REVIEW PAPER

Metformin intolerance in type 2 diabetes mellitus – the possibility of using a multi-strain probiotic

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ABSTRACT

Metformin is a widely used drug in the management of type 2 diabetes (T2DM); however, its administration is linked with the elevated incidence of gastrointestinal (GI) adverse events (AEs) limiting its use or treatment intensification. The complex interplay between metformin and the gut ecosystem has emerged as a additional of interest, particularly the drug's impact on the composition and function of the gut microbiota. Therefore, in this review we present the possibility of interfering with microbiota by using multi-strain probiotic to mitigate the GI AEs in patients with metformin intolerance. We synthesise findings from various research studies that explore the modification of gut microbiota as a means to reduce GI AEs in T2DM patients with metformin intolerance. As we discuss the available evidence, the narrative outlines the mechanisms through which probiotics may exert beneficial effects and evaluate the efficacy of different probiotic formulations. The results of research on gut microbiota modification in patients with T2DM and metformin intolerance appear promising in alleviating GI AEs.

KEY WORDS: type 2 diabetes mellitus, metformin intolerance, multi-strain probiotic.

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Introduction

A total of 537 million adults worldwide are living with diabetes, and over 90% of them present type 2 of the disease [1]. Metformin has been commonly used among patients with type 2 diabetes mellitus (T2DM) for almost 7 decades and was recommended as a first-line drug choice in T2DM in the guidelines released by the International Diabetes Federation in 2005 [2]. According to the newest American Diabetes Association and European Association for the Study of Diabetes recommendations, which introduced the concept of patient-centred care, there is a need to consider other new glucose-lowering drugs, which could be the first choice of therapy when cardiovascular (CV) and renal comorbidities or CV risk factors are present [3]. Nevertheless, new glucose-lowering drugs are usually evaluated as an add-on to existing metformin therapy as a standard procedure [3], and metformin remains a drug with good treatment efficacy, improving glycaemic control, with a good safety profile, neutral weight or weight loss, no associated hypoglycaemia, beneficial effects on the CV system, and low cost [4].

Metformin intolerance

As assessed more than 20 years ago, among patients treated with metformin, 20–30% experience gastrointestinal (GI) adverse events (AEs) [5], which is related to worse health-related quality of life [6] and lower adherence and discontinuation of the treatment in approximately 5% of patients [5]. Recently, in our meta-analysis and meta-regression of randomised controlled trials (RCTs), we proved that the risk of GI AEs such as diarrhoea, abdominal pain, and nausea is higher in T2DM patients treated with metformin compared with other antidiabetic drugs or placebo. Specifically, when compared to placebo, the relative risk was 98% higher for abdominal pain, 184% higher for diarrhoea, 168% higher for nausea, 228% higher for vomiting, and 36% higher for constipation [7].

The pathophysiology of the GI disorders related to metformin use remains poorly understood. There are several hypotheses explaining the mechanisms for metformin intolerance, including increased lactate production [8] and serotonin accumulation [9]. The concentration of metformin in the gut is higher than in the blood [10] and may be even higher in metformin-intolerant individuals. This results in prolonged contact between the enterocyte and metformin, leading to increased glucose utilisation and lactate production, which can lead to symptoms of intolerance [11]. Metformin, by its structural relation to selective agonists of the serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor, induces 5-HT3 receptor-independent release of 5-HT from human duodenal mucosa [12]. 5-HT affects 5-HT3 receptors located on visceral afferent fibres of the vagus nerve [12]. This modulates the excitability and activity of GI vagal afferent fibres and may be involved in GI AEs, including bloating, nausea and vomiting, and visceral hypersensitivity [12]. Moreover, metformin treatment leads to disturbances in the entero-hepatic circulation of bile salts by reducing ileal bile salt reabsorption, which causes elevated colonic bile salt concentrations [13]. It reduces the amount of *Bacteroides fragilis*, which in turn causes the conversion of primary bile acids to secondary bile acids via bile salt hydrolase (BSH), thereby increasing glycoursodeoxycholic acid, which is an antagonist of the nuclear farnesoid X receptor, leading to increased production of bile acids in the liver and increased sensitivity to insulin [13]. The increased osmotic burden in the colon is a possible explanation for watery stool formation in patients treated with metformin [14]. Dujic *et al.* suggested that reduced transport of metformin via organic cation transporter 1 (OCT1) could increase metformin concentration in the gut [15], which might then affect the balance of incretins, ghrelin, bile acids, or serotonin, leading to increased risk of GI AEs and drug discontinuation [16]. They also showed that the concomitant use of OCT1-inhibiting drugs such as citalopram, proton pump inhibitors, verapamil, doxazosin, and codeine was significantly associated with metformin intolerance, with verapamil increasing the odds of intolerance sevenfold [15].

