BMC Women's Health

RESEARCH

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MCT-modified ketogenic diet as an adjunct to standard treatment regimen could alleviate clinical symptoms in women with endometriosis

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Abstract

Background Endometriosis as a chronic gynecological condition impairs the quality of life of affected women because it usually accompanied by painful clinical symptoms such as persistent severe acyclic pelvic pain, dyspareunia, and dyschezia. The aim of the present study was to examine the effects of MCT-modified ketogenic diet as an adjunct to standard treatment regimen in women with endometriosis.

Methods This is a 12-weeks randomized controlled clinical trial that was conducted on 50 patients with endometriosis who referred to Yas hospital complex infertility clinic, Tehran, Iran. Participants were randomly allocated to intervention group receiving MCT-modified ketogenic diet plus standard treatment regimen (n = 25) and control group receiving standard treatment regimen (n = 25). Clinical symptoms, anthropometric parameters, lipid profile, and serum aminotransferases were measured at the beginning and end of the study. Statistical analysis was done by SPSS version 27 software and P-value < 0.05 was regarded significant.

Results Finally, 44 patients including 19 subjects in the intervention group and 25 subjects in the control group completed the study. Dyspareunia and dyschezia significantly reduced in the MCT-modified ketogenic diet group compared to the control group at the end of the study (P = 0.02 and P = 0.001, respectively). Also, there was a marginally significant reduction in the final values of pelvic pain (P = 0.07). However, no significant differences in the final value of anthropometric indices including weight, BMI, and WC, serum levels of TG, TC, HDL-C, LDL-C, and aminotransferases including ALT and AST was detected.

Conclusions MCT-modified ketogenic diet as an adjunct to standard treatment regimen could alleviate clinical symptoms including pelvic pain, dyspareunia, and dyschezia in women with endometriosis.

Trial registration Iranian Registry of Clinical Trials IRCT20131125015536N15. Registered on 24 July 2024. https://www.irct.ir/trial/78113.

Keywords MCT-modified ketogenic diet, Pelvic pain, Dyspareunia, Dyschezia, Endometriosis

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Background

Endometriosis, an estrogen-dependent chronic condition, characterized by the ectopic implantation of functional tissue lining the uterus outside of the uterine cavity [1]. Endometriosis as the most perplexing gynecological condition affecting women of reproductive age manifests in infertility, chronic pelvic pain, severely painful menstrual periods, dyspareunia, dyschezia, abdominal bloating, and constipation [2–4]. The prevalence of endometriosis was high in developing countries. The incidence of endometriosis in women of reproductive age ranges from 5 to 15% [5]. Endometriosis increases healthcare resource utilization and costs because of its high burden of comorbidities [6].

A great variety of treatments for endometriosis-associated symptoms have been implemented [7]. The combined oral contraceptive pill and progestogens as the first-line treatments and surgical approaches as the second- and third-line treatments are recommended [8]. However, the recurrence rate of symptoms after five years is 50% [9]. Thus, developing novel therapeutic strategies focus on inflammatory and angiogenesis pathways as the most important mechanisms responsible for endometriosis is of paramount importance [10]. Activation of estrogen signaling, systemic inflammation, oxidative stress, angiogenesis, cell division, and inhibition of apoptosis are the main factors involved in the pathogenesis of endometriosis [11]. Also, based on the available evidence, Wnt/B-catenin signaling pathway is the most well-known pathway responsible for initiation and progression of the endometriosis lesions [12].

