

KUŚMIERSKA, Martyna, KUŚMIERSKI, Jakub, JANIĆ, Izabela, MARTYKA, Anna and UJMA, Przemysław. Significance of the Gut-Brain Axis in the Development of Overweight and Obesity. *Journal of Education, Health and Sport*. 2024;70:49434. eISSN 2391-8306.

<https://dx.doi.org/10.12775/JEHS.2024.70.49434>

<https://apcz.umk.pl/JEHS/article/view/49434>

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. 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 2024; This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited. The authors declare that there is no conflict of interests regarding the publication of this paper. Received: 16.03.2024. Revised: 10.05.2024. Accepted: 14.05.2024. Published: 17.05.2024.

Significance of the Gut-Brain Axis in the Development of Overweight and Obesity

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ABSTRACT

Introduction: The global obesity crisis results from inactive lifestyles and poor diets, increasing the risk of metabolic disorders. Emerging research links obesity with gut microbiome changes influenced by factors like age, genetics, and diet. Gut-brain communication via neural, endocrine, and inflammatory pathways, influenced by microbial compounds, affects nervous system function.

Materials and Methods of Research: A thorough literature review was performed using PubMed and Google Scholar, employing keywords related to the gut-brain axis and obesity.

Results: Obesity shifts gut microbiota composition due to factors like childbirth method, diet, antibiotics, and environment. This imbalance impacts metabolism, appetite, and insulin sensitivity. Gut microbes influence the brain, regulating energy balance and inflammation. Dysregulated tryptophan metabolism leads to insulin resistance. Gut-brain communication via the vagal nerve affects nutrient metabolism. Hormones like insulin and leptin, along with microbial metabolites, affect lipid metabolism and appetite. Gut microbiota abundance correlates with leptin signaling, and changes in ghrelin levels relate to microbiota composition. Microbial presence affects food cravings. Inflammation in obesity is linked to gut microbiota changes, mediated by bile acids and microbial metabolites. Interventions like probiotics and fecal microbiota transplantation offer potential for managing obesity. Emerging therapies like peptide D3 hold promise but require further study.

Conclusion: The microbiome-gut-brain axis is vital in obesity, affecting metabolism, inflammation, and appetite. Utilizing interventions such as dietary adjustments and probiotics targeting gut-brain signaling shows promise in managing obesity. Personalized approaches are crucial due to microbiome complexity. Further research is needed to develop effective therapies for the obesity epidemic.

Keywords: Gastrointestinal Microbiome; Brain-Gut Axis; Overweight; Obesity.

I. Introduction

The global prevalence of excess body weight is a significant health concern, driven by sedentary lifestyles and unhealthy dietary habits, impacting approximately 2 billion people worldwide. Obesity stands as a primary risk factor for metabolic disorders. [1] WHO defines overweight and obesity as follows: overweight is a BMI greater than or equal to 25; and obesity is a BMI greater than or equal to 30. It's evident that obesity stems primarily from disrupted energy homeostasis, rather than mere passive accumulation of excess body fat. Yet, the mechanisms underlying chronic energy imbalances and the subsequent chain of altered biochemical signaling leading to weight gain and biological defense of increased body fat mass remain less understood. [2] Obesity poses a significant health threat, significantly elevating the risk of conditions such as type 2 diabetes mellitus, fatty liver disease, hypertension, heart attack, stroke, dementia, osteoarthritis, obstructive sleep apnea, and various cancers. This contributes to a decrease in both life expectancy and quality of life. [3] Currently, an increasing number of association studies are establishing connections between obesity and overweight and microbiome alterations. [4]

Human body harbors a diverse microbiome across various niches. Primary sites of microbial colonization in humans include the skin, airways, urogenital tract, eyes, and gastrointestinal tract. [5]. The human gut microbiota is composed of diverse microorganisms, such as bacteria, archaea, eukaryotes, viruses, and parasites. The composition and metabolic phenotype of the gut microbiota are influenced by various factors, including age, host genetics, geographical location, and dietary habits. [6] Clearly defined pathways exist for bidirectional communication, encompassing neural, endocrine, and inflammatory mechanisms, which connect the gut and the brain. The primary mode of communication from the gut microbiome to the central nervous system (CNS) involves intermediates derived from microbes, with well-documented examples including short-chain fatty acids (SCFAs), secondary bile acids (2BAs), and metabolites of tryptophan. [7] The metabolites produced by the gut microbiota play a role in modulating the physiology and behavior of both the central nervous system (CNS) and enteric nervous system (ENS). Furthermore, the vagus nerve's afferent branch serves as the primary neural pathway linking the gastrointestinal tract to the nucleus of the solitary tract and higher emotion-regulating networks in the mammalian brain. While direct interaction with the gut microbiota is not observed, research indicates that the vagus nerve can detect microbial signals, such as bacterial metabolites. [8]

