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Clinical Significance of Nitric Oxide Measurement in Assessing the State of The Small Intestinal Mucosa in Children with Intestinal Malabsorption Syndrome

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Abstract

Betel Intestinal malabsorption syndrome (IMS) in children is a clinically heterogeneous condition that may result from functional and enzymatic disorders, inflammatory processes, and structural changes in the small intestinal mucosa. It is therefore important to search for non-invasive biomarkers that can help assess the activity of the pathological process and distinguish between the inflammatory and functional-enzymatic components of intestinal damage. One such potential marker is nitric oxide (NO), which regulates microcirculation, intestinal

motility, and mucus secretion, and maintains the epithelial barrier.

Aim of the study — to summarize current scientific data on the physiological role of nitric oxide and its diagnostic value in assessing the state of the small intestinal mucosa in children with intestinal malabsorption syndrome, and to determine the prospects for the practical application of this approach in pediatrics.

Materials and methods. An analytical review of the literature was conducted in the PubMed, Scopus, and eLibrary databases for the period from 1994 to 2025. Search queries included the following keywords and their combinations: “nitric oxide”, “nitric oxide synthase”, “intestinal mucosa”, “intestinal permeability”, “malabsorption syndrome”, “fecal nitric oxide”, “exhaled nitric oxide”, and “children”, as well as the corresponding Russian-language terms. Of the 62 publications initially identified, 28 were included in the analysis after the exclusion of duplicates and irrelevant sources.

Results. The literature analysis showed that nitric oxide (NO) plays a fundamental role in maintaining normal homeostasis of the intestinal mucosa. Epithelial inflammation is accompanied by activation of inducible NO synthase (iNOS), which leads to a significant increase in NO synthesis and changes in the levels of its stable metabolites, nitrites and nitrates. These metabolites are important markers of the inflammatory process. Increased NO production and iNOS activation are characteristic of inflammatory bowel diseases, celiac disease, and other enteropathies.

The assessment of fecal and serum NO metabolites, as well as direct measurement of NO concentrations in biological media, is regarded as a promising non-invasive or minimally invasive approach to evaluating inflammatory activity. However, data on the diagnostic value of these parameters in children with intestinal malabsorption syndrome (IMS) remain insufficient and require further investigation.

Conclusion. Measurement of nitric oxide metabolites is a promising method for the non-invasive assessment of the small intestinal mucosa in children with IMS. At present, this method should be regarded as an additional diagnostic tool that does not replace standard clinical, laboratory, endoscopic, and histological examinations. Further prospective clinical studies are needed to establish its diagnostic capabilities, define reference values, and determine its place in the diagnostic algorithm for children.

Keywords: Nitric oxide, NO synthase, iNOS, small intestinal mucosa, intestinal malabsorption syndrome, children, intestinal permeability, enteropathy, non-invasive diagnostics.

1. Introduction

Intestinal malabsorption syndrome (IMS) in children is a clinically heterogeneous condition caused by multiple pathological mechanisms. These include functional and enzymatic dysfunctions, inflammatory processes, structural modifications of the small intestinal mucosa, and impaired intestinal barrier function [1,2]. The clinical manifestations of IMS include diarrhea, changes in stool consistency and frequency, symptoms of maldigestion, weight loss, delayed physical development, and nutrient deficiencies.

Developing an effective diagnostic and treatment strategy requires an accurate determination of the nature of the mucosal lesion. Traditional methods of morphological verification, such as endoscopy with targeted biopsy and histological examination, require special preparation and, in most cases, sedation, which limits their repeated use during patient follow-up [3]. Therefore, the search for accessible and safe non-invasive biomarkers capable of indirectly reflecting the activity of inflammatory and destructive processes in the intestinal mucosa is a relevant task.

One promising biological marker is nitric oxide (NO), a short-lived signaling molecule that regulates a wide range of physiological processes in the gastrointestinal tract. NO is synthesized from L-arginine by enzymes of the NO synthase (NOS) family, which includes endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) isoforms [4].

