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Name of Journal: *World Journal of Clinical Pediatrics*

Manuscript NO: 74057

Manuscript Type: ORIGINAL ARTICLE

Case Control Study

Effects of Adherence to the Mediterranean Diet in Children and Adolescents with Irritable Bowel Syndrome

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder in children and adults, which increased over the past twenty years. The Mediterranean diet (MD) is a well-known diet full of antioxidants and anti-inflammatory ingredients.

AIM

² We evaluated the safety, tolerability, and effects of adherence to MD on disease patterns in children and adolescents with irritable bowel syndrome (IBS).

METHODS

This prospective, cross-sectional case-controlled study included 100 consecutive IBS patients diagnosed according to Rome IV criteria, aged 12-18 years. Patients were subdivided into two groups (50 patients each); Group I received MD and Group II on their regular diet for six months. Besides IBS scores (IBS-SSS, IBS-QoL, and total score), different clinical and laboratory parameters were evaluated at the start and end of the study.

RESULTS

MD was safe and well-tolerated in IBS patients. IBS children and adolescents with good adherence to MD (KIDMED Score ≥ 8 points); group I showed significant improvement in IBS scores. IBS-SSS in the MD group was 237.2 ± 65 at the beginning of the study and decreased to 163.2 ± 33.8 at the end of the study ($p < 0.001$). It did not show a significant improvement in the group with a regular diet (248.3 ± 71.1 at the beginning of the study compared to 228.5 ± 54.3 at the study end with $P < 0.05$). The mean IBS-SSS in the MD group significantly improved compared with the group with a regular diet.

Mean IBS-QoL in group I improved from 57.3 ± 12.9 at the start of the study to 72.4 ± 11.2 at the study end ($p < 0.001$), and significantly improved when compared to its level in group II at the study end (59.2 ± 12.7) with $p < 0.001$, while group II showed no significant improvement in IBS-QoL at the study end when compared to the beginning of the study (59.2 ± 11.7 with $p > 0.05$). The mean total IBS score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($p < 0.05$), and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5) with $p < 0.05$, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.8 ± 13.5) with $p > 0.05$.

CONCLUSION

MD was safe and associated with significant improvement in IBS scores in children and adolescent patients with IBS.

Key Words: Mediterranean diet (MD); irritable bowel syndrome (IBS); children and adolescents.

Al-Biltagi M, ²El Amrousy D, El Ashry H, Maher S, Mohammed MA, Hasan S. Effects of Adherence to the Mediterranean Diet in Children and Adolescents with Irritable Bowel Syndrome. *World J Clin Pediatr* 2022; In press

Core Tip: Diet is an essential factor in the pathogenesis and management of irritable bowel syndrome (IBS) patients. Studies involving different modalities of diets in IBS are lacking with contradictory results. Mediterranean diet (MD) is a well-known balanced diet with anti-inflammatory properties. We prospectively studied 100 pediatric and adolescent patients with IBS, divided into two equal groups: group I received MD and group II had a regular diet for six months. Different clinical and laboratory parameters besides IBS scores were evaluated at the start and end of the study. The current study showed that MD is a safe and effective low-cost new strategy in pediatric and adolescent patients with IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the highly prevalent gastrointestinal disorders in children and adults, which increased over the past twenty years. It has a significant effect on the lives of affected children and their families and poses a significant burden on healthcare systems (1). It is classified as one of the functional gastrointestinal disorders; characterized by varying degrees of abdominal pain or discomfort, abdominal distension, altered bowel habits, and flatulence, and can be divided into four subtypes; IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M) and IBS unsubtyped (IBS-U) (2).

IBS pathogenesis is a poorly recognized disorder. Many theories were proposed to explain its pathogenesis [3]. It could be related to low-grade inflammation of the bowel mucosa. Dysbiosis with dysregulation of brain-gut axis function and bacterial overgrowth are commonly seen in IBS and are accepted theories that can explain the occurrence of IBS. Immune activation and visceral hypersensitivity are possible pathogenetic mechanisms associated with disturbed gastrointestinal motility [4, 5]. A possible mechanism is dysregulated neurotransmitters such as cholecystokinin, vasoactive intestinal peptides, and serotonin with the abnormal gut-brain axis [6]. Moreover, food allergy or vitamin deficiency may play a role [7, 8].

