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SIFO - an insufficiently researched, but clinically significant issue. What do we know so far? Can physical activity help to relieve gastrointestinal symptoms?

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Abstract

Introduction and purpose: Small intestinal fungal overgrowth (SIFO) presents as an excessive presence of fungi in the small intestine, often associated with gastrointestinal (GI) symptoms like unexplained gas, bloating, pain, malabsorption, and irregular bowel movements, including constipation or diarrhea. The study aims to organize information regarding this condition, emphasizing the lack of specific guidelines regarding diagnosis and treatment and need for treatment that are not only based on systemic drugs but also additional ways such as physical activity.

Materials and methods: We conducted a literature review utilizing the medical databases PubMed and Google Scholar, retrieving articles in English using keywords such as "small intestinal fungal overgrowth," "SIFO," "gastrointestinal symptoms," "enterocolitis," "exercising," and "brain-gut axis" in various combinations. Our analysis included data from 33 scientific references published between 1931 and 2023.

Summary: Small intestinal fungal overgrowth (SIFO) is more often acknowledged as a potential factor for unexplained gastrointestinal symptoms. More and more clinicians attach importance to this issue, as it is a serious clinical burden which significantly reduces quality of life. Nevertheless, the precise clinical impact of SIFO within the community remains uncertain as the available literature primarily consists of isolated case reports or observations from autopsies of patients undergoing cancer treatment. There still are no specific guidelines for diagnosis and treatment. Clinicians use systemic antifungal drugs. There is a potential in physical activity as an additional way to treat this condition.

Key words: small intestinal fungal overgrowth, SIFO, gastrointestinal symptoms, exercising, brain-gut axis

Introduction

Small intestinal fungal overgrowth (SIFO) manifests as an abundance of fungi within the small intestine, which is correlated with gastrointestinal (GI) symptoms such as unexplained gas, bloating, pain, malabsorption, irregular bowel movements - including constipation or diarrhea. The human digestive tract contains diverse concentrations of fungi, typically comprising commensal flora that have adapted to the host immune system. Disruptions to this equilibrium can result in fungal overgrowth occurring in different areas of the digestive system. Among the fungal species, *Candida* is the most frequently encountered within the small intestine and its presence is connected with above-mentioned symptoms in immunocompromised individuals, those undergoing immune-lowering treatments e.g. using steroids or antibiotics and those with chronic disorders. Some studies also indicated that those symptoms connected with excessive amounts of fungus can also be found in non-immunocompromised patients. There are no official standards in case of SIFO treatment. Along with systemic antifungal drugs, exercising and sport in general can influence in a positive way the microbiome-gut-brain axis.

Pathophysiology

The gut microbiota refers to the collection of all microorganisms present in the human digestive system - it mostly (up to 90%) consists of the Firmicutes and Bacteroidetes bacterial phyla. Besides bacteria - viruses, fungi, archaea and Protozoa can be found.

Generally, microbiota plays a crucial role in supporting the body's health - it takes part in:

- digestion;
- generating vitamins;
- supporting production of short-chain fatty acids and amino acids;
- maintaining intestinal integrity;
- forming the intestinal epithelium;
- protecting against pathogens.

Dysbiosis is characterized as an altered composition or quantity of microorganisms. There is several types of this condition:

- Small Intestinal Bacterial Overgrowth (SIBO),

- Large Intestinal Bacterial Overgrowth (LIBO),
- Small Intestinal Fungal Overgrowth (SIFO),
- Intestinal Methanogen Overgrowth (IMO).

