Metformin: old friend, new ways of action–implication of the gut microbiome?

Julie Rodriguez, Sophie Hiel, and Nathalie M. Delzenne

Purpose of review
Gut dysbiosis was recently associated with the occurrence of type 2 diabetes (T2D). In addition to this finding, an increasing number of studies performed upon the last 5 years have also shown that metformin treatment leads to changes in gut bacterial composition in diabetic patients. This review focuses on the articles describing the effects of metformin on gut homeostasis (including the gut microbiota) and proposes potential mechanisms involved in those effects.

Recent findings
Several human and animal studies emphasized that metformin alters the gut microbiota composition by enhancing the growth of some bacteria, such as *Akkermansia muciniphila*, *Escherichia* spp. or *Lactobacillus* and by decreasing the levels of some other ones like *Intestinibacter*. In-vitro studies also demonstrated a direct action of metformin on the growth of *A. muciniphila* and *Bifidobacterium adolescentis*. Moreover, in the intestines, metformin does not only improve the glucose uptake, but it also promotes the short-chain fatty acid (SCFA) production, protects the intestinal barrier and regulates the secretion of gut peptides

Summary
It is now clear that gut microbiota participates to the glucose-lowering effects of metformin in the context of diabetes. Further work is now needed to determine the exact mechanisms of action of the drug and to understand by which processes metformin is able to enhance the growth of some bacteria exhibiting beneficial effects for the host.

Keywords
diabetes, gut microbiota, intestinal function, metformin

INTRODUCTION

Metformin is the most prescribed pharmacotherapy for the treatment of individuals with type 2 diabetes (T2D) due to its safety and its glucose-lowering effects. However, its mechanisms of action remain to be clarified. It is well established that the liver is a major site of metformin action [through an activation of the hepatic AMP-activated protein kinase (AMPK) protein]. There is growing evidence suggesting that the gut microbiota would be another target involved in the antidiabetic effects of metformin. During the last 10 years, an increasing number of studies have indicated several changes in gut bacterial composition or function in T2D patients. This dysbiosis observed during T2D pathology and hyperglycemia is mostly due to a depletion of butyrate-producing bacteria (including *Clostridium* species, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* or *Roseburia inulinivorans*) and an enrichment of opportunistic pathogens, as recently reviewed [1]. In addition, emerging evidence also highlighted the role for the gut microbiota in diabete prevention, glycemic control and in the treatment of T2D [2]. Following the hypothesis that metformin could act on gut microbiota to control glucose homeostasis, a recent review by McCreight *et al.* [3▪] described the passage of metformin through the gastrointestinal tract and supported the fact that a large accumulation of metformin into the intestine could contribute to the glucose-lowering effect of this drug,

Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium

Correspondence to Prof. Nathalie M. Delzenne, Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université catholique de Louvain, av. E. Mounier 73 bte B1.73.11, B-1200 Brussels, Belgium. Tel: +32 764 73 69; e-mail: nathalie.delzenne@uclouvain.be

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KEY POINTS

- Emerging hypotheses suggest that metformin could target the gut microbiota to exert its glucose-lowering effects.
- Metformin reverses some bacterial changes occurring during T2D, especially by increasing SCFA-producing bacteria and by decreasing opportunistic pathogens.
- Metformin largely increases the abundance of *A. muciniphila* in both human and animal models of obesity and T2D. The growth of this bacterium is promoted by metformin *in vitro*, suggesting that metformin acts as a growth factor for some gut microbes.
- Metformin ameliorates the intestinal functions by improving the intestinal glucose sensing, enhancing the production of SCFA and gut peptides or by protecting the gut permeability.

perhaps by regulating the gut microbiota composition. Indeed, Cabreiro *et al.* [4] firstly demonstrated that metformin slows aging in a model of *Caenorhabditis elegans* by altering microbial metabolism, suggesting the possibility that this drug might similarly affect microbial metabolism and gut microbiota composition in mammals. Since, a number of studies performed in animals and humans explores the possibility that gut microbiota could contribute to the antihyperglycemic effects of metformin.

