

Ketogenic diet in pharmaco-resistant epilepsies: a clinical nutritional assessment

Dieta cetogênica na epilepsia fármaco-resistente: avaliação clínica-nutricional

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Abstract

Background Epilepsies are among the most prevalent chronic neurological diseases, usually beginning in childhood. About 30% of children with epilepsies develop seizures that are difficult to control with medication. Recurrent epileptic seizures hinder diet intake, impairing the nutritional status. Although non-pharmacological interventions (e.g., ketogenic diet therapy) can improve epileptic seizure frequency, few studies analyzed their impact on the nutritional status of children and adolescents with epilepsies.

Objective The aim was to evaluate the effects of a ketogenic diet on the nutritional status and clinical course of patients with pharmaco-resistant epilepsies.

Methods This cross-sectional study included patients under 18 years of age followed up at the Ketogenic Diet Ambulatory Clinic of the Instituto de Medicina Integral Prof. Fernando Figueira between December 2015 and December 2021. Socioeconomic, clinical, nutritional, and laboratory data were collected from medical records at different time points during the ketogenic diet.

Results The sample comprised 49 patients aged between 5 months and 17 years (median = 4.4 years), mostly male (62.1%), and from Recife and the metropolitan region (51%). Underweight patients (BMI-for-age) improved their nutritional status in six months. However, patients who were normal weight and overweight maintained their nutritional status. Dyslipidemia was a common and short-term adverse effect. Moreover, the treatment decreased epileptic seizure frequency and antiseizure medication intake.

Conclusion The ketogenic diet prevented malnutrition from worsening and reduced epileptic seizures and antiseizure medication intake.

Keywords

- ▶ Seizures
- ▶ Diet, Ketogenic
- ▶ Malnutrition
- ▶ Drug Resistant Epilepsy

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Resumo

Antecedentes A epilepsia, uma das doenças neurológicas crônicas mais prevalentes, tem geralmente início na infância. Cerca de 30% das crianças com epilepsia desenvolvem crises de difícil controle medicamentoso. As crises epiléticas recorrentes dificultam a ingestão alimentar, prejudicando o estado nutricional. Intervenções não farmacológicas, como a terapia com dieta cetogênica, podem melhorar a frequência das crises epiléticas, mas existem poucos estudos sobre a repercussão no estado nutricional da criança/adolescente.

Objetivo Avaliar o efeito da terapia cetogênica sobre o estado nutricional e a evolução clínica da epilepsia fármaco-resistente.

Métodos Estudo tipo corte transversal envolvendo menores de 18 anos acompanhados no Ambulatório de Dieta Cetogênica do Instituto de Medicina Integral Prof. Fernando Figueira entre dezembro de 2015 e dezembro de 2021. Dados socioeconômicos, clínicos, nutricionais e laboratoriais foram coletados nos prontuários dos pacientes em vários momentos da terapia cetogênica.

Resultados A amostra foi composta por 49 pacientes com idades entre cinco meses e 17 anos (mediana = 4,4 anos), a maioria do sexo masculino (62,1%) e procedentes de Recife e região metropolitana (51%). Pacientes com baixo peso (de acordo com o IMC para idade) melhoraram seu estado nutricional em seis meses. No entanto, os pacientes com peso adequado e com sobrepeso mantiveram seu estado nutricional. A dislipidemia foi um efeito adverso frequente e de curta duração. Além disso, o tratamento reduziu a frequência de crises epiléticas e a dose de fármacos anticrises.

Conclusão A dieta cetogênica preveniu o agravamento da desnutrição e reduziu as crises epiléticas e a dosagem de fármacos anticrises.

