

Abstract

Crohn's disease (CD) is a recurrent inflammatory disease of the gastrointestinal tract. In the last decades, a continuous increase in the disease incidence has been observed, both in children and adults, and the younger the age of the diagnosed patient, the less optimistic prognosis. Typical signs include those of the gastrointestinal tract, although there may be less specific extraintestinal manifestations and/or complications of advanced inflammation which occur concurrently or as the only manifestation. The multiplicity of symptoms which are often difficult to control has a negative effect on the patient's quality of life.

Despite an indisputable progress of knowledge, the Crohn's disease is still incurable. Therapy is chronic in nature and its primary focus is on mitigating symptoms and preventing disease progression, and in the case of children, also on ensuring normal growth, development and maturation. A treatment strategy of fundamental importance for long-term maintenance of therapeutic effects is to induce deep remission, i.e. eliminating clinical symptoms and healing inflammation of the gastrointestinal tract. A pharmacological therapy used for this purpose, however, has numerous limitations, and effective treatment of the Crohn's disease remains a big challenge for specialists.

Scientific achievements of the last years show a huge potential of nutritional therapy used as an alternative to pharmacological treatment in the active CD. Promising results presented in consecutive scientific reports create a need to conduct further studies on the possibility of using this therapeutic method. Determining the place of nutritional treatment in the therapeutic algorithm of CD is especially important in the paediatric population, where each postponement of pharmacological treatment is of great importance for the child's development and prognosis in a chronic disease.

The objective of my PhD thesis was to evaluate the efficacy of two methods of nutritional therapy, i.e. exclusive enteral nutrition and an innovative Crohn's Disease Exclusion Diet in the treatment of children with an active Crohn's disease.

The history of nutritional treatment of CD dates back to the first half of the 20th century, when enteral nutrition was used to improve the nutritional status of patients in a severe condition/prepared for surgical procedures. In the course of time it was observed that such treatment had a good effect not only on the nutritional status of patients but also on their clinical condition and laboratory test results (including inflammatory markers). In subsequent years, high efficacy of exclusive enteral nutrition (EEN) in inducing clinical remission in children was

demonstrated in numerous studies. In first years of the 21st century there appeared reports indicating similar efficacy of EEN and glucocorticoids in inducing clinical remission, with a higher safety profile and significantly more positive effect of nutritional treatment on intestinal mucosa healing and on growth and development of treated children. For this reason, 10 years ago, exclusive enteral nutrition took the place of steroids and is still recommended as the first line treatment in an active luminal paediatric CD.

EEN involves the use of a complete liquid diet (enteral formula) with the exclusion of normal dietary components for several (usually 6-8) weeks. A difficult to accept taste of formulas intended for administration via a feeding tube significantly reduced the possibility of implementing EEN via the oral route. The necessity to insert a nasogastric tube, aside from high costs, was one of the key factors causing patients to resign from this method of treatment. In 2013, Modulen IBD - a liquid diet intended for nutritional treatment of CD patients was introduced on the Polish market. Essential characteristics differentiating new formula from available equivalents is an additive of bioactive peptides TGF- β (transforming growth factor beta) with confirmed anti-inflammatory effect, and an attractive taste. The possibility of implementing oral EEN was a potential factor improving its general acceptance and, therefore, enabling wider use of this therapeutic method. The paper **“Oral exclusive enteral nutrition for induction of clinical remission, mucosal healing, and improvement of nutritional status and growth velocity in children with active Crohn's disease - a prospective multicentre trial”** summarised the results of a multicentre, prospective study conducted in 2014, which assessed tolerance of oral exclusive enteral nutrition, and the effect of such treatment on the disease activity and nutritional status in 20 Polish children with an active CD. This was one of the first projects in the world assessing the efficacy of a several-week EEN with the Modulen IBD. An additional value of the study was the fact that a new non-invasive marker, i.e. faecal calprotectin level, was used to assess intestinal inflammation. Oral EEN with Modulen IBD was used in all the patients for 6 weeks. Lack of acceptance of oral administration constituted an indication for treatment continuation via feeding tube. Clinical disease activity assessed with the Paediatric Crohn's Disease Activity Index (PCDAI), faecal calprotectin level, and the nutritional status were analysed at baseline and in week 10 (i.e. 4 weeks after EEN completion). The implementation of nutritional recommendations and tolerance of the new formula were assessed based on an interview with the child's parent/guardian.

