Modulator Role of Oral Antidiabetic Metformin on Intestinal Microbiota

Oral Antidiyabetik Metforminin Bağırsak Mikrobiyotası Üzerine Modülatör Rolü

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ÖZET

Metformin (1,1-dimetilbiguanidhidroklorür), tip 2 diabetes mellitus (T2DM) için birinci basamak tedavi olarak yaygın olarak kullanılmakta olup ABD'de en çok reçete edilen antidiyabetik ilaçtır. Metforminin karaciğer glikoz üretimini inhibe ettiği, hem karaciğer hem de iskelet kasındaki periferik glikoz alımını düzenlediği ve insülin duyarlılığını artırdığı gösterilmiştir. Metforminin karaciğerde adenozinmonofosfat (AMP) ile aktive olan protein kinaz (AMPK) bağımlı ve AMPK bağımsız yolakların aktivasyonu yoluyla hepatik glikoz çıkışını baskılayarak anti-hiperglisemik etki gösterdiği düşünülse de yapılan çalışmalar bağırsaktaki yolaklar aracılığıyla da etki gösterebileceğini ortaya koymaktadır. Metforminin hem terapötik hem de advers etkilerinin nedeni olduğunu öne sürülen mikrobiyota aracılı etkileri ve bu etkilerin mekanizmaları konu ile ilgili mevcut makalelere dayanarak incelenmiştir.

Anahtar Sözcükler: Metformin, Tip 2 Diyabet, Bağırsak Mikrobiyotası, Mikrobiyom, Biguanidler, Bakteriler.

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ABSTRACT

Metformin (1,1-dimethylbiguanidhydrochloride) is widely used as a first-line treatment for type 2 diabetes mellitus (T2DM) and is the most prescribed antidiabetic drug in the USA. Metformin has been shown to inhibit liver glucose production, regulate peripheral glucose uptake in both liver and skeletal muscle, and increase insulin sensitivity. Even though metformin is thought tohave an anti-hyperglycemic effect bysuppressing the hepatic glucose output through activation of adenosinemonophosphate (AMP)-activated protein kinase (AMPK) dependent and AMPK independent pathways in the liver, studies reveal that it may also act through pathways in the intestine. Microbiota-mediated effects of metformin, which are claimed to be the cause of both therapeutic and adverse effects and the mechanisms of these effects have been investigated based on currentarticles on the subject.

Key Words: Metformin, Type 2 Diabetes, Intestinal Microbiota, Microbiome, Biguanides, Bacteria.

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INTRODUCTION

Diabetes is a common disease worldwide and according to the latest data from the World Health Organization (WHO), the prevalence of diabetes among adults has increased from 4.7% to 8.5% in the last 34 years (1).

Type 2 diabetes mellitus pathogenesis is a process in which blood sugar levels gradually increase due to increased insulin resistance and decreased beta cell function (2). Although genetic and environmental risk factors are known, eating habits, sedentary lifestyle and intestinal-microbiota relationship are increasingly accepted (3, 4, 5, 6).

Metformin is a first-line treatment for patients with T2DM, with lifestyle changes, as noted in guidelines published by the American Diabetes Association and the European Diabetes Research Association (7).

Metformin is a biguanide derivative obtained from "Goat's rue" or "French lilac" (Galega officinalis) (8). This herb which contains galegine, at first was used to relieve the symptoms of diabetes mellitus (9). Galegine is an izoprenilguanidin (9). While stronger biguanides, phenformin and buformin were very popular in the USA and Europe in the 1960s, they were removed from the market in most countries in the late 1970s due to the risk of lactic acidosis (10). Metformin has been widely used in the UK since 1958 and in the United States since 1995 to treat type 2 diabetes (T2D) (9).

The fasting glucose-lowering activity of metformin is equal or better than other oral agents without causing hypoglycemia or weight gain (11). However, metformin can be successfully combined with all other currently used glucose-lowering agents including insulin (11).

