REVIEW PAPER

Dual-edged health benefit of *Akkermansia muciniphila*: impact on metformin and insulin resistance in type 2 diabetes – a perspective

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ABSTRACT

The gastrointestinal tract inner mucus layer, primarily composed of mucins, serves vital functions, including facilitating food movement and providing a barrier against microorganisms and toxins. *Akkermansia muciniphila* bacteria, thriving on mucins, bolster the gut barrier and outcompete pathogens. Their abundance correlates with mucin content, production of short-chain fatty acids, lowering of intestinal inflammation, and enhances tight junction proteins expression. Metformin medications, used in type 2 diabetes mellitus (T2DM), and metformin's benefits in T2DM involve modulation of the microbiome, notably increasing *Akkermansia muciniphila* and short-chain fatty acid (SCFAs) production, aiding glucose balance via gut-liver crosstalk. A relative increase of *Akkermansia muciniphila* in the gut has a beneficial effect, but its overabundance may thin the mucus layer, compromising the gut barrier function. Excessive *Akkermansia muciniphila*, possibly from prolonged metformin use, could disrupt the gut barrier and increased lipopolysaccharide challenge, fostering inflammation and potential metformin resistance. Thus, clinically, leveraging metformin-induced microbiome changes warrants caution, especially in chronic T2DM management, due to potential inflammation exacerbation via mucin breakdown, urging contextual evaluation before therapeutic decisions.

KEY WORDS: metformin, short-chain fatty acids (SCFAs), Akkermansia muciniphila.

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Introduction

In recent years, research into the interplay between gut microbiota and metabolic health has uncovered intriguing connections, with *Akkermansia muciniphila* emerging as a central player in modulating both glucose and lipid metabolism as well as maintaining intestinal barrier function. *Akkermansia muciniphila*, a mucin-degrading bacterium residing in the gastrointestinal tract, exerts pleiotropic effects on host physiology, impacting various metabolic pathways and immune responses [1, 2]. Its presence in the gut positively correlates with improved glucose tolerance and lipid profiles [3, 4]. Additionally, *Akkermansia muciniphila* promotes the synthesis of short-chain fatty acids (SCFAs), particularly propionate and butyrate, which further dampens inflammation and reinforces the intestinal barrier [5] (Fig. 1). Furthermore, the relationship between metformin, a widely used medication for type 2 diabetes mellitus (T2DM), and *Akkermansia muciniphila* in modulating gut health and metabolic outcomes is gaining attention. Metformin glucose-lowering effects are partly mediated by alterations in the gut microbiota, including the enrichment of *Akkermansia muciniphila* and subsequent production of SCFAs [6–9] (Fig. 2). However, prolonged use of metformin may have adverse effects due to an overabundance of *Akkermansia muciniphila* in the gut, compromising gut barrier function through excessive mucin degradation [10]. In this perspective, I have summarised recent findings on the roles of *Akkermansia muciniphila* in health benefits, the relationship between metformin use and *Akkermansia muciniphila* abundance, and highlighted the dangers associated with prolonged use of metformin alone or with insulin in T2DM patients. Furthermore, suggest some mitigation strategies to overcome the threats associated with prolonged use of metformin.

Akkermansia muciniphila has pleotropic roles in glucose, lipid, and bile acid metabolism

The abundance of *Akkermansia muciniphila* in the gut significantly influences the metabolism of glucose, lipids, and bile acids (BAs) in the host. Propionate and butyrate SCFAs secreted by *Akkermansia muciniphila* trigger the synthesis of the glucagon-like peptide-1 (GLP-1) hormone, which is a key metabolic regulator at the gut surface, aiding in insulin secretion and suppressing appetite [11–13] (Fig. 1). *Akkermansia muciniphila*-derived protein P9 interacts with intercellular adhesion molecule 2, an immune cell integrin, further bolstering GLP-1 production [14]. Additionally, *Akkermansia muciniphila* has been shown to improve glucose and lipid metabolism through the activation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathway [15]. *Akkermansia muciniphila* also regulates lipid metabolism mainly in the liver, small intestine, and adipose tissue. For example, propionate affects the expression of genes associated with fatty acids uptake and oxidation (Gpr43, Fiaf, HDACs, and PPARγ) [14, 16]. In mouse adipose tissue, *Akkermansia muciniphila* administration reduces white adipose tissue volume and enhances thermogenesis by upregulating the uncoupling protein 1 [17].