Palavras-chave

- ▶ Convulsões
- ▶ Dieta Cetogênica
- ▶ Desnutrição
- ▶ Epilepsia Resistente a Medicamentos

INTRODUCTION

Epilepsies are one of the most common neurological diseases.¹ Epilepsies can be classified as pharmaco-resistant when two antiseizure medications (ASMs), taken as prescribed and properly chosen, whether monotherapy or combined, fail to stop or control the seizures.² Thus, patients with pharmaco-resistant epilepsies benefit from non-pharmacological or non-conventional interventions, such as the ketogenic diet (KD).³

Severe epileptic syndromes impair nutritional status. However, the relationship between malnutrition and epilepsies is yet to be determined.⁴ Studies suggest muscle spasms increase energy expenditure, and ASMs hamper nutrient absorption.⁵ In this sense, KD helps the nutritional treatment of patients with pharmaco-resistant epilepsies using a high-fat, low-carbohydrate, and adequate-protein approach in a 3:1 or 4:1 ratio (3 or 4 grams of fat to 1 gram of protein + carbohydrate).⁶ Other less restrictive and palatable KD may also be used, such as modified Atkins (MAD) and low-glycemic-index diets (LGI).^{7,8}

KD aims at improving the clinical course of epilepsies and reducing ASMs dosage and adverse effects. Also, this diet reduces treatment costs, improves the quality of life, promotes the well-being of families, and reduces the risk of sudden death.³ Although KD reduces epileptic seizures, its effects on the nutritional status of pediatric and adolescent patients need verification.⁹ Therefore, this study aimed to

evaluate the effects of KD on the nutritional status and clinical course of patients with pharmaco-resistant epilepsies.

METHODS

This cross-sectional retrospective study included patients under 18 years diagnosed with pharmaco-resistant epilepsies. Patients were followed up for at least six months at the Ketogenic Diet Ambulatory Clinic of the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) from December 2015 to December 2021. Patients who started KD in other services were excluded from the sample, and those with incomplete medical records were considered losses.

The IMIP is in Recife, the capital of the state of Pernambuco, and is one of the most important hospital structures in Northeast Brazil (the region with the lowest socioeconomic development). The Ketogenic Diet Ambulatory Clinic for Pharmaco-resistant Epilepsies was established in December 2015, is the first in North and Northeast Brazil, and has trained professionals in Child Neurology and Nutrition.

Caregivers were informed about the study via telephone. If they chose to participate, their consent was recorded and signed by a witness that was not from the research team and who accompanied the interview. The researcher kept this document and delivered it to the caregiver on their next visit to the clinic or sent a copy via WhatsApp or telephone message (SMS).

Socioeconomic, clinical, nutritional, and laboratory data were collected from medical records. The socioeconomic variables involved the age, sex, and origin of the patients. Clinical variables comprised epilepsies etiology according to the International League Against Epilepsy – ILAE criteria,¹⁰ number of daily epileptic seizures, ASMs use and dosage, and ketosis measurement. Ketosis state was assessed using the daily measure of ketonuria, indicated by +++ urine ketones or levels above 150 mg/dL.^{11,12}

At each consultation, a team of nutritionists assessed the nutritional status; results were analyzed in the follow-up periods. Nutritional status was assessed using body mass index (BMI)-for-age.^{13,14} Total serum cholesterol \geq 170 mg/dL characterized hypercholesterolemia, while triglycerides $>$ 100 mg/dL for patients up to ten years and $>$ 130 mg/dL for those over ten years characterized hypertriglyceridemia.^{15,16}

Data on KD characteristics (KD ratio [transition, 2:1; 3:1; 4:1, MAD, or LGI], feeding route [oral or enteral via nasogastric tube or gastrostomy], duration, treatment status, and adverse effects) were collected at different time points (3, 6, 12, 18, and 24 months of KD). Treatment was complete when patients achieved well-controlled epilepsies and discontinued when patients presented adverse effects or no improvement in epileptic seizures. Also, the treatment was discontinued or abandoned if the family did not attend the consultations.

Epileptic seizure frequency was reported by caregivers using a calendar. These data were compared to baselines obtained previously (frequency per month before KD). Moreover, response to KD was measured after three, six, 12, 18, and 24 months. Reduction in epileptic seizure frequency was classified according to the Huttenlocher criteria¹⁷; a reduction of over 50% indicated well-controlled epilepsies.^{18,19}

Descriptive analysis was performed using Stata® software, version 13.0. The relative frequencies were used for categorical variables, and central tendency and dispersion measures for continuous variables.

The study followed Resolution No. 466/2012 and Circular Letter No. 2/2021/CONEP/SECNS/MS (Brazil) concerning research in digital media and was approved by the research ethics committee of the Instituto de Medicina Integral Professor Fernando Figueira (no.: 50599821.0.0000.5201).

