LEWANDOWSKI, Mateusz, SIEKIERKO, Nikola, ŚWIĘTOCHOWSKI, Jakub, KOTUSIEWICZ, Wiktoria, ŻOŁNIEREK, Maja, LUBCZYŃSKA, Zuzanna, BIENIA, Grzegorz, POPRAVKO, Yevheniia, PRZERADZKI, Jakub & KUCHARSKI, Jakub. What do we know about the connection between gut microbiota and pain? Journal of Education, Health and Sport. 2023;20(1):62-68. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.20.01.007
https://apcz.umk.pl/JEHS/article/view/43233
https://zenodo.org/record/7825004

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 20.03.2023. Revised: 21.03.2023. Accepted: 13.04.2023. Published: 13.04.2023.

What do we know about the connection between gut microbiota and pain?

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Abstract
Introduction and objective
The relationship between gut microbiota and pain is crucial. Several studies demonstrate the evidence that gut microbiota play a key role in visceral, neuropathic and inflammatory pain. The proper profile of microbiota is also important in patients after surgeries and injuries who suffer from postoperative pain. In the present review study we assessed a comprehensive range of relevant literature to present the role of gut microbiota as the key factor in maintaining the structural integrity of the intestinal mucosal barrier, pain perception and modulation of the immune system.
Review methods
We conducted a literature review in February, 2023 searching for terms “Gut microbiome and pain", “Probiotic supplementation”, “Fecal microbial transplantation in patients with pain”. This publication includes the analysis of several case reports, which describe patients who were successfully treated with modification of gut microbiota composition.
Brief description of the state of knowledge
The gut microbiota is a diversity of many different microorganisms. They inhabit our gut and are the key to many aspects of human health. To understand how important the gut microbiome is we have to be aware of a bidirectional connection between the gut and the brain. The gut microbiota has an impact on the nervous system via the microbiome-gut-brain axis and the hypothalamic-pituitary-adrenal axis.
Summary
We propose novel therapeutic methods like probiotics or prebiotics or fecal microbiota transplantation as the new strategy for the management of pain. To reach this goal we need more clinical evidence to implement our theoretical knowledge to clinical practice.

Key words: gut microbiome, pain, hypothalamic-pituitary-adrenal axis, probiotic supplementation, fecal microbial transplantation, inflammation

Streszczenie
Wprowadzenie i cel pracy
Związek między mikrobiomem jelitowym a bólem ma istotne znaczenie. Liczne badania wykazały, że mikroflora jelitowa odgrywa kluczową rolę w odczuwaniu bólu trzewnego, neuropatycznego jak i zapalnego. Właściwy skład mikrobiomu ma również znaczenie u pacjentów po operacjach i urazach, u których występuje ból pooperacyjny. W niniejszym badaniu przeglądowym oceniono obszerny zakres literatury naukowej, aby przedstawić rolę mikroflory jelitowej jako kluczowego czynnika w utrzymaniu integralności strukturalnej bariery śluzowej jelit, odczuwaniu bólu i modulacji układu odpornościowego.
Materiał i metody
W lutym 2023 roku przeprowadzono przegląd literatury w poszukiwaniu terminów „Mikrobiom jelitowy a ból”, „Suplementacja probiotykami”, „Przeszczep drobnoustrojów kałowych u pacjentów z bólem”. Publikacja ta zawiera analizę opisów pacjentów pomyślnie leczonych poprzez modyfikacją składu mikroflory jelitowej.
Opis stanu wiedzy
Mikrobiota jelitowa to różnorodność wielu różnych mikroorganizmów. Zamieszkują one nasze jelita i są kluczem do wielu aspektów zdrowia człowieka. Aby zrozumieć, jak ważny jest mikrobiom jelitowy, musimy być świadomi dwukierunkowego połączenia między jelitami a mózgiem. Mikrobiota jelitowa ma wpływ na układ nerwowy poprzez oś mikrobiom-jelita-mózg oraz oś podwzgórze-przysadka-nadnercza.
Podsumowanie
Nowe metody terapeutyczne, takie jak probiotyki, prebiotyki lub przeszczepy mikroflory kałowej mogą stanowić nową strategię leczenia bólu. Aby osiągnąć ten cel, potrzeba więcej dowodów klinicznych, aby wdrożyć wiedzę teoretyczną do praktyki klinicznej.