In this context, we propose to review the last findings highlighting the gut-related activities of metformin. This review starts with a description of both in-vivo and in-vitro studies relating the changes in gut microbiota following metformin administration. In a second part, the review focuses on the regulation of intestinal functions by metformin, and the involvement of gut microbes in these processes.

METFORMIN PARTIALLY REVERSES THE DYSBIOSIS RELATED TO TYPE 2 DIABETES

To investigate how metformin could alter the gut microbiota composition, several studies were performed in human and animal models.

Human studies

A recent work by Wu *et al.* [5▪▪] demonstrated that metformin treatment-induced significant alteration in the composition of the gut microbiota of treatment-naïve patients, recently diagnosed T2D. In this study, all participants were fed with a hypocaloric diet. The whole-genome shotgun sequencing revealed that 1700 mg/day of metformin-induced significant changes in the relative abundance of 81 bacterial strains after 2 months and regulated 86 bacterial strains after 4 months of treatment, whereas only one bacterial strain was altered in the placebo group. Most of these changes were detected in the Firmicutes and Proteobacteria phyla. Significantly, these changes correlated with those observed in a subset of the placebo group that switched to the metformin treatment 6 months after the start of the clinical trial. Unlike the first assay, they also reported a metformin-induced increase in *Bifidobacterium* in this subgroup [5▪▪]. Moreover, the comparison of gut microbiota composition between T2D-metformin treated versus untreated patients revealed that the treatment significantly increased the relative abundance of *Escherichia* spp. and reduced the abundance of *Intestinibacter* genus [6]. Actually, it is not excluded that the increased abundance of *Escherichia* spp. could mediate the adverse events reported with metformin treatment, such as gastrointestinal symptoms. Wu *et al.* [5▪▪] also found the same changes after 2 and 4 months of treatment in treatment-naïve T2D patients, as well as an increase in the abundance of *Akkermansia muciniphila* in individuals receiving metformin for 4 months. In addition, metformin partially reverted T2D-associated changes, as similar abundance of *Subdoligranulum* and *Akkermansia* were found between T2D-treated metformin patients and control healthy subjects [6]. Moreover, in a cohort of 145 European women with T2D, patients receiving metformin had increased levels of *Enterobacteriaceae* (including *Escherichia, Shigella, Klebsiella* and *Salmonella*) and decreased levels of *Clostridium* and *Eubacterium* [7]. The higher levels of *Enterobacteriaceae* were also found in basal conditions in Nordic T2D patients (having both parents born in Scandinavia) treated with metformin versus untreated patients [8]. In a Columbian adult population diagnosed with T2D, the *16S rRNA* gene sequencing revealed no differences in the number of observed operational taxonomic unit (OTUs) between groups (treated with metformin versus untreated group) [9▪]. Nonetheless, the β-diversity was significantly reduced by the treatment, suggesting that metformin alters the bacterial community structure in the gut microbiota of T2D patients. In this Columbian T2D population, metformin significantly increased the OTUs belonging to *Megasphaera* and *Prevotella* genus, whereas the treatment reduced the OTUs from Clostridiaceae 02d06 and *Barnesiellaceae* family, as well as the *Oscillospira* genus [9▪].

Animal studies

In rodent models fed with a high fat diet (HFD), metformin administration reduced both richness and diversity of the gut microbiota [10,11], except in aged obese mice where no difference was found after the treatment [12]. Significantly, unlike the HFD, metformin had no impact on the α-diversity of gut microbiota from mice fed with a standard diet, suggesting the diet-dependent effects of metformin on gut microbiota diversity [11]. Principal component analysis and UniFrac distance-based principal coordinate analysis showed that metformin treatment resulted in obvious changes of gut microbiota in rodents, observed by a clear separation between groups [10–12]. Among 134 key OTUs analyzed in fecal samples from rats, 70 were decreased by the treatment, whereas 56 were increased. Metformin did not modify the Firmicutes/Bacteroidetes ratio but increased the Proteobacteria and Verrucomicrobia phyla. At the genus level, metformin significantly enriched some genus such as *Allobaculum, Akkermansia, Bacteroides, Blautia, Butyricicoccus, Klebsiella, Lactobacillus, Parasutterella, Phascolarctobacterium* and *Prevotella* while it decreased *Clostridium XlVa, Flavonifractor, Lachnospiracea_incertae_sedis, Roseburia* and *Clostridium XI*.