Akkermansia muciniphila has been shown to have an impact on bile acid metabolism and the gut-liver axis. Research has shown that *Akkermansia muciniphila is* linked with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic and alcohol related/associated liver disease [4, 18–20]. *Akkermansia muciniphila* correlated with circulating BAs and liver lipids, suggesting a role of this bacterium in BA signalling, and presented benefits in preventing hepatic fat accumulation and inflammation in Nonalcoholic fatty liver disease (NAFLD) [19]. Additionally, the anti-MASLD activity of *Akkermansia muciniphila* correlated with lipid oxidation and improved gut-liver interactions through regulating the metabolism of L-aspartate [4]. Together, *Akkermansia muciniphila* influences host metabolism by promoting GLP-1 production and activating the PI3K-Akt pathway, impacting glucose, lipid, and bile acid metabolism (Fig. 1). Thus, *Akkermansia muciniphila* is a potential agent for clinical intervention in liver and bile acid metabolic disorders [2, 21].

Akkermansia muciniphila plays a vital role in maintaining intestinal barrier function

The maintenance of intestinal barrier integrity necessitates the presence of intact epithelial boundaries, the upkeep of tight junctions, regular mucus secretion, a balanced gut microbiome, and a fine-tuned immune system [5]. *Akkermansia muciniphila* can alleviate inflammatory responses and help in maintaining intestinal barrier function. This beneficial impact is achieved by the interaction of *Akkermansia muciniphila* cell wall components with Toll-like receptor 2 (TLR2) on intestinal epithelial cells (IECs). This interaction leads to enhanced activation of Adenosine monophosphate (AMP)-activated protein kinase (AMPK) and inhibition of nuclear factor-kappa B (NF-κB), leading in turn to