Both therapeutic and GI AEs of metformin may be associated with changes in the gut microbiota [17]. Bryrup *et al.* showed that metformin intake influences the composition of the gut microbiota in men with normal glucose metabolism and that pre-treatment bacterial genera may determine the development of adverse GI reactions to metformin treatment [18]. Shortly after this discovery metformin was considered to be one of the key drugs affecting the gut microbiota [19].

Gut microbiome and metformin intolerance

The gut microbiome studies are receiving increasing attention due to the hypothesis that disrupted gut microbiota contributes to the development of metabolic diseases including obesity and

T2DM [20–22]. One of the metagenome association studies has shown that intestinal dysbiosis is associated with T2DM and is characterised by reduced butyrate-producing bacteria, which alters colon permeability and leads to endotoxaemia [23]. These changes, in turn, increase the production of reactive oxygen species, and inflammation and inflammatory markers [24]. Forslund *et al.* analysed 784 available human gut metagenomes, and showed how metformin was associated with gut microbial dysbiosis [17]. They confirmed the detected changes in the gut microbiome in patients with T2DM treated with metformin, including a decrease in butyrate-producing taxa [17]. Butyrate is a short-chain fatty acid (SCFA) of greater physiological importance than the other major SCFAs (acetate and propionate) [25]. It is used by colonocytes to maintain the anaerobic environment in the gut, maintains the integrity of the intestinal barrier by regulating the expression of claudin-1 and synaptopodin, and limits pro-inflammatory cytokines (IL-6, IL-12) [25]. Inadequate butyrate secretion results in alleviation of histone deacetylase 3 inhibition and an increase in the production of reactive oxygen species (ROS), nicotinamide adenine dinucleotide phosphate oxidase 4 proteins, IL-1β, and a reduction in IL-10 and IL-17α. However, butyrate treatment restores inflammatory markers in appropriate levels and reduces ROS production in mice [23].

Patients with diabetes who were not treated with metformin had higher abundances of *Eubacterium* and *Clostridiaceae* SMB53 [26] and lower levels of SCFA producers such as *Roseburia*, *Subdoligranulum*, and the cluster of *Clostridiales* that produce butyrate [17]. Mueller *et al.* confirmed in their study that patients treated with metformin had a significantly altered microbiota composition compared to controls [27]. They enrolled 121 overweight adults and randomly assigned them to 3 groups: metformin treatment, coach-directed behavioural weight loss, and self-directed care. Microbial DNA was then collected and extracted from faeces at baseline, 6 months, and 12 months, and SCFAs were measured from fasting serum. Consequently, metformin treatment increased amplicon sequence variants for *Escherichia* and *Ruminococcus torques* and decreased *Intestinibacter bartlettii* and the genus *Roseburia*, including *Roseburia faecis* and *Roseburia intestinalis*. Metformin also increased butyrate, acetate, and valerate compared to the control group [27]. Whereas Huang *et al.* suggested that metformin promotes the secretion of gut hormones such as GLP-1 by increasing the number of SCFA-producing bacteria, which not only has an anti-diabetic role, but may also cause GI side effects [28]. Notably, administration of metformin for the duration of only 7 days among healthy volunteers resulted in significant reduction of diversity of gut microbiome. Moreover, the relative abundance of opportunistic pathogens such as *Escherichia-Shigella spp.* was associated with severity of GI AEs [29]. Thus, the potential causal and personalised role of the human gut microbiota in metformin treatment has been elucidated, and it has been hypothesised that modulation of the gut microbiota may influence the metabolic state in patients with T2DM [30].

Multi-strain probiotic and metformin intolerance

The existence of microorganisms was discovered by Robert Hooke and Antoni van Leeuwenhoek during the period 1665–1683 [31]. Subsequently, the role of microorganisms in causing infectious diseases was noticed, and in the last 20 years bacteria have not been considered only as disease causing factors but there have also been studies performed to understand the possibility of the potential use of bacteria in disease therapy [32]. In 2013, a great discovery was made when gut microbiota was transplanted for the first time into a patient with recurrent *Clostridioides difficile* infection (CDI) proving that this is a more effective treatment method than commonly recommended vancomycin [33].

At the beginning of the 20th century Louis Pasteur discovered the microorganisms responsible for fermentation, while Metchnikoff attributed the longer life expectancy of Bulgarian farmers to their regular use of fermented dairy products like yogurt. Then he proposed lactobacilli as a potential remedy for the putrefactive effects of GI metabolism, which he claimed contributed to disease and aging [34] and considered it as a probiotic. According to expert consensus, probiotics are defined as *live microorganisms that, when administered in adequate amounts, confer a health benefit to the host* [35].

Because patients who do not tolerate metformin due to GI AEs present with a different gut microbiota composition than patients who do not experience this side effect, the question has been raised whether modifying the gut microbiota with a microbiota modulator or probiotic could reduce the occurrence of GI AEs during metformin use.