Dysbiosis can disrupt the body's balance and contribute not only to onset of unexplained gastrointestinal symptoms, but also favors conditions like inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diabetes, obesity, and allergies. [1]

In the case of fungus, it is present in the gut of approximately 70% of healthy adult subjects and it is mainly *Candida* species. The mouth and anorectum contains the highest amount of fungi, while the stomach and jejunum exhibit the lowest concentration. [2] When it comes to substantial yeast or fungal colonization in the gut, it seldom occurs unless the protective barriers have been compromised. One of these protective mechanisms involves the interaction between bacteria in the gut's commensal flora and the proliferation of fungi and it was demonstrated by researches conducted in both human and animal models. [3,4]

Risk factors

Factors that have been identified as contributors to the onset of candidiasis in the gastrointestinal tract include compromised immune function due to underlying medical conditions with e.g. HIV infection, cancer, and diabetes mellitus and some drugs including anti-cancer chemotherapy, immunosuppressants, steroids, parenteral antibiotics and proton pump inhibitors. [5,6,7,8]

There was a case report of a 48-year-old woman with Sjögren's syndrome and cervical cancer (stage II). This patient underwent radiation therapy complicated by rectovaginal fistula, which treatment required both colectomy and ileostomy. It subsequently resulted in watery diarrhea and weight loss (about 18 kg in 5 months) with no results in nutritional treatment. After admission to the hospital and endoscopy - overgrowth of *Candida tropicalis* in the small intestine was found. The patient was treated using central parenteral nutrition (CPN) and fluconazole (3-week course), her condition and symptoms slowly improved, she gradually gained weight (about 5 kg) and returned to work 4 months after discharge from hospital. [9]

In a recent study Jacobs et al reported an increased incidence of SIFO in patients utilizing PPIs and experiencing small bowel dysmotility. Patients, who had negative endoscopy and radiology tests and presented unexplained gastrointestinal symptoms, completed previously prepared form and had ambulatory antro-duodeno-jejunal manometry performed. This procedure was combined with a collection of duodenal aspirates - for cultures of aerobic and

anaerobic bacteria and fungi. One hundred and fifty patients were tested and ninety four among them had overgrowth - respectively - SIFO 32/94, SIBO 38/94, mixed SIBO/SIFO 32/94. It was also indicated that it was Candida which was responsible for SIFO. 80/150 subjects had dysmotility and 65/150 patients were taking IPP - those two factors had increased significantly risk for overgrowth ($P < 0.05$). [10]

Age, including both infants and the elderly, malnutrition, along with prolonged hospitalization, especially those in intensive care units, seems to be additional risk factors contributing to fungal proliferation and GI symptoms. [2]

Individuals undergoing transplantation are also susceptible to fungal infections. In a study from 2010 Florescu et al reported that 98 pediatric patients who underwent small bowel transplantation were observed. Twenty five of them had in total fifty nine episodes of Candida infections and four episodes of invasive aspergillosis. [11]

Individuals who have undergone colectomy exhibit notably higher rates of SIBO/SIFO and experience more severe gastrointestinal symptoms. In 2018 Rao SSC et al conducted a study in which patients with unexplained symptoms from gastrointestinal tract with ($n=50$) and without ($n=50$) colectomy were tested. Glucose breath test, previously prepared symptom questionnaires and/or duodenal aspiration/culture were used. Subjects who had colectomy performed showed a notably higher prevalence of mixed SIBO/SIFO (12/50) compared to controls (4/50), with statistical significance ($p = 0.017$). Although the prevalence of SIFO was higher in the colectomy group, the difference did not reach statistical significance ($p = 0.08$) [12]. In 2015 Abdulla et al also stated that SIFO and SIBO are significant and often overlooked complications following colectomy, which can elucidate gastrointestinal symptoms. In this study in total - 62% (31/50) of patients who had previously undergone colectomy and experienced chronic gastrointestinal symptoms were found to have undiagnosed SIBO, 39% (12/31) had coexisting SIFO and 4% (2/50) had SIFO (only Candida was found). [13]