II. Purpose of the Study

Currently, there is a growing body of evidence linking intricate interplay between dysregulation of the gut microbiome and the gut-brain axis to the pathomechanism of overweight and obesity development. The primary objective of this review is to delve into the intricate connections between the gut-brain axis and obesity. By synthesizing current research findings and elucidating underlying mechanisms, this study aims to offer a deeper understanding of the complex interplay between these factors within the realm of medical science. Through an extensive examination of the literature, this review seeks to provide insights into potential therapeutic targets and strategies for addressing obesity through modulation of the gut-brain axis.

III. Materials and Methodology

A comprehensive literature search was conducted using electronic databases including PubMed and Google Scholar. The search strategy utilized a combination of keywords related to the gut-brain axis (e.g., “gut microbiota”, “microbiom”, "gut-brain axis," "enteric nervous system," "vagus nerve") and obesity (e.g., "obesity," "overweight," "body mass index"). The search was limited to articles published in English from inception to 2017. Additional studies were identified through manual searches of reference lists of relevant articles.

IV. Description of the State of Knowledge

Characteristics of Gut Microbiota in Individuals with Obesity vs. Individuals with Normal Body Weight

Microbiota in healthy adult humans primarily consist of Firmicutes and Bacteroidetes, accounting for about 70% of the total microbiota. Additionally, Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria may also be present, although in smaller proportions. [9] Regarding the bacterial groups involved, the comparison of gut microbiota between individuals with obesity and those with a lean phenotype demonstrated a greater abundance of Firmicutes and a reduced proportion of Bacteroidetes in obesity. [10] Of particular interest, obese individuals undergoing a 1-year low-calorie diet exhibit a reduction in Firmicutes and an increase in Bacteroidetes proportions, aligning more closely with the Firmicutes/Bacteroidetes ratios observed in lean individuals. [11]

Other significant variables affecting the gut microbiota and potential obesity development.

Numerous factors contribute to the formation of the typical gut microbiota. These factors encompass the method of childbirth (vaginal or cesarean), dietary patterns during

infancy (breast milk or formula), and throughout adulthood (plant-based or animal-based), as well as the use of antibiotics or antibiotic-like substances originating from the environment or the gut commensal community. [12] Research suggests that changes in the gut microbiome in response to high-fat diets vary significantly, influenced by the types of dietary fats consumed. For example, diets high in saturated fatty acids reduce microbiota diversity, richness, and Bacteroidetes levels, whereas diets rich in unsaturated fatty acid have the opposite effect, increasing microbiome diversity, richness, and Bacteroidetes abundance. [13] Furthermore, a diet abundant in dietary fiber, such as mediterranean diet, serves as a valuable reservoir of "microbiota accessible carbohydrates" (MACs), which microbes can utilize to furnish the host with energy and a carbon source. Consequently, they have the capacity to alter the intestinal environment. [14, 15]. Additionally, it is impossible to overlook the influence of antibiotics. While their impact on the gut microbiota has long been recognized, an increasing body of literature draws attention to their role in obesity development through the influence on the microbiome-gut-brain axis. [16] Multiple studies have indicated a heightened risk of obesity associated with early-life exposure to antibiotics, highlighting the significance of the critical period during which the influence of the gut microbiome on host metabolism may be molded and solidified. [17]

Specific Correlations Between Gut Microbiota and the Brain

Intestinal microbiota and their metabolites might target the brain directly via vagal stimulation or indirectly through immune-neuroendocrine mechanisms, and they can regulate metabolism, adiposity, homeostasis and energy balance, and central appetite and food reward signaling, which together have crucial roles in obesity. [18] The gut microbiota generates a variety of metabolites that can influence host metabolism, including bile acids. These acids are initially synthesized from cholesterol in the liver and are subsequently metabolized by the gut microbiota into secondary bile acids. [19] In obesity-related gut dysbiosis, the decline in Bacteroides and Lactobacillus leads to decreased levels of bile acids, hampering energy expenditure primarily by impairing bile acid-mediated signaling pathways. This exacerbates the progression of the disease. [20] Moreover, the gut microbiota synthesizes SCFAs by efficiently extracting energy from the diet through metabolizing various components, including dietary fibers, proteins, peptides, and glycoproteins. These are transformed into easily absorbable products by the host, such as short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. SCFAs function as signaling molecules to regulate the secretion of anorectic (hunger-suppressing) hormones, such as GLP-1, PYY, and

