Akkermansia muciniphila, una bacteria contra la obesidad y su relación con la dieta. Revisión sistemática

Akkermansia muciniphila, a bacteria against obesity and its relationship with diet. Systematic review

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RESUMEN

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Palabras clave:
Akkermansia muciniphila, obesidad, intervención dietética

La bacteria anaerobia *Akkermansia muciniphila* ha demostrado su papel en la regulación del metabolismo y los marcadores de inflamación desde su descubrimiento. Es una bacteria Gram negativa que se clasifica dentro del filo Verrucomicrobiae. Es reconocida como una bacteria no patógena, desprovista de factores de virulencia y carente de una interacción significativa con el huésped que conduzca a la infección o enfermedad. Forma parte del microbioma intestinal humano y su mayor concentración se encuentra en los individuos de peso normal. Se realizó una revisión sistemática para analizar intervenciones clínicas dietéticas que examinan la asociación entre el fenotipo o estado de obesidad y la concentración de *A. muciniphila* en la microbiota intestinal, después de modificaciones nutricionales específicas en pacientes humanos con sobrepeso. La búsqueda de artículos se realizó utilizando Pubmed y Clinicalkey como motores de búsqueda. La terminología booleana ((*Akkermansia muciniphila*) and (obesidad)) and (intervención or nutrición or dieta or nutriente) se utilizó para seleccionar artículos relevantes para nuestra investigación. De los 301 artículos originales identificados, solo se seleccionaron aquellos que involucran intervenciones dietéticas en humanos. Los resultados indican que el aumento de *A. muciniphila* (ya sea mediante suplementación directa o intervención dietética) se asoció con efectos beneficiosos como disminución de la inflamación, reducción del riesgo cardiovascular, aumento de la sensibilidad a la insulina y reducción de los niveles de colesterol. En conclusión, se necesitan más intervenciones en seres humanos para determinar los beneficios y riesgos del aumento de las concentraciones de *A. muciniphila*.

ABSTRACT

Keywords:

Akkermansia muciniphila, obesity, dietary intervention

The anaerobic bacterium Akkermansia muciniphila has demonstrated its role in regulating metabolism and markers of inflammation since its discovery. It is a Gram-negative bacteria that is classified within the phylum Verrucomicrobiae. It is recognized as a non-pathogenic bacteria, devoid of virulence factors and lacking a significant interaction with the host that leads to infection or disease. It is part of the human intestinal microbiome and its highest concentration is found in individuals of normal weight. A systematic review was performed to analyze clinical dietary interventions examining the association between obesity phenotype or status and the concentration of A. muciniphila in the intestinal microbiota, after specific nutritional modifications in overweight human patients. The search for articles was carried out using Pubmed and Clinicalkey as search engines. The Boolean terminology ((Akkermansia muciniphila) and (obesity)) and (intervention or nutrition or diet or nutrient) was used to select articles relevant to our research. Of the 301 original articles identified, only those involving dietary interventions in humans were selected. The results indicate that increasing A. muciniphila (either through direct supplementation or dietary intervention) was associated with beneficial effects such as decreased inflammation, reduced cardiovascular risk, increased insulin sensitivity, and reduced cholesterol levels. In conclusion, further interventions in humans are needed to determine the benefits and risks of increasing A. muciniphila concentrations.

Introduction

Global curiosity surrounding anaerobic bacteria *Akkermansia muciniphila* has spiked in the last decade. Gut microbiota is closely related to overall human health, providing a physical and chemical barrier between pathogenic bacteria and enterocytes, as well as aiding in cellulose digestion, formation of vitamins, such as vitamin K, thiamine, riboflavin and vitamin B12. As well as, maintaining normal levels of inflammation and having an impact on the immune system especially during neonatal life (1,2).

Multiple interventions have been following gut microbiota changes after certain dietary interventions. For example, diets based on fiber, fats, or milk products such as fermented milk modulate the gut microbiota levels for each specific bacteria. What's more interesting is the consumption of breast milk in infants and the direct impact in regulating gut microbiota. Receiving human oligosaccharides, some bacteria including *A. muciniphila* are able to use them as an energy source using some enzymes, contributing to an increase in their concentration levels. *Akkermansia* also has a beneficial effect in the production of short chain fatty acids, which have been proven to improve metabolic functions (3).

Since its discovery in 2004, multiple studies have described its behavior surrounding dysbiosis in patients with obesity, diabetes, metabolic syndrome, among other diseases (4). Higher concentrations of *A. muciniphila* have been associated with the activation of CREBH (cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H) transcriptional factor that regulates triglycerides metabolism in the gastrointestinal tract, protecting it from hyperlipidemia and hypertriglyceridemia (5). Additionally, *A. muciniphila* is associated with the regulation of adipocyte differentiation and, moreover, its abundance is related to a reduction in visceral fat and body weight in trials involving mice (3-4,6-7).

Previous studies had shown the significance of *A. muciniphila* in metabolic functions and its inverse correlation with obesity (4,8-9). The most intriguing studies are those that involve dietary interventions, either with prebiotics, food components or supplementation with *A. muciniphila*, since their results show the potential to become a novel approach to obesity management (10). However, most of the available information has animals as subjects of study, without replicating its methodology on humans (4, 11).

There are very few studies conducted with human subjects that evaluate the fluctuations of *A. muciniphila* related with dietary interventions (7). Hence, it is important to review the current available literature in order to understand utterly the role of nutrition in the abundance of the gut microbiome and its effects on obesity biomarkers.

Our aim is to evaluate the correlation between dietary interventions in patients with obesity and the abundance of *A. muciniphila*; and its relationship with inflammation markers.