Ketogenic diet, a high-fat and very low-carbohydrate diet, could consider as promising therapeutic option for the management of various disorders including epilepsy, diabetes, dyslipidemia, cardiovascular disease, malignancies and diseases of the female reproductive system [13]. By suppressing inflammation and oxidative stress, attenuating angiogenesis and cell division, promoting apoptosis, and inhibiting Wnt/B-catenin signaling pathway, ketogenic diets may alleviate endometriosis and its related symptoms [14–17]. Among different kinds of ketogenic diets, MCT-modified ketogenic diet accelerates the process of ketogenesis [18]. Also, risk of some complications such as drowsiness, nausea, vomiting, possible low blood sugar, increased blood cholesterol, increased liver enzymes, and gastrointestinal complications is very low in modern ketogenic diets, such as the MCT oil-based ketogenic diet [19]. For example, a study conducted on breast cancer patients undergoing radiotherapy showed that the administration of an MCT-based ketogenic diet formula, compared to a standard diet, not only did not cause the deleterious complications associated with the classic ketogenic diet, but also significantly improved liver and kidney function indicators such as creatinine and liver enzymes, as well as improved serum triglyceride levels [20].

An animal study by Wang et al. [21] demonstrated that ketogenic diet could attenuate cell division and promote apoptosis in mouse with induced colorectal cancer. Also, the authors reported that Wnt/B-catenin signaling pathway was suppressed and the expression of B-catenin as a main mediating protein in this pathway was decreased [21]. In addition, a systematic review concluded that ketogenic diets could be helpful for inflammation-associated pain, such as pelvic pain of endometriosis, by attenuating inflammatory cascade [22].

Since no clinical trial has investigated the effects of ketogenic diets in the management of endometriosis, this study aims to assess the effects of MCT modified-ketogenic diet as an adjunct to standard treatment regimen in women with endometriosis.

Methods

Study design

This current research is a randomized controlled clinical trial that is registered at the Iranian Registry of Clinical Trials (ID: IRCT20131125015536 N15. https://www.irct.ir/trial/78113. Registered on 24 July 2024.) and received approval from Medical Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICNE.REC.1403.167). The present investigation conducted at the Yas Hospital Complex, Tehran, Iran in accordance with the Declaration of Helsinki. Also, this study adheres to CONSORT guidelines. Researchers obtained written informed consent from study subjects before participation in the clinical trial. Study subjects selected from women with endometriosis who were diagnosed by a skilled specialist based on laparoscopic and pathological findings. Women with endometriosis enrolled from the clients of Yas hospital complex infertility clinic. An expert gynecologist diagnosed women with endometriosis according to the laparoscopic and pathological findings. Patients that satisfy the following inclusion criteria were eligible to participate in the present clinical trial. We included individuals aged between 25 to 35 years, subjects whose BMI ranged between 21 to 25 kg/m^2, patients with diagnosis of endometriosis by an adept gynecologist according to the laparoscopic and pathological findings (patients affected by endometriosis stage I or II based on diagnostic laparoscopy, or patients with a higher stage who underwent diagnostic-therapeutic laparoscopy and the stage of their disease was reduced to I or II, three months after laparoscopy), and who fill out a written informed consent. Also, having a visual analog scale (VAS) score of 3 out of 10 or greater than 3 out of 10 for pelvic pain, dyspareunia, and dyschezia

was considered as another inclusion criterion. Women who were pregnant or breastfeeding or menopause, who were afflicted by liver and kidney disorders, kidney stones, cancer, intestinal malabsorption, diabetes, cardiovascular diseases, and endocrine abnormalities, and who were smokers or addicted to alcohol were excluded. Also, patients with uterine myoma or polyp and subjects who take medications including anti-depressant drugs, clomifene, letrozole, and gonadotropins were excluded.

Randomization

Random allocation was done by the Permuted Block Randomization method at the termination of the Run-in period. In this method, eligible people who met the eligibility criteria were selected and then randomly assigned using 4 blocks based on the severity of endometriosis (stage I or stage II) in a random allocation method. They were assigned to either MCT-modified ketogenic group or control group. In random allocation, based on the list of random numbers, the letters A and B are assigned equally to the random numbers. In this way, the letters A and B spread between the patient codes. Numbers assigned to patients according to the order of participants'entry, and patients received standard treatment regimen (oral contraceptive pill (OCP)) plus MCT-modified ketogenic diet or standard treatment regimen lonely based on specific letters (A or B). The intervention group received MCT-modified ketogenic diet plus standard treatment regimen and only standard treatment regimen was assigned to control group.

