REVIEW ARTICLE

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Review of Literature on *Akkermansia muciniphila* and its Possible Role in the Etiopathogenesis and Therapy of Type 2 Diabetes Mellitus

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Abstract

Akkermansia muciniphila is a promising gut microbiota for the treatment of type 2 diabetes mellitus (T2DM). *A. muciniphila* stimulates intestinal wall integrity, is an anti-inflammatory agent, and reduces endoplasmic reticulum stress, lipogenesis and gluconeogenesis. These properties make *A. muciniphila* a potential treatment option for T2DM by reducing insulin resistance and increasing insulin sensitivity and glucose tolerance in different tissues. This article explores the possible role of *A. muciniphila* in T2DM management, along with the various methods known to modulate *A. muciniphila*.

Key words: Akkermansia muciniphila, ER stress, gut microbiota, insulin resistance, probiotic, type 2 diabetes mellitus

INTRODUCTION

The complex etiopathogenesis of type 2 diabetes mellitus (T2DM) includes dysbiosis or the imbalance of gut microbiota composition as a contributory factor.[1] Dysbiosis may induce systemic low-grade inflammation which leads to insulin resistance.[2] An important gut microbiota in T2DM is *Akkermansia muciniphila* (*A. muciniphila),* a butyrate-producing microbiota which stimulates the secretion of incretin hormones, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2) and peptide YY (PYY). Incretins stimulate insulin secretion from pancreatic beta cells.[3] Furthermore, *A. muciniphila* improves intestinal wall integrity and reduces endoplasmic reticulum (ER) stress, lipogenesis and gluconeogenesis.[4]

Management of T2DM currently focuses on controlling the symptoms and preventing complications through lifestyle intervention and administration of antidiabetic drugs. The modulation of *A. muciniphila* is a simple and potentially disease-modifying treatment of T2DM. This literature review will discuss the role of *A. muciniphila* in the treatment of T2DM to date and its prospects in the future.

METHODOLOGY

We searched PubMed, Cochrane Database, Science Direct, and Google Scholar for relevant studies about *A. muciniphila* and T2DM that were published in English between the 2nd up to the 23rd of April 2020. The keywords included "*Akkermansia muciniphila*" AND "type 2 diabetes mellitus" OR "obese" OR "insulin resistance." Titles and abstracts were screened to avoid duplication, and reviews of the complete manuscripts were done to determine the appropriateness of the studies to be included. Additionally, the reference lists of the selected articles were reviewed to identify other relevant articles. Selected studies have met the inclusion and exclusion criteria of the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework. We included studies involving subjects with T2DM or metabolic syndrome who received intervention to increase *A. muciniphila* or improve metabolic parameters in comparison to a control group. The outcomes considered were the measured levels of *A. muciniphila* and/or improvement in other metabolic parameters. We excluded non-English-language studies, unavailable full texts, case reports and letters for this review article. Ultimately, 42 studies were included as references in the synthesis of this review article, and 9 were used for the methods of modulation of *A. muciniphila*.

Gut microbiota and type 2 diabetes mellitus

T2DM is a multifactorial metabolic disease characterized by hyperglycemia. The factors that cause hyperglycemia are the egregious eleven, namely: pancreatic beta-cells failure to produce insulin; increased pancreatic alpha cell glucagon secretion; increased liver gluconeogenesis; impaired insulin action in skeletal muscles; increased lipolysis and free fatty acids from adipose tissue; intestinal GLP-1 deficiency; decreased gastric production of amylin; increased kidney reabsorption of glucose through sodium-glucose contransporters-2 (SGLT-2); low-grade systemic inflammation; neural stimulation to increase appetite due

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to high levels of insulin and changes in the composition of the gut microbiota.[2]