In another study, metformin administration into the upper small intestine of HFD fed rats 1 day prior the collection of samples revealed a shift of the microbiota composition from untreated rats with the Bray–Curtis distances analysis [13▪▪]. Therefore, in this study, there was no difference in the β-diversity between groups. The main change observed, following the metformin treatment, was an increase in the relative abundances of *Lactobacillaceae* family and *Lactobacillus* genus. At the species level, the treatment increased the abundance of *Lactobacillus salivarius* without having a significant effect on *Lactobacillus gasseri*. All these results were confirmed in a model of gut microbiota transfer from rats receiving the upper small intestinal infusion of metformin into recipient rats. It has also been demonstrated that metformin restored the abundance of the beneficial bacteria *Lactobacillus* and *A. muciniphila* in HFD fed mice developing insulin resistance [14]. In addition to these reported effects, metformin also rescued the relative abundance of others genus altered during a HFD, such as *Anaerotruncus, Lactococcus, Parabacteroides, Odoribacter, Alistipes, Lawsonia, Blautia* and *Lactonifactor* [15]. The large increase of *Akkermansia* is actually responsible for the enrichment of Verrucomicrobia phylum observed in the metformin-treated group. In the study of Lee and Ko [11], metformin significantly increased the relative abundance of Bacteroidetes and Verrucomicrobia phylums. Metformin enriched the *Verrucomicrobiaceae* family, and particularly *A. muciniphila*. Metformin had also positive effects on the enrichment of the *Clostridium cocleatum* genus. Recently, in aged obese mice, the same authors showed that metformin decreased the Firmicutes/Bacteroidetes ratio, together with increased *Bacteroides, Butyricimonas, Parabacteroides* genera and the *A. muciniphila* species [12].

In vitro studies

It has been recently reported that metformin also directly enhances the growth of *A. muciniphila* and *Bifidobacterium adolescentis* in pure cultures [5▪▪]. In addition, the incubation of fecal samples from treatment-naïve patients with metformin, in a gut simulator, also stimulates the growth of *A. muciniphila*, proving the direct metformin–microbiota interactions.

To conclude, all these analysis performed in human and animal models prove that metformin induces rapid changes in the gut microbiota composition and could partially counteract the gut microbiota alterations observed during T2D or hyperglycemia. Some specific bacteria seem to be highly regulated by metformin, such as *A. muciniphila,* since a higher abundance of this bacteria was found following metformin administration in both human and animal models. Significantly, the in-vitro results suggest that metformin could act as a growth factor for some bacterial species.

EFFECT OF METFORMIN ON KEY INTESTINAL FUNCTIONS: A LINK WITH THE GUT MICROBIOTA?

Even if the main effects of metformin are described in the liver, an increasing number of evidences now confirm that metformin treatment also affects the intestine by acting on key processes related to glucose homeostasis (Fig. 1).

Metformin regulates the intestinal glucose uptake and glucose homeostasis

The emergence of metformin as a regulator of the gastrointestinal function and its essential role for glucose homeostasis has been recently reviewed [16]. Since, the last discoveries in animal models highlighted a new mechanism responsible for the decrease in glucose production by metformin linked to the modification of upper intestinal microbiota [13▪▪]. The authors showed that metformin restored the HFD-altered upper intestinal glucose sensing, by normalizing sodium glucose co-transporter 1