Methods

The chosen databases were PubMed and Clinical Key. The inclusion criteria for our study were: Study type being a dietary intervention or supplementation of *Akkermansia muciniphila*, randomization of patients, original language English, time of publication between 2016 and 2023, human patients with overweight and/or obesity, and

measurements of the abundance of *Akkermansia muciniphila* before and after the intervention as one of the measured variables. The exclusion criteria for our study were: Pharmacological or surgical interventions, systematic reviews, meta-analysis, cross sectional and disclosure studies, patients included in the study having non-related diseases and articles with expressed conflicts of interest. The Boolean terminology used for the search was: ((Akkermansia muciniphila) AND (obesity)) AND (intervention OR nutrition OR diet OR nutrient). These terms were selected in order to retrieve the articles that breach the subject of *Akkermansia muciniphila* and obesity and also included dietary interventions in the subjects. Date filters were applied to exclude articles that were published prior to 2016.

The results of this search in each database yielded the following number of articles. PubMed 257 articles relating to the search were found. Clinical Key yielded another 44 articles relating to the search. Two articles appeared in both databases. In total, 301 unique articles regarding *Akkermansia muciniphila*, obesity and interventions were found. After applying the exclusion criteria a total of 25 articles were reviewed. The search began on 15 June 2021 and concluded on 13 July 2023.

To collect reports data, a spreadsheet was made, and the reviewers summarized each individual article. The data included in the spreadsheet was: purpose of the trial, how *Akkermansia muciniphila* was directly affected by the intervention, patient's characteristics, method used on the intervention and metabolic measurements used. This information guided us towards comparing the available information from different studies and the fluctuations on the abundance of the bacteria.

Not all interventions employed the same obesity measurement markers. Besides these we decided to collect any marker that was compared before and after the dietary intervention and that demonstrates a modification increasing or decreasing relating to *A. muciniphila.* Also, time intervals manage a range from a minimum of one month.

In order to ascertain bias-free articles, a conscious search of a conflict-of-interest disclaimer was made. Added to this, a final search of Google Academic was made to be certain that no article that could be included in this review was ignored.

The chosen articles were summarized in a spreadsheet in order to compare the results of different nutritional interventions. Qualitative data was sorted out and our findings will be explained further. Bias was not found within the chosen articles, and no other articles were found on Google Academic that could be included in our study.

Results

Microbiology

Akkermansia muciniphila is a gram negative strictly anaerobic bacteria, taxonomically classified within the phylum *Verrucomicrobiae,* with a characteristic lack of motility. Morphologically, the bacterium features an oval-shaped cell with an axial diameter ranging from 0.6 to 10 μm. Cultivated under suitable conditions, *A. muciniphila* showcases diverse growth patterns, appearing as solitary cells, pairs, short chains or forming conglomerates. The genomic architecture of *A. muciniphila* MucT strain is characterized by a singular circular chromosome of 2.66 mbp. Further investigation divided *A. muciniphila* into three species phylogroups, however MucT is the most studied strain (12).

A prominent characteristic of *A. muciniphila* is its exceptional metabolic versatility. Specifically, it demonstrates a remarkable ability to thrive in environments enriched with

gastric mucin, utilizing this complex glycoprotein as a source of essential carbon, energy and nitrogen. This adaptive metabolic strategy not only underscores the ecological significance of the bacteria, but also implies potential implication in host-microbiome interactions (12) .

Regarding specific requirements for its growth, *A. muciniphila* thrives optimally at a temperature of 37°C and a pH of 7.5, without the need for exogenous vitamins. The strict anaerobic nature of the bacteria emphasizes its preference for environments devoid of oxygen, introducing an additional layer of complexity to its in vitro cultivation (12-13).

Akkermansia muciniphila has been documented to establish colonization within the human gut through a symbiotic relationship, typically initiated in the early stages of life, potentially within the first year of life. Noteworthy traces of this bacterium have been identified in human milk, implying a potential mode of transmission from mother to infant. Consequently, detectable quantities of the bacterium could be observed in the gastrointestinal tract of newborns (8, 13).

The abundance of *A. muciniphila* exhibits a distinctive pattern across the human lifespan. In healthy adults, this bacterium constitutes a noteworthy proportion, accounting for approximately 1 to 4% of the total gut microbiota, emphasizing its integral role within the complex microbial environment contributing to overall host health. However with advancing age, there is a reported decrease in the abundance of *A. muciniphila* within gut microbiota, suggesting a potential correlation between the aging process and its concentration on the microbiome. The mechanisms and implications of this decline in elderly populations warrant further investigations, to properly comprehend the dynamic interplay between *Akkermansia muciniphila* and the hosts physiological changes over the course of time (12-13).

Akkermansia muciniphila is acknowledged as a non-pathogenic bacterium, devoid of virulence factors and lacking a significant host interaction leading to infection or disease. Instead, disturbances in the abundance of this bacterium have been linked to certain pathological conditions, emphasizing its potential role as a biomarker or contributing factor to disease states such as obesity, type 2 diabetes mellitus, inflammatory bowel disease, atopy, and autism[12]. Even in diseases like cancer, it has been found that immunotherapy in combination with *A. muciniphila* administered as probiotic through microbiota transplantation has the potential to achieve better clinical results (12).

Its role in the microbiome is to maintain mucosal integrity, influence on metabolic processes and regulate immune responses, because of its anti-inflammatory properties. These characteristics are fundamental to maintain a healthy human microbiota (12-13).

Mechanisms of action

It was first postulated that the mechanism of action of *A. muciniphila* could be related to the endocannabinoidome, the endogenous system related to regulation of appetite, metabolism and inflammation. However, new hypotheses suggest that *A. muciniphila* has a positive effect on two endocannabinoidome lipids (1-Palmitoyl-glycerol and 2-Palmitoyl-glycerol), which in turn activate peroxisome proliferator-activated receptor alpha (PPARα) which could be one of the mechanisms for producing the benefits further described (14).