The conducted study has provided the following results:

Exclusive enteral nutrition with Modulen IBD administered orally for 6 weeks:

- was well tolerated by most patients - the recommendation on daily intake of the formula was implemented by 95% of the treated children, with only one patient requiring a nasogastric tube;
- had a positive effect on the clinical disease activity - in week 10, a significant decrease in PCDAI score was observed, with clinical remission in 65% study patients, and a clinical response in further 30%.
- promoted intestinal mucosal healing - in week 10, a significant decrease in the faecal calprotectin level was observed, wherein a normalization of this parameter was stated in ¼ of the study children;
- improved the nutritional status - in week 10, normal Body Mass Index (BMI) according to percentile charts was recorded in 2/3 of patients with malnutrition at baseline.

Faecal calprotectin level is currently a standard marker in the assessment of intestinal inflammation in CD. Since 2017, Modulen IBD has been reimbursed in Poland in an induction therapy in children with active CD, and it is the only reimbursed enteral formula administered orally in this group of patients. The confirmed efficacy of oral exclusive enteral nutrition with Modulen IBD, as well as solving the problem of a financial barrier, made it possible to popularise this therapeutic method in the group of Polish children with an active CD. Nevertheless, the necessity to exclusion of normal dietary components for a few weeks was still a serious obstacle for many patients. What is more, subsequent scientific reports showed that most patients who completed the EEN course and returned to their previous diet quickly experienced a relapse of the disease.

The limitations of EEN were the starting point in a search for other possibilities of nutritional treatment. Results of studies conducted over the last years assessing the possibility of using various known elimination diets (e.g. a specific carbohydrate diet, a low fermentable oligo- di- and monosaccharides and polyols diet or a vegetarian diet) in the treatment of active CD in children and adults have not demonstrated a sufficient efficacy of any of them. More than 10 years ago, a team led by Professor Arie Levine developed an innovative Crohn's Disease Exclusion Diet (CDED) for patients with CD. The scientists used the available knowledge according to which selected components of western (or industrialised) diet were engaged in the pathomechanism of CD and had a negative effect on the course of the disease. On this basis it was assumed that elimination of these pro-inflammatory factors, combined with a daily intake of products supporting bowel recovery, may be an effective treatment method of inflammation. In subsequent years (2014 and 2017), first results of studies were presented

showing a potential efficacy of CDED used in combination with partial enteral nutrition (PEN) in the treatment of children and adults with CD. The year 2019 was a breakthrough since it marked the publication of results of a multicentre randomised study, showing a similar efficacy of CDED + PEN and EEN in the treatment of children with an active CD, while the tolerance of the new method and its long-term efficacy were remarkably higher. In both study groups the liquid formula used was Modulen IBD. These issues were discussed in two review papers “**Nutritional Therapy in Paediatric Crohn's Disease - Are We Going to Change the Guidelines?**” and “**Crohn's Disease Exclusion Diet – modern nutritional treatment of Crohn's disease**”, whose aim was to summarise current knowledge on the effect of the western diet on the development and course of CD, and to discuss the mechanism of action, protocol and results of the study on the efficacy of the new elimination diet.

A literature review allowed drawing the following conclusions:

- the analysis of the disease incidence across the world and results of epidemiological studies indicate that external environmental factors play a significant role in the CD aetiology;
- according to the current knowledge, it may be assumed that due to the effect of external factors, genetically predisposed subjects develop a dysfunction in the intestinal barrier integrity and uncontrolled bacterial penetration through intestinal mucosa, which in turn leads to the development of chronic inflammation;
- epidemiological as well as cellular and animal model studies have revealed that the so-called western diet, by its negative effect on gut microbiome and intestinal mucosa, is one of the key external factors responsible for triggering the pathomechanism in CD;
- a demonstrated good EEN efficacy confirms that the dietary modification primarily by eliminating pro-inflammatory factors constitutes an effective way of treatment in children with active CD; however, the disadvantages of this method may be discouraging as far as its wider usage is concerned;
- the innovative CDED used in combination with partial enteral nutrition seems to be equally effective and an easier to use alternative to exclusive enteral nutrition in inducing remission in children with active CD;
- additional advantages of the new method of nutritional treatment, i.e. its demonstrated positive effect on the intestinal permeability and microbiota composition, as well as inclusion

of both the remission inducing and maintaining phase in the diet protocol, give hope to improve the long-term effects of nutritional treatment;

- establishing the position of CDED + PEN in the treatment algorithm of CD requires confirmation of its efficacy in further studies.