RESULTS

The eligibility criteria were applied to 81 patients. Five patients were excluded because they started KD in another service, and 27 were lost due to unavailable contact or lack of information on medical records. Therefore, the study included 49 patients (men = 62.1%) between five months and 17 years of age (median of 4.4 years).

Most patients were from Recife (state capital) and metropolitan region (51.0%), followed by the inland of Pernambuco (38.8%) and other states of Northeast Brazil (10.2%). According to medical records, the pharmacoresistant epilepsies etiology was likely genetic (55.1%), structural (26.5%), infectious (12.2%), or unknown (6.1%).

The feeding route, KD duration, and treatment status at the end of the study are shown in ►Table 1. About 77.6% of the

Table 1 Characterization of the ketogenic diet performed by 49 patients with pharmacoresistant epilepsies followed at IMIP

		n (%)
Feeding route	Oral	39 (79.6)
	Enteral via nasogastric tube	2 (4.1)
	Enteral via gastrostomy	8 (16.3)
Diet duration (months)	3 to 6	6 (12.2)
	7 to 12	15 (30.6)
	13 to 24	11 (22.5)
	25 to 36	5 (10.2)
	Over 36	12 (24.5)
Treatment status in December 2021	Followed up	21 (42.9)
	Completed	8 (16.3)
	Discontinued*	7 (14.3)
	Discontinued by the family**	13 (26.5)
Adverse effects	Yes	38 (77.6)
	No	11 (22.4)

Notes: *Discontinued due to adverse effects or lack of improvement; **Treatment discontinued by family choice.

patients presented adverse effects. Most occurred in the short term (less than three months) and were related to the gastrointestinal tract (nausea, vomiting, constipation, diarrhea, and lack of appetite); sleepiness and irritability occurred in low proportion. These data are not presented in the table.

►Table 2 shows the KD ratio modified at each time point according to the clinical response and the estimated percentage of reduced epileptic seizure frequency. The number of patients gradually reduced in each period. At six months of treatment, 69.3% of the patients showed a reduction in epileptic seizure frequency by over 50%, 14.3% by below 50%, and 16.3% showed no reduction. Seventeen patients were under KD for 24 months, and two (11.8%) had poorly controlled epilepsies. ►Figure 1 shows the ketosis and ASMs dosage reduction at each time point.

Nutritional status (BMI-for-age) is presented in ►Figure 2. Patients before the KD presented normal weight (51.0%), overweight (28.6%), and underweight (20.4%). Five of ten patients who were underweight presented normal weight after six months of KD; no patient presented overweight after the same period. Among the 17 patients who remained on the KD for 24 months, 58.8% were normal weight, and 41.2% were overweight.

►Table 3 shows the evolution of the lipid profile. After 12 months of KD, the number of patients with hypertriglyceridemia and hypercholesterolemia increased, decreasing at 18 and 24 months.