A focal point of investigation pertains to *A. muciniphila's* role in sustaining the intestinal barrier. According to Bian, et al (2019), the Amuc_1100 protein derived from *A. muciniphila* demonstrated a noteworthy reduction in inflammatory cell populations within the colon. This reduction targeted macrophages, cytotoxic T lymphocytes, and key

inflammatory cytokines such as TNF-a, IL-1a, IL-6, IL-12, MIP-1a, GCSF, and CXCL1. Beyond the colon, a decrease in CD16/32+ was observed in the spleen and lymph nodes of the mesentery, signifying broader immunomodulatory effects within extracolonic regions (15).

A recent investigation by Qian, et al. (16) has unveiled that Amuc_2109, an enzyme actively secreted by A. muciniphila, exhibits a mitigating impact on DSS-induced colitis in mice. This enzymatic intervention is characterized by increased expression of tight junctions (TJs) and at the same time, a reduced expression of NLRP3 inflammasome. Interestingly, the protective nature of viable *A. muciniphila* against colitis is dependent on NLRP3 activation. Notably, the regulatory role of NLRP3 in maintaining intestinal homeostasis has been previously delineated, evidenced by increased susceptibility to experimentally induced colitis in NLRP3-/- mice. Furthermore, administration of *A. muciniphila* has been shown to induce the proliferation of intestinal stem cells, while simultaneously enhancing the differentiation of Paneth and goblet cells in both the small intestine and colon. This phenomenon is observed in both healthy mice and those with gut damage induced by radiation and methotrexate.

Added to the former, the study establishes a correlation between the favorable effects of *A. muciniphila* in the intestinal tract and increased levels of acetic and propionic acids in the cecal content of treated mice. This elucidates the bacterium's contribution to tissue repair in the intestinal mucosa, implicating short-chain fatty acids (SCFAs) as crucial players in this reparative process. Thus, the study underscores the multifaceted role of *A. muciniphila* in intestinal health, spanning from immune modulation to the promotion of tissue repair through the production of SCFAs (16-17).

In the investigation of Ashrafian, et al. (18) regarding murine high-fat diet (HFD)–induced intestinal dysbiosis, the outer membrane vesicles derived from *Akkermansia muciniphila* demonstrated a capacity to enhance the intestinal mucosal barrier function. This was evident through augmented expression of tight junctions and IL-10, coupled with the inhibition of inflammatory markers within the colon.

Moreover, in Chelakot, et al. (19) *Akkermansia muciniphila's* outer membrane vesicles exhibited the ability to mitigate intestinal permeability, elevate tight junction expression via AMP-activated protein kinase (AMPK), suppress TLR-4 and interferon-alpha (IFN-α) expression, and enhance TLR-2 expression and IL-4 production in Caco-2 cell lines in vitro. This comprehensive exploration unveils the diverse mechanisms by which *Akkermansia muciniphila's* outer membrane vesicles contribute to intestinal health, encompassing mucosal barrier fortification, immune modulation, and regulatory effects on cellular signaling pathways.

Akkermansia muciniphila as a supplement

Considering the background of existing studies in mice and the benefits of *A. muciniphila* concentration, the simplest way to study its effects on the body is by supplementation. This bacteria can be ingested either live or pasteurized at 70°C for 30 min. The effects of ingesting live vs pasteurized *A. muciniphila* were extremely similar, including lowering fasting insulin levels, improving insulin sensitivity, lower white blood cell levels, lower total levels of cholesterol, all of these markers are related to levels of LPS which the supplementation of *A. muciniphila* reduced. However similar they may, ingesting the pasteurized version of *A. muciniphila* instead of the live sample lowered the activity of the enzyme dipeptidyl peptidase-IV, that decreased activity is related to improved glucose modulation, reduced cardiovascular risk and lowered levels of inflammation (7).

Druart et. al (20) have concluded that pasteurized *A. muciniphila* presents no genotoxicity nor subchronic toxicity, making it a safe food ingredient according to the FDA and EFSA guidelines on toxicology for non absorbable ingredients .

Pasteurized supplementation has shown its viable capacity to regulate hepatic molecules associated with the expression of atherosclerosis in mice. Specifically, gen Fmo3 from the liver reduced its expression after the intervention with pasteurized bacteria, subsequently reducing metabolites linked to thrombus development. However, it has been observed that the mechanisms responsible for reducing pro-inflammatory conditions and thrombus generation in lab mice may not precisely replicate those found in the bloodstream of human patients (21). Consequently, doubts have arisen regarding these mechanisms for reducing atherosclerosis through the hepatic route.

The effects of dietary interventions and supplements in A. muciniphila concentration

The available scientific evidence supports the influence of dietary interventions and the consumption of distinct nutrients on the concentration of *Akkermansia muciniphila.* The evidence supports the idea that adhering to a Mediterranean diet, having an elevated fiber intake, and operating under a caloric deficit in overweight individuals, resulting in an increase of the concentration of *A. muciniphila* in fecal material (20) .

Derrien et al (13) proved that food components like conjugated linoleic acid, polyamines, pectine, fructooligosaccharides, corn starch, fermentable oligosaccharides disaccharides monosaccharides polyols (FODMAP), have a beneficial effect increasing the abundance of the bacteria. A follow-up study in which an augmentation of fiber consumption, for the most part FODMAPS, in an overweight and obese population for 6 weeks, resulted in an increase in the abundance of *A. muciniphila* in fecal material .