Under normal conditions, NO, generated mainly by the constitutive NOS isoforms, plays a key role in regulating mucosal microcirculation, intestinal motility, mucus secretion, and intercellular interactions in the intestinal wall [5]. During inflammation, pro-inflammatory cytokines activate iNOS, leading to increased NO production. Prolonged and pronounced activation of this mechanism may contribute to oxidative and nitrosative stress and to impaired barrier function of the intestinal epithelium [6,7].

Interest in NO as a biomarker of intestinal status emerged in the 1990s following studies that demonstrated a marked increase in luminal NO concentrations in inflammatory diseases, particularly ulcerative colitis [8,9]. Subsequently, a number of methods for assessing NO production were developed, including the measurement of nitrite and nitrate levels in feces and blood, as well as the measurement of NO in the intestine and in exhaled air [10,11].

However, data on the diagnostic value of NO in children with IMS remain limited. Most studies have been conducted in patients with inflammatory bowel diseases, celiac disease, and certain forms of enteropathy [12]. Therefore, extrapolation of

these data to children with IMS requires caution and additional clinical validation.

Thus, it appears relevant to systematize data on the physiological and pathophysiological role of NO, current methods for its measurement, and the possibilities of using these parameters to assess the state of the small intestinal mucosa in children with intestinal malabsorption syndrome.

Aim of the study — to analyze current scientific data on the role of nitric oxide and its metabolites in the diagnostic assessment of the small intestinal mucosa in children with intestinal malabsorption syndrome.

The study addresses the following objectives:

1. To study the physiological functions of nitric oxide in the small intestinal mucosa.

2. To identify the main mechanisms of altered nitric oxide production in damage and inflammation of the intestinal epithelium.

3. To review current methods for measuring the levels of nitric oxide and its metabolites.

4. To evaluate the scientific validity of using nitric oxide in the diagnosis of diseases involving damage to the intestinal mucosa.

5. To identify the prospects and conditions for using nitric oxide measurement in the diagnosis of intestinal malabsorption syndrome in children.

2. Materials and Methods

This work was performed as an analytical review of the scientific literature on the subject.

Publications were searched for and selected in the international databases PubMed and Scopus and the Russian database eLibrary for the period from 1994 to 2025. The search strategy used keywords and their combinations such as “nitric oxide”, “nitric oxide synthase”, “intestinal mucosa”, “intestinal permeability”, “malabsorption syndrome”, “fecal nitric oxide”, “exhaled nitric oxide”, and “children”. Equivalent Russian-language terms were also used: “nitric oxide” (oksid azota), “NO synthase”, “intestinal mucosa”, “intestinal permeability”, “impaired absorption syndrome”, “malabsorption syndrome”, and “children”.

The review included full-text original studies and systematic reviews addressing the physiological and pathophysiological aspects of the role of NO in the gastrointestinal tract, methods of its measurement, and its diagnostic significance in diseases involving damage to the intestinal mucosa.

Exclusion criteria were publications without available full text, non-peer-reviewed conference abstracts, and works unrelated to gastrointestinal pathologies and conditions.

At the initial stage, 62 publications were identified. After the exclusion of duplicate sources and materials that did not meet the inclusion criteria, 28 scientific papers were selected for the final analysis and formed the basis of this review.

3. Results

1. Physiological role of nitric oxide in the small intestinal mucosa

Nitric oxide (NO), a key regulator of physiological processes, is synthesized in the human body from L-arginine by NO synthases in the presence of oxygen. Three main isoforms of NO synthase have now been identified: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS), each of which plays a specific role in maintaining homeostasis [4,5].

The endothelial (eNOS) and neuronal (nNOS) isoforms of NO synthase are constitutive and provide a basal level of NO production. In the intestinal mucosa, NO performs an important function in regulating vascular tone, microcirculation, intestinal motor activity, neurohumoral interactions, and the state of the epithelial barrier. These processes play a critical role in maintaining the physiological integrity and function of the intestinal tract.