A few potential therapeutic modalities are available to treat children with IBS, fewer of them have shown some benefits. Additionally, most of the described pathophysiological mechanisms and treatment choices are adult studies. These have surfaced as challenges when dealing with pediatric IBS, and they need to be overcome for effective management of children with IBS (9).

The Mediterranean Diet (MD) is characterized by many vegetables, fruits, bread, and other forms of cereal, rice, beans, and nuts. It also includes virgin olive oil as the principal source of fat, moderate amounts of dairy products (basically cheese and yogurt), moderate amounts of fish, and red meat in low quantities. The value of this dietary model is related to being a balanced and diverse diet that can provide most of the recommended macronutrients in proper proportions. It is characterized by a low

content of saturated fatty acids, high monounsaturated fatty acids, high amounts of fiber, complex carbohydrates, and essential antioxidants (10). They play a crucial role in preventing ⁴ cardiovascular and cerebrovascular diseases, diabetes, obesity, neurodegenerative illnesses, and cancer (11-12).

Data suggests that the MD might be beneficial in alleviating the functional gastrointestinal symptoms through the increased fiber and antioxidant consumption and the low intake of saturated fats and oligosaccharides (13-14). However, information about the compliance and efficacy of MD in children and adolescents with IBS is lacking. We aimed to study the effects of MD on the symptoms of IBS in children and adolescents.

MATERIALS AND METHODS

We designed the study to evaluate MD's tolerability, safety, and potential efficacy in children and adolescent patients with IBS. After explaining the study design, goals, and rights, all patients/caregivers were provided written consent or assent. We conducted the study according to the Helsinki Declaration of 1975. This prospective randomized, case-controlled study was carried out in the Pediatric and Gastroenterology departments, Tanta University Hospital, Egypt, between September 2020 and July 2021. We included one hundred consecutive children and adolescents with IBS diagnosed according to Rome IV criteria (15), aged 12-18 years old. We divided the patients into two groups (50 patients each); the group I received MD with good adherence (KIDMED Score ≥ 8 points) and Group II received a regular diet. Allocation to the groups was done using simple randomization. The study was not blind as we need to do patient and family education about the MD.

Inclusion criteria: patients with IBS; aged 12-18 years diagnosed with childhood irritable bowel syndrome according to ROME IV criteria (15)

Exclusion criteria: recent change in IBS therapy, gastrointestinal infection, history of gut surgery or radiation, celiac disease, overweight or underweight according to the centile

curve, (16) chronic disease such as renal failure or diabetes mellitus, and patients not adherent to the dietary protocol.

Study Intervention

During the study period (6 mo), the patients in group I had the MD as a sole intervention besides their regular treatment. Patients (and their caregivers) received one-to-one education and counseling by a dietitian trained in the MD during each visit. Before each visit, patients and their families completed a 3-day food intake record to help assure compliance with the diet. We closely followed up with the patients with the study team, including the dietitian, research pediatrician, and research gastroenterologist, for questions and problem intervention during the study period.

All participants had complete history taking, including dietetic history, and thorough clinical examination including anthropometric measurements such as height, weight, and body mass index (BMI). All participants with IBS filled out the IBS symptoms severity score (IBS-SSS) questionnaire (17). IBS-SSS consists of 5 items (severity and frequency of abdominal pain, bloating, satisfaction with bowel habits, and quality of life) collected by direct interview using the visual analog scale (VAS). We scored each item on a scale from 0 to 100. A score below 75 means that the patient is in remission. The mild, moderate, and severe boundary scores are 75–175, 175–300, and above 300. A decrease in the score of 50 or more was considered a significant improvement. The patients also had an IBS quality of life (IBS-QoL) questionnaire (18). Effectiveness, reliability, and sensitivity of IBS-SSS to treatment are verified by IBS-QoL, which has 34 items, using a 5-choice scale (0–4). We transformed the summed total score to a 100-scale ranging from 0 (lowest) to 100 (highest). A total score of IBS measured by a VAS of 100 scales is used to evaluate the total IBS symptoms impact the quality of life, which was done at the same frequency as IBS-SSS and IBS-QoL scores.