Several clinical interventions had been conducted to show the correlation of Mediterranean diet and the augmentation of *A. muciniphila* (3,21). A study targeting Mexican men with metabolic syndrome involved the supplementation of polyphenol resveratrol, a naturally found compound in Mediterranean diet foods such as cranberries and grapes. This intervention has been observed to induce a notable enhancement in glucose homeostasis, consequently leading to an increase in the concentration of *A. muciniphila* in the fecal samples of the participants (22).

In another intervention conducted in 2021, a total of 210 hypercholesterolemic subjects were prescribed with a daily consumption of 85 grams of oats; which are rich in phenolic compounds known to increase the fecal excretion of cholesterol. Over a course of 45 days, this dietary intervention resulted in an increase of the fecal concentration of *A. muciniphila* and a significant reduction in serum levels of total cholesterol and LDL (23).

Additionally, a separate study in 2020 (3), showed that a traditional Mediterranean diet reduced insulin resistance in individuals and improved their serum glucose levels. A possible correlation exists with the potential involvement of dietary fiber and butyric acid and their effects on improving the gut metabolism. Notably, the improvement of glucose metabolism coincided with an elevation in the concentration of *A. muciniphila* in the studied population.

Another clinical intervention was conducted by Tagliamonte et al. (21) in which an overweight population was administered a Mediterranean diet, increasing their consumption of fruits, vegetables, fish and olive oil. After a four-week intervention, the fecal levels of *A. muciniphila* were increased, which can be attributed to the dietary change.

Through the implementation of a caloric deficit diet, where the daily caloric intake was reduced from 2400 kcal/day to 1680 kcal/day in men and from 2100 kcal/day to

1470 kcal/day in women, the gut microbiome of overweight participants was restored. The ingested calories were provided from nutritious food such as fruits, vegetables, fiber and local produce. Coincidentally, the dietary changes were similar to the ones on a traditional Mediterranean diet. Over the course of six months, this dietary intervention resulted in a significant increase in the abundance of *A. muciniphila* in fecal material (24).

Obesity and its effect on A. muciniphila concentration

Although the etiology of obesity is complex and multifactorial, it is well known its main cause is the consumption of excessive energy through dietary intake, disproportionate to the individual's energy loss rate via metabolic and physical activity (25).

High-fat diets, consisting of excessive intake of fats and refined carbohydrates, are not only linked to obesity and metabolic diseases, but also to the gut microbiota since they have been associated with dysbiosis and its reduction of intestinal bacterial diversity, disruptions in intestinal membrane integrity and permeability, increased LPS transfer to the bloodstream and systemic inflammation (26).

An example of high-fat diet-induced dysbiosis is the generation of the "obese microbiome", which has been typified as a reduced percentage of the *Bacteroidetes* phylum and an equivalent increase in the percentage of the *Firmicutes* phylum in the gut microbiota (27); this altered ratio of *Bacteroidetes:Firmicutes* was present at baseline in 12 obese people who went through two types of low-calorie diets interventions, after which the ratio was restored and the increased abundance of *Bacteroidetes* was correlated with the percentage of body weight loss (28).

Another type of obese microbiome was the decrease in *Bifidobacterium spp.* abundance and the increase in Clostridia XIV and Enterobacteriales in mice fed with a high-fat diet (9); the reduction in bifidobacteria alters the intestinal membrane integrity because that type of bacteria maintains and improves intestinal barrier function as well as prevents the passage of toxins to the bloodstream (26). In addition, studies in humans have associated higher intake of monounsaturated fatty acids with lower levels of *Bifidobacteria spp* and only slightly higher levels of *Bacteroides spp.;* and *in vitro* studies have found that high levels of polyunsaturated fatty acids, like linolenic, arachidonic and α-linolenic acids at up to 10-40 µg/ml^{-1}, can inhibit both mucus adhesion and growth of all tested *Lactobacillus* strains (29-30); hence, demonstrating how high-fat diets diminish the concentration of beneficial bacteria.

More studies in human subjects have proven this high-fat diet induced dysbiosis by demonstrating that the *Bacteroidetes:Firmicutes* ratio alongside LPS levels, of up to 7.8 EU/ml, are elevated in patients with obesity. Interestingly, other studies have shown healthy human subjects that are exposed to a 5-day high-fat diet intervention have an enhanced abundance in detrimental bacteria such as *Firmicutes* and *Proteobacteria* [31]. Thus showing how a high-fat proinflammatory environment has an effect in the gut microbiota.

All these examples of high-fat diet-induced dysbiosis can be attributed to *A. muciniphila* since mucin-degrading bacteria are highly influenced by high-fat diets (26). The latter can be proven by data of several studies that increased the abundance of *A. muciniphila* through dietary interventions but whose participants, at baseline, had a very low percentage of *A. muciniphila* in stool samples due to their obesity phenotype and their lifestyle habits of consuming a high-fat diet, (3,6-7).

The theorized mechanisms by which chronic consumption of high-fat diets induces dysbiosis, thus decreasing the concentration of beneficial bacteria in the gut like *A.*

muciniphila, are thought to be two (31). The first one consists in alterations in lipid metabolism-related genes that cause an overflow of fat from the diet to the distal small intestine, the higher concentrations of fatty acids in this location of the intestine are hypothesized to have an antimicrobial effect, reducing the bacterial diversity and altering the *Bacteroidetes:Firmicutes* ratio, characteristic of the obese microbiome (32-33). The second one is related to changes in the host bile composition since high-fat diets increase the production of bile acids, which raises the number of species capable of metabolizing them and lowers the abundance of other bacterial species due to the bile acids' antimicrobial activity (34).

Now that a high-fat diet induced dysbiosis environment is established, a cascade of inflammatory pathways is unraveled which leads to adipose tissue dysfunction, ultimately promoting the obese phenotype. What is proposed is that Toll-like receptors (TLRs), specially TLR4, are constantly activated in dysbiosis by a high amount of LPS-producing Gram Negative bacteria, causing the ongoing activation of nuclear factor kappa β (NF-κB)-dependent transcription factors for proinflammatory cytokines such as IL-1β, IL-18, IL-6, IL-33, tumor necrosis factor α (TNFα) and interferon-gamma (IFNγ), all of which contribute to colonic inflammation (31).