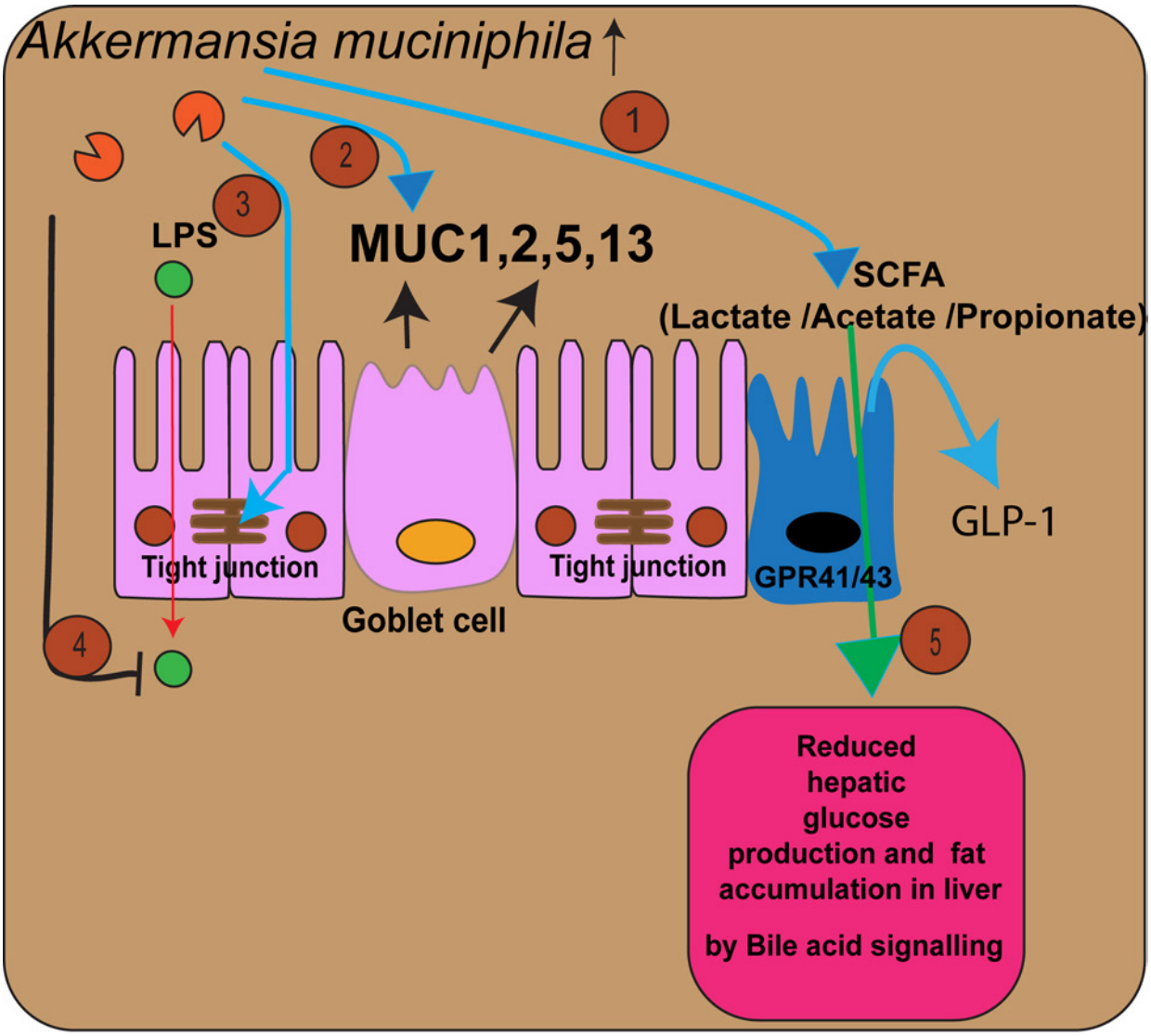

Fig. 1. The beneficial effect of *Akkermansia muciniphila* on intestinal cells and glucose metabolism at the gut surface. The relative increased abundance of *Akkermansia muciniphila* in the gut triggers the synthesis of short-chain fatty acids (SCFAs), particularly propionate and butyrate (1). These SCFAs, in turn, suppress the build-up of inflammatory cytokines and boost the production of the glucagon-like peptide-1 hormone via G-protein-coupled receptors (GPR41/43). The abundance of *Akkermansia muciniphila* correlates positively with intestinal mucin content, as mucin degradation by *Akkermansia muciniphila* activates transcription of key mucin gene (MUC1, MUC2, MUC5, and MUC13) through elevated levels of SCFAs or by enhancing histone acetylation and methylation on the MUC promoter (2). Additionally, *Akkermansia muciniphila* could alleviate inflammation of intestinal epithelial cells (IECs) and improve the expression of tight-junction proteins (ZO-1 and occludin) and reduce the serum lipopolysaccharide level by improving the barrier functions of IECs (3, 4). SCFAs also contribute to the reduction of hepatic glucose production and fat accumulation by bile acid signalling of the gut-hepatic axis (5)

amelioration of inflammatory responses [22]. Furthermore, *Akkermansia muciniphila* triggers the synthesis of SCFAs, particularly propionate and butyrate. This SCFA, in turn, suppresses the buildup of inflammatory cytokines and dampens the activity of the TLR2/Myd88/NF-κB pathway, thus displaying anti-inflammatory properties while preserving the integrity of the intestinal barrier [23, 24] (Fig. 1).