Słowa kluczowe: mikrobiom jelitowy, ból, oś podwzgórzowo-przysadkowo-nadnerczowa, suplementacja probiotykami, przeszczep drobnoustrojów kałowych, zapalenie

Introduction

The gut microbiome is a diversity of many different microorganisms, which once created our microsystem including bacteria, yeast, parasites and viruses [1]. They inhabit our gut and are included in vital functions such as immunological, metabolic and neurobehavioral traits. They are the key to many aspects of human health such as protection from pathogens, host nutrient metabolism, production of vitamins, xenobiotic and drug metabolism, maintenance of structural integrity of the gut mucosal barrier and modulation of the immune system [2]. This specific environment is susceptible to many factors such as diet, exercise, smoking, age and frailty [3], environment, body mass index, anesthesia or just our lifestyle [4]

To understand how important the gut microbiome is we have to be aware of the microbiome-gut-brain axis. This is a bidirectional connection between the gut and the brain. This communication includes stimulation of host immunological responses with cytokines as signaling mediators, tryptophan metabolism, the vagus nerve and alteration of neuronal circuits by bacterial metabolites [5]. The bacteria and their metabolites can stimulate the enteric nervous system. This afferent stimulation goes through the vagal nerve to the brain where it initiates an efferent signal. That stimulates an anti-inflammatory reflex in which mediators such as acetylcholine are released through interaction with immune cells in order to reduce or prevent inflammation [6].

Another important route connecting the brain and gut microbiome is the hypothalamic-pituitary-adrenal axis (HPA). This main neuroendocrine axis indicates the importance of systemic release of cortisol caused by psychological stress. This can impact and alter the microbiome composition. The HPA axis is also significantly linked with other systems, such as the immune system, the intestinal barrier and blood–brain barrier, microbial metabolites, and gut hormones, as well as the sensory and autonomic nervous systems [7].

Unfortunately the amount of disorders connected with an altered gut microbiota is still increasing. They are associated with states linked with acute and chronic stress, pain but also gut inflammation disorders [8]. This should prompt us to look for development of new therapeutic methods.

Methods

We conducted a literature review in February, 2023 searching for terms “Gut microbiome and pain", “Probiotic supplementation”, “Fecal microbial transplantation in patients with pain”. We used PubMed and Google Scholar databases to inquire about case reports which describe patients with pain who were successfully treated with modification of gut microbiota composition.

Discussion

The sensation of pain can be increased by inflammation [8]. This common knowledge was used in a study which investigated whether inflammatory pain was modified in the absence of the microbiota [9]. Authors of the study assess nociceptive responses induced by a range of inflammatory stimuli in germ-free and

conventional mice. The inflammatory pain, as measured by hypernociceptive response and increase in pain response, is seen in inflammatory conditions with mediators such as adenosine 5′-triphosphate (ATP), H+, prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α), interleukin 1beta (IL-1β), C–C motif chemokine ligand 2 (CCL2), and chemokine (C-X-C motif) ligand 1 (CXCL1) being released from immune cells [10]. This experiment shows that germ-free mice have reduced inflammatory hypernociception induced by carrageenan, lipopolysaccharide, TNF-α, IL-1β, and the chemokine CXCL1. The study implies that contact with commensal microbiota is essential for mice to develop inflammatory hypernociception. Furthermore, colonization of the mice with commensal microbiota caused increased levels of inflammation and pain [11].

The diversity of specific bacteria in the gut microbiota is connected with symptom severity in the chronic pelvic pain syndrome(CPPS). Shoskes at al. [12] revealed that microbiomes were significantly different between the group of patients who suffered from severe pelvic pain and the comparator group which reported none or mild symptoms of CPPS. The most important difference was less diversity of the gut microbiota species in patients with symptomatic chronic pelvic pain syndrome. In the feces of patients who experienced severe pain, there was under-represented bacterial taxa such as Prevotella compared to controls. It leads to a hypothesis that this bacteria protects the organism from inflammation and may be a possible novel approach to treatment of patients with inflammatory diseases.