Alterations of the gut microbiota induce inflammation and play an important role in the complex pathogenesis of T2DM. Gut microbiota promote fermentation of undigested carbohydrates, stimulate insulin secretion, inhibit gluconeogenesis, increase insulin sensitivity and have anti-inflammatory effects. Gut microbiota convert undigested carbohydrates into short-chain fatty acids (SCFA),[5] metabolites which stimulate intestinal L cells to secrete incretin hormones (GLP-1, GLP-2 and PYY) that trigger pancreatic beta-cells to release insulin.[6] Dysbiosis decreases intestinal wall integrity and induces systemic low-grade inflammation. This metabolic endotoxemia state is precipitated by the dependent attachment of lipopolysaccharide (LPS) to the CD14 / toll-like receptor (TLR) 4 complex on the surface of intestinal cells leading to inflammation and subsequent insulin resistance.[7-9]

Akkermansia muciniphila

A. muciniphila belongs to the *Verrucomicrobia* (phylum), *Verrucomicrobiae* (class), *Verrucomicrobiales* (order), *Verrucomicrobiacaea* (family), dan *Akkermansia* (genus) and is a microbiome that is abundant in the human intestine. It makes up 3% of the entire gut microbiota colony and is a butyrate-producing bacteria.[10] Derrien et al. discovered *A. muciniphila* in 2004 and it has since become a popular research field because of its potential as a probiotic.[11] It ferments mucin as a source of carbon, energy, and nitrogen, then releases sulfate after the mucin fermentation is complete.

A. muciniphila colonizes the mucosal lining of the intestine,[4] and various studies have shown that the amount of *A. muciniphila* in the intestines of healthy people is significantly greater than those who have diabetes and obesity.[12,13] Another study by Schneeberger et al. in 2015 also found an inversely proportional relationship between the number of *A. muciniphila* and body weight, inflammation and the metabolic syndrome.[14]

The role of *Akkermansia muciniphila* in type 2 diabetes mellitus

A. muciniphila has a role in the pathogenesis of T2DM through several mechanisms (Figure 1). An increase in the number of bacterial colonies improves the integrity of the intestinal wall by colonizing the mucus layer of the cell surface and protects the cells from LPS, which attaches itself independently. The amount of *A. muciniphila* in the intestine also depends on the amount mucin – their energy source – present. In addition, the administration of *A. muciniphila* also enhances the expression of regenerating islet-derived protein (Reg3γ), a peptide that stimulates aggregation between microbiota in the intestinal epithelium.[15]

A. muciniphila improves insulin sensitivity and glucose tolerance through its anti-inflammatory mechanisms. The inflammatory process begins with the entry of LPS into the intestinal cell mucosa as an endotoxin, which then attaches to the lipopolysaccharide binding protein (LBP) which initiates activation of nuclear factor-KB (NF-KB) and Jun N-terminal Kinase (JNK).[16] *A. muciniphila* can reduce the amount of phosphor-JNK significantly and increases the NF-KB inhibitor protein and IKBA protein levels in the liver, indicating that the inactivation of the NFKB and JNK pathways results in an anti-inflammatory reaction. This is supported by an increase in the concentration of both α-tocopherol (an essential antioxidant and anti-inflammatory factor),[17] and β-sitosterol, which maintain