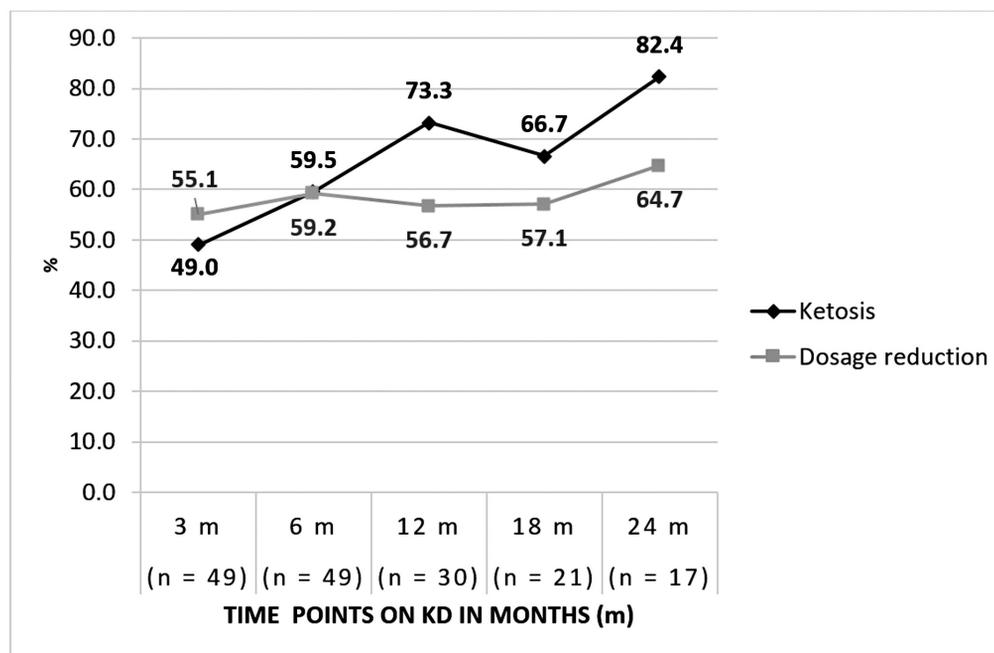
DISCUSSION

In this study, KD prevented malnutrition worsening and reduced epileptic seizure frequency and ASMs dosage.

Table 2 Ketogenic diet ratio and reduced epileptic seizure frequency according to time points on KD

		Time points on KD (months)				
		3 n = 49	6 n = 49	12 n = 30	18 n = 21	24 n = 17
		n (%)	n (%)	n (%)	n (%)	n (%)
Type of KD	Transition or 1:1	2 (4.1)	3 (6.1)	–	2 (9.5)	1 (5.9)
	2:1 or 2.5:1	16 (32.7)	9 (18.4)	4 (13.3)	1 (4.8)	–
	3:1 or 3.5:1	14 (28.6)	14 (28.6)	6 (20.0)	2 (9.5)	3 (17.7)
	4:1 or 4.5:1	13 (26.5)	18 (36.7)	16 (53.3)	13 (61.9)	12 (70.6)
	MAD	4 (8.2)	3 (6.1)	3 (10.0)	3 (14.3)	1 (5.9)
	LGI	–	2 (4.1)	1 (3.3)	–	–
Classification of the reduction in epileptic seizure frequency (per month)	Excellent (100%)	8 (16.3)	10 (20.4)	5 (16.7)	3 (14.3)	4 (23.5)
	Very good (90% - 99%)	7 (14.3)	11 (22.4)	5 (16.7)	3 (14.3)	7 (41.2)
	Good (50% - 90%)	16 (32.7)	13 (26.5)	9 (30.0)	6 (28.6)	4 (23.5)
	Regular (< 50%)	11 (22.5)	7 (14.3)	8 (26.7)	5 (23.8)	1 (5.9)
	No reduction	7 (14.3)	8 (16.3)	3 (10.0)	4 (19.1)	1 (5.9)

Abbreviations: LGI, low-glycemic index diet; MAD, modified Atkins diet.

**Figure 1** Percentage of ketosis (urinary ketones > 150mg/dL) and reduction in the antiseizure medication dosage.

Most patients with epilepsies were men, corroborating the literature.^{20,21} Despite physical and neurological limitations, most patients performed oral feeding, a more physiological feeding route. However, in oral feeding patients, a low-palatability KD may cause treatment refusal and interruption.⁷

All KD was outpatient and started with fat offered in low proportions and gradual progression, favoring palatability and adherence. Also, the diet became more restrictive as the fat proportion increased. After three months, about half of the patients presented ketosis (urinary ketones > 150 mg/dL), a frequency that increased according to KD duration

and adjustments to optimize the ketogenic effect. High-fat diets (3:1 or 4:1 ratio) promoted the highest levels of ketosis.

A high prevalence of patients on the 4:1 ratio diet was observed after 24 months. A randomized clinical trial with 158 children on KD (4:1 ratio), modified Atkins diet, and the low-glycemic index diet showed that all diets reduced epileptic seizure frequency.²²

About 40% of the patients discontinued the KD: 14.3% due to adverse effects or lack of improvement in epileptic seizure frequency, and about 25% did not attend consultations. In a review of the applicability of KD, the dropout rate was between