Study interventions

Women with diagnosed endometriosis who met the inclusion criteria and volunteer to participate in the study entered a two-week run-in period to obtain sufficient data about their food habits and dietary intakes. Also, compliance to the diet measured in this period of time. Fifty eligible patients with endometriosis were randomly allocated to intervention (n = 25) and control group (n = 25). The intervention group received MCT-modified ketogenic diet plus standard treatment regimen (OCP) for 12 weeks and the control group received only standard treatment regimen (OCP) for 12 weeks. It should be noted that there was no dietary intervention in the control group and they were recommended to follow their regular diet. MCT-modified ketogenic diet contains 70–80% fat, 15–20% protein and 5–10% carbohydrates. The calories of the diets were calculated based on the Mefflin formula and based on the current body weight. The ratio of grams of fat and protein to carbohydrates was 3:1. A limited amount of pistachios, almonds, or olives was recommended for snacks. Consumption of water, tea and spices was not limited. It was recommended not to use rice, bread, sugar, sweets, potatoes, pasta and dairy products during the intervention period. The amount of protein was limited and comes from eggs, cheese, fish, chicken, quail and meat. The amount of fruit in the diet was very limited and vegetables could be used in the amount allowed in the diet. Ketogenic diet started and stopped gradually. Patients advised to consume two meals of regular diet and one meal of ketogenic diet on the first two days. Two meals of ketogenic diet and one meal of regular diet consumed on the third and fourth day and finally on the 5 th day, the consumed completely. Along with the diet, 500 cc of MCT oil was given to the patients every three weeks to accelerate the process of ketosis. Since MCT oil was tasteless, patients advised to take 8 cc of it (based on the amount prescribed in the diet) with a salad or on its own after a main meal. Consumption of MCT oil was gradually started with a dose of 5 ml and within 3 days, it reached the final dose calculated in the diet. About 40 food menus were planned for patients to use any menu they like based on their individual preferences. Multivitamin supplements and calcium-vitamin D supplements were also prescribed for patients in both study groups.

To assess adherence to the diet during the intervention, a three-day food recall questionnaire was collected from the participants by phone calls at the beginning of the study and every two weeks. If the study patients did not answer phone calls more than twice or consumed 3 inappropriate meals per week for more than 2 consecutive weeks, they considered non-compliant. Also, the patients were asked to measure their urinary ketones daily, while fasting and using a urine ketone strip, during the first two weeks and once a week after that. Persistent ketonuria was determined by urinary ketones above 0.5 mmol/L. If there was not even one day of stable ketonuria after the complete start of the diet (the fifth day), patients were considered non-compliant and excluded from the study. About follow-up schedule, all parameters except body weight and dietary intakes were assessed at the initiation of the study and after the intervention period, 12 weeks.

Measurements and assessments

Assessment of anthropometric parameters

Body weight was estimated fasting, without shoes, with minimal clothing and using a digital scale (Seca, Hamburg, Germany) with an accuracy of 100 g at the beginning and end of the study. Also, once every 2 weeks, body weight of participants was asked by phone call. The height of people standing without shoes was measured with a tape measure installed on the wall with an accuracy of 0.5 cm. BMI was calculated using the formula of dividing weight in kilograms by the square of height in meters. We measured waist circumference (WC) using