Post-GI-surgical complications can be implicated by the gut microbiota environment [13]. Guyton et al. revealed that there is a probable connection between an imbalance in the profile of gut microbiota and increased susceptibility of the post-operative pain development. The anesthesia and surgery are proven to have an impact on the reduction of Lactobacillus species [14]. That is associated with behavioral changes such as elevated levels of anxiety and stress. As the study explores, application of Lactobacillus salivarius has a positive influence on the microbioms [14]. Hypothetically, there is a possibility to manipulate the microbiota by introducing the probiotics prior to surgery in order to minimize the deleterious impact on the profile of microbiota.

In this case report the authors suggested that probiotics supplementation can reduce the number of recurrences of acute anterior uveitis (AAU) in patients. They present a 21-year-old woman with ocular redness and pain which was connected with her 3-year history of AAU. She was successfully treated with dietary probiotic and steroids. The possible explanation is that gut dysbiosis can influence the prognosis of uveitis by inducing a loss of the gut's immune homeostasis, thus promoting inflammation [15]. The results of this study are consistent with another case report. Askari et al. effectively treated a 49-year-old woman with an ocular manifestation of Behcet’s syndrome with a symbiotic supplementation (probiotics and prebiotics). After 7-month treatment the symptoms improved and serum inflammatory markers were suppressed [16].

There are some significant studies which focus on determining whether administration of probiotics is beneficial in functional abdominal pain (FAP) during childhood [17,18,19]. The authors of the first study enrolled a total of 101 children in a randomized double-blind, placebo controlled trial. Those patients randomly received either Lactobacillus reuteri DSM 17938 or placebo for 4 weeks, with further follow-up of 4 weeks. In this randomized controlled trial administration of probiotics significantly reduced the abdominal pain in children with FAP as compared to the control group [17]. According to Newlove-Delgado and al. [18] administration of probiotics may improve abdominal pain in children in the short-term. Their article based on 19 studies suggested that clinicians could consider probiotics in management strategy in recurrent abdominal pain. Giannetti and al.

[19] assessed the efficacy of a probiotic mixture of Bifidobacteria in 48 children with IBS. The primary parameter was abdominal pain resolution. The study indicated improved abdominal pain and quality of life in children with IBS. Another clinical trial showed that probiotics alleviate pain in patients with rheumatoid arthritis [20]. In the group of 45 adults, individuals who received Bacillus coagulans GBI-30, 6086 experienced a significant reduction of pain. The results of the study support the role of probiotics for inflammatory diseases and the role of the gut microflora in pain relief.

Another case study concerns a 46-year-old female with diabetic neuropathy. She had a fecal microbiota transplantation (FMT) and thus achieved relief in her symptoms. The authors proposed that FMT could be a successful treatment in patients with complications of diabetes such as painful diabetic neuropathy. Results of the discussed case are promising, as since her first FMT the patient did not use any drugs for alleviating the pain [21]. The case study drew attention to the role of the fecal microbiota transplantation in the regulation of gut-brain axis, which is another example of the crucial role of the gut microbiome.

Conclusion

To summarize, the emerging role of the gut microbiota is the key to identify new therapeutic pathways in development of pain treatment. We are getting better at understanding the profile of microbiota and we already have the theoretical background to take steps to conduct clinical studies concerning the influential role of the gut microbiota in pain relief. The increasing attention drawn to these subjects may have an impact on the future investigations about gut-brain axis and the influence of gut microbiota dysregulation which participates in visceral pain, inflammatory pain or neuropathic pain. Therefore, we showed several cases of patients successfully treated with tools including probiotics or prebiotics or fecal microbiota transplantation, which were influential for gut microbiota composition.

This review paper does have several limitations. Despite all the information aforementioned, there is not enough data or publications regarding the role of the gut microbiome in the development of pain. We need more clinical evidence to implement our theoretical knowledge to clinical practice. In our opinion, the identification of novel therapeutic tools like probiotics or prebiotics or fecal microbiota transplantation in pain treatment represents a research priority.

Conflict of interest statement

Competing interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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