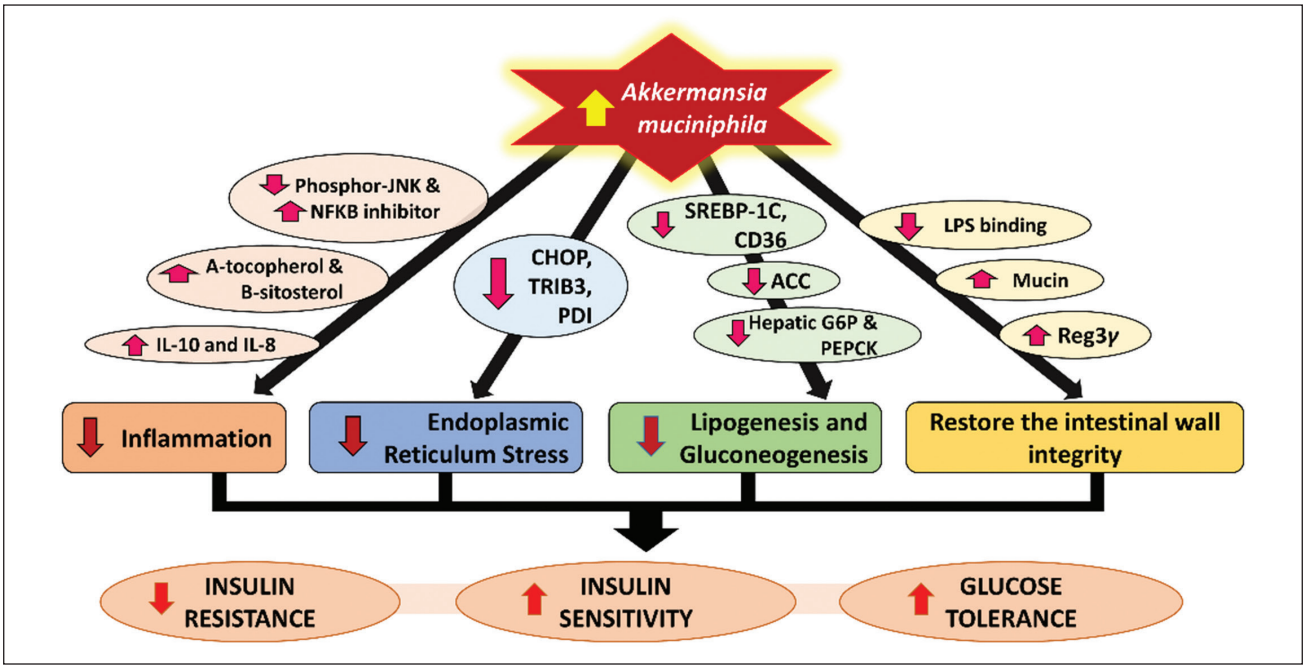

Figure 1. The role of *Akkermansia muciniphila* in type 2 diabetes mellitus.

the immune system and provide anti-inflammatory activity in the intestinal endothelial cells.[18] *A. muciniphila* also induces the release of anti-inflammatory cytokines, namely IL-10 and IL-8.[19]

The improvement in glucose tolerance is due to decreased lipotoxicity and ER stress. *A. muciniphila* reduces unfolded protein levels inside the cell – a marker of ER stress – such as immunoglobulin heavy chain-binding protein / glucose-regulated protein 78 (BiP / GRP78) and PKR-like ER kinase (PERK) in the liver and skeletal muscle. In addition, *A. muciniphila* decreases genes contributing to the ER stress process, namely, a decrease in the concentration of mRNA C / *EBP homologous protein* (CHOP) and *tribbles homolog 3* (TRB3) in the large intestine, and a decrease in mRNA of *protein disulfide isomerase* (PDI) in the jejunum. These genes activate the unfolded protein response, which triggers ER stress.[20] This mechanism suggests that *A. muciniphila* can reduce ER stress and interfere with the genetic process.

A. muciniphila also plays a role in the process of lipogenesis and gluconeogenesis. *A. muciniphila* supplementation significantly reduces the expression of genes that participate in lipogenesis, namely *sterol regulatory element-binding proteins* (SREBP1c) and *fatty acid translocase* (CD36) in the liver and muscles. A 2015 *in vivo* study by Schneeberger et al., found a low amount of *acetyl-CoA carboxylase* (ACCase) in muscle after *A. muciniphila* supplementation.[14] ACCase is an enzyme needed to form *malonyl-CoA* from acetyl-CoA as a substrate for fatty acid biosynthesis. The decrease in the amount of ACCase indicates that *A. muciniphila* decreases fat deposition in hepatic tissue and muscle, thereby increasing insulin sensitivity.[8]

In gluconeogenesis, *A. muciniphila* supplementation is known to deplete visceral fat mass and increase glucose tolerance based on an intraperitoneal glucose tolerance test (IPGTT). Its administration induces a rise in phosphorus AKT Ser473 in the liver and muscles a marker of increased insulin sensitivity in these tissues. *A. muciniphila* also depresses the expression of gluconeogenic enzymes hepatic glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK). Normally, these enzymes are suppressed by insulin. A decrease in their levels indicates improved hepatic insulin sensitivity.[21]

Current insights on *Akkermansia muciniphila* modulation as a therapeutic innovation for type 2 diabetes mellitus

The modulation of *A. muciniphila* can be done through several methods such as direct administration as a probiotic, administration of prebiotics and by other interventions like administration of metformin and through bariatric surgery (Table 1).