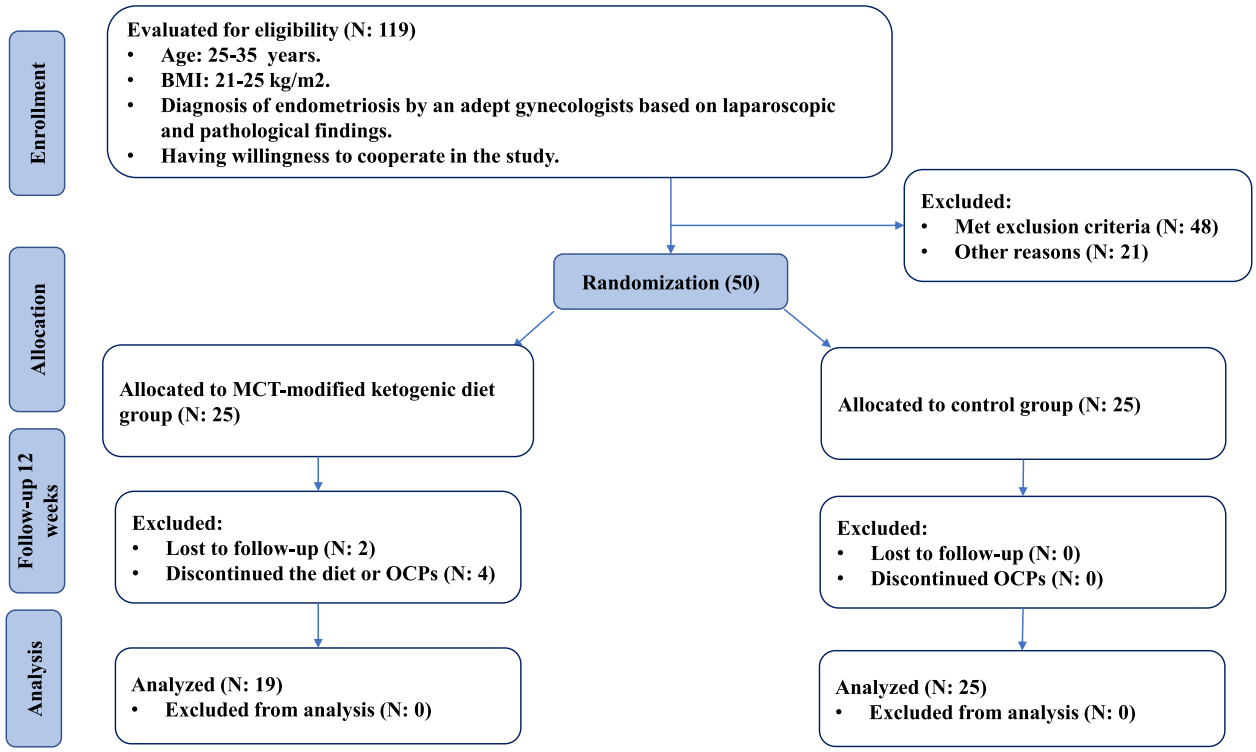

Fig. 1 Study flowchart. OCPs, oral contraceptive pills

the middle of the lowest gear, the high point of the iliac crest and on the biggest environmental gluteal muscle, respectively.

Laboratory assessments

Blood samples (10 mL) were drawn following an 8 to 12-h overnight fasting before and after the intervention. It was used to separate the serum by centrifuging at a speed of 3500 rpm for 10 min. The serum was transferred into sterile microtubes and kept in a −80 ℃ freezer until the test. Commercial kits (Pars Azmoon Inc. kit, Tehran, Iran) used to measure the concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and liver transaminases including aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Clinical assessments

Clinical symptoms including pelvic pain, dyspareunia, and dyschezia were estimated at the beginning and termination of the study using a visual analog scale (VAS) questionnaire that its validity and reliability have been confirmed. Blood pressure was checked out using a mercury sphygmomanometer after at least five-minutes resting. The measurement was carried out on two occasions.

Sample size calculation

By considering type I error of 5% ($\alpha = 0.05$) and power of 90%, the sample size was calculated to be 19 for each group according to the two sided t test. We upraised the final sample size to 25 women in each group to compensate for drop-out rate of 25% during the research period.

Statistical analysis

Descriptive and analytical statistics was applied for data analysis and all analyzes were run using SPSS version 27 software. The normal distribution of the variables was checked through scatter diagram, histogram and Shapiro–Wilk test. Median (interquartile range) applied for variables with non-normal distribution. Mean (standard deviation) and number (percentage) were respectively used for quantitative and qualitative variables. Between-group differences were assessed using a general linear mixed model (GLM) for continuous variables and chi-square test for categorical variables. P-value < 0.05 was accounted statistically significant.