In addition to the anti-inflammatory function of *Akkermansia muciniphila* at the intestinal surface, this organism offers protective roles against the intestinal pathogen, *Citrobacter rodentium* (a bacteria known to induce bacterial colitis) [25]. This protective function of *Akkermansia muciniphila* against *Citrobacter rodentium*-induced colitis was attributed to its ability to enhance the mucus barrier, as shown by the upregulation of mucin gene expression including muc1, muc5, and muc13, along with bolstered anti-microbial responses such as the upregulation of CRAMP, Reg3γ, and IL-22. *Akkermansia muciniphila* also shown to offer protective mechanisms against *Clostridioides dif-*

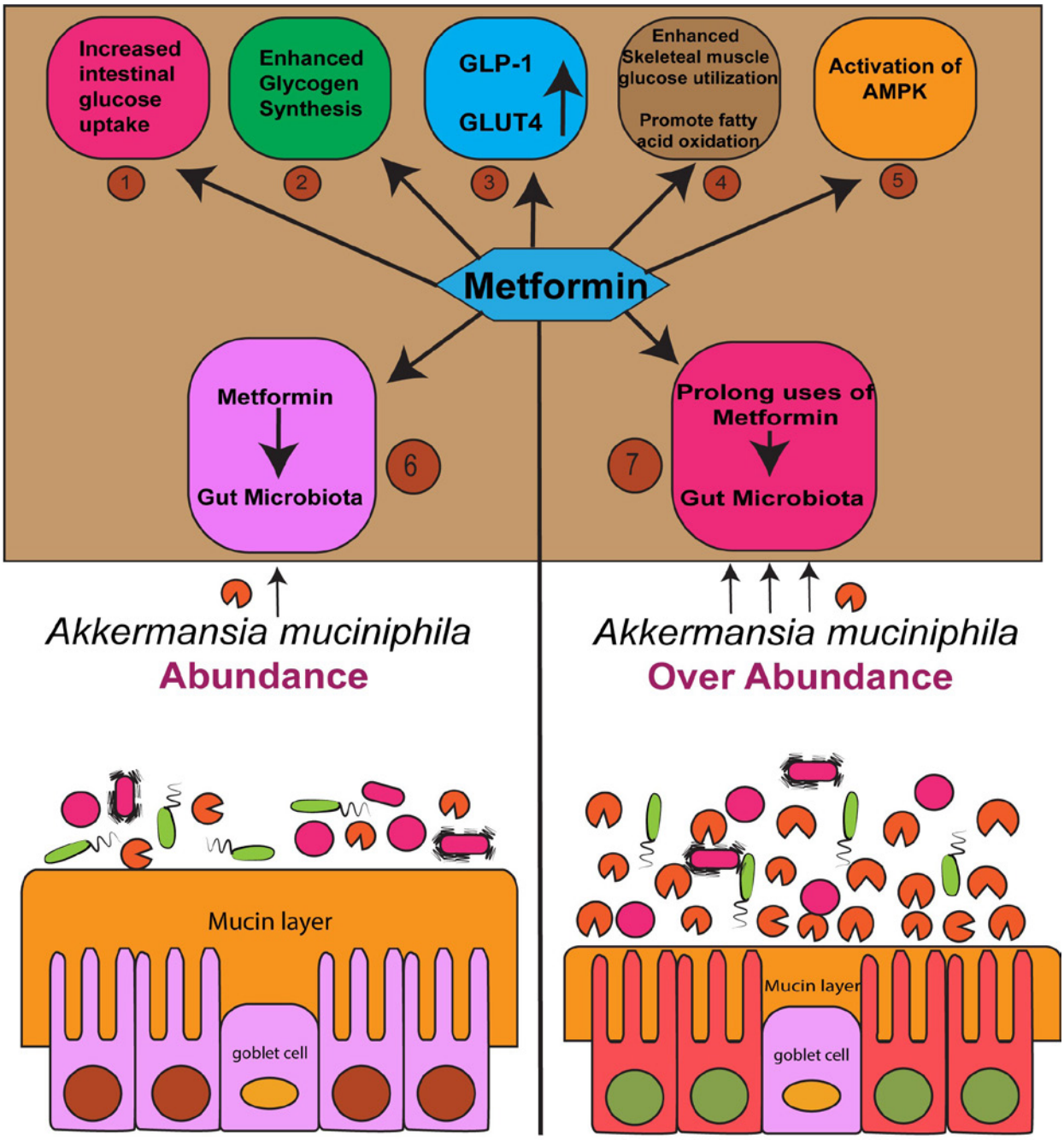

Fig. 2. Molecular mechanisms of metformin action in type 2 diabetes. Metformin, a commonly prescribed medication in the clinical management of type 2 diabetes mellitus, is predominantly known for its capacity to lower blood glucose levels. It achieves this by increasing intestinal glucose uptake (1), improving glycogen synthesis (2), boosting glucagon-like peptide-1 production, and enhancing the recruitment and activity of GLUT4 glucose transporters (3). Furthermore, it enhances skeletal muscle glucose utilisation, promotes fatty acid oxidation, and increases insulin receptor tyrosine kinase activity (4), and inhibition of mitochondrial complex I and other pathways may activate adenosine 5′-monophosphate-activated protein kinase (5). Additionally, it is suggested that the hypoglycaemic effects of metformin are through interactions with gut microbes, specifically through increased relative abundance of *Akkermansia muciniphila* and gut barrier function by elevated production of intestinal mucin layer (6). Prolonged use of metformin may cause overabundance of *Akkermansia muciniphila* and defective gut barrier function because excessive *Akkermansia muciniphila* growth disrupts the mucin production and degradation equilibrium of goblet cells at the gut surface (7)