In recent studies, in addition to diabetes and obesity, metformin has also been shown to be effective in the treatment of multiple metabolic disorders such as non-alcoholic fatty liver (12), polycystic ovarian syndrome (PCOS) (13), cardiovascular disease (14), aging (15) and even cancer (16).

When the adverse effects of metformin are examined, it is seen that gastrointestinal intolerance is of great priority (11). Approximately 15-25% of patients using metformin have metformin-related gastrointestinal side effects, and some of these patients cannot tolerate metformin due to lactic acidosis (17).

It is difficult to explain the mechanisms of a single compound that has multiple effects against different diseases, but recent evidence about the gut microbiota's role in all the above-mentioned disorders suggests a reasonable explanation for the multiple activities of metformin (18).

DISCUSSION

Although metformin has been used for more than 60 years to treat T2DM, the exact mechanism (or mechanisms) of glucose's effect on blood levels is still uncertain (19).

It is known that activating AMPK with metformin is the primary mechanism for improving hyperglycemia (20). It has been suggested that increases in cytosolic AMP with metformin may be a mechanism of AMPK activation (21).

Intestinal microbiota is a new target in metformin action mechanisms and plays a role in both the therapeutic and adverse effects of the drug (8).

Microbiota is a complex and heterogeneous ecosystem of taxonomically identified and unidentified microorganisms located in several areas of the human body, localized in the gastrointestinal tract over 70% and typed by two dominant bacterial phyla, namely *Bacteroidetes* and *Firmicutes* (22). Importantly, recent data have shown that glucose lowering effects of metformin are mediated by changes in composition and function of the gut microbiota (23).

Studies have provided evidence that intravenous administration of metformin is less effective than the oral dose for stimulating the glucose-lowering effect (24, 25, 26). Unlike oral administration, intravenous administration of metformin in humans does not improve glycemia (24), suggesting that this gastrointestinal tract may be the primary area of this drug, although these mechanisms are not currently open. In addition, after an oral administration, the metformin half-life in the blood is about 3-4 hours, which seems to be inconsistent with the duration of its glucose-lowering effect (22).

Metformin accumulates in the small intestine and large intestine at concentrations 30-300 times higher than in plasma (27, 28), thereby making the intestine the primary reservoir for metformin in humans (28).

In the light of the data presented to the literature, it has been reported that the glucose-lowering effect of metformin disappears as a result of oral administration of a broad spectrum antibiotic cocktail with oral metformin in mice (29). However, the non-reduced levels of metformin effects in AMPK knockout animalmodels increased interest in the effects of metformin on intestinal pharmacology (30).

Metformin delayed release (DR), a new formulation of metformin, has been recently developed and formulated by targeting ileum by pH-dependent dissolution of the tablet (17). Compared to metformin immediate release (IR) or metformin extended release (XR), the bioavailability of metformin DR is lower, but its glucose-lowering efficacy is similar despite low systemic metformin exposure (31). It emphasizes ileum as a region of intake and an important area of metformin in lowering blood glucose (17).

The link between the effects of metformin and intestinal microbiota has been supported by many recent studies;

Shin NR et al. examined the therapeutic effect of metformin on healing of the diabetic phenotype and investigated the possible contribution of intestinal microbiota in obese and diabetic mouse models induced by a high-fat diet (HFD) (29). This study provides detailed evidence that intestinal microbial community modulation with metformin treatment or *Akkermansia* administration may lead to an improved metabolic profile in patients with T2DM (29).

Lee H et al., in their study published in 2014, investigated metformin-induced changes in the composition and metabolic functions of the gut microbiota in HFD-fed obese mice and in normal diet-fed mice (30). Results show that the variety and composition of the gut microbiota change significantly during metformin treatment of HFD-fed mice and the changes are related to the levels of various metabolic biomarkers (30). They suggested that the specific composition of intestinal microbiota during metformin therapy had therapeutic effects on metabolic diseases, including obesity and T2DM, and that specific pathways associated with lipid metabolism may play a role in the improvement induced by metformin therapy (30).