Results

As demonstrated in Fig. 1, among the 119 women examined for the eligibility criteria, 50 met the inclusion criteria and recruited in the study. As six of the patients were

Table 1 Baseline characteristics of the study subjects

variables		Groups		*P*-Value*
		MCT-modified KD (*n* = 25)	control (*n* = 25)	
Age (years)		27 ± 4	29 ± 4	0.1[a]
weight (kg)		60.3 ± 8.4	61.4 ± 6.3	0.65[a]
Height (cm)		163 ± 7	163 ± 6	0.87[a]
Marital status	married	22 (88%)	21 (84%)	0.68[b]
	divorced	3 (12%)	4 (16%)	
Education	Diploma and lower	5 (20%)	6 (24%)	0.73[c]
	Bachler and higher	20 (80%)	19 (76%)	
occupation	Housewife	8 (32%)	4 (16%)	0.4[b]
	Employee	11 (44%)	13 (52%)	
	Self-employed	6 (24%)	8 (32%)	
Socio-economic status	High	13 (52%)	10 (40%)	0.39[c]
	moderate	12 (48%)	15 (60%)	
Endometriosis grade	grade 1	9 (47%)	13 (52%)	0.76[c]
	grade 2	10 (53%)	12 (48%)	

Data are presented as mean ± SD for quantitative and frequency (%) for qualitative variables

KD ketogenic diet

* based on [a]independent sample t test, [b]chi-square, and [c]mann-whithney test

lost to follow up, finally, 44 (19 in the intervention group and 25 in the control group) completed the trial.

Table 1 indicated baseline characteristics of study patients. The mean age of the patients was 27 ± 4 years and 29 ± 4 years in the intervention and control group, respectively. Fifty-three percent of the women in the intervention group and forty-eight percent of them in the control group were affected with endometriosis grade II. There were no statistically significant differences between the two groups in terms of age, weight, height, marital status, educational level, occupational position, socio-economic status, and grade of endometriosis ($P_{value} > 0.05$).

The anthropometric parameters of the participants are shown in Table 2. There were no significant within- or between-group differences in terms of weight, BMI, and WC in the study groups post-intervention ($P_{value} > 0.05$). Also, comparing change-from-baseline values for all the mentioned parameters indicated no statistical significant difference between study groups ($P_{value} > 0.05$). As indicated in Table 3, after adjusting for baseline values and weight changes, no significant differences in the final value of serum levels of TG, TC, HDL-C, LDL-C, and aminotransferases including ALT and AST were observed in the intervention group compared to the control group post-intervention ($P_{value} > 0.05$). Also, comparing change-from-baseline values for all the mentioned parameters except TC indicated no statistical significant difference between study groups ($P_{value} > 0.05$). There was a significant increase in change-from-baseline value for TC in the intervention group compared to the control group ($P_{value=}0.04$). However, regarding within-group differences, serum levels of AST was significantly reduced in both of the MCT-modified ketogenic diet group and control group at the end of the trial ($P_{value=}0.02$ *and* $P_{value=}0.03$, *respectively*).

Table 4 reported clinical symptoms of the participants during the study. After adjustment for potential confounders including baseline values, weight changes, and endometriosis grade, dyspareunia ($MD = 0.82$; 95% $CI = 0.12, 1.52$; $p = 0.02$) and dyschezia ($MD = 1.06$; 95% $CI = 0.46, 1.6$; $p = 0.001$) significantly reduced in the MCT-modified ketogenic diet group compared to the control group at the end of the study. Comparing change-from-baseline values for dyspareunia ($p = 0.05$) and dyschezia ($p = 0.001$) showed a significant decrease in the intervention group. Also, there was a marginally significant reduction in the final values of pelvic pain ($MD = 0.42$; 95% $CI = -0.04, 0.88$; $p = 0.07$) in the intervention group compared to the control group at the termination of the trial. However, comparing change-from-baseline values for pelvic pain demonstrated no statistical significant difference between the study groups ($P_{value} > 0.05$). Regarding within-group differences, a significant decrease in the scores of pelvic pain, dyspareunia, and dyschezia was detected in both of the study groups ($P_{value} < 0.005$).