ficile infection (CDI), which involve bolstering the intestinal barrier through a heightened expression of tight junction proteins and dampening both local and systemic immune responses [26, 27]. Collectively, these findings underscore the protective roles of *Akkermansia muciniphila* in modulating gut barrier integrity and immune responses against enteric infectious diseases.

Molecular mechanisms of metformin action in type 2 diabetes

Metformin, a widely prescribed drug in T2DM management clinical practice, is primarily recognized for its role in reducing plasma glucose levels. Additionally, it is also prescribed to patients recommended for the insulin-sensitising agent [28]. The action of metformin spans multiple biological pathways, primarily focusing on glucose homeostasis (Fig. 2). It achieves this by enhancing glycogen synthesis, increasing intestinal glucose uptake, and boosting GLP-1 production. Additionally, it lowers hepatic glucose production, enhances skeletal muscle glucose utilisation, promotes fatty acid oxidation, increases insulin receptor tyrosine kinase activity, and enhances the recruitment and activity of GLUT4 glucose transporters. These mechanisms collectively improve insulin-stimulated glucose disposal in peripheral tissues [29–31]. Furthermore, the benefits of metformin in T2DM are attributed to gut-liver crosstalk, which influences hepatic glucose production [32]. Additionally, metformin inhibition of mitochondrial complex I and other pathways may activate adenosine 5′-monophosphate-AMPK, a crucial cellular energy sensor [33, 34] (Fig. 2). Moreover, metformin can stimulate insulin secretion through the release of GLP-1, thereby boosting and lowering plasma glucose levels [35, 36]. In recent years, there has been a growing volume of research examining the connection between metformin and gut microbiota. This research suggests that metformin may achieve some of its hypoglycaemic effects through interactions with gut microbes [6, 37–40] (Fig. 2). Together, research suggested that metformin achieves its therapeutic benefits through both direct and indirect molecular mechanisms, potentially overcoming molecular defects associated with insulin resistance. However, further scientific research is needed to understand the conclusive and the molecular basis of metformin action.