Napolitano A et. al., in their study, used the paradigm of metformin release and restart following the rise and fall of fasting blood glucose as a marker of the metformin effect (32). As a result, they reported the pleotropic effects of metformin, including the alteration of enterohepatic recirculation of bile acids, modulation of the gut microbiota, and changes in intestinal hormones, particularly glucagon like peptide 1 (GLP1) (32).

Zhang Xet al. found that berberine and metformin, clinically effective drugs in the treatment of diabetes, altered the intestinal microbiota structure and significantly reduced microbial diversity in the gut of obese rats (18). They suggested that selective enrichment of short chain fatty acid (SCFA)-producing bacteria and reduction of intestinal microbial diversity with both drugs may be common mechanisms for improving gastrointestinal health and eventually mediate their beneficial effects on the host, particularly in metabolic and cardiovascular diseases (18).

Many of the early studies on gut microbiome did not control treatment regimens in T2DM patients, leading to different results (33). The study by Forslund K et al. emphasizes the need to differentiate the effects of specific diseases from drugs in human microbiome studies (33). Forslund K et al. published a comprehensive study combining multi-country (Denmark, Sweden and China) datasets available from 784 human intestinal metagenomas (33). Here, they showed how the antidiabetic drug affects these results using the existing 784 human metagenomas and analyzed the effects of metformin, the most commonly used antidiabetic drug (33). Study results show partial intestinal microbial mediation of both therapeutic and side effects of metformin (33). The results also provide evidence consistent with the hypothesis that metformin alters the intestinal microbiota composition by mucin-degrading *A. muciniphilla*, along with enrichment of SCFA-producing bacteria(33).

BurtonJHet al. conducted a study with metformin using a gastrointestinal microbiome modulator (GIMM) or placebo in patients with metformin intolerance with T2DM (11). They found that treatment in combination with metformin and GIMM resulted in lower fasting glucose levels and suggested that metformin treatment was better tolerated for a longer period or at a higher dosage (11). The data observed in this pilot clinical study show that GIMM can both relieve metformin-mediated gastrointestinal symptoms and improve glucose regulation (11).

De la Cuesta Zuluaga et al., in their study, aimed to test the effect of metformin on T2DM and intestinal dysbiosis relationship on Colombian adults in line with previous observations (34).Their study provides evidence compatible with the hypothesis that metformin has direct effects on the gut microbiota composition, by increasing mucin-degrading *A. muciniphila*, as well as various SCFA-producing bacteria(34).

The study conducted by Wu H et al. is among the first studies showing that there is a link between metformin and metal binding proteins produced by intestinal microbiota (35). Study data show that metformin interacts with different gut bacteria, possibly through regulation of metal homeostasis (35). The findings support the idea that altered gut microbiota mediates the antidiabetic effects of metformin (35).

Ma W et al. treatedhealthy micewith metformin to for 30 days and obtained significantly altered microbes compared to saline-treated controls (36). The results show that metformin changes intestinal microbiomes of healthy mice and the gut microbiota may play an important role in the anti-inflammatory effect of metformin in non-diabetic conditions (36).

Elbere I et al. evaluated the short-term effect of oral metformin use on the composition and diversity of human intestinal microbiome in healthy individuals, and the possible link between these changes and metformin-related gastrointestinal side effects (37).Although it induces side effects associated with the gastrointestinal tract, it has been suggested that metformin can also show its effects with its ability to modulate the intestinal microbiome (37).The findings indicating a decrease in the internal diversity of the intestinal microbiome immediately after the first two or three doses of metformin are consistent with the effects of metformin previously observed in mouse and rat models (18, 30). However, for the first time, they proved that metformin has a short-term effect on the intestinal microbiome in humans (37).

Lee H et al, in their study published in 2018, examined the effect of metformin on gut microbiota in elderly subjects and the mechanisms underlying this effect (38).In aged mice with HFD-induced obesity, treatment with merformin has significantly shifted the gut microbiota(38).The results show that modulation of the intestinal microbiota by metformin has a therapeutic effect on metabolic disorders in elderly subjects and these effects are associated with inflammatory immune responses(38).