It was also stated that inherited connective tissue disorders such as Ehlers Danlos Syndrome (EDS) can be connected with SIFO. Hyperelasticity, that occurs in such disorders, also influences gut smooth muscle, resulting in gastrointestinal motility dysfunction. That may be the reason why gastrointestinal (GI) symptoms are prevalent. Studies suggest occurrence 35-38,5% while testing individuals using breath tests for SIBO. In the matter regarding SIFO there were less studies conducted. Nevertheless such disorders can be the reason for SIFO in a similar way to SIBO. In 2021 there was a study performed, where adult patients ($n=24$, all female) with EDS and unexplained GI symptoms lasting over a year underwent endoscopy. Duodenal aspirates were collected and aerobic, anaerobic, and fungal cultures were obtained. Tests in

twelve participants (50%) were positive for SIBO/SIFO - among them, three patients (25%) showed both SIBO and SIFO, seven (58%) had SIBO exclusively, and two (17%) had SIFO alone. There were similar prevalence of GI symptoms rates compared to the negative aspirates group, therefore such symptoms alone are weak predictors of SIBO and SIFO. There is still a need for future, standardized research on larger groups of patients. [14]

Another experiment conducted in mice by Yang et al in 2017 demonstrated that prolonged ethanol administration led to an decrease in fungal diversity and overgrowth of Candida within the intestines. [15]

Risk factors
underlying medical conditions with compromised immune function e.g. HIV infection, cancer, diabetes mellitus, malnutrition, transplantation
drugs: anti-cancer chemotherapy, immunosuppressants, steroids, parenteral antibiotics, proton pump inhibitors
age - infants and elderly people
hospitalization (especially intensive care units)
small intestine dysmotility
colectomy
inherited connective tissue disorders eg. Ehlers Danlos Syndrome
chronic ethanol consumption

Clinical manifestation

The most frequently reported symptoms in patients with SIFO are unexplained gas, bloating, belching, flatulence, indigestion, nausea, irregular bowel movements, malabsorption, abdominal pain, along with chest pain. [10,16] It has also been found that in more severe cases, SIFO can manifest as bloody diarrhea and colonic erosions. There were also described sequences when fungal overgrowth leads to diarrhea and it consequently leads to dehydration, imbalance in electrolytes and hyperchloremic metabolic acidosis. Many studies tried to explain

the way *Candida* overgrowth can cause diarrhea, but any of them have valid evidence. The clinical manifestation of *Candida*-induced diarrhea resembles other intestinal infections, and physical examination findings offer limited assistance in distinguishing it from other forms of infectious diarrhea. [17]

When it comes to immunocompetent patients - there was one experiment performed, in which one healthy patient voluntarily consumed a saline suspension with concentration of 10^{12} *Candida albicans* cells. Two hours later there was a transient toxic reaction observed - high fever, chills, headache, which lasted up to 9 hours after the initiation of the test. The administration of a cathartic and oral nystatin gave an almost immediate remission of symptoms. No permanent damage occurred as a result of this experiment. After the test it was suggested that *C. albicans* cells have the ability to traverse the intestinal wall - most likely through the mechanism of "persorption," and consequently enter the bloodstream and urine. Given that the population of *C. albicans* in the intestine resembled that occasionally observed after the administration of broad-spectrum antibiotics, it appears plausible that antibiotic-induced fungal overgrowth could similarly lead to fungemia, even in immunocompetent patients. [18] Numerous additional case reports document the occurrence of fungi, particularly *Candida albicans*, in the small intestine in patients who are immunocompetent and without any underlying medical conditions, who experienced abdominal pain or diarrhea and those symptoms were alleviated after following antifungal therapy [17,19].

Diagnosis

There are no official guidelines regarding diagnosis of SIFO. Gastrointestinal symptoms of this condition are non-specific, therefore a diagnosis can not be made based on them alone. The method currently used is endoscopy with collection of small intestinal juice aspirates and then cultures for fungi. Without a positive outcome of it, it can not be proved that fungal overgrowth is responsible for symptoms. The huge limitation is that not every fungi can be cultured using in vitro. There is also no specific number of fungi whose presence in the small intestine would indicate SIFO. Four studies suggest that the cut off of fungal organisms should be $\geq 10^3$ cfu/mL. Also, the detection of fungi in the stool is not equivalent to the diagnosis of SIFO, because fungi found there is usually a normal commensal in patients with compromised immune systems. It was suggested that confirmation of fungal overgrowth can be made using urinary organic acids e.g. D-arabinitol, but there is yet no proven alternative to endoscopy.