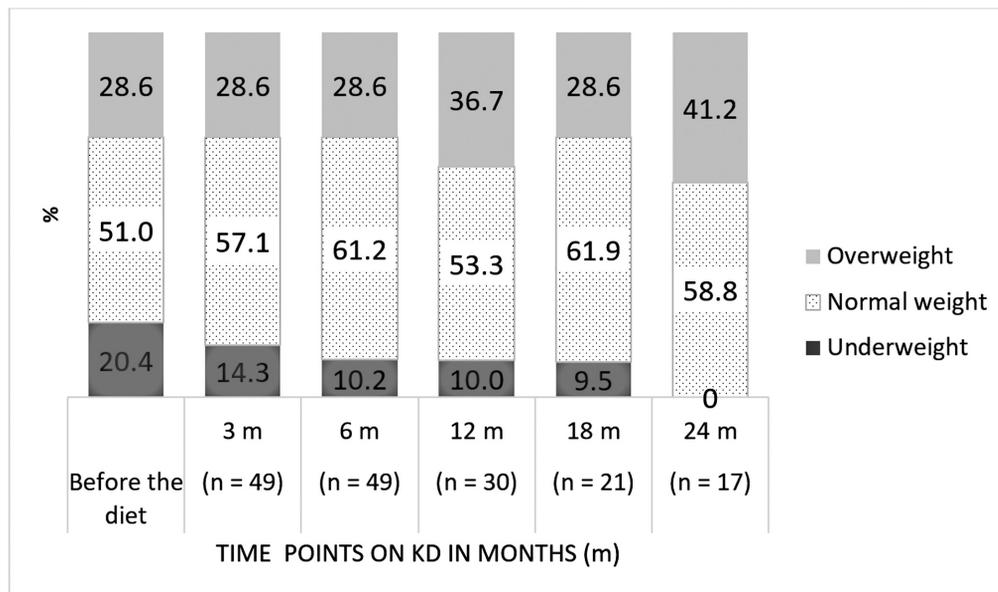


Figure 2 Nutritional status (BMI-for-age) according to time points on KD of patients with pharmacoresistant epilepsies.

Table 3 Lipid profile according to time points on KD

Before the diet n = 4		3months n = 49	6months n = 49	12months n = 30	18months n = 21	24months n = 17
		n (%)	n (%)	n (%)	n (%)	n (%)
Total cholesterol	Adequate	25 (51.0)	14 (28.6)	11 (22.5)	9 (30.0)	7 (41.2)
	Inadequate*	21 (42.9)	20 (40.8)	25 (51.0)	15 (63.3)	9 (52.9)
	No registry	3 (6.1)	15 (30.6)	13 (26.5)	2 (6.7)	1 (5.9)
Triglycerides	Adequate	31 (63.3)	20 (40.8)	20 (40.8)	16 (53.3)	7 (41.2)
	Inadequate**	15 (30.6)	13 (26.5)	16 (32.7)	12 (40.0)	8 (47.0)
	No registry	3 (6.1)	16 (32.7)	13 (26.5)	2 (6.7)	2 (11.8)

Abbreviation: IMIP, Instituto de Medicina Integral Prof. Fernando Figueira. Notes: *Hypercholesterolemia (≥ 170 mg/dL)^{15,16}; **Hypertriglyceridemia (> 100 mg/dL for patients up to 10 years and > 130 mg/dL for those over 10 years).

20% and 54%.²² This occurred because families had difficulties preparing and administrating the KD and attending consultations.²² In our study, many patients were from the inland of Pernambuco or other states (covering distances > 500 kilometers) and did not receive financial support to access the reference center, corroborating the literature. Studies also reported discontinuation because of delayed improvement of epilepsies, adverse effects, and non-adherence due to low palatability.^{7,22,23}

Most patients (75%) presented gastrointestinal adverse effects (nausea, vomiting, diarrhea, and constipation), possibly due to intolerance to KD. Sleepiness and irritability were also presented in low frequency in the first months of treatment. Families were instructed on these mild adverse effects after KD adjustments.⁷

A systematic review included 11 studies (n = 778 participants) on the effects of KD on pharmacoresistant epilepsies. The main reasons for discontinuation were adverse effects and non-adherence. All studies reported adverse effects,

mainly short-term gastrointestinal symptoms.²⁴ Other less common effects were anorexia, lethargy, lower respiratory tract infections, and hyperammonemic encephalopathy.²⁴