Table 2 Anthropometric parameters of the study subjects at baseline and after the 12-weeks of intervention

parameter	Time	Groups		Mean difference	95% CI		*P*[*]
		MCT-Modified KD (*n* = 19)	Control (*n* = 25)		Lower	Upper	
weight	Before	60.3 ± 8.4	61.4 ± 6.3	1.05	−3.65	5.76	0.65[a]
	After	60.2 ± 8.4	61.4 ± 6.1	0.21	−0.45	0.87	0.52[b]
	Change	−0.11 ± 0.78	0.08 ± 1.2	0.18	−0.43	0.81	0.55[a]
	P-within[**]	0.54	0.76				
BMI	Before	22.6 ± 1.8	22.9 ± 1.2	0.34	−0.64	1.34	0.48[a]
	After	22.6 ± 1.9	22.9 ± 1.3	−0.005	−0.28	0.27	0.97[b]
	Change	0.02 ± 0.4	0.02 ± 0.49	0	−0.26	0.27	0.97[a]
	P-within[**]	0.86	0.84				
WC	Before	79.2 ± 3.6	81.2 ± 5.02	1.9	−0.63	4.61	0.13[a]
	After	79.1 ± 3.4	81.2 ± 4.6	0.23	−0.29	0.76	0.38[b]
	Change	−0.05 ± 0.5	0.01 ± 1.1	0.06	−0.46	0.58	0.81[a]
	P-within[**]	0.69	0.97				

Data are presented as mean ± standard deviation

BMI Body mass index, *WC* waist circumference, *KD* ketogenic diet

[*] based on [a]independent sample t test, and [b]general linear model adjusted for baseline values

[**] based on paired sample T test

Discussion

Currently, no curative treatment for endometriosis exists since pathogenesis of this disorder is not fully recognized [23]. Even after treatment of these patients using hormonal suppression, surgery, or a combination of both, the severity of endometriosis remained unchanged in most of the cases [24]. Therefore, investigating an adjuvant therapy such as an appropriate diet could be beneficial for the management of endometriosis [25, 26]. To the best of our knowledge, this is the first randomized controlled trial investigating the effects of MCT-modified ketogenic diet as an adjuvant therapy in patients with endometriosis. Based on our main findings, dyspareunia and dyschezia significantly reduced in the MCT-modified ketogenic diet group compared to the control group at the end of the study. Also, there was a marginally significant reduction in the final values of pelvic pain. However, no significant differences in the final value of anthropometric indices including weight, BMI, and WC, serum levels of TG, TC, HDL-C, LDL-C, and aminotransferases including ALT and AST was detected.

In line with our findings, a systematic review by Masino et al. [22] concluded that ketogenic diets could be helpful for inflammation-associated pain like pelvic pain in endometriosis by attenuating inflammatory cascade. Also, a recent prospective study conducted by Cirilo et al. [27] disclosed that there was a clear tendency toward a relationship between pain relief in endometriosis and Mediterranean diet. After 3 months of intervention, dyspareunia, non-menstrual pelvic pain, dysuria, and dyschezia were significantly reduced. Moreover, after six months of intervention, there was a significant decrease in terms of dyspareunia and dyschezia [27].

Another clinical study by Haaps et al. [28] found that patients who were on both a low-FODMAP diet and an endometriosis-specific diet for 6 months experienced less pelvic pain and had better quality of life scores compared to the control group. Overall, the study concluded that nutritional interventions including both a low-FODMAP diet and an endometriosis-specific diet improved pain and quality of life in patients with endometriosis [28].

Marziali et al. [29] indicated that prescription a gluten-free diet for 12 months can significantly reduce painful symptoms associated with endometriosis. Another study by Moore et al. [30] revealed that prescribing a low-FODMAP diet for 4 weeks in patients with endometriosis who had IBS significantly improved pain in the abdomen and pelvis. The hypothesis for the effectiveness of these diets in patients with endometriosis is that they often have intestinal disorders such as IBD, IBS, and celiac disease, and the presence of these disorders and their associated abdominal pain doubles the amount of pelvic pain associated with endometriosis. Therefore, following a gluten-free diet or low-FODMAP diet, due to the improvement in abdominal pain of the aforementioned intestinal disorders, generally reduces abdominal and pelvic pain [29, 30].