The reports from 2019 have initiated a new era of nutritional treatment of CD, and many centres across the world, including ours, have begun their own studies aiming at the assessment of the usefulness of the new therapeutic tool. The paper “**Effect of the Crohn's Disease Exclusion Diet (CDED) on the Faecal Calprotectin Level in Children with Active Crohn's Disease**” is the first and so far the only publication presenting results of a study assessing the efficacy of CDED + PEN used in a group of Polish children with active CD. The analysis included 48 children treated at the Department of Gastroenterology, Hepatology, Feeding Disorders and Paediatrics of the Children's Memorial Health Institute. In previous projects, the main inclusion criterion in the analysis and the basis to assessment of the therapy efficacy was the result in PCDAI - a partially subjective scale of clinical disease activity. In the analysed group, the principal eligibility criterion and the basis to assess the efficacy of nutritional treatment was the faecal calprotectin level - a non-invasive and objective marker of intestinal inflammation. All the patients received induction treatment for 12 weeks, in accordance with the CDED + PEN protocol. At baseline and in week 12, the analysis of inflammatory parameters was conducted, i.e. faecal calprotectin level and C-reactive protein (CRP), as well as assessment of the clinical disease activity (using PCDAI), and nutritional status.

The conducted study has provided the following results:

- CDED + PEN had a positive effect on mucosal healing - after 12 weeks of treatment, a significant decrease in faecal calprotectin level was observed, while normalization of this parameter was observed in 1/3 children, and a decrease by at least 50% in more than half of the patients;

- in patients presenting clinical symptoms of CD at baseline, a 12-week nutritional treatment with CDED + PEN led to clinical remission in half of the children, and clinical response in nearly 3/4 of them;

- in children presenting clinical symptoms at baseline, intestinal inflammation was more advanced than in those with clinical remission at the time of qualification to the nutritional treatment (median value of faecal calprotectin level 1410 µg vs 939.5 µg, respectively);

- this observation was manifested in the efficacy of nutritional treatment in both subgroups - the percentage of children with normalised faecal calprotectin level after a 12-week course of treatment with CDED + PEN was twice higher in the group with clinical remission at baseline than in the patients presenting clinical symptoms at the time of introducing nutritional therapy;
- all patients with normal faecal calprotectin level in week 12 were in clinical remission, and 94% of them had normal CRP value;
- all the children with recorded malnutrition at baseline who completed a 12-week course of nutritional treatment showed improvement in the nutritional status, with a BMI increase by one percentile channel in more than half of them.

Thanks to subsequent reports from centres all over the world, in 2023, CDED + PEN was for the first time included in the recommendations of nutritional treatment of CD. According to current guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), new nutritional therapy is recommended as an alternative to EEN in the treatment of mild to moderate active luminal CD in children. Available scientific reports show that the role of CDED + PEN in a severe/complicated CD should not be neglected; however, it requires verification in further studies.

Conclusion.

The western diet is one of the potential negative factors in the development and course of CD. Scientific studies have identified the components of this nutrition style, which, by a negative effect on the intestinal barrier, constitute a potential cause of development of chronic inflammation. According to the most recent literature, dietary modification by eliminating those pro-inflammatory factors represents an effective method of CD treatment in children.

Exclusive enteral nutrition is recommended by most scientific societies as the first line therapy of active CD in children. No side effects, a chance to postpone pharmacotherapy and a positive effect on development are unquestionable advantages of this treatment method in a paediatric population. The possibility of oral administration, as well as introducing reimbursement of Modulen IBD in Poland have facilitated the use of EEN in practice. Nevertheless, the monotony of exclusive nutrition with the liquid diet for a few weeks still constitutes a serious obstacle for undertaking this therapy among young patients. On the other hand, being aware of the high risk of rapid loss of therapeutic effects, specialists may have a limited trust in this method.

Confirmed efficacy and additional advantages of the CDED used in combination with PEN seem to create a sufficient basis for changes in the CD treatment algorithm. According to the latest ESPEN guidelines (2023), this new nutritional therapy should be considered as an alternative to EEN in children with a mild to moderate active luminal disease. The analysis of our own results and experience of other researchers shows that a 12-week course of CDED + PEN has a positive effect on the clinical disease activity and on mucosa healing, but it does not result in complete healing of intestinal inflammation in the majority of the children treated. It appears that effects of the applied nutritional treatment depend on the initial disease severity. It may be concluded that in patients with advanced inflammation, prolonged use of CDED + PEN, depending on the outcomes of a planned period of induction treatment, may constitute a potential strategy improving the final efficacy of this therapeutic method; however, results of such analyses have not been published to date.