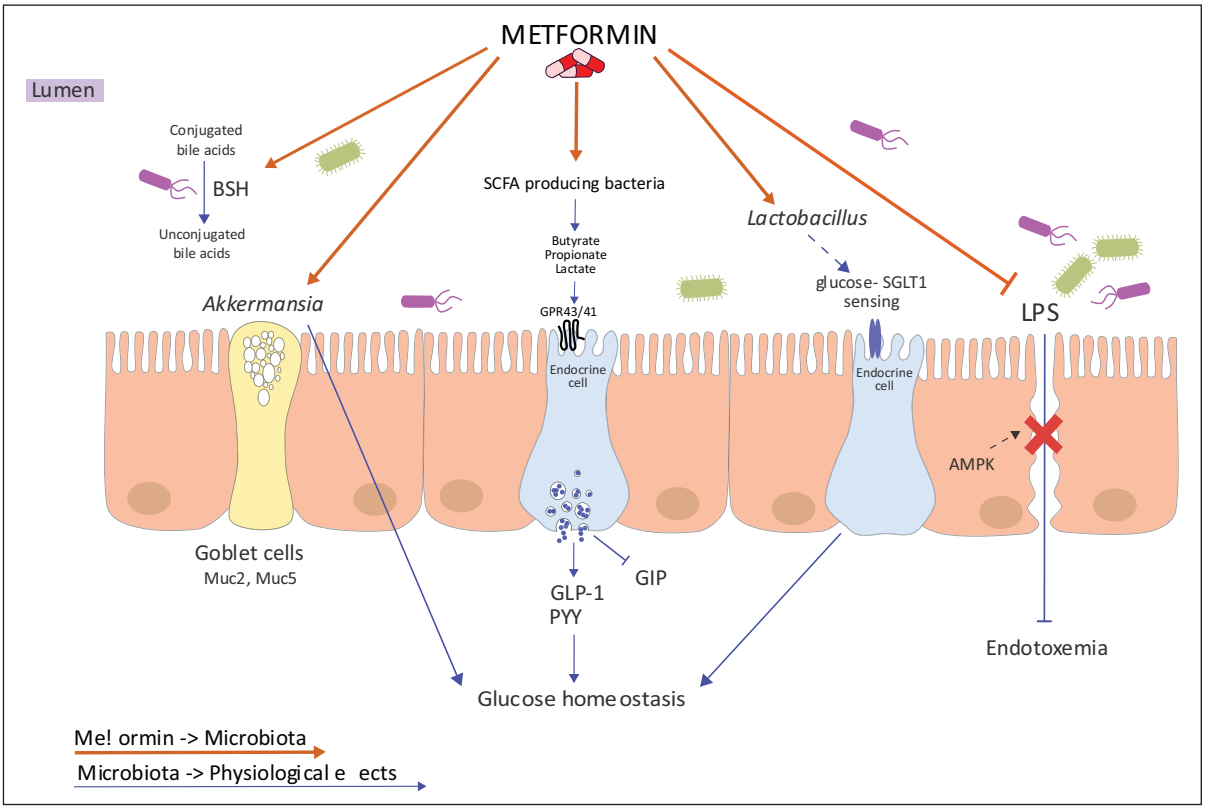

FIGURE 1. Impact of metformin on gut function linked to gut microbiota activity and composition. Human and animal studies have revealed that metformin is able to modify gut microbiota composition and activity, which impacts several pathways involved in the improvement of the diabetic phenotype at the intestinal level. Orange arrows indicate direct effect of metformin on microbiota, blue arrows shows microbiota-mediated physiological effects. Dashed arrows indicate putative effects. For more details, please refer to the main text.

expression in rats. This effect was dependent on the composition of the upper intestinal microbiota. They show that transplant with the homogenate from upper small intestinal microbiota contents from metformin-pretreated donors restored glucose sensing in HFD recipient rats. In this study, the increased abundance of *Lactobacillus* was pointed out as potentially involved in the restoration of upper small intestinal glucose sensing [13▪▪]. Moreover, in T2D patients, a short-term administration of metformin (7 days) inhibited the rate of small intestinal glucose absorption [17▪], whereas another study showed that a long-term administration of metformin (26 weeks) increased two-fold the glucose utilization in the small intestine and three-fold in the colon [18]. These last studies conclude that metformin alters the glucose absorption and utilization in the small intestine, participating to the improvement of glucose homeostasis.

