

Research Article

The Cross-talk Relationship between Metformin and Gut Microbiota

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Abstract

Background: Metformin is the first-line oral therapy for type 2 diabetes mellitus. However, its mode of action is poorly defined. There is an increasing awareness regarding the cross talk of gut microbiota and metformin. The current review aimed to assess the bidirectional relationship between metformin and gut microbiota.

Methods: Electronic search was conducted in Pub Med and the first 100 articles in Google Scholar published until November 2019. However, only randomized controlled trials on humans published in the English language were included. The terms “gut microbiota,” “gut flora ”and “ metformin” were as keywords to perform the search. Although 124 articles were retrieved, only six met the inclusion criteria of the study.

Results: Of the six full texts of randomized controlled trials included in the study, two-thirds were published in Europe, one in the USA, and one in China. Six hundred-thirty five patients were included and the duration of the studies ranged from seven days to six months. The studies concluded that microbiota modulates some metformin actions on plasma glucose; while metformin enhances the abundance of microbiota that positively affect insulin resistance and plasma glucose.

Conclusion: The current review showed that microbiota dysbiosis may mediate metformin antidiabetic effects. Whereas metformin shifted the gut microbiota toward the beneficial species ameliorating insulin resistance. The present study might provide insights into a novel therapeutic approach to treat type 2 diabetes mellitus.

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1. Introduction

Over decades of clinical use as the first-line drug for the treatment of diabetes mellitus, metformin has proved to be safe and well tolerated. Metformin enhances insulin action in the liver and skeletal muscles to decrease insulin production and increase non-oxidative disposal of glucose. When taken together, these actions reduce insulin in the hyperglycemic state with little potential for hypoglycemia [1]. However, the mechanism of action of metformin is not completely understood. There is an increasing awareness about the role of the gastrointestinal tract in the regulation of plasma glucose, mainly through microbiota effects on incretins, bile acids, and glucagon-like peptide [2].

The inhibition of the mitochondrial respiratory chain mediated by activation of adenosine monophosphate-activated protein kinase (AMPK) thought as the center of metformin action has been challenged and it may account for indirect changes in insulin sensitivity [3]; blocking this pathway is not followed by loss of metformin effects on glucose. In addition, oral metformin is more effective than intravenous, raising the possibility of an important gut role.

The gut microbiota is the first protection system of the gastrointestinal tract; it is composed of thousands of species and more than 15,000 kinds of bacteria in weight equal to 1 kg [4]. Recent studies showed that the gut microbiota might play an important role in the pharmacodynamics and pharmacokinetics of metformin, while the drug metformin alters the functional capacity of gut microbiota [5, 6]. The gut microbiota is an area of extensive research due to its associations with various diseases including diabetes mellitus. An interesting recent study conducted among patients with type 2 diabetes mellitus (50%), overweight/obesity (78%), co-morbid psychiatric (65%), and opioid use (45%) disorders in the USA concluded the interaction between metformin, gut microbiota, and opioid use [7].

The current review assessed the role of metformin on the gut microbiota, and whether the gut microbiota mediates the actions of metformin.

2. Methods

An electronic search was conducted in Pub Med database and the first 100 articles in Google Scholar for relevant articles in the English language; the search was limited to randomized controlled trial on humans from the first published article to November 2019. The terms "gut flora" "metformin," and "gut microbiota were used as keywords with protean and/or OR. Articles published in languages other than English and studies on animals were not included. One hundred twenty-four articles were retrieved. The titles and abstracts of the articles were screened for the removal of duplications and irrelevant articles. Only six articles fulfilled the inclusion criteria. Figure 1 illustrates the different phases of the search process.

3. Results

The six selected randomized controlled trials (four from Europe, one from the USA, and one from Asia) included 635 patients who received metformin for a duration ranging from seven days to six months, the dose ranged from 1 gr/day to 1.7 gr/day. All studies showed that metformin altered microbiota and improved glucose tolerance. In addition, metformin increased the gut microbiota species with positive effects on insulin resistance and plasma glucose, some studies reported a favorable effect on lipids as well (Table 1).