Moreover, the persistent activation of these pathways maintain a chronic inflammatory state that damages the intestinal epithelial barrier. This integrity is jeopardized by a decrease in tight-junction proteins like zonulin, occludin, and claudin-1/5 which allow LPS, cytokines and bacteria to get into the bloodstream, causing endotoxemia, and translocate to peripheral targets such as the adipose tissue. This exact translocation is what impairs adipose tissue, hence perpetuating the obese phenotype (31). However, further research is needed to fully understand the exact pathophysiological mechanisms by which high-fat diets, thus an obesity phenotype, induce gut dysbiosis in humans and lowers the abundance of *A. muciniphila* specifically.

Table 1. Type of interventions in obesity individual and effects in *Akkermansia muciniphila* levels

Author	Study type	Country	Year	Relevant finding
Dao, et al (6)	Non randomized trial	France	2016	There was a decrease in *A.muciniphila* abundance in a high genes group related to the bacteria after the nutrition intervention period, but it remained consistently and significantly higher then the low genes group.
Roshanravan, et al (35)	Randomized double-blind trial	Iran	2017	A group of 60 patients with obesity and diabetes were divided in 4 groups of supplements intervention: sodium butyrate, inuline, both and placebo. After 45 days, both supplements groups have an increase in *Akkermansia muciniphila* group.
Deppomier, et al (7)	Randomized, double-blind	United States	2019	The abundance of *A.muciniphila* was similar between 3 groups of patients at baseline. Whereas the supplementation significantly increased by 1.7 to 2.6 Log the quantity of *A.muciniphila* recovered in the feces of Pasteurized *A.muciniphila*

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				and Alive *A.muciniphila* groups, and not in placebo.
Payahoo, et al (36)	Randomized double blind trial	Iran	2019	From 60 obese patients, the trial proved that the group that were receiving Oleoylethanolamide supplementation for 8 weeks have an increase of *Akkermansia muciniphila* abundance compared to the placebo group, through a quantitative real-time PCR.
Walker, et al (22)	Randomized, placebo controlled clinical trial	United States	2019	*Akkermansia muciniphila* abundance increased in 11 caucasian subjects out of 28 subjects in total with metabolic syndrome after a 35 day administration of 1 g orally of polyphenol resveratrol twice daily. Insulin sensitivity and glucose homeostasis also improved in these subjects.
Guevara-Cruz, et al (37)	Randomized double-blind trial	Mexico	2020	Interestingly, five genera, including Paraprevotella, Suterella, Anaeroplasma, Akkermansia and Oscillospira, were increased in the Gestein intervention groups, representing 41% of all genera of the gut in contrast to the 7%–10% represented in the placebo group.
Tagliamonte, et al (21)	Randomized and controlled trial	Italy	2021	A dietary intervention consisting of a switch from a Western diet to a tailored Mediterranean diet in 82 subjects with overweight and obesity increased the fecal abundance of *Akkermansia muciniphila*.
Vitale, et al (3)	Randomized, controlled, parallel group designed study	Italy	2021	Improved postprandial glucose metabolism and insulin sensitivity was reported in 16 subjects with overweight and obesity after following a 8 week isoenergetic Mediterranean diet intervention. These changes were accompanied by an increase in the abundance of *A. muciniphila*.
Jie et al (24)	24-week dietary intervention cohort	China	2021	83 participants (29 with overweight, 43 with obesity and 11 with normal weight) underwent a 6-month dieting program in which fecal microbiome data was analyzed. *A. muciniphila* abundance was reported to be increased after the dietary intervention.

Discussion

The proinflammatory state of obesity and the concentration of *A. muciniphila* are closely intertwined. However, as the exact mechanism of action remains unclear, it is uncertain whether the decline of *A. muciniphila* is a predisposing factor for increased inflammation or if the inflammatory state of the body leads to a reduction of the bacteria. Nevertheless, it is well-established that dysbiosis significantly influences inflammation within the microbiome (29-30). Further colonization has gathered attention from the pediatric care after knowing human milk capacity to transfer bacteria from the mothers gut, that initiates new approaches that symbiosis and the microbiome could play an important role in proinflammatory conditions since the transmission of mother's own microbiome to its child (38).

Regardless of this uncertainty, the increment of *A. muciniphila,* whether through direct supplementation, prebiotic consumption, or dietary changes, confers beneficial effects to overweight individuals. Increased levels of *A. muciniphila* in the gut microbiota have been associated with reduced cardiovascular risk, improved insulin sensitivity, lower cholesterol levels, reducing proinflammatory endotoxins (TLR and TLR4) and cytokines (IL-6, TNF, C-reactive protein), improved barrier function decreasing its permeability, reduce anthropometric measurements such as waist-to-hip ratio and subcutaneous adipocyte diameter, weight loss, and an overall healthier metabolic status (25). With all of these revolutionary studies that should be done could finally understand completely the exact mechanisms that *A. muciniphila* impacts in all these metabolic factors including if there's a direct correlation in atherosclerosis prevalence besides the improvement in cardiovascular health and health parameters.

All these benefits have been documented in studies on obesity, where patients initially exhibited low levels of *A. muciniphila* in their stool samples, reflecting the dysbiosis commonly observed in obese individuals. The chronic consumption of high-fat diets induces dysbiosis through antimicrobial effects, such as fatty acid deposition in the distal small intestine or increased bile acid production, promoting the growth of pathogenic bacterial strains and selectively inhibiting beneficial bacteria. This leads to the formation of proinflammatory microbiota frequently observed in obese patients. It is possible that patients with obesity have a lower baseline concentration of this bacterium due to their obese phenotype, although further studies are needed to establish a significant correlation.