NO is essential for adequate blood supply to the mucosa, regulating vascular tone and ensuring optimal conditions for the delivery of oxygen and nutrients and the removal of metabolites. In addition, NO is involved in controlling intestinal peristaltic activity via the nitrergic neuronal system, which underlines its importance in maintaining normal gastrointestinal motility.

At physiological concentrations, NO performs predominantly protective functions: it supports microcirculation, modulates the interaction of inflammatory cells with the endothelium, and participates in the restoration of the epithelial layer. These mechanisms help maintain the structural and functional integrity of the intestinal mucosa.

Unlike the constitutive isoforms, iNOS expression is low under normal conditions. However, under the influence of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interferon-gamma (IFN-γ), iNOS activity increases significantly, resulting in elevated and prolonged NO production [6].

Moderate activation of iNOS is adaptive, contributing to an effective response to inflammatory stimuli. However, excessive and prolonged NO production in chronic inflammation may become pathogenic [5,7]. The interaction of NO with the superoxide anion leads to the formation of peroxynitrite, which can damage lipids, proteins, and nucleic acids, potentially resulting in impaired cellular function and loss of tissue structural integrity [6,7,13].

Strong activation of NO-dependent mechanisms disrupts the structure of intercellular junction proteins, leading to increased paracellular permeability of the intestinal barrier and reduced protective function. These changes may contribute to the development of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

Thus, the physiological role of NO in the intestine is multifactorial and ambiguous. At normal levels, NO maintains homeostasis and the protective functions of the mucosa. However, excessive iNOS activation and NO overproduction during inflammation can damage the epithelial barrier, promoting the development of pathological conditions.