Several years ago Burton *et al.* evaluated the impact of a GI microbiome modulator (GIMM), composed of inulin from agave, β-glucan from oats, and polyphenols from blueberry pomace, on GI intolerance induced by metformin [36]. The study enrolled 10 patients with T2DM who previously reported symptoms of metformin intolerance. Utilising a 2-period crossover design with randomised treatment sequences, either placebo followed by GIMM or vice versa, the study found that co-administration of GIMM with metformin over 2 weeks significantly improved GI tolerance scores when compared to placebo. In addition, fasting glucose levels were notably lower in the group receiving metformin and GIMM as opposed to the group receiving metformin and placebo. These findings suggest that concurrent use of GIMM has the potential to improve both GI tolerance and therapeutic efficacy of metformin in T2DM management. The study's limitations include a small sample size that was not justified by power calculations. The sample predominantly consisted of African American women, limiting the study's generalisability to a broader population. The choosing of the GIMM ingredients was grounded in their specific metabolic and microbiome effects. β-glucan and inulin are oligosaccharides that undergo fermentation by colonic microbiota, leading to the production of SCFAs [37]. These SCFAs activate free fatty acid receptors and stimulate the secretion of peptides such as GLP-1 and peptide YY [38]. The polyphenols, derived from blueberries, offer antioxidant properties, altering the intestinal redox state but also modulating the GI microbiota [39].

Building on these premises, researchers in a recent meta-analysis extended the inquiry to the role of probiotics in mitigating metformin intolerance in T2DM. The meta-analysis, which synthesised results from multiple RCTs, found that probiotic supplementation can significantly reduce GI discomfort associated with metformin use [40]. Beyond symptom mitigation, the analysis also indicated that probiotics contributed to improved glycaemic control, similarly to GIMM. While many studies utilised single-strain probiotics [41], some used multi-strain as well [42, 43]. Unfortunately, it remains unknown whether the use of additional strains provides benefit. Commonly used strains included that of *Lactobacillus casei, Lactobacillus acidophilus,* and *Lactobacillus rhamnosus.* These strains have been proven to be effective in the prevention of CDI [44, 45]. Qu *et al.* demonstrated in an animal model of T2DM, that *Lactobacillus casei* enriched SCFA producing bacteria, increased SCFA concentration and downstream GLP-1 and peptide YY secretion [46]. These effects are opposite to the changes associated with metformin treatment [17]. The results of the mentioned meta-analysis of RCTs, while promising, come with caveats that must be acknowledged. The study grapples with issues such as outcome reporting inconsistencies, potential publication bias, and a mostly unclear risk of bias for allocation concealment across the included RCTs. These limitations compromise the certainty of the evidence, emphasising the need for future research. The meta-analysis concludes that larger, more robust studies are needed to corroborate these promising findings and to elucidate the underlying mechanisms.

On that note, Nabrdalik *et al.* recently conducted a rigorous 32-week, randomised, double-blind, placebo-controlled, single-centre, crossover trial aiming to lower the GI AEs related to metformin intolerance with a multi-strain probiotic. The study found that a multi-strain probiotic could effectively alleviate GI side-effects of metformin in T2DM patients [47]. Notably, the study was conducted under challenging conditions due to the COVID-19 pandemic, complicating patient recruitment. Despite these hurdles, the study successfully enrolled patients with T2DM, aged 18–75 years, with a minimum duration of diabetes of at least 6 months, and treated with a stable metformin dose of up to 1500 mg daily, who were experiencing GI AEs related to metformin use. The study used a multi-strain probiotic under the brand name Sanprobi Barrier, which included an array of bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Levilactobacillus brevis* W63, *Lacticaseibacillus casei* W56, *Ligilactobacillus salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58 in a daily dose of 2×10^9 colony forming units. A total of 37 metformin-intolerant patients were randomly allocated to receive either the probiotic or a placebo. After 12 weeks the patients crossed over to the alternate treatment arm. The outcomes of the trial revealed significant reductions in the incidence, frequency, and severity of nausea and abdominal bloating/pain, as well as an overall improvement in the self-assessed tolerability of metformin while under probiotic supplementation [47]. The trial was supported by a scientific Grant from Diabetes Poland and industry (Sanprobi sp. z o. o. sp. k.), which provided the probiotic for-

mulations, thereby emphasising the translational aspect of this research.

Conclusions

The results of research on gut microbiota in alleviating GI AEs in patients with T2DM and metformin intolerance appear promising. Based on the reviewed body of evidence, it seems crucial to use a multi-strain probiotic to alleviate GI AEs in patients with metformin intolerance and enable wider use of metformin to improve T2DM management.

Disclosures

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2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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