Metformin treatment also triggers specific modifications of the gut microbiota in the large bowel that can be related to the improvement of glucose homeostasis. For instance, Lee and Ko [11] showed that in HFD fed mice treated with metformin, *A. muciniphila* was negatively correlated with serum glucose level, whereas other bacteria such as *Clostridium orbiscindens, Blautia producta* and *Allobaculum* sp. strain ID4 were negatively correlated with the hepatic levels of peroxisome proliferator-activated receptor alpha and glucose transporter 2. *A. muciniphila* is one of the most abundant single species in the human intestinal microbiota and a well known mucin-utilizing specialist inversely associated with obesity, diabetes and cardiovascular disease [19]. Several recent studies reported that metformin significantly increased the abundance of the Verrumicrobia phylum, due to an enrichment of the genus *Akkermansia,* and particularly *A. muciniphila* species in both models of T2D patients and HFD-induced obesity in mice [5▪▪,9▪,10,11,14,15].

In this context, several treatment strategies using *A. muciniphila* in murine models already show promising results to counteract the diabetic phenotype. Oral administration of *A. muciniphila* to HFD-fed mice significantly enhanced glucose tolerance [15,20]. However, antidiabetic properties of *A. muciniphila* have not yet been shown in humans, due to difficulties encountered with growth conditions of

this bacteria and the difficulty to use living *Akkermansia* as a feasible approach in patients. Plovier *et al.* [21] recently addressed this issue by using the pasteurized *A. muciniphila* bacteria which showed increased capacity to reduce fat mass development, insulin resistance and dyslipidemia versus the live bacteria in mice. The isolation and the treatment with a specific membrane protein of *Akkermansia* – *Amuc1100* – also recapitulates the improvement of glucose homeostasis in mice, thereby suggesting that specific components of certain bacteria promoted by the metformin treatment, may play a role in the improvement of host physiology [21]. The use of this bacterium, or of its bioactive component, could also be envisioned as a new strategy for ameliorating the diabetic phenotype, if proven in humans.

Fecal microbiota transplantation was also successful in reproducing metformin antidiabetic effect, proving that a substantial part of therapeutic effect could come from a more global modulation of the composition or activity of the gut microbiota. Indeed, transfer of fecal material coming from metformin-treated individuals in germ-free mice fed with HFD improved glucose tolerance of the recipient mice [5▪▪]. These new findings highlight the potential of integrate microbiota targeted therapy in the management of T2D.

Metformin promotes the short-chain fatty acid-producing bacteria

Metabolites produced by gut microbes may also be related to the development of T2D and insulin resistance. Short-chain fatty acid (SCFA) are produced by anaerobic bacteria from undigestible food, such as carbohydrates, which are catabolized into acetate, propionate, butyrate or lactate [22]. These SCFA have important metabolic functions and are crucial for intestinal health [23]. In addition to the reported effects of SCFA in gut health, SCFA exhibited beneficial effects in peripheral tissues such as adipose tissues, skeletal muscles and liver by controlling substrate metabolism and function, leading to improvement of insulin sensitivity [23]. A recent work highlighted that intestinal dysbiosis is associated with altered SCFA levels in humans [24]. Significantly, recent animal study has demonstrated that butyrate and propionate activate the intestinal gluconeogenesis, displaying beneficial effects on glucose signaling and energy homeostasis [25].

In this context, human studies revealed an increase of both butyrate, propionate and lactate by metformin in T2D patients [5▪▪,6]. However, another recent study performed in Nordic T2D patients fed with an Okinawan-based Nordic diet found contradictory results showing that the use of metformin did not affect SCFA concentrations [8]. In this study, we cannot ensure that the use of different diet and the ethnicity may have a possible influence on this parameter.