In the clinical study conducted by Tong X et al., intestinal microbial structure was observed to be changed by metformin in humans(39). The results suggest that inhibition of potential pathogen-like bacteria may be involved in the glucose lowering effect of metformin(39). The data obtained suggest that the metformin and Chinese herbal formula AMC containing coptis chinensis and berberine can improve type 2 diabetes with hyperlipidemia by enriching beneficial bacteria such as *Blautia* and *Faecalibacterium*(39).

Bauer PVet al suggested that metformin therapy modifies the upper small intestine microbiota by increasing the abundance of *Lactobacillus*, and changes in metformin-related intestine microbiota restores a sodium glucose cotransporter-1 (SGLT1) dependent glucose sensitive pathway to regulate glucose homeostasis in the upper small intestine (40).

Sun L et al., in their study, revealed that *Bacteroides fragilis* decreased and bile acid glycoursodeoxycholic acid (GUDCA) increased in the gut as a result of metformin treatment and these changes were accompanied by inhibition of the intestinal farnesoid X receptor (FXR) signal (41). Study results show that metformin inhibits the growth of *B. fragilis* by altering the metabolism of folate and methionine, and reducing the abundance of *B. fragilis* and bile salt hydrolase (BSH) activity contributes to the improvement of glucose intolerance with metformin(41).The current study revealed that metformin therapy increased bile acid GUDCA levels in the gut by reducing the abundance of *B. fragilis* species and BSH activity in the intestines of people with T2D. As a result of inhibition of intestinal FXR with GUDCA treatment, it significantly increased serum active GLP1 levels. The results suggest that the *B. fragilis* - GUDCA - intestinal FXR axis mediates the improvement in metformin-related metabolic disorders, including hyperglycemia(41). The results also showed that metformin inhibited the gut FXR signal by modulation of the gut microbiota, not by the gut AMPK signal(41).

The primary purpose of the clinical study of Bryrup T et al., in young and healthy men,was to investigate composition changes in the intestinal microbiota following metformin intake, regardless of the physiological changes induced by the diabetic condition (42). The secondary aim was to examine whether the pre-treatment gut microbiota was associated with gastrointestinal side effects reported during metformin therapy (42). They showed that administration of metformin had an effect on the composition of the human intestinal microbiota in healthy young men, and these changes were reversed after discontinuation of metformin (42). They suggested that the pre-treatment composition of a subset of a bacterial species may predict the risk of developing gastrointestinal side effects against metformin and proposed the potential involvement of bacterial fermentation, intestinal barrier, and histamine into metformin intolerance (42).

Zhang W. et. al., in their study, observed changes in mucosal inflammation and intestinal barrier structure in response to berberine or metformin treatment in T2DM and obesity db/db mice, and compared their effects on weight, food intake and blood glucose(43). Based on the results obtained, they suggested that metformin and berberine are effective in modulating intestinal inflammation, repairing intestinal integrity, controlling weight gain and blood sugar, and supporting a healthy gut microbiome(43). Observations of the gut microbiome have shown an increase in SCFA-producing bacteria following berberine and metformin treatment, which positively affects imbalances in db/db mice(43).

CONCLUSION

Clinical research is currently approved as one of the first-line drugs for the treatment of T2DM, as metformin shows that it has a low risk of hypoglycaemia, persistent antihyperglycemic effect, cardiovascular safety, and moderate weight loss (44). Although it is accepted that it exerts its anti-hyperglycemic effect mainly through the activation of AMPK in the liver (20), recent studies in both rodents and (18, 29, 30, 36, 38, 41, 43) and humans (4, 33, 34, 32, 35, 37, 39, 41, 42) show that intestinal microbial changes may contribute to the antidiabetic effect of metformin. Although the data provide evidence that metformin exerts its antidiabetic effect through modulation of the intestinal microbiota, the mechanism of action (or mechanisms) that have not yet been clarified and needs to be clarified by future studies.

Conflict of interest

No conflict of interest was declared by the authors.

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