However, by correcting this dysbiosis through dietary interventions, individuals can reach the associated benefits, including improved cellulose digestion, reduced inflammation, and enhanced synthesis of vitamins such as Vitamin K and B12.

It is important to note that most of these health benefits in patients with obesity have been achieved through dietary interventions involving modifications such as a polyphenol-rich diet, hypocaloric diets, Mediterranean diet, and fiber-rich diets, rather than direct supplementation with the bacteria. We believe that dietary modifications have the potential to serve as a remarkable therapeutic approach for treating obesity by increasing the abundance of beneficial bacteria like *A. muciniphila*, as dietary changes may be more accessible to patients rather than direct supplementation with *A. muciniphila*, whether in live or pasteurized form. We also believe that dietary modification could be strategic for changing genetic transmission of obesity By implementing a diet based on

the approaches that increase *A. muciniphila,* breast feeding ,with enough presence of the bacteria in mother´s microbiome, could make new generations to stop transmitting the complete genetic sequence of obesity DNA information, through healthy epigenetic factors of a healthy lifestyle.

Conclusions

In conclusion, the relationship between the proinflammatory state of obesity and the concentration of *Akkermansia muciniphila* (*A. muciniphila*) in the gut microbiota is complex and not fully understood. *A. muciniphila* is a strict anaerobic gram negative bacteria that possess an outstanding metabolic versatility, which provides the human being a symbiotic relationship that offers intestinal barrier integrity protection and anti-inflammatory based benefits that aids in several metabolic processes and even immune responses. Additionally, since it is a non-pathogenic bacterium devoid of virulence factors it lacks a significant host interaction pathway that could lead to disease.

Quite opposite, disturbances in its percentage within the gut microbiome have been linked to pathological conditions, and the abundance of *Akkermansia muciniphila* has an inverse correlation with the augmentation of inflammation markers and an "obese" microbiome. Despite the exact mechanisms for this are not completely understood, new hypotheses have arisen, and one of them suggests that *A. muciniphila* lowers obesity biomarkers by having a positive effect on two endocannabinoidome lipids and synthesizing the Amuc_1100 protein which reduces inflammatory cell populations within the colon.

Adjustments on dietary intake of nutrients that increase the ampleness of *A. muciniphila* in the gut microbiome will create a favorable environment for the augmentation of cellulose digestion; thus reducing the risk of metabolic diseases and its further complications.

It is worth noting that most of the health benefits observed in obese patients have been achieved through dietary interventions rather than direct supplementation with *A. muciniphila*. Dietary modifications offer a more accessible therapeutic approach for treating obesity as they can be easily adopted by patients. Further research is needed to establish a significant correlation between the baseline concentration of *A. muciniphila* and obesity. Nonetheless, dietary modifications hold great potential for increasing the abundance of beneficial bacteria like *A. muciniphila* and can serve as an effective strategy in the treatment of obesity.

Conflict of Interest
There are no conflicts of interest

References

1. Guyton AC, John Edward Hall. Textbook of Medical Physiology. Saunders; 2006.
2. Servin AL. Antagonistic Activities of Lactobacilli and Bifidobacteria against Microbial Pathogens. FEMS Microbiology Reviews. 2004 Oct;28(4):405–40.
3. Vitale M, Giacco R, Laiola M, Della Pepa G, Luongo D, Mangione A, et al. Acute and Chronic Improvement in Postprandial Glucose Metabolism by a Diet Resembling the Traditional Mediterranean Dietary pattern: Can SCFAs Play a role? Clinical Nutrition. 2021 Feb;40(2):428–37.

4. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between Akkermansia Muciniphila and Intestinal Epithelium Controls diet-induced Obesity. Proceedings of the National Academy of Sciences. 2013 May 13;110(22):9066–71.

5. Shen J, Tong X, Sud N, Khound R, Song Y, Maldonado-Gomez MX, et al. Low-Density Lipoprotein Receptor Signaling Mediates the Triglyceride-Lowering Action of Akkermansia Muciniphila in Genetic-Induced Hyperlipidemia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016 Jul;36(7):1448–56.

6. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al. Akkermansia Muciniphila and Improved Metabolic Health during a Dietary Intervention in obesity: Relationship with Gut Microbiome Richness and Ecology. Gut. 2015 Jun 22;65(3):426–36.

7. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with Akkermansia Muciniphila in Overweight and Obese Human volunteers: a proof-of-concept Exploratory Study. Nature Medicine. 2019 Jul;25(7):1096–103.

8. Roshanravan N, Bastani S, Tutunchi H, Kafil B, Nikpayam O, Mesri Alamdari N, et al. A Comprehensive Systematic Review of the Effectiveness of Akkermansia muciniphila, a Member of the Gut microbiome, for the Management of Obesity and Associated Metabolic Disorders. Archives of Physiology and Biochemistry. 2021 Jan 15;129(3):1–11.

9. Mujico JR, Baccan GC, Gheorghe A, Díaz LE, Marcos A. Changes in Gut Microbiota Due to Supplemented Fatty Acids in diet-induced Obese Mice. The British Journal of Nutrition [Internet]. 2013 Aug 1 [cited 2023 Jun 6];110(4):711–20. Available from: https://pubmed.ncbi.nlm.nih.gov/23302605/

10. Abuqwider JN, Mauriello G, Altamimi M. Akkermansia muciniphila, a New Generation of Beneficial Microbiota in Modulating Obesity: a Systematic Review. Microorganisms. 2021 May 20;9(5):1098.