Direct administration of probiotic *Akkermansia muciniphila*

A. muciniphila can be administered directly but the dose and viability of the bacteria require further investigation. The effective dose of *A. muciniphila* in humans is unknown,

Table 1. Modulation of intestinal *Akkermansia muciniphila*

Author (year)	Intervention	Subjects	Findings	Ref
In vitro				
Marcial-Coba et al. (2019)	Microencapsulation in xanthan and gellan gum matrix. Stored aerobically or anaerobically for 1 month at 4 °C or 25 °C.	*A. muciniphila* DSM22959 and *Lactobacillus plantarum subsp. plantarum* ATCC14917 as the comparator	Cryoprotectant solutions improved the survival of both strains (survival rate 64–76%; p < 0.001). Survivability of *A. muciniphila* was significantly better when stored anaerobically at 4 °C.	22
In vivo				
Everard et al. (2011)	Prebiotic administration; oligofructose (0.3 g/mouse/day) for 5 weeks.	High-fat diet-induced obese mice	Increased in the abundance of *Akkermansia muciniphila* by ~100 fold.	25
Roopchand et al. (2015)	Grape polyphenols administration for 13 weeks	High-fat diet-induced obese mice	Increased in the abundance of *Akkermansia muciniphila*. (cecal sample: 6.2 ± 4.6% on control group, versus 49.1 ± 2.0% on intervention group; Fecal sample: 7.5 ± 4.7% on control group, versus 54.8 ± 2.5% on intervention group.	26
Tu et al. (2018)	Dietary black raspberry (*Rubus occidentalis*, BRB) for 7 weeks	Normal and specific-pathogen free C57BL/6 mice	*A. muciniphila* population increased by 157-fold in the intervention group compared to control group	27
Shin et al. (2014)	300 mg/kg/day of metformin treatment by oral gavage for 6 weeks	Diet-induced obese mice (C57BL/6 mice, fed either a normal-chow diet or a high-fat diet)	Metformin treatment significantly improved the glycaemic profile of HFD-fed mice and increased the number of mucin-producing goblet cells (p<0.0001)	30
Clinical				
Depommier et al. (2019)	Daily oral supplementation of 10^{10} *A. muciniphila* bacteria either live or pasteurized for three months.	Overweight/obese insulin-resistant volunteers	Pasteurized *A. muciniphila* improved insulin sensitivity (p = 0.002), reduced insulinemia (p = 0.006) and plasma total cholesterol (p = 0.02); slightly decreased body weight (p = 0.091), fat mass (p = 0.092) and hip circumference (p = 0.091) compared to placebo group	24
de la Cuesta-Zuluaga et al. (2016)	Metformin treatment	459 participants (28 with diabetes, 14 taking Metformin, and 84 participants without diabetes)	Participants with metformin-taking diabetes had higher relative abundance of *Akkermansia muciniphila* compared with those without diabetes (p = 0.003, q value = 0.01)	31
Murphy et al. (2016)	RYGB compared to SG	14 obese T2DM patients underwent laparoscopic SG (n = 7) or RYGB (n = 7)	RYGB resulted in increased *Firmicutes* and *Actinobacteria* phyla but decreased *Bacteroidetes* phyla. SG resulted in increased *Bacteroidetes* phyla.	33
Dao et al. (2019)	RYGB compared to GB	65 women with severe obesity	A significant increase in *A. muciniphila* relative abundance after RYGB, but not correlated with metabolic improvement.	37

Abbreviation: GB, gastric binding; GIT, gastrointestinal tract; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy

but the standard dose of probiotics is in the range 10^9 to 10^{11} colony-forming units (CFU).[22]