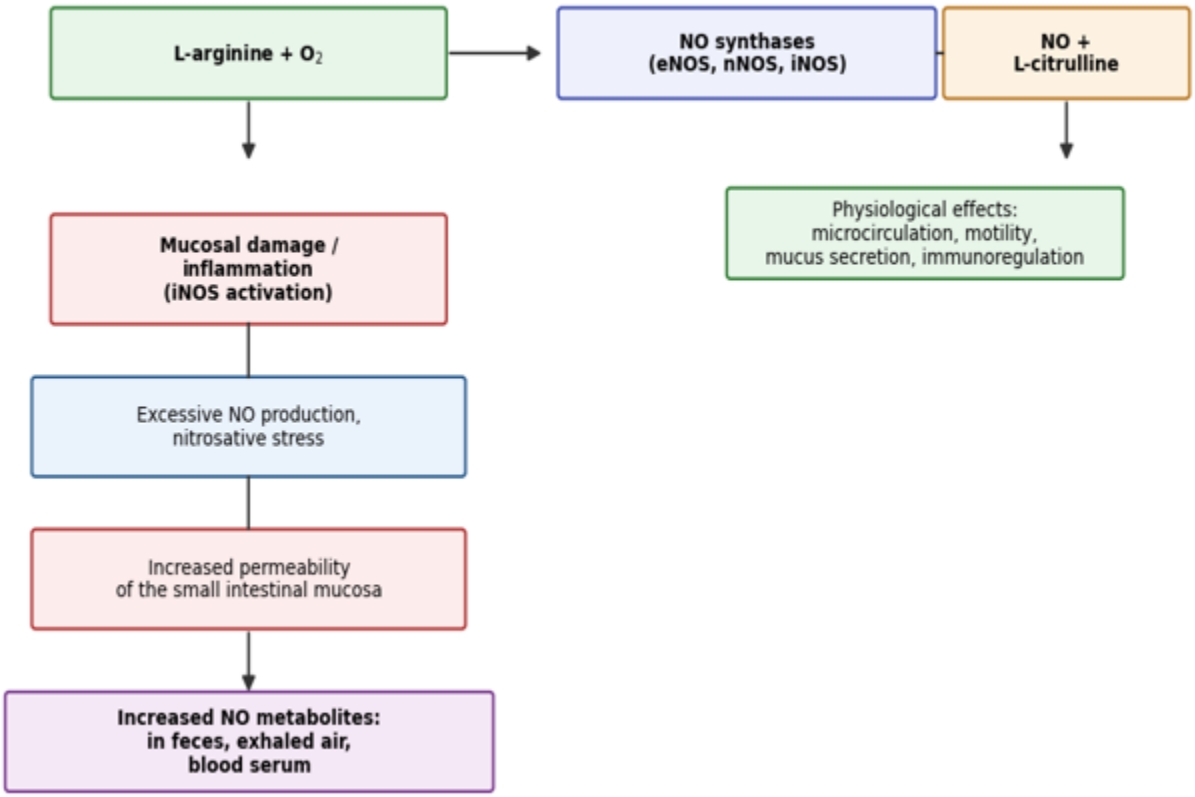


Fig. 1. Scheme of nitric oxide metabolism in the small intestinal mucosa under normal conditions and in mucosal damage

2. Current methods for measuring nitric oxide and its metabolites

Measuring nitric oxide (NO) levels in biological tissues and fluids is challenging because of its short half-life. In clinical and experimental practice, this problem is often addressed by methods that measure stable end products of NO metabolism, such as nitrites and nitrates, as well as by methods for the direct detection of NO in the gas phase [10].

The most common approaches include:

1. Analysis of fecal nitrites and nitrates.
2. Measurement of serum nitrite and nitrate concentrations.
3. Direct luminal or rectal measurement of NO.
4. Measurement of NO in exhaled air.

5. Immunohistochemical analysis of inducible NO synthase (iNOS) expression in mucosal biopsy specimens.

Each of these methods has its own advantages and limitations, which requires careful consideration when choosing the optimal approach for a particular research or clinical task.

Analysis of fecal NO metabolites is of particular interest in pediatric practice because it is non-invasive. However, fecal nitrite and nitrate concentrations can vary considerably depending on many factors, including local NO production by the mucosa, the composition of intestinal contents, the activity of the gut microbiota, and diet, which may complicate the interpretation of the data obtained.

Measurement of serum nitrites and nitrates makes it possible to assess the systemic level of NO metabolites; however, this parameter is not specific to pathological processes in the intestine. It may reflect the general condition of the body, which makes it less informative for diagnosing intestinal diseases.

Luminal or rectal measurement of NO provides a more accurate assessment of local NO production in the intestine. However, this method involves technical difficulties and requires specialized equipment, which limits its use in routine clinical practice.

Measurement of exhaled NO is a non-invasive method that makes it possible to assess NO levels in the airways and may be used to evaluate systemic inflammation. However, interpreting this parameter as a specific marker of intestinal damage requires caution, since it may reflect processes occurring not only in the intestine but also in the respiratory system.

Immunohistochemical analysis of iNOS expression in mucosal biopsy specimens is the most direct and accurate method for assessing local enzyme activity [10,11,14]. However, this method requires endoscopy and tissue sampling, which limits its use in clinical practice owing to its invasiveness and the need for specialized equipment.

Table 1.

Main methods for measuring nitric oxide and its metabolites used in the study of gastrointestinal diseases

Method	Biological material	Invasiveness	Main diagnostic/research value
Measurement of nitrites/nitrates	Feces	Non-invasive	Indirect assessment of intestinal inflammatory activity
Luminal/rectal NO measurement	Intestinal lumen	Minimally invasive	Assessment of local NO production, mainly in inflammatory bowel diseases
Measurement of nitrites/nitrates	Venous blood	Minimally invasive	Assessment of the systemic level of NO metabolites
Measurement of exhaled NO	Exhaled air	Non-invasive	Assessment of airway NO; potential additional systemic marker of inflammation
Immunohistochemical detection of iNOS	Mucosal biopsy specimen	Invasive	Assessment of local iNOS expression and morphofunctional verification of the inflammatory process

3. Diagnostic significance of nitric oxide measurement in diseases involving damage to the intestinal mucosa

A substantial body of data on the diagnostic significance of nitric oxide (NO) has been accumulated in the context of inflammatory bowel diseases (IBD). Since the 1990s, studies have demonstrated a significant increase in luminal NO production during the active phase of inflammation, particularly in ulcerative colitis [8, 9]. These data indicate that NO plays a key role in the pathogenesis of IBD as an important mediator of the inflammatory response.