11. Medina-Larqué AS, Rodríguez-Daza MC, Roquim M, Dudonné S, Pilon G, Levy É, et al. Cranberry Polyphenols and Agave Agavins Impact Gut Immune Response and Microbiota Composition While Improving Gut Barrier function, inflammation, and Glucose Metabolism in Mice Fed an Obesogenic Diet. Frontiers in Immunology. 2022 Aug 16;13.

12. Zhang T, Li Q, Cheng L, Buch H, Zhang F. Akkermansia Muciniphila Is a Promising Probiotic. Microbial Biotechnology. 2019 Apr 21;12(6):1109–25.

13. Derrien M, Belzer C, de Vos WM. Akkermansia Muciniphila and Its Role in Regulating Host Functions. Microbial Pathogenesis. 2017 May;106:171–81.

14. Depommier C, Vitale RM, Iannotti FA, Silvestri C, Flamand N, Druart C, et al. Beneficial Effects of Akkermansia Muciniphila Are Not Associated with Major Changes in the Circulating Endocannabinoidome but Linked to Higher Mono-Palmitoyl-Glycerol Levels as New PPARα Agonists. Cells. 2021 Jan 19;10(1):185.

15. Bian X, Wu W, Yang L, Lv L, Wang Q, Li Y, et al. Administration of Akkermansia Muciniphila Ameliorates Dextran Sulfate Sodium-Induced Ulcerative Colitis in Mice. Frontiers in Microbiology. 2019 Oct 1;10.

16. Qian K, Chen S, Wang J, Sheng K, Wang Y, Zhang M. A β-N-acetylhexosaminidase Amuc_2109 from Akkermansia Muciniphila Protects against Dextran Sulfate Sodium-induced Colitis in Mice by Enhancing Intestinal Barrier and Modulating Gut Microbiota. Food & Function. 2022;4.

17. Rodrigues VF, Elias-Oliveira J, Pereira ÍS, Pereira JA, Barbosa SC, Machado MSG, et al. Akkermansia Muciniphila and Gut Immune System: a Good Friendship That Attenuates Inflammatory Bowel Disease, Obesity, and Diabetes. Frontiers in Immunology [Internet]. 2022 Jul 7;13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9300896/pdf/fimmu-13-934695.pdf

18. Ashrafian F, Shahriary A, Behrouzi A, Moradi HR, Keshavarz Azizi Raftar S, Lari A, et al. Akkermansia muciniphila-Derived Extracellular Vesicles as a Mucosal Delivery Vector for Amelioration of Obesity in Mice. Frontiers in Microbiology. 2019 Oct 1;10.

19. Chelakkot C, Choi Y, Kim DK, Park HT, Ghim J, Kwon Y, et al. Akkermansia muciniphila-derived Extracellular Vesicles Influence Gut Permeability through the Regulation of Tight Junctions. Experimental & Molecular Medicine. 2018 Feb;50(2):e450–0.

20. Druart C, Plovier H, Van Hul M, Brient A, Phipps KR, Vos WM, et al. Toxicological Safety Evaluation of Pasteurized Akkermansia Muciniphila. Journal of Applied Toxicology. 2020 Jul 28;41(2):276–90.

21. Tagliamonte S, Laiola M, Ferracane R, Vitale M, Gallo MA, Meslier V, et al. Mediterranean Diet Consumption Affects the Endocannabinoid System in Overweight and Obese subjects: Possible Links with Gut microbiome, Insulin Resistance and Inflammation. European Journal of Nutrition. 2021 Mar 24;60.

22. Walker JM, Eckardt P, Aleman JO, Correa J, Liang Y, Tadasu Iizumi, et al. The effects of trans-resveratrol on insulin resistance, inflammation, and microbiota in men with the metabolic syndrome: A pilot randomized, placebo-controlled clinical trial. PubMed. 2019 Jan 10;4(2):122–35.

23. Xu D, Feng M, Chu Y, Wang S, Shete V, Tuohy KM, et al. The Prebiotic Effects of Oats on Blood Lipids, Gut Microbiota, and Short-Chain Fatty Acids in Mildly Hypercholesterolemic Subjects Compared with Rice: a Randomized, Controlled Trial. Frontiers in Immunology [Internet]. 2021 Dec 9;12:787797. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8697019/

24. Jie Z, Yu X, Liu Y, Sun L, Chen P, Ding Q, et al. The Baseline Gut Microbiota Directs Dieting-Induced Weight Loss Trajectories. Gastroenterology [Internet]. 2021 May 1 [cited 2022 Oct 14];160(6):2029-2042.e16. Available from: https://www.gastrojournal.org/article/S0016-5085(21)00096-2/fulltext

25. Wright SM, Aronne LJ. Causes of Obesity. Abdominal Radiology [Internet]. 2012 Mar 18;37(5):730–2. Available from: https://link.springer.com/article/10.1007/s00261-012-9862-x

26. Netto Candido TL, Alfenas R de CG, Bressan J. Dysbiosis and Metabolic Endotoxemia Induced by high-fat Diet. Nutrición Hospitalaria. 2018 Oct 17;35(6).