To understand the increase of SCFA production by metformin, a recent review by Montandon and Jornayvaz [26▪] summarizes the last studies showing the contribution of antidiabetic drugs (including metformin) on the enrichment of SCFA-producing bacteria. Metformin treatment increased the OTUs belonging to SCFA-producing bacteria, including *Allobaculum*, *Bacteroides, Blautia, Butyricoccus, Lactobacillus, Akkermansia* and *Phascolarctobacterium* genus in rats [10,11,15]. An enrichment of some bacterial taxa producing SCFA, including for instance *Bacteroides* or *Butyricimonas* genus, was also found in aged obese mice [12]. In humans with T2D, metformin also increased the relative abundances of genus involved in the SCFA production: *Akkermansia, Lactobacillus, Bifidobacterium, Prevotella, Megasphaera, Shewanella, Blautia* or *Butyrivibrio* [5▪▪,6,9▪].

To conclude, the enrichment of the SCFA-producing bacteria by metformin could be a mediating mechanism for inducing beneficial effects on the host, particularly during metabolic diseases such as obesity and T2D.

Metformin promotes the mucin-degrading bacteria

The higher abundance of *Akkermansia* following metformin administration – described before – could be explained by the regulation in the number of mucin-producing goblet cells in the intestine, providing more substrate for the growth of *A. muciniphila*. Indeed, Shin *et al.* [15] demonstrated that metformin increases the number of goblet cell population in mice, regardless of metabolic profile or dietary composition. Moreover, the number of goblet cells was positively correlated with the abundance of *Akkermansia*. In addition, expression of *MUC2* and *MUC5* genes, two markers for analyzing mucin levels, significantly increased in HFD-fed female mice treated with metformin [11]. However, Bauer *et al.* [13▪▪] did not find an increase of *A. muciniphila* with metformin; this is probably due to the fact that the analysis was done in the upper small intestine and *A. muciniphila* colonized more cecum and colon.

Metformin enhances the gut-related peptides secretion

As reviewed by McCreight *et al.* [3▪], metformin may also affect glucose metabolism by increasing

glucagon-like peptide-1 (GLP-1) secretion in both mouse and human studies. In a clinical intervention study with T2D patients stopping and restarting the metformin treatment, it appeared that the metformin withdrawal was associated with a reduction of active and total GLP-1 in the serum, whereas this effect was reversed when metformin was restarted [27]. A similar profile was also found for the concentration of circulating peptide tyrosine-tyrosine (PYY) during metformin treatment but the effects were less pronounced than those observed for GLP-1. In addition, the authors found correlations between the abundances of Firmicutes and Bacteroidetes phyla and the levels of serum PYY suggesting the potent implication of gut bacteria in the regulation of this hormone [27]. Metformin also increased the level of total GLP-1, in nondiabetic subjects and metformin-treated diabetic patients, independently of changes in weight or glycemia [28]. In addition, both delayed-release metformin and immediate-release metformin (using different tablets including or not a proprietary enteric coat) resulted in comparable increases of plasma GLP-1 and PYY concentrations, in T2D patients [29]. Bronden *et al.* [30] demonstrated that single-dose metformin enhances bile acid-induced secretion of plasma GLP-1 following cholecystokinin-mediated gallbladder emptying in T2D patients. Moreover, in diabetic rats, intraduodenal infusion of metformin lowered blood glucose through a GLP-1 dependent mechanism [31]. This study highlighted the importance of the gut–brain–liver communication for acute metformin action, as inhibition of duodenal AMPK suppressed the hepatic glucose production-lowering effect of intraduodenal metformin, suggesting that acute metformin effect is AMPK-dependent and required the activation of PKA by GLP-1 in duodenal enterocytes [31].