One alternative to safely and effectively deliver *A. muciniphila* to the intestine is by microencapsulation.[23] An *in vitro* study simulated the administration of microencapsulated *A. muciniphila* through the digestive tract and showed its viability was reduced 2.01 log CFU ml^{-1} under fasting conditions (pH 2) and by 0.3 log CFU ml^{-1} at post-meal conditions (pH 4) with a survival rate of 0.97% and 49.76%, respectively. The unencapsulated cells had a more significant decrease in viability at fasting and post-meal of 3.12 log CFU ml^{-1} and 1.53 log CFU ml^{-1} respectively. This implies that microencapsulation effectively protects the bacteria to reach the intestine *in vitro*.[22] Administration of probiotics after meals is also the best way to maintain bacterial viability.[22,23]

A proof-of-concept randomized-controlled exploratory study was conducted by administering live and pasteurized *A. muciniphila* to 40 overweight/obese volunteers with insulin resistance. There were no significant changes in inflammatory markers associated with hematology, liver, kidney and muscle function. However, *A. muciniphila* increased insulin sensitivity and decreased total plasma cholesterol, body weight and fat mass.[24] This first human trial indicated that both live and pasteurized *A. muciniphila* was well-tolerated, safe and improves several metabolic parameters.

Prebiotic as growth enhancing substance of intestinal *Akkermansia muciniphila*

The use of prebiotics together with the consumption of probiotics has become popular in recent years. Oligofructose, an oligosaccharide of short-chain inulin fragments, is a widely used prebiotic. In 2011, Everard et al., found that oral administration of oligofructose restored the level of *A. muciniphila* in high-fat- diet-fed (HFD) mice and those with genetic manipulation of leptin deficiency and obesity. Baseline *A. muciniphila* levels were 100 and 3300 times less than the control group, respectively.[25]

Polyphenol is another substance increasingly being used as prebiotic. It is derived from grapes and nourishes gut microbiota, stimulates growth, increases metabolic function and reduces inflammation.[26] This is seen as reductions in levels of tumor necrosis factor α (TNF-α), bacterial LPS and the absence of serum IL-6. Roopchand et al., in 2015 compared clinical differences between a group of mice given polyphenol plus soy protein isolate (SPI) and a group given SPI alone. Mice given polyphenol-SPI had a lower body weight, liver mass and liver fat, and significantly higher glucose tolerance than the SPI-diet-alone group.[26] Moreover, a 2008 study by Tu et al., evaluated the administration of black raspberries containing polyphenol and oligosaccharide in normal mice. They showed an elevation in the proportion of *A. muciniphila* by as much as 157 times compared to normal mice without the intervention.[27] Apples are another rich source of this substance, with procyanidin as the dominant polyphenol. The procyanidin macromolecules in apples may suppress pro-inflammatory factors in the intestinal mucosa, inhibit weight gain and improve the *Firmicutes*/*Bacteroidetes* ratio, including *A. muciniphila*, as a trigger factor of intestinal barrier function repair.[28]

Roopchand et al., added that the relatively low absorption of polyphenol is vital to how it fights oxygen radicals. This study also found an increase in *A. muciniphila* on HFD mice fecal concentration from 7.5% to 54.8%.[26]

The effect of metformin on *Akkermansia muciniphila* abundance in the intestine

Metformin is the most commonly prescribed drug in the management of T2DM.[29] Its accumulation in the intestine is approximately 300 times higher than in plasma, making the intestine the body's main reservoir of metformin.[23] A 2014 study by Shin et al., attempted to prove the effect of metformin on gut microbiota composition. The prevalence of *Verrucomicrobe* associated with *A. muciniphila* was significantly lower in mice given HFD than those who were on normal diet (ND). However, after metformin administration, *Verrucomicrobe* increased significantly in the HFD group, while no significant change was observed in the ND group. Metformin was also found to significantly increase goblet cells in the HFD and ND groups of mice, independent of the metabolic profile or diet. Furthermore, they found a positive correlation between the number of goblet cells and the availability of *A. muciniphila* in the intestine.[30]

A 2015 study by Forslund et al., showed that the abundance of *A. muciniphila* in the intestine of T2DM patients was similar to non-diabetic patients after metformin administration. Those who were treated with metformin also showed an increased production of propionate, a substance produced through mucin fermentation by *A. muciniphila*.[29] A recent study by De La Cuesta-Zuluaga et al., also revealed that T2DM patients treated with metformin had 3.4 times more *A. muciniphila* in their intestines than those who did not receive this therapy.[31] Metformin enhances the intestinal protective barrier which may work synergistically with *A. muciniphila* in maintaining the integrity of the mucus layer.[29] Although further investigation into other bacterial genus/species that may be involved in the metformin-induced improvement of metabolic parameters is required, these findings may suggest that an increase in *A. muciniphila* may contribute to the antidiabetic properties of metformin.