Metformin and *Akkermansia muciniphila* interaction in type 2 diabetes: balancing gut health and therapeutic considerations

In the gastrointestinal tract, the inner mucus layer is primarily composed of heavily glycosylated proteins called mucins. This layer serves pivotal functions, including facilitating the smooth movement of food, engaging in cellular signalling pathways, and providing a barrier against commensal microorganisms, pathogens, toxins, and environmental irritants [41, 42]. *Akkermansia muciniphila* bacteria feed on mucins as their primary carbon and nitrogen source within the intestinal mucus layer, outcompeting pathogens and fortifying the gut barrier [43, 44] (Fig. 1). The abundance of *Akkermansia muciniphila* correlates positively with intestinal mucin content, as mucin degradation by *Akkermansia muciniphila* activates key mucin gene (MUC1, MUC2, MUC5, and MUC13) transcription through elevated levels of SCFAs or by enhancing histone acetylation and methylation on the MUC promoter [45–47]. Furthermore, SCFAs play a role in regulating the expression of the *Na+/H+ exchanger 3* (*NHE3*) gene, facilitating the formation of a dense inner mucus layer on the surface of epithelial cells and regulating gut-hepatic axis [32, 48]. Additionally, *Akkermansia muciniphila* could alleviate inflammation of IECs and improve the expression of tight junction proteins (ZO-1 and occludin proteins) in IECs [45, 49] (Fig. 1).

Metformin, a widely used medication for T2DM, is known for its safety, affordability, and efficacy in reducing HbA_{1c} levels [50]. Research highlights its influence on the microbiome, potentially reversing dysbiosis associated with diabetes by increasing mucin-degrading organisms like *Akkermansia muciniphila* [6–9]. Additionally, *Akkermansia muciniphila* presence positively correlates with the number of mucin-producing goblet cells post-metformin treatment, contributing to the thickness, stability, and integrity of the intestinal mucus layer and barrier [6] (Fig. 2). Furthermore, evidence suggests that its glucose-lowering effects are partly mediated by changes in intestinal microbiota [8, 9]. Metformin alters the gut microbiota composition, particularly by promoting the growth of specific bacteria like *Akkermansia muciniphila*, which consequently enhances the production of SCFAs such as butyrate and propionate. These SCFAs play a vital role in regulating glucose balance [51] (Fig. 1). The metformin-induced change in gut microbiota notion is further supported by the following:

- studies indicating that metformin's effects are nullified when broad-spectrum antibiotics are administered to high-fat-diet-fed mice prior to metformin treatment, strongly implicating gut bacteria role, notably *Akkermansia muciniphila*, in mediating metformin's actions [6],
- experiments showing that the beneficial effects of metformin on glucose metabolism, insulin signalling, and redox status are abolished by exogenous lipopolysaccharide (LPS)

administration in mice, highlighting the pivotal role of LPS in mediating metformin's effects [52]. Additionally, research has shown that administering *Akkermansia muciniphila* to mice reduces serum LPS levels [53, 54].

Thus, it is plausible to assume that the enrichment of *Akkermansia muciniphila* species in the gut microbiota of T2DM patients may not necessarily represent defining characteristics of T2DM disorders themselves. Instead, the inherent imbalances in gut microbiota are associated with patients' prolonged use of metformin for the treatment of T2DM [8]. Furthermore, it is suggested that the relative abundance of *Akkermansia muciniphila* promotes the dynamic equilibrium of mucin degradation by gut bacteria, and production by intestinal goblet cells is maintained [3, 55, 56]. However, recent findings suggest that the overabundance of *Akkermansia muciniphila* progressively thins the mucus layer, allowing harmful bacteria direct access to epithelial cells, damaging them and disrupting tight junctions [10]. Persistent mucin deficiency impairs mucus layer repair, weakening epithelial cell repair capacity, and thereby