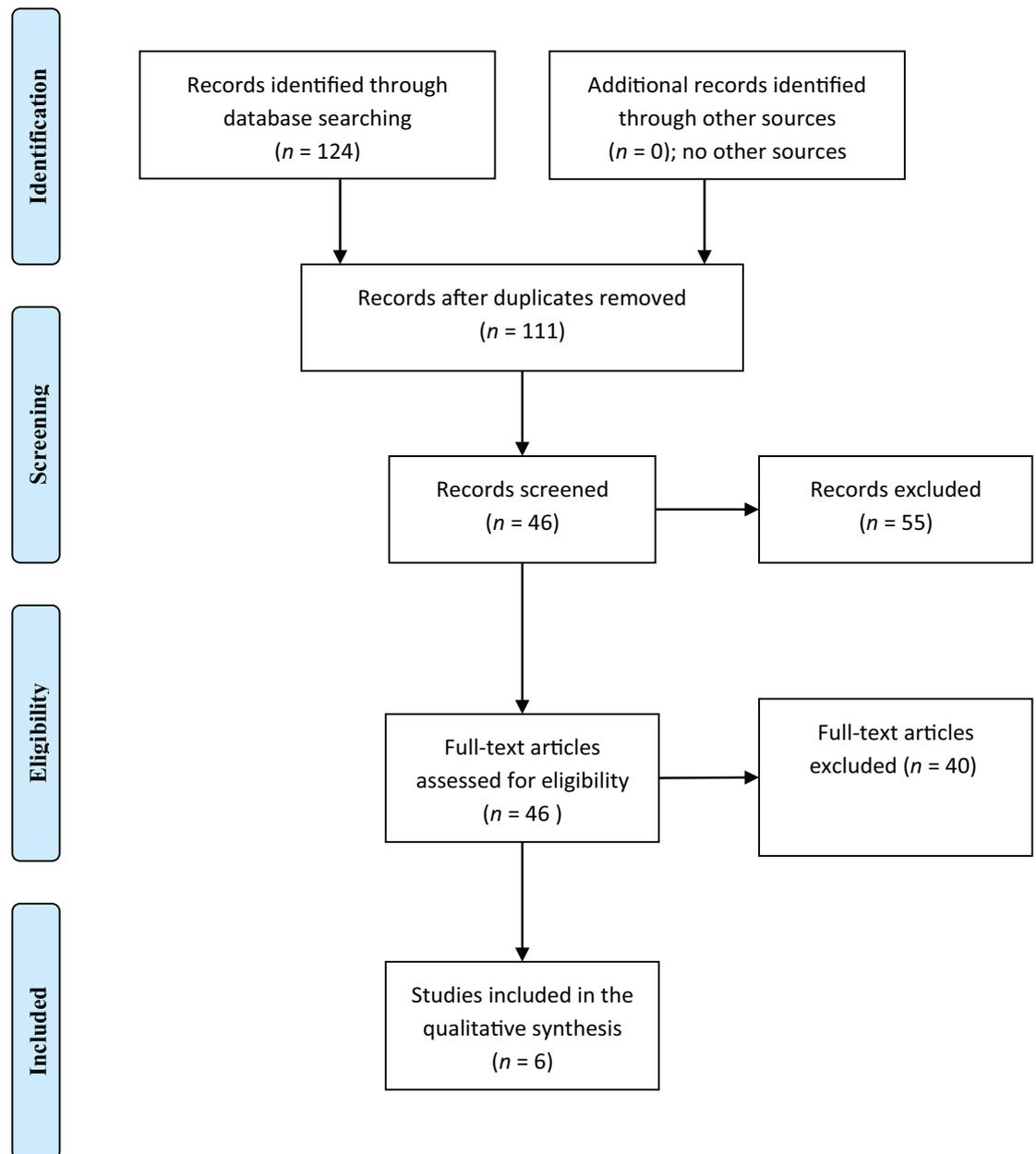


Figure 1: Flow diagram of the different phases of the systematic review (PRISMA flowchart).

4. Discussion

In the present review of randomized controlled studies, Napolitano *et al.* [8] assessed 14 patients on metformin 1000 mg/day and followed them up for three months. The study assessed gut microbiota, gut hormones including glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine, glucose-dependent insulinotropic peptide), and blood and fecal bile acids at four points (baseline, after metformin withdrawal, when the fasting plasma glucose was 25% above normal, and after the drugs were reintroduced). The researcher observed an increased level of GLP-1 and reduction in bile acids with

TABLE 1: The relationship between metformin and gut microbiota.

Author	Year	Country	Number of patients	Study duration	Results
Napolitano <i>et al.</i>	2014	UK	14	Three months on metformin 1000 mg/day	Metformin changed gut microbes (phylum Firmicutes and Bacteroidetes abundance) in patients with type 2 diabetes
Burton <i>et al.</i>	2015	USA	14	Two weeks on 1500 mg/day with microbiome modulator	Microbiome modulator (NM504) in addition to metformin increased efficacy and tolerability of the drug
Pendersen <i>et al.</i>	2016	UK	29 patients	Prebiotics for 21 weeks	No effect of prebiotics on microbiota proposed that metformin may play a role
Wu <i>et al.</i>	2017	Sweden		120 days on metformin or placebo with a washout period	Microbiota mediates some metformin antidiabetic effects; moreover, fecal transplantation from metformin-treated patients improved glycemia among mice
Albere <i>et al.</i>	2018	Latvia	18	Metformin 850 twice daily for seven days	Metformin had an immediate effect on gut microbiota
Tong <i>et al.</i>	2018	China	400	12 weeks	Metformin shifted the gut microbiota (the abundance of the <i>Blautia</i> spp. that improved insulin resistance), ameliorated hyperlipidemia, and improved glycemic control

metformin, while the reverse happened with metformin withdrawal. Furthermore, the researchers observed that the abundance of Bacteroidetes was negatively correlated with changes in cholic acid and conjugates, while phylum Firmicutes abundance was positively correlated. These results imply that metformin exerts gut-based pharmacology. A study published in the United States [9] found that the addition of microbiome modulator to metformin increased both efficacy and tolerability in the form of glucose profile improvement and lesser gastrointestinal manifestations (the most common side effects of metformin). The aforementioned findings supported the previous observations regarding the role of gut microbiota on metformin. Also, it may pave the way for more use of this essential first-line antidiabetic medication. Pendersen *et al.* [10] assessed the effects of prebiotics on gut microbiota and found no positive results. However, the authors proposed that metformin might play a role. A study [11] with a long period of follow-up (120 days) observed that microbiota mediates some metformin antidiabetic effects; moreover, fecal transplantation from metformin-treated patients improved glycemia among mice. This observation suggested that metformin may play a major role in fecal transplantation, and supporting the previous finding, fecal transplantation was an effective measure including diabetes mellitus, autism, and inflammatory bowel disease among various diseases [12–14]. It is interesting to note that metformin had an immediate effect on the gut microbiota starting from the first 24 hr [15], a study with a relatively large sample size [16] showed that metformin shifted the gut microbiota, ameliorated hyperlipidemia, and improved glycemic control.

5. Conclusion

The current review showed that microbiota dysbiosis might mediate the antidiabetic effects of metformin. While metformin shifted the gut microbiota toward the beneficial species, the current review showed that gut microbiota might serve as a promising target for diabetes control, which has become a worldwide public health threat.

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Ethical considerations

The study has been approved by the University