The patients also had routine laboratory investigations such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum calcium, random blood sugar, renal and hepatic functions, serum proteins, urine, and stool analysis. Fecal calprotectin was measured, and fecal blood in the stool was done in all included patients to exclude

patients with inflammatory bowel disease. Follow-up visits were done at one, three, and six months. All IBS scores, laboratory parameters, and growth parameters (body weight, height, and BMI) were repeated at the end of our study.

KIDMED test (Table 1)

The Mediterranean Diet Quality Index for children and teenagers (KIDMED test) is an instrument developed and validated by Serra-Majem *et al.* It is used to evaluate the adherence of children and youths to MD (19). The index ranges from 0 to 12. It is based on a 16-questions test that can be self-administered or conducted by interview (pediatrician, dietitian, *etc.*). Questions indicating a negative association concerning the MD are assigned a value of -1 and those with a positive aspect +1. The total values from the processed test are categorized into three degrees: 1) ≥ 8 , optimal adherence to the Mediterranean Diet; 2) 4–7, adherence improvement is needed to adjust intake to Mediterranean patterns; 3) ≤ 3 , poor adherence to MD (20).

The primary outcome of the current study was to assess the effects of adherence to the Mediterranean diet for six months on the IBS symptoms and severity score. The secondary outcome was to evaluate the safety and tolerability of the Mediterranean diet in children and adolescents with IBS.

Ethical considerations

This clinical study was conducted following the principles of the Declaration of Helsinki. At the beginning of the study, all subjects (and caregivers) were fully informed about the study objectives and their rights. They signed a written informed consent to participate in the study. The local Ethical Committee approved the study. The study is registered with the registration number PACTR202008711997928. All authors had access to the study data and have reviewed and approved this final manuscript.

Statistical analysis

A sample size of 45 IBS patients in each group was required to achieve a power of more than 80 to detect a difference of 60 in the mean of the primary outcome point (IBS-SSS) based on a previous study (21). We recruited more than the estimated sample size,

expecting a possible lack of adherence to MD or withdrawal from the study, undermining our results. We collected and analyzed the data using SPSS version 17 (SPSS Inc., Chicago, IL). We expressed the continuous data as mean \pm standard deviation. We used the paired t-test to compare the same group before and after treatment. An independent t-test was used for comparison between group 1 and group 2. we expressed the categorical variables as numbers and percentages and analyzed them using the Chi-square test. We used the Pearson correlation to evaluate the correlation between MD with IBS scores. The statistical significance was defined as $P < 0.05$.

RESULTS

This study included 100 children and adolescent patients with IBS aged 12-18 years; divided into two groups included 50 patients. Group-I had 27 meals and 23 females with a mean age of 15.5 ± 1.8 years, and group II had 26 males and 24 females with a mean age of 15.2 ± 1.5 years. Before the study, the average duration of IBS symptoms was 34.4 ± 9.1 mo in group I and 35.3 ± 9.8 mo in group II. We illustrated the demographic, growth parameters, clinical subtypes, IBS severity, treatment drugs, and IBS scores in both groups in table 2. We found no significant differences between the two groups in all measured parameters at the start of our study.

Basic laboratory data in all patients done at start of our study(table 3) with non-significant differences between both groups regarding serum albumin(4.1 ± 0.9 g/dL in Group-I and 4.3 ± 0.88 in Group-II with $P = 0.93$) ,serum triglycerides(120.7 ± 45.6 mg/dL in Group I and 112.9 ± 49.4 in Group-II with $P = 0.44$),serum cholesterol (154.0 ± 36.6 mg/dL in Group I and 163.6 ± 44.1 in Group II with $P = 0.35$),random blood glucose level(86.2 ± 20.2 mg/dL in Group I and 85.7 ± 9.7 in Group II with $P = 0.91$),hemoglobin level(13.1 ± 1.6 g/dL in Group-I and 13.6 ± 1.8 in Group II with $P = 0.47$).Fecal calprotectin was normal in both groups(12 ± 9.1 ug/g in group I and 11 ± 8.8 in Group II with $p = 0.52$), and it was done to exclude patients with inflammatory bowel disease.