There should be established guidelines with new tools and techniques of detective that are easier to implement and more cost effective. [6,10,20,21]

Treatment

Systemic medications are used to treat SIFO. The choice depends on the general condition of the patient, his immune status, the severity of the disease, contraindications to specific antifungal drugs and the resistance of *Candida* and other fungi to drugs. The medications used to treat SIFO include azoles, echinocandins and polyenes.

In the azole group, fluconazole is the drug of choice. It is safe, cheap, and used orally. It can be used in people with HIV and mucosal candidiasis. [22,23] Studies indicate that in patients with GI candidiasis who were treated with fluconazole (azole antifungal) for 2-3 weeks symptoms resolved rapidly. [24]

As for echinocandins (caspofungin, anidulafungin, micafungin) - they are mostly used to treat invasive candidiasis, as well as infections caused by *C. glabrata* and *C. krusei*. [25]

Polyenes include nystatin and amphotericin B. Nystatin is not absorbed from the intestine or skin, making it suitable for treating oral and skin candidiasis. Toxicity is rare with nystatin. [26] When it comes to amphotericin B, the main weakness is its nephrotoxicity and the fact that it needs to be administered intravenously daily. [27]

Influence of physical activity on the microbiome-gut-brain axis

The microecosystem within the gut maintains a symbiotic relationship with the host organism, where a balanced and diverse array of microorganisms promotes overall health. Reduced diversity and disturbed balance in gut microorganisms leads to systemic repercussions, including gastrointestinal symptoms, psychological discomfort and therefore decreased quality of life. Correlation between above-mentioned elements is recognized as the microbiome-gut-brain axis. Among the things that can influence the intestinal microecosystem are probiotic supplementation as well as exercising.

There is evidence which suggests that exercise could facilitate a bidirectional connection between the gut and brain by modulating the microbiome and therefore physical activity can be used as a therapeutic approach for both psychological and gastrointestinal disorders. [28] Studies have shown that exercising enhances the diversity of the gut microbiome and modifies gut biodiversity both quantitatively and qualitatively. It prevents imbalance in gut

microbiota and therefore prevents different types of overgrowth - fungal, bacterial etc. [29,30] Information about disturbance in this specific balance is received to the central nervous system from the gut via the vagus nerve and CNS will then determine if an inflammatory response is needed. [31]

Studies have indicated that too intense exercise has a negative impact on the intestines by increasing intestinal permeability, causing damage and leading to mild endotoxemia. [32,33] What helps relieve symptoms are targeted exercise therapies, which also improves psychological state, quality of life and reduces stress. [28]

Summary

Small intestinal fungal overgrowth (SIFO) is more often acknowledged as a potential factor for unexplained gastrointestinal symptoms. More and more clinicians attach importance to this issue, as it is a serious clinical burden which significantly reduces quality of life. It might be more prevalent than it was previously assumed, particularly among patients with underlying medical conditions such as diabetes, gut dysmotility, drugs which lower the immune response (e.g. PPI, steroid and antibiotic usage) as well as it can manifest in individuals with compromised immune systems. Nevertheless, the precise clinical impact of SIFO within the community remains uncertain as the available literature primarily consists of isolated case reports or observations from autopsies of patients undergoing cancer treatment.

Diagnosis typically involves small bowel aspiration and culture. Future research is essential in this matter and should focus on finding a simpler, less invasive and more cost-effective way to diagnose this clinical issue. There is also a need to create diagnostic criteria as well as treatment regimes, which will acknowledge both antifungal treatment and underlying risk factors through randomized controlled trials. The impact of physical activity on symptom relief should also be more widely explored as a non-invasive approach.

Disclosure

Authors do not report any disclosures.

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