leptin. Additionally, they influence gut motility, transit time, and fat storage in adipose tissue. [21, 22] Other microbiota metabolites also warrant notable consideration. Metabolites stemming from the essential aromatic amino acid tryptophan (Trp) in the gut also hold significant importance. The three primary metabolic pathways of Trp, which yield serotonin (5-hydroxytryptamine), kynurenine (Kyn), and indole derivatives, are influenced by the microbiota, either directly or indirectly. [23] Dysregulation of tryptophan metabolism is linked to inflammation, insulin resistance, and decreased secretion of the incretin hormone glucagon-like peptide 1 (GLP-1) from intestinal enteroendocrine L cells. Additionally, reduced biosynthesis of serotonin (5-HT) from intestinal enterochromaffin cells occurs due to a decline in the production of microbiota-derived metabolites that stimulate host 5-HT production. [24]

Central nervous system (CNS) and enteric nervous system (ENS) interact with gut microbiota to regulate nutrient metabolism. The vagal nerve system mediates communication between the CNS and ENS, governing gastrointestinal functions and feeding behavior. Vagal afferent neurons also express receptors for gut peptides secreted by enteroendocrine cells (EECs), including CCK, ghrelin, leptin, PYY, GLP-1, and serotonin. Gut microbiota modulate levels of these gut peptides, influencing the vagal afferent pathway and thereby regulating intestinal metabolism via the microbiota-gut-brain axis. [25] The physiological control of appetite is mediated by circulating orexigenic and anorexigenic hormones (e.g., leptin, insulin, and ghrelin) produced by peripheral organs, including gut, adipose tissue, and pancreas. [26] Insulin, an anabolic hormone, triggers numerous cellular reactions. Its hormonal effects involve enhancing protein synthesis, initiating de novo lipogenesis and cell growth, and suppressing lipolysis. However, during hyperinsulinemia, insulin's ability to regulate glucose is compromised due to decreased insulin signaling efficiency, often termed "insulin resistance". [27] Evidence indicates that SCFAs (especially acetate) play a crucial regulatory role in controlling body weight and insulin sensitivity by influencing lipid metabolism and maintaining glucose homeostasis. [28] Leptin, originating from white adipose tissue, functions within the brain to relay information about fuel availability, suppress hunger after meals, stimulate energy expenditure, and regulate blood glucose levels. [29] Research indicates a correlation between gut microbial abundance and richness and leptin signaling. For instance, individuals with lower bacterial richness tend to exhibit higher levels of circulating leptin, regardless of obesity status. Furthermore, both in vivo and in vitro studies have demonstrated that the migration of living gut microbiota to adipose tissues, prompted by

heightened intestinal permeability, impacts energy metabolism by suppressing leptin signaling in both obese humans and mice. [18] Ghrelin is famously known as the 'hunger hormone'. Among the various metabolic effects of ghrelin, its primary roles include stimulating appetite by activating orexigenic hypothalamic neurocircuits and promoting lipogenesis independently of food intake. These actions collectively result in weight gain and increased adiposity. [30, 31] Alterations in ghrelin levels in the bloodstream have been associated with shifts in gut microbiota composition, indicating potential regulation of the ghrelinergic system by commensal gut microbes. It has been demonstrated that short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, along with lactate, as well as bacterial supernatants from the *Bifidobacterium* and *Lactobacillus* genera, can influence GHSR-1a signaling. [32] It's also crucial to acknowledge that the presence of microbiota triggers the activation of the reward system, consequently heightening food cravings, whereas their absence may depress the reward system and diminish food cravings. [33]

It is important to also acknowledge that mild inflammation serves as a distinguishing feature of metabolic conditions such as obesity. New findings suggest that these conditions involve changes in the composition of gut microbiota and their byproducts. These substances traverse a compromised intestinal barrier, reaching different metabolic organs like the liver and adipose tissue, consequently fostering metabolic inflammation. [34] As an example, bile acids function as signaling agents, modulating metabolism and inflammation through the nuclear farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5). These receptors trigger transcriptional networks and signaling pathways that regulate the expression and function of genes related to bile acid, lipid, and carbohydrate metabolism, energy utilization, and inflammation. They primarily operate in enterohepatic tissues but also exert effects in peripheral organs. [35] In inflammation research, SCFAs are consistently found to diminish inflammation while promoting fatty acid oxidation, inhibiting synthesis, enhancing heat generation, and reducing fat storage. Despite their robust metabolic regulatory capacity, the intricate network and molecular mechanism governing SCFAs remain unclear. [36]

Possible points of intervention.