Activation of estrogen signaling, systemic inflammation, oxidative stress, angiogenesis, cell division, and inhibition of apoptosis are the main factors involved in

Table 3 Biochemical parameters of the study subjects at baseline and after the 12-weeks of intervention

parameter	Time	Groups		Mean difference	95% CI		P*
		MCT-modified KD (*n* = 19)	Control (*n* = 25)		Lower	Upper	
AST	Before	18 (17, 24)	19 (16, 24)	1.6	−1.9	5.2	0.82[c]
	After	18 (16, 21)	19 (17, 22)	0.8	−0.13	1.73	0.09[b]
	Change	−1 (−3, 0)	0 (−3, 0)	0.31	−1.1	1.8	0.53[c]
	P-within**	0.02[e]	0.03[e]				
ALT	Before	19.7 ± 6.7	17.8 ± 7.1	−1.8	−6.1	2.3	0.37[a]
	After	18.9 ± 6	17.6 ± 6.1	0.14	−1.02	1.32	0.8[b]
	Change	−0.84 ± 2.5	−0.28 ± 2.03	0.56	−0.87	1.9	0.43[a]
	P-within**	0.16[d]	0.49[d]				
TG	Before	111 ± 36	100 ± 42	−11.5	−35.07	12.03	0.32[a]
	After	109 ± 36	102 ± 35	2.9	−2.2	8.2	0.25[b]
	Change	−2.2 ± 8.3	2.36 ± 10.4	4.57	−1.16	10.3	0.11[a]
	P-within**	0.26[d]	0.27[d]				
TC	Before	143 ± 30	171 ± 26	27.8	10.58	45.11	0.02[a]
	After	147 ± 28	164 ± 21	−3	−12.05	6.04	0.5[b]
	Change	3.7 ± 17.7	−6.3 ± 11.7	−10.1	−19.7	−0.48	0.04[a]
	P-within**	0.36[d]	0.01[d]				
HDL	Before	52 ± 14	53 ± 12	1.05	−7.1	9.2	0.79[a]
	After	52 ± 12	54 ± 12	0.66	−1.5	2.8	0.55[b]
	Change	0.05 ± 5.2	0.6 ± 2.8	0.54	−2.17	3.23	0.68[a]
	P-within**	0.96[d]	0.3[d]				
LDL	Before	101 ± 22	95 ± 23	−6.8	−20.69	7.06	0.32[a]
	After	107 ± 27	96 ± 17	−4.9	−11.05	1.08	0.1[b]
	Change	5.58 ± 12.5	1.32 ± 7.93	−4.2	−10.81	2.29	0.19[a]
	P-within**	0.06[d]	0.41[d]				

Data are presented as mean ± standard deviation or Median (IQR)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *KD* ketogenic diet

* based on [a]independent sample t test, [c]mann-whithney, and [b]general linear model adjusted for baseline values and weight changes

** based on [d]paired sample T test or [e]Wilcoxon

the pathogenesis of endometriosis [11]. ketogenic diets might alleviate endometriosis and its-related complications by targeting main factors involved in its pathogenesis. They suppress inflammation and oxidative stress, attenuates angiogenesis and cell division, and promotes apoptosis. Also, as a theoretical explanation, ketogenic diets could inhibit Wnt/B-catenin signaling pathway as the most well-known pathway responsible for initiation and progression of the endometriosis lesions [12, 14–17, 21]. They suppress Wnt/B-catenin signaling pathway by decreasing the expression of B-catenin, main mediating protein in this pathway [21].