Bariatric surgery and the improvement of intestinal microbiota composition

Bariatric surgery (BS) is an effective option in the management of obese patients and their complications.[32] One interesting outcome related to BS is the improvement

in the gut microbiota population and diversity after the procedure, despite no observed difference in the parameters of glucose homeostasis. In 2017, Murphy et al., report a significant increase in general gut microbiota diversity from baseline to 3 months post-Roux-en-Y Gastric Bypass (RYGB) and even up to 1-year post-treatment.[33]

Although BS improves gut microbiota composition, the mechanisms as to how are still not fully understood. Aside from modification of the digestive tract anatomy, there are several factors that can affect post-BS intestinal microbiota including post-surgery food preferences, reduced food consumption and nutritional malabsorption.[13,34,35]

A study by Ulker et al., in 2018 has shown that a difference in post-BS diet therapy options, namely a low-fat-high-carbohydrate diet compared to a high-carbohydrate-low-glycemic index diet affects the number of specific strains of the gut microbiota.[32] The second factor that affects the post-BS intestinal microbiota are hormonal changes in leptin and ghrelin. Circulating serum leptin levels are reported to positively impact the growth of *Mucispirillum, Lactococcus* and *Lachnospiraceae*.[36] Finally, the composition of the gut microbiota is influenced by the gastrointestinal pH. The pH level in each component of the gastrointestinal tract distal to the stomach becomes more basic after surgery due to the decrease in gastric acid production from its reduced volume.[32] Alterating the pH affects microbiota level to a significant extent. A study by Murphy et al., in 2017 demonstrated a decrease in *Bacteroidetes* and an increase in *Firmicutes* and *Actinobacteria* groups due to post-BS pH changes.[33]

A post RYGB study by Dao et al., in 2019 revealed an increase in the mean relative number of *A. muciniphila* after 3 months. By 1 year-post operative follow-up, *A. muciniphila* levels increased 200-fold, although the total number was still lower than non-obese subjects. Furthermore, patients with a relatively low level of *A. muciniphila* at baseline had the greatest increase in numbers regardless of the type of BS performed.[37] Hence, an improvement in the intestinal microbiota composition is one of the positive effects after any BS procedure.

Future perspectives

A. muciniphila as a potential therapy for T2DM can be facilitated by fecal microbiota transplantion (FMT), already in use for *Clostridium difficile* infection and inflammatory bowel disease.[38,39] The complex interaction between patients and their gut microbiota should trigger further consideration regarding other factors that may influence the modulation of *A. muciniphila* and the intestines, in particular a comprehensive dietary review to maintain the homeostasis and efficiency of *A. muciniphila.* The mechanisms related to the gut microbiome and the selection between different strains require more data. Administration of probiotics has been noted to trigger disturbances in the horizontal transfer of genes between microbiota.[40] Several studies have found the occurrence of horizontal antibiotic-resistant gene transfer by lactic acid bacteria in fermented foods.[41,42] *A. muciniphila* is known to be related to increase insulin sensitivity and glucose tolerance. However, an actual reduction in the glucose parameters (Hba1c, fasting blood glucose) is still limited to be found. Thus, this gaps in knowledge should be further explored in the future researches.

CONCLUSION

Alterations of the gut microbiota is one of the patho-physiologic changes that underlies the development of T2DM. The amount of *A. muciniphila* is inversely correlated with body weight, inflammation and the metabolic syndrome, and can be a potential intervention for T2DM by improving these parameters. Increasing the levels of *A. muciniphila* can be achieved through several modulations such as functional food or probiotic intake, metformin and bariatric surgery. However, clinical studies are still sparse and further research is needed to determine its definite role and safety among patients with T2DM.

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