27. Sun L, Ma L, Ma Y, Zhang F, Zhao C, Nie Y. Insights into the Role of Gut Microbiota in obesity: pathogenesis, mechanisms, and Therapeutic Perspectives. Protein & Cell [Internet]. 2018 May [cited 2019 Nov 4];9(5):397–403. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5960470/

28. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Human gut microbes associated with obesity. Nature [Internet]. 2006 Dec;444(7122):1022–3. Available from: https://www.nature.com/articles/4441022a

29. Bibbò S, Ianiro G, Giorgio V, Scaldaferri F, Masucci L, Gasbarrini A, et al. The Role of Diet on Gut Microbiota Composition. European Review for Medical and Pharmacological Sciences [Internet]. 2016 Nov 1;20(22):4742–9. Available from: http://pubmed.ncbi.nlm.nih.gov/27906427

30. KankaanpÃ¤Ã¤ PE, Salminen SJ, Isolauri E, Lee YK. The Influence of Polyunsaturated Fatty Acids on Probiotic Growth and Adhesion. FEMS Microbiology Letters [Internet]. 2001 Jan;194(2):149–53. Available from: https://academic.oup.com/femsle/article/194/2/149/489490

31. Rosendo-Silva D, Viana S, Carvalho E, Reis F, Paulo Matafome. Are Gut dysbiosis, Barrier disruption, and Endotoxemia Related to Adipose Tissue Dysfunction in Metabolic disorders? Overview of the Mechanisms Involved. Internal and Emergency Medicine. 2023 Apr 4;18.

32. Patterson E, O' Doherty RM, Murphy EF, Wall R, O' Sullivan O, Nilaweera K, et al. Impact of Dietary Fatty Acids on Metabolic Activity and Host Intestinal Microbiota Composition in C57BL/6J Mice. British Journal of Nutrition. 2014 Feb 20;111(11):1905–17.

33. de Wit N, Derrien M, Bosch-Vermeulen H, Oosterink E, Keshtkar S, Duval C, et al. Saturated Fat Stimulates Obesity and Hepatic Steatosis and Affects Gut Microbiota Composition by an Enhanced Overflow of Dietary Fat to the Distal Intestine. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2012 Sep 1;303(5):G589–99.

34. Tidjani Alou M, Lagier JC, Raoult D. Diet Influence on the Gut Microbiota and Dysbiosis Related to Nutritional Disorders. Human Microbiome Journal. 2016 Sep;1:3–11.

35. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Naimeh Mesri Alamdari, et al. The Effects of Sodium Butyrate and Inulin Supplementation on Angiotensin Signaling Pathway via Promotion of Akkermansia Muciniphila Abundance in Type 2 diabetes; a randomized, double-blind, placebo-controlled Trial. Journal of Cardiovascular and Thoracic Research. 2017 Nov 25;9(4):183–90.

36. Payahoo L, Khajebishak Y, Alivand MR, Soleimanzade H, Alipour S, Barzegari A, et al. Investigation the Effect of Oleoylethanolamide Supplementation on the Abundance of Akkermansia Muciniphila Bacterium and the Dietary Intakes in People with obesity: a Randomized Clinical Trial. Appetite. 2019 Oct;141:104301.

37. Guevara-Cruz M, Godinez-Salas ET, Mónica Sánchez-Tapia, Torres-Villalobos G, Pichardo-Ontiveros E, Rocío Guizar-Heredia, et al. Genistein Stimulates Insulin Sensitivity through Gut Microbiota Reshaping and Skeletal Muscle AMPK Activation in Obese Subjects. Open Diabetes Res Care. 2020 Mar 1;8(1):e000948–8.

38. Łagowska K, Drzymała-Czyż S. A Low Glycemic Index, Energy-restricted Diet but Not Lactobacillus Rhamnosus Supplementation Changes Fecal short-chain Fatty Acid and Serum Lipid Concentrations in Women with Overweight or Obesity and Polycystic Ovary Syndrome. European Review for Medical and Pharmacological Sciences [Internet]. 2022 Feb 1 [cited 2023 Apr 30];26(3):917–26. Available from: https://pubmed.ncbi.nlm.nih.gov/35179758/

39. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining Trained Immunity and Its Role in Health and Disease. Nature Reviews Immunology. 2020 Mar 4;20(6):375–88.

40. Bäck M, Yurdagul A, Tabas I, Öörni K, Kovanen PT. Inflammation and Its Resolution in atherosclerosis: Mediators and Therapeutic Opportunities. Nature Reviews Cardiology [Internet]. 2019 Mar 7;16(7). Available from: https://www.nature.com/articles/s41569-019-0169-2

41. Guevara-Cruz M, Godinez-Salas ET, Mónica Sánchez-Tapia, Torres-Villalobos G, Pichardo-Ontiveros E, Rocío Guizar-Heredia, et al. Genistein Stimulates Insulin Sensitivity through Gut Microbiota Reshaping and Skeletal Muscle AMPK Activation in Obese Subjects. Open Diabetes Res Care. 2020 Mar 1;8(1):e000948–8.

42. Pogue A, Jaber I, Zhao Y, Lukiw W. Systemic Inflammation in C57BL/6J Mice Receiving Dietary Aluminum Sulfate; Up-Regulation of the Pro-Inflammatory Cytokines IL-6 and TNFα, C-Reactive Protein (CRP) and miRNA-146a in Blood Serum. Journal of Alzheimer's Disease & Parkinsonism. 2017;07(06).

43. Ouyang J, Lin J, Isnard S, Fombuena B, Peng X, Marette A, et al. The Bacterium Akkermansia muciniphila: a Sentinel for Gut Permeability and Its Relevance to HIV-Related Inflammation. Frontiers in Immunology. 2020 Apr 9;11.

44. Rodríguez-Daza MC, de Vos WM. Polyphenols as Drivers of a Homeostatic Gut Microecology and Immuno-Metabolic Traits of Akkermansia muciniphila: from Mouse to Man. International Journal of Molecular Sciences. 2022 Dec 20;24(1):45.

45. Cao MZ, Wei CH, Wen MC, Song Y, Srivastava K, Yang N, et al. Clinical Efficacy of Weight Loss Herbal Intervention Therapy and Lifestyle Modifications on Obesity and Its Association with Distinct Gut microbiome: a Randomized double-blind Phase 2 Study. Frontiers in Endocrinology. 2023 Mar 22;14