The mechanisms of regulation of GLP-1 secretion by metformin are well discussed in the review of Bahne *et al.* [32]. In this review, the authors hypothesized that metformin could probably increase directly the GLP-1 concentration by increasing its secretion from L cells, or by reducing its degradation by dipeptidyl peptidase-4 in the intestinal mucosa and portal system. One other explanation is that metformin could indirectly enhance the GLP-1 secretion, via alterations in the bile acid pool or via modulation of the gut microbiota [32]. This last point is particularly of interest in the current review. Indeed, we have discussed above that metformin increases the production of SCFA by the gut microbiota. Propionate, acetate and butyrate have been shown to act on G protein-coupled receptors, resulting in GLP-1 secretion [33]. Thus, the action of metformin on gut microbiota composition could explain the regulation of GLP-1 concentration. Significantly, one earlier study also demonstrated that metformin decreased the levels of plasma GIP (glucose-dependent insulinotropic polypeptide) in rats fed with a high-fat/high-sucrose diet [34]. Elevated GIP levels are associated with glucose intolerance and hyperinsulinemia, and the authors found that a combined action of metformin and oligofructose maximally attenuates GIP release [34]. These new findings support that metformin strongly regulates the intestinal hormones GLP-1, PYY and GIP involved in the insulin secretion and this mechanism could participate to the glucose-lowering effects by metformin.

Metformin regulates the bile acids turnover

Bile acids are amphipathic water-soluble steroid-based molecules well known for their important lipid-solubilizing role in the assimilation of fat. In addition to their lipid-solubilizing function, bile acids are also able to modulate both lipid and glucose metabolism by activating the 7-transmembrane bile acid receptor 7-transmembrane bile acid receptor and the nuclear farnesoid X receptor farnesoid X receptor [35].

The impact of metformin on the bile acids turnover and homeostasis has been well documented and reviewed [3▪,32]. Recent work also indicated that metformin may help to improve glucose metabolism by regulating the level of serum total bile acids in diabetic rats [36]. After 4 months of metformin treatment, Wu *et al.* [5▪▪] observed large increases in plasma bile acid concentrations (total, primary, secondary and unconjugated), whereas the levels of bile acids remained unchanged in fecal samples. The authors showed that 2 months of metformin increased the abundance of *bsh,* a gene encoding bile salt hydrolases enzymes produced by the gut microbiota. On the contrary, to our knowledge, there is no study showing correlation between specific bacteria and the concentration of bile acids following metformin treatment.

Metformin maintains the integrity of the intestinal barrier

It has been well established that a high-fat diet alters the gut microbiota composition, and increases the plasma concentration of lipopolysaccharide (LPS) in mice, which contribute to an alteration of intestinal permeability and a reduced glucose tolerance [37]. Metformin has been shown to limit the HFD-induced increases in serum LPS level, probably due to a modification of the gut microbiota composition [15]. Few time later, another team confirmed

that metformin lowered the blood LPS level and protected gut barrier function in a model of HFD-induced obesity and insulin resistance in mice [14]. Moreover, the exogenous administration of LPS blocked the enhancing effects of metformin on glucose control and insulin signaling. These results suggest a role of metformin in modulating gut microbiota and blood LPS level for both enhancing insulin signaling and reducing glucose level. As also recently reviewed by two teams, AMPK could play a role in maintaining the intestinal barrier integrity, and thus, the metformin-mediated activation of AMPK could participate to the decrease of LPS leakage from the gut [38,39].

CONCLUSION

The discovery of the gut microbiota as a metabolic partner in the management of T2D led to several studies investigating whether metformin could target the gut microbes to mediate its glucose-lowering effects in the organism. During the last 5 years, a number of evidences have indicated that metformin induces rapid changes in gut bacterial composition and improves intestinal functions. First, metformin enhances the SCFA production, promotes the activity of endocrine cells by releasing more GLP-1 and PYY peptides, regulates the bile acids turnover and reduces endotoxemia. Second, metformin increased the relative abundance of some specific bacteria known to induce beneficial effects in the host, such as *A. muciniphila* or *Lactobacillus*.

Taken together, all these mechanisms could participate to the glucose-reducing effects of metformin. Even if, during several years, the liver was considered as the main target of metformin action, the recent knowledge confirmed that gut microbiome is also mainly targeted by this drug and may be potentially the first site of action in the control of glucose homeostasis by metformin. It is now widely accepted that gut microbiota plays a crucial role in the management of T2D development and future strategies (as metformin administration coupled with nutritional advices and physical activity) should focus on the analysis of gut microbiota modulation to improve the diabetic phenotype.

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Conflicts of interest

There are no conflicts of interest.

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