption.[24] An animal experiment indicated that MCFA and their derivatives had some anti-microbial effects and may influence the composition of intestinal microbiota.[25] An in vitro study proposed that dietary MCFAs may lead to less insulin resistance and lipotoxicity compared with LCFAs.[26]

Limitation of our study

Lack of control groups, small sample size and limited duration of follow-up are the main limitations of our study.

Conclusion

MCTs therapy is not widely applied in clinical arenas at present, despite a growth trend in the last 2 years. Some

beneficial effects of MCTs therapy could be observed in diseases with gastrointestinal malabsorption, exocrine pancreatic insufficiency, intestinal lymphangiectasia and dyslipidemia. More randomized control trials, with larger samples and longer follow-up, are required to further testify the efficacy of MCTs intervention in these diseases and other medical specialities. Furthermore, the knowledge on MCTs was poor in most clinicians and more education programs are needed to expand knowledge of MCTs therapy.

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The research has been approved by the institutional review board of the ethical matters in Peking Union Medical College Hospital (PUMCH) (Approval number S-054).

AUTHOR DISCLOSURES

The authors have no financial disclosures or conflicts of interest to declare. The article was written independently, and the work described in the paper was original.

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Original Article

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中国综合医院中链甘油三酯膳食及肠内临床应用现状

目的：中链甘油三酯（median chain triglycerides，MCTs）由于其摄入、吸收、代谢方面的特殊作用而广受关注，但目前其在中国住院患者的膳食及肠内临床应用尚无报道且现状不明。本文首次报告 MCTs 临床应用现状，以期进一步阐明其应用的指征和规范。**方法：**回顾性分析纳入北京协和医院 2012 年 1 月至 2013 年 12 月两年间应用 MCTs 进行膳食及肠内营养干预的住院患者 46 例次及其治疗 2 周后临床情况变化。所有患者的治疗指征及治疗结局均进行循证评价。同时，随机选取 77 名临床医师进行问卷调查，进一步阐明临床医师对 MCTs 营养治疗的认知度。**结果：**46 例次接受 MCTs 营养干预的患者临床表现及 MCTs 应用指征各异，其中包括 21 例胃肠消化功能障碍（15 例治疗 2 周后好转），15 例淋巴循环障碍（7 例好转），5 例血脂异常（3 例好转），4 例胰腺外分泌功能不全（2 例好转）以及 1 例癫痫发作（未好转）患者。病例的 MCTs 治疗指征均进行循证评价。针对医师的问卷调查显示，尽管应用 MCTs 治疗的患者例数正在逐渐增加，临床医师对 MCTs 的理化特点、应用指征以及 MCTs 治疗机制的认知仍存在普遍不足。**结论：**MCTs 治疗可改善胃肠道吸收不良、胰腺外分泌功能不全、小肠淋巴管扩张以及血脂异常患者的临床表现，但目前尚需针对较大样本人群、具有足够随访时间的临床随机对照试验以进一步评价其疗效。同时更多的 MCTs 知识宣教应在临床医师中进行普及以提高临床医务人员对其的认知程度。

关键词：中链甘油三酯、膳食、肠内营养、指征、结局