Several studies have found a correlation between increased local NO production and the severity of inflammation as assessed by endoscopic and histological criteria [8-11]. This observation provided the rationale for studying NO and its metabolites as potential markers of disease activity.

Changes in NO levels during treatment are of particular interest. In some studies, a decrease in the concentration of NO metabolites was accompanied by clinical improvement and a reduction in inflammatory markers, which allows this parameter to be considered an additional tool for monitoring the course of the disease over time [10, 11].

However, the diagnostic significance of NO should not be considered in isolation. Increased NO production reflects the activation of inflammatory and cellular mechanisms but does not make it possible to establish the specific etiology of the disease.

Activation of inducible NO synthase (iNOS) and increased NO production have also been described in celiac disease and a number of other diseases associated with enterocyte damage, impaired intestinal permeability, and changes in mucosal structure [12, 13]. The common pathogenetic mechanism of these conditions is activation of the inflammatory response mediated by pro-inflammatory cytokines and subsequent iNOS expression [1,2,12]. This mechanism provides a theoretical basis for studying the role of NO in other conditions associated with intestinal malabsorption.

It is important to note that pathogenetic similarity does not imply proven diagnostic equivalence. Data obtained in IBD and celiac disease cannot be automatically extrapolated to all patients with intestinal malabsorption syndrome (IMS). IMS is a heterogeneous condition, and in each patient malabsorption may be caused predominantly by enzymatic, functional, inflammatory, or structural disorders.

Thus, elevated levels of NO metabolites may indicate the presence of an inflammatory component in the mucosal lesion. However, clinical studies in the pediatric IMS population are needed to confirm this assumption.

4. Prospects for the use of nitric oxide measurement in children with intestinal malabsorption syndrome

Measurement of nitric oxide (NO) and its metabolites in biological fluids is a promising method that may serve as an additional diagnostic tool for intestinal malabsorption syndrome (IMS) in children. In terms of non-invasiveness, the analysis of fecal NO metabolites is the most preferable. Where technically feasible, it is also advisable to measure NO in exhaled air. However, it should be borne in mind that the interpretation of this parameter requires caution because of its potential non-specificity with regard to intestinal pathology.

In the presence of clinical and coprological signs of impaired digestion, elevated levels of fecal NO metabolites may indicate an active inflammatory process in the intestinal mucosa [1,2,10]. In this case, the results of the NO metabolite analysis may serve as a basis for an in-depth diagnostic workup, including endoscopy if necessary.

On the other hand, normal levels of fecal NO metabolites in the presence of signs of maldigestion may indicate a predominantly functional-enzymatic mechanism of impaired digestion. It should be noted, however, that a normal NO level is not a sufficient criterion for ruling out an inflammatory or structural lesion of the mucosa.

Thus, the most rational approach is to integrate the analysis of NO metabolites into a comprehensive diagnostic algorithm that includes clinical assessment, coprological examination, laboratory tests, assessment of exocrine pancreatic function, and endoscopy when indicated. This comprehensive approach allows for a more accurate and thorough diagnosis of intestinal malabsorption syndrome in children.