Strengths and weaknesses of the trial

The strengths of our trial included long duration of the intervention, a personalized and prescription-based dietary intervention, and robust statistical analysis that adjusted findings for probable confounders to minimize biases. Also, investigating the effects of MCT-modified ketogenic diet as an adjunct to standard treatment regimen in women with endometriosis, for the first time, would be considered as another strong points. Our trial also has some notable limitations. First, our results could not be generalized to patients with moderate to severe disease (endometriosis grade III and IV) because we exclusively included patients with endometriosis grade I and II. Also, narrow inclusion criteria for age (25–35 years) and BMI (21–25 kg/m^2) may limit the external validity of the study. It should be noted that the findings may not apply to populations with overweight/obesity or older reproductive-age women. Second, due to the remarkable drop-out rate, the sample size seems to be not sufficient. Third, some other unknown confounders could affect the obtained results despite of considering probable confounding variables in statistical analysis. And finally, given the anti-inflammatory

Table 4 Clinical symptoms of the study subjects at baseline and after the 12-weeks of intervention

parameter	Time	Groups		Mean difference	95% CI		P*
		MCT-modified KD (*n* = 19)	Control (*n* = 25)		Lower	Upper	
Pelvic pain	Before	5 (4, 8)	5 (4, 7)	−0.29	−1.63	1.04	0.63[c]
	After	4 (3, 5)	4 (3, 6)	0.42	−0.04	0.88	0.07[b]
	Change	−1 (−2, 0)	−1 (−1, 0)	0.5	−0.11	1.12	0.13[c]
	P-within**	0.001	< 0.001				
Dyspareunia	Before	6 (3, 8)	6 (3, 7)	−0.34	−1.87	1.17	0.61[c]
	After	4 (3, 6)	4 (3, 7)	0.82	0.12	1.52	0.02[b]
	Change	−2 (−2, 0)	−1 (−1, 0)	0.89	0.05	1.73	0.05[c]
	P-within**	0.001	0.001				
Dyschezia	Before	4 (3, 6)	3 (3, 5)	−0.48	−1.5	0.54	0.33[c]
	After	3 (2, 4)	3 (2, 4)	1.06	0.46	1.6	0.001[b]
	Change	−2 (−3, 1)	0 (−1, 0)	1.09	0.47	1.71	0.001[c]
	P-within**	< 0.001	0.002				

Data are presented as or Median (IQR)

KD ketogenic diet

* based on [c]mann-whithney and [b]general linear model adjusted for baseline values, weight changes, and endometriosis garde

** based on Wilcoxon test

hypothesis of the ketogenic diet, it is a missed opportunity not to measure biomarkers such as CRP, IL-6, or TNF-α.

Conclusion

Altogether, MCT-modified ketogenic diet as an adjunct to standard treatment regimen could significantly alleviate clinical symptoms including dyspareunia and dyschezia in women with endometriosis. Also, there was a marginally significant reduction in pelvic pain. Future well-designed randomized controlled trials with greater sample size enrolling patients with all stages of endometriosis are recommended to establish the benefits of the MCT-modified ketogenic diet as an adjuvant therapy in the management of endometriosis. Also, it is important to incorporating validated quality of life assessment tools such as the SF-36 or EHP-30 questionnaires to evaluate the broader impact of the MCT-modified ketogenic diet on patients' well-being in future studies.

Abbreviations

BMI	Body mass index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
PBMCs	Peripheral blood mononuclear cells
WC	Waist circumference
VAS	Visual analog scale
TG	Triglyceride
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol

Acknowledgements

We sincerely thanked Tehran university of medical sciences (TUMS) for its financial support.

Authors' contributions

FN and FD contributed to the conception of research and searched databases, data collection was done independently by 2 reviewers (FN and FD), MM and HA performed the statistical analysis, FN wrote the manuscript, and MJHA critically revised the manuscript.

Funding

The trial funding was supported by Tehran University of Medical Science (Grant number: 73845). The funder is not involved in the study design, collection, management, analysis and interpretation, writing of the manuscript, and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities.

Data availability

The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from participants before participation in the research project. The current trial received approval from Medical Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICNE.REC.1403.167). This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 1 April 2025 Accepted: 9 May 2025
Published online: 16 May 2025

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