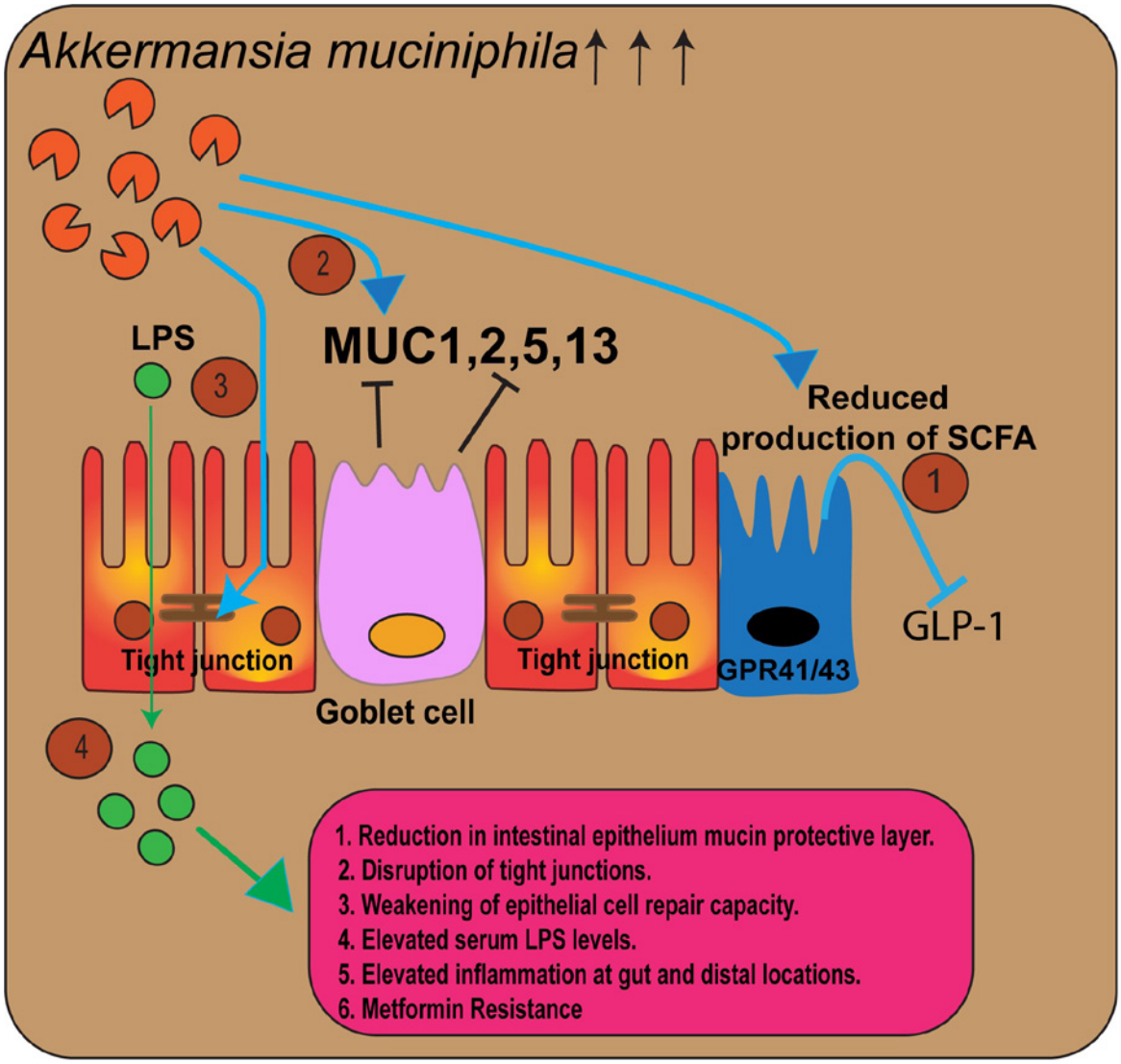

Fig. 3. The possible perspective of the detrimental effect of metformin-induced overabundance of *Akkermansia muciniphila* in the gut. Prolonged use of metformin potentially aggravates inflammation in specific circumstances, possibly by promoting the breakdown of mucin products and weakening intestinal barrier functions in chronic type 2 diabetes mellitus patients. The possible mechanisms involve the following: reduced production of SCFA and glucagon-like peptide-1 (1), disruption in mucin production and degradation equilibrium by an overabundant *Akkermansia muciniphila* population at the gut surface, and reduction of MUC1, 2, 5, and 13 protein production (2). Additionally, defective tight junctions lead to the disruption of gut barrier function (3) and an upsurge in inflammation-related disorders at the gut interface and other distal locations, with elevated serum lipopolysaccharide (LPS) (4). Together, this leads to the creation of a malfunctioned gut barrier function associated with increased serum LPS levels, creating a favourable environment for the upsurge of pathogenic bacteria and metformin resistance development

compromising the intestinal epithelium barrier function in mice [10].