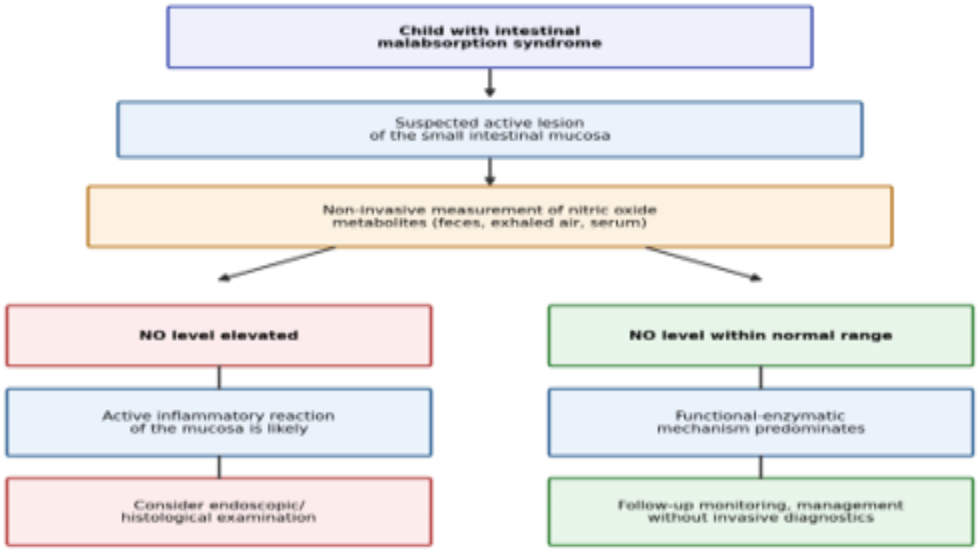


Fig. 2. Proposed algorithm for the use of nitric oxide measurement in children with intestinal malabsorption syndrome

4. Discussion

Nitric oxide (NO) occupies a central place in the regulation of physiological processes in the intestinal mucosa and, at the same time, may be a key factor in the mechanisms of its damage. Under normal conditions, NO generated by constitutive NO synthase (eNOS) performs regulatory and protective functions, maintaining microcirculation, intestinal motility, and the integrity of the epithelial barrier [5,6,7]. However, during an inflammatory process accompanied by activation of inducible NO synthase (iNOS), NO production increases significantly, which may lead to oxidative and nitrosative stress.

This dual action of NO underlies its importance as a potential marker of pathological changes in the intestinal mucosa [8–11]. In recent years, particular attention has been paid to the quantitative assessment of NO and its metabolites, such as nitrites and nitrates, in biological fluids and tissues, which allows them to be used as diagnostic indicators of inflammatory bowel diseases.

Studies have shown that increased local production of NO and its metabolites correlates with the activity of the inflammatory process, and changes in these parameters over time may serve as an indicator of treatment effectiveness. These data point to the high diagnostic value of NO in inflammatory bowel diseases such as Crohn's disease and ulcerative colitis.

There are also data on the role of NO in the pathogenesis of celiac disease and other enteropathies associated with damage to the intestinal epithelial layer. However, for children with intestinal malabsorption syndrome (IMS), a clinical and pathophysiological syndrome of diverse etiology, the evidence base remains less developed. This must be taken into account when interpreting study results, since the levels of NO metabolites may vary depending on the specific pathogenetic mechanisms underlying the different forms of IMS.

Nitrite and nitrate concentrations in biological samples can vary considerably depending on the analytical method, dietary habits, the composition of the gut microflora, the presence of inflammation, and other factors. This creates certain difficulties in directly comparing the results of different studies.

At this stage, NO should be regarded not as a stand-alone diagnostic criterion but as an additional potential biomarker that can be integrated into a comprehensive assessment of the intestinal mucosa. Prospective studies in children with various forms of IMS, including the assessment of NO metabolites, clinical manifestations, coprological findings, and the endoscopic picture, could significantly expand our understanding of the role of NO in the pathogenesis of this syndrome.

A promising direction for further research is the establishment of reference intervals for NO metabolites in children of different age groups, as well as evaluation of their potential to differentiate between inflammatory and functional-enzymatic forms of intestinal malabsorption. Such an approach would improve diagnostic accuracy and help develop effective strategies for treating intestinal diseases in children.

Limitations of the study

This work has limitations, as it is an analytical review based on data concerning inflammatory bowel diseases and individual enteropathies, which substantially limits its potential for broader generalizations. In particular, data obtained directly from studies of children with intestinal malabsorption syndrome (IMS) are limited and require further investigation.