Mediterranean diet was well tolerated in IBS patients. Only three patients could not tolerate it and were withdrawn from the study (one after one month, and two patients after three months, replaced by other patients; Figure 1). No adverse events regarding MD were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group-II at the end of our study (Table 4). At the end of our study, there was a significant improvement in all IBS scores in IBS patients who received MD (group I) compared to such scores at the start of the study and when compared to group II at the end of the study (Table 4). The mean IBS-SSS in group-I became 163.2 ± 33.8 at the study end compared to 237.2 ± 65 at the start ($p < 0.001$), with significant improvement, when compared to group-II at the study end (228.5 ± 54.3) with $p < 0.001$, while in group-II, there was no substantial improvement in IBS-SSS at the study end compared to its mean level at the start of the study (228.5 ± 54.3 vs. 248.3 ± 71.1 with $p 0.29$). Mean IBS-QoL in group-I became 72.4 ± 11.2 at the end of our study compared to 57.3 ± 12.9 at the start ($p < 0.001$), and significantly improved when compared to its level in group II at the end of the study (59.2 ± 12.7) with $p < 0.001$, while in group II, non-significant improvement in IBS-QoL at the end of our study compared to its mean level at the start of the study (59.2 ± 12.7 vs. 59.1 ± 11.7 with $p 0.77$). The mean total score in group I became 28.8 ± 11.2 at the end of our study compared to 24.1 ± 10.4 at the start ($P = 0.02$), and significantly improved when compared to its level in group II at the end of the study (22.1 ± 12.5) with $P = 0.03$, while in group II, non-significant improvement in the total score at the end of our study compared to its mean level at the start of the study (22.1 ± 12.5 vs. 22.8 ± 13.5 with $p 0.94$). These changes reflect MD's positive impact on symptoms and lifestyle of IBS children and adolescents.

DISCUSSION

What should we ²eat? This question is one of the most frequently asked questions by ⁶patients with IBS and their caregivers. Many patients also seek dietary guidelines because the diet is considered safer than medical therapies. Treating IBS symptoms by modifying the patient's diet has been one of the most desirable therapeutic strategies for ⁶a long time. Unfortunately, the scarcity of high-quality evidence supporting a specific dietary intervention resulted in unnecessary exclusion diets despite lacking evidence of efficacy and safety, especially in pediatric age groups (22). The current study found that MD was safe and well-tolerated in IBS patients. Compared to the control group, good adherence to MD resulted in significant improvement in IBS scores and IBS-QoL and total IBS score. Many previous studies in children and adolescents showed a negative correlation between compliance with the MD and the development of various diverse pathological conditions, such as obesity, asthma, and recurrent cold (23-24).

Considering the potential association of adherence to MD with the development of functional gastrointestinal disorders (FGIDs), many data from the adult populations support the beneficial effect of the MD on preventing the development of or lessening the gastrointestinal (GI) symptoms in patients with GI disorders, both functional (IBS, functional dyspepsia, gastroesophageal reflux) or organic (inflammatory bowel disease) (25). Elmaliklis *et al* showed that adherence to MD (including functional foods containing probiotics, prebiotics, antioxidants, fiber, vitamins, minerals) was significantly lower in adults patients with various gastrointestinal disorders such as IBS, Crohn's disease, ulcerative ³colitis, and gastroesophageal reflux than in controls (26).

Another Southern Italian study by Zito *et al* investigated the association between adherence to the MD and onset of symptoms in adults with functional dyspepsia or IBS. They demonstrated a negative correlation between compliance with the MD and the development of gastrointestinal symptoms. They concluded that good adherence to the MD could prevent the development of gastrointestinal symptoms in adults. Moreover, they showed that patients with functional dyspepsia and IBS between 17 and 24 years had significantly poorer MD adherence than the respective age-matched control groups. Interestingly, Strisciuglio *et al* studied the adherence to the MD in children and

adolescents suffering from inflammatory bowel disease with an age-matched population with FGIDs (gastroesophageal reflux and functional constipation). It was found that children/adolescents with inflammatory bowel syndrome had poorer adherence to the MD than those with FGIDs. However, there is no data on the association of MD adherence with the prevalence of FGIDs in children and adolescents (28).