Hence, it is conceivable to assume that the advantageous effects of metformin, facilitated by the augmentation of *Akkermansia muciniphila* within the gut, may fluctuate based on their relative prevalence. When the relative abundance falls within the gut-microbe equilibrium threshold, the metformin-driven augmentation of *Akkermansia muciniphila* might play a beneficial role in maintaining the delicate balance between mucin production and degradation dynamics (Fig. 1). However, an excessive presence of *Akkermansia muciniphila* in the gut could yield divergent and detrimental effects on host well-being, such as the attenuation of intestinal barrier integrity and the reduction of the intestinal epithelium mucin protective layer (Fig. 3). Individuals with T2DM who consume metformin medications might replicate circumstances where prolonged usage of metformin could result in a relative overabundance of *Akkermansia muciniphila* in the gut, potentially leading to compromised gut barrier functions and elevated serum LPS levels. Such circumstances, particularly the disruption of gut barrier function, could precipitate an upsurge in inflammation-related disorders at the gut interface and other distal locations, with elevated serum LPS potentially fostering the emergence of metformin resistance in patients, reminiscent of findings from murine studies [52] (Fig. 3). These suppositions find partial substantiation in studies underscoring the significance of intestinal barrier integrity, with its disruption possibly contributing to autoimmune afflictions like type 1 diabetes or systemic lupus erythematosus [57, 58]. Moreover, an abundance of *Akkermansia muciniphila* has been linked to a spectrum of human ailments including Parkinson's, Multiple Sclerosis, and Alzheimer's, hinting at a potential dualistic role [59–62]. Additionally, conflicting findings exist regarding its impact on inflammatory bowel disease [63].

Therefore, in light of all available data on the use of metformin and its effects on the gut microbiome and overall health, a cautious strategy is warranted. Clinicians can consider leveraging metformin-induced microbiome rebalancing in newly diagnosed T2DM patients. However, managing chronic T2DM patients with metformin or other antidiabetic medications, either alone or in combination with insulin therapy, requires a nuanced and careful approach. Prolonged metformin use potentially aggravates inflammation in specific circumstances, possibly by promoting the breakdown of mucin products and weakening of intestinal barrier functions in chronic T2DM patients, thereby creating a favourable environment for pathogenic bacteria. These factors are crucial to bear in mind when contemplating the clinical application of metformin or interventions involving *Akkermansia muciniphila*, underscoring the necessity for a contextual assessment prior to therapeutic utilisation. Moreover, considering the varied research outcomes regarding the positive and negative impacts of *Akkermansia muciniphila* on gut health, it is recommended that the balance of *Akkermansia muciniphila* and other gut microbiota be evaluated in individuals with chronic T2DM. Introducing a high-fibre diet or reducing metformin doses alongside insulin therapy could potentially rebalance the gut microbiome, particularly in patients with excessive levels of *Akkermansia muciniphila*, thus enhancing the management of T2DM.

Conclusions

The intricate interplay between mucin dynamics, gut microbiota, and metformin treatment in the context of T2DM presents a multifaceted landscape. While metformin's ability to modulate *Akkermansia muciniphila* levels holds promise in ameliorating glucose metabolism and gut health defects, its prolonged usage warrants careful consideration due to the potential for perturbing gut barrier integrity and fostering inflammation, as shown by murine studies. The delicate balance between mucin production, microbial composition, and host response underscores the need for a cautious and individualised approach in clinical practice. Further research is imperative to elucidate the nuanced effects of metformin on mucin dynamics and gut microbiota and their implications for overall health, paving the way for more tailored therapeutic interventions in the management of T2DM and related metabolic disorders.

Disclosures

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