Another significant limitation is the variety of methods used to measure nitric oxide (NO) and its metabolites. Different studies use different types of biological material, measurement methods, units of measurement, and cut-off values, which hampers direct quantitative comparison of the data and precludes a full meta-analysis. This methodological heterogeneity reduces the possibility of obtaining accurate and reproducible results, which in turn complicates the interpretation of the data and their application in clinical practice.

Therefore, statements regarding the potential use of NO in IMS should be regarded as scientifically grounded hypotheses requiring confirmation under controlled clinical conditions. Achieving this goal requires further studies using unified methods and standardized approaches to the measurement of NO and its metabolites, which will improve the accuracy and reliability of the data obtained.

5. Conclusion

Nitric oxide (NO) plays a key role in regulating physiological processes in the small intestinal mucosa and is also involved in inflammatory and oxidative-nitrosative damage to the intestinal epithelium. Inflammatory processes activate inducible NO synthase, leading to increased NO production and changes in the levels of its stable metabolites, nitrites and nitrates. These changes have been studied in particular detail in inflammatory bowel diseases and certain enteropathies, such as celiac disease.

Studies demonstrate that the measurement of NO metabolites, in particular fecal nitrites and nitrates, may be a promising non-invasive method for assessing the activity of pathological processes in the intestinal mucosa. However, the diagnostic value of this method in children with intestinal malabsorption syndrome has not yet been established. Consequently, this approach cannot replace standard clinical, laboratory, endoscopic, and histological diagnostic methods.

Assessing the prospects of this approach requires prospective studies involving children of different age groups and with different variants of intestinal malabsorption syndrome. These studies should compare the levels of NO metabolites with clinical manifestations, coprological findings, and endoscopic and histological data. This will make it possible to determine the diagnostic accuracy of the method, establish age-specific norms, and define the role of NO metabolites in the comprehensive diagnosis and monitoring of children with intestinal malabsorption syndrome.

Practical recommendations

1. Analysis of nitric oxide metabolites is a promising non-invasive approach for assessing the state of the intestinal mucosa in children with intestinal malabsorption syndrome. This method is particularly relevant in the presence of clinical and coprological signs of an inflammatory process.

2. Fecal nitrites and nitrates can be considered the priority target of analysis in terms of minimizing invasiveness. However, interpreting the results requires taking into account the clinical picture and the findings of other laboratory tests.

3. An elevated level of NO metabolites cannot serve as a stand-alone diagnostic criterion for inflammatory bowel disease. This finding should be regarded as grounds for a more detailed examination of the patient, including a decision on endoscopy in accordance with clinical indications.

4. A normal level of NO metabolites does not rule out structural or inflammatory lesions of the mucosa. Therefore, a negative test result should not be a reason to forgo a standard diagnostic workup when clinically indicated.

5. Measurement of NO metabolites should not replace conventional methods for diagnosing intestinal malabsorption syndrome, such as clinical assessment, coprological examination, fecal pancreatic elastase-1 testing, and endoscopy with biopsy when indicated.

6. In research settings, the methodology for measuring NO metabolites must be standardized. This includes the choice of biological material, the conditions for its collection and storage, the analytical method, the units of measurement, and the criteria for interpreting the results.

7. Prospective clinical studies are needed to establish reference values for NO metabolites in children of different age groups. It is also important to determine their diagnostic sensitivity and specificity in different variants of intestinal malabsorption syndrome.

8. When introducing the method into pediatric practice, age-related and technical limitations should be taken into account, especially in young children. The possible influence of concomitant inflammatory diseases and other factors on the concentration of NO metabolites should also be considered.

9. In the future, it is advisable to consider the measurement of NO metabolites as part of a comprehensive panel of non-invasive markers. This will make it possible to compare the results with clinical, laboratory, endoscopic, and morphological data, thereby improving diagnostic accuracy and treatment effectiveness.

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