In a randomized clinical trial involving 48 children with epilepsies (26 in KD and 22 on ASMs, about 58% of the KD group completed the 16-month follow-up. Despite the high cost of treatment, the amount and severity of epileptic seizure frequency were reduced. However, data were inconclusive regarding the best cost-benefit among KD and ASMs.²⁵

KD is used for rapid weight loss²⁶; however, weight loss is not the aim for pharmacoresistant epilepsies. Patients who were underweight, overweight, and with obesity may benefit from an ideal caloric value, according to age-adjusted protein-calorie needs, favoring the improvement or maintenance of their nutritional status.⁷

In this study, half of the patients who were underweight before KD increased their BMI-for-age at six months of treatment, being classified as normal weight. Moreover, the percentage of patients who were overweight was

maintained. The reduction in the sample may explain changes in the nutritional status after six months of KD. Most patients in each duration point had normal weight.

The effects of KD on nutritional status are still controversial. A study showed that weight gain in children with epilepsies on KD is similar to healthy children.²⁷ However, early and long-term KD may highly impair anthropometric values and bone mass, highlighting nutritional status monitoring concerns.^{28–31}

The lipid profile complements the nutritional status assessment.³² Despite the prolonged and high fat intake, this study indicated that the lipid profile alternated between adequate and inadequate after 12 months of KD. The human body presents compensatory mechanisms to maintain balance in fat metabolism.³³ Less saturated fat intake may favor a normal lipid profile and controlled atherogenic fractions.³⁴ In addition, dyslipidemia is a common and short-term adverse effect of KD, occurring at any time and controlled with adequate monitoring and adjustment.⁷ Statins may also be used if dyslipidemia remains severe and persistent.⁷

KD is an unconventional, safe, and effective treatment that reduces epileptic seizures and the use of ASMs.^{35–38} A multicenter study indicated that 33% of children with pharmacoresistant epilepsies achieved complete control, and 33% decreased ASMs use. In addition, a longitudinal study demonstrated reduced ASMs use; about 15% of the children could live without these epileptic seizures.^{36,37}

Most patients in our study showed reduced epileptic seizure frequency by over 50% after six months of treatment, corroborating the literature. In a multicenter study, 54% of the 51 children who presented a mean of 230 epileptic seizures per month showed a decrease by 50% after KD within three months of follow-up.³⁸

KD is efficient if epileptic seizure frequency is reduced by at least 50%.^{18,19} Although some patients did not reach this percentage, reducing epileptic seizure frequency improved the cognitive and neurodevelopment, behavior, and quality of life of the patient and family, justifying the maintenance of treatment.⁷

Although no difference was found in the mean number of ASMs used before and after KD, 6% of our patients showed dosage reduction, and one patient (2%) stopped using ASMs. In another study, the dosage reduction occurred in 33% of the sample.³⁹ Drug polytherapy is high-cost and presents adverse effects, limiting its use.³⁶ Moreover, a high dosage of ASMs impacts the behavior and cognition of children, justifying early withdrawal or reduction.³⁶ A study evaluated the main adverse effects of drug polytherapy using the perception of parents, indicating altered behavior, increased irritability, depressive symptoms, changes in cognitive function, motor and coordination problems, visual changes, headache, and dermatological, gastrointestinal, and hormonal complaints.¹⁹

This study presents some limitations. The sample was small, and many losses occurred due to the lack of information in medical records. In addition, losses occurred because some patients were still undergoing treatment or did not adhere to KD and gave up before 24 months.

KD requires dedication, work, and organization, and most adverse effects can be prevented and controlled.⁷ Important steps must be verified for treatment success: the initial lipid profile; the record of epileptic seizures; replacing drugs containing sugar; the type of diet to be followed; and products that are not part of the eating habit. In the follow-up, ketosis control is essential during the month before the consultation. Therefore, the family must participate in the treatment for the patient to feel included in the family context.^{5,7}

In conclusion, KD prevented malnutrition worsening and reduced epileptic seizures and ASMs use. Changes in the lipid profile occurred, and adverse effects were reported; however, they were short-term and controlled with diet adjustments.

Authors' Contributions

All authors equally contributed to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review, and editing. All authors approved the submitted version of the manuscript.

Conflicts of Interest

There is no conflict of interest to declare.

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