In the current study, the Mediterranean diet was well tolerated in IBS patients; only three patients could not tolerate it and were withdrawn from the study (one after one month, and two patients after three months, and were replaced by other patients). No adverse events regarding MD were reported as reflected by non-significant changes in growth parameters (height, weight, and BMI), laboratory parameters (serum albumin, triglycerides, cholesterol, glucose, and hemoglobin levels) at the end of our study when compared to the same parameters at the start of the research and when compared to group II at the end of our research.

Our study found positive effects of MD in children and adolescents with IBS with significant improvements in all IBS scores compared to the patients on the regular diet. These effects may be due to the specific components of MD, which is characterized by high intake of plant-based foods (vegetables, legumes, fruits, nuts, whole grain cereals), olive oil as the primary fat source, moderate amounts of dairy products (yogurt and cheese), and low or moderate amounts of fish and meat, with well-known antioxidant and anti-inflammatory properties (10). Regular consumption of such products induces an accumulation of nitrate/nitrite/NO, polyunsaturated fatty acids (PUFA), and polyphenolic compounds, such as resveratrol, in the human body (12). The most important dietary sources of NO₃⁻ for the human body include green vegetables such as spinach, lettuce, collard greens and radishes, beets, and meat. At the organ level, NO₂⁻-dependent vasorelaxation plays a role in hypoxic blood flow regulation and improves tissue microcirculation (29, 30).

Mediterranean diet traditionally includes an abundance of vegetables and fish; both contain a substantial amount of diverse PUFA (ω -3, 6, 9). Briefly, PUFAs are divided

into three classes based on the position of the first double bond from the methyl carbon, labeled "ω": ω-3 (DHA-docosahexaenoic, EPA-eicosapentaenoic, and ALA-α-linolenic), ω-6 (LA-linoleic, GLA-γ-linolenic, and AA-arachidonic); and ω-9 (OA-oleic). Extensive studies have revealed that the protective effects of EPA and DHA could be mediated by forming reactive lipid molecules called Resolvins (31). Resolvins (E1 and D1) have a well-known anti-inflammatory property through preventing polymorphonuclear neutrophil (PMN) activation and translocation into the tissue (32-33). Resolvin E1 regulates cytokine/chemokine production (34) and inhibits TNFα-induced nuclear translocation of NF-κB (35). Freeman *et al* characterized several electrophilic oxo-derivatives of DHA and EPA, synthesized in activated macrophages via the cyclooxygenase-2 dependent pathway. Like Resolvins, these also possessed strong anti-inflammatory properties (36).

Regular consumption of grape wine is an integral element of the Mediterranean diet. The anti-inflammatory benefits of grape wine could be attributed to its phenolic components. Polyphenolic compounds such as quercetin, resveratrol, or catechins are potent antioxidants; thus, one of the mechanisms of protection they provide might be the inhibition of oxidative stress (37). Moreover, the effect of the MD on gut microbiota may be an additional factor. Previous studies demonstrated that good adherence to the MD was associated with lower *Escherichia coli* counts and a higher *Bifidobacteria* to *E. coli* ratio (38).

The strength of the current study is that it is the first report on the association between adherence to MD and IBS symptoms in children and adolescents. The main limitation is the cross-sectional design, which allows the assessment of good associations but not conclusions on causality. The study was also from a single-center, so the data cannot be generalized.

CONCLUSION

Results of the current study indicate that good adherence to the MD is safe and associated with significant improvement in IBS-score in children and adolescents. The

mechanisms underlying this association and the causality between the MD and IBS need further clarification. If further studies with extensive metabolomic analysis and microbiome assessments confirm the current study's findings, this will complete the picture of the diet–health interaction and relationship. Until then, we should encourage children and adolescents to follow the MD to have a place among other measures in minimizing the symptoms.

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