Various probiotics, whether used independently or as part of symbiotic blends, can exert their anti-obesity effects through species- and strain-specific mechanisms. These mechanisms include modulation of gut microbiota, reduction in insulin resistance, and enhancement of satiety. Specifically, species such as *Lactobacillus* (e.g., *L. Casei*, *L. Gasseri*, *L. Rhamnosus*,

L. Plantarum) and *Bifidobacterium* (e.g., *B. Infantis*, *B. Longum*, and *B. Breve B3*) have been effectively employed in obesity due to their limited pathogenicity and low antibiotic resistance levels. [37] Prebiotic oligosaccharides have been shown to selectively modify the intestinal microbiota, leading to significant reductions in body weight, percentage of body fat, percentage of trunk fat, and serum interleukin-6 levels in children with overweight or obesity. [38] What's intriguing is that studies have demonstrated that synbiotics, which are a combination of prebiotics and probiotics, exhibit greater efficacy in modulating gut microflora compared to prebiotics and probiotics when used individually. [39] Fecal microbiota transplantation (FMT) presents an intriguing avenue for modifying gut microbiota and enhancing clinical outcomes, predominantly utilized in treating *Clostridium difficile* infection. However, its utilization in metabolic contexts lacks extensive data. In individuals with metabolic syndrome and obesity, receiving FMT from lean donors notably boosts insulin sensitivity, albeit with varying clinical responses. [40] There is currently a wealth of research focused on exploring novel therapeutic avenues. For example, a small peptide, D3, distinct from GLP-1 analogues, demonstrates the ability to mitigate obesity progression by curbing appetite and modulating gut microbiota. This investigation provides new insights, suggesting the UGN-GUCY2G axis as a promising therapeutic focal point for anti-obesity medication development. Nevertheless, additional investigation is needed to delve deeper into this matter. [41]

V. Conclusion

In summary, the microbiome-gut-brain axis emerges as a fundamental player in the multifaceted landscape of obesity. By virtue of intricate bidirectional signaling, the gut microbiota exerts profound effects on diverse metabolic pathways, encompassing energy metabolism, inflammation modulation, and appetite regulation, all of which are intricately linked to the development and progression of obesity. Notably, alterations in gut microbial composition and function have been associated with the pathophysiology of obesity, with specific microbial taxa and their metabolites implicated in influencing host energy balance and adiposity. Furthermore, the gut-brain axis serves as a critical conduit through which signals from the gut microbiota are transmitted to the central nervous system, modulating appetite, satiety, and food intake regulation. Dysregulation of this axis, whether through perturbations in gut microbial diversity, aberrant gut barrier function, or altered production of microbial metabolites, can disrupt energy homeostasis and contribute to the onset of obesity.

Moreover, the role of the microbiome extends beyond traditional metabolic pathways, encompassing the intricate interplay between gut microbiota, immune function, and systemic inflammation, all of which are intricately linked to obesity development and progression. The gut microbiota influences immune cell development, function, and responsiveness, shaping the immune landscape in adipose tissue and promoting low-grade chronic inflammation, a hallmark of obesity-related metabolic dysfunction. Furthermore, microbial metabolites, such as short-chain fatty acids, bile acids, and tryptophan derivatives, have emerged as key mediators in modulating immune function and inflammatory tone, further underscoring the intricate interplay between the microbiome and obesity-associated inflammation.

In light of these insights, harnessing the therapeutic potential of the microbiome-gut-brain axis holds considerable promise in the management and prevention of obesity. Strategies aimed at modulating the gut microbiota composition and function, such as dietary interventions, prebiotics, probiotics, and fecal microbiota transplantation, offer novel approaches to ameliorating obesity-related metabolic disturbances. Moreover, targeting gut-brain signaling pathways, including the manipulation of gut hormone secretion, neural signaling, and central appetite regulation, represents an exciting frontier in obesity therapeutics. However, it is essential to recognize the complexity of the microbiome-gut-brain axis and the heterogeneity of individual responses to microbial interventions, emphasizing the need for personalized and precision medicine approaches in tackling obesity and its associated comorbidities. Thus, continued research efforts are warranted to elucidate the mechanistic underpinnings of microbiome-host interactions and to translate these findings into effective therapeutic strategies for combating the global obesity epidemic.

DISCLOSURE

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All authors have read and agreed with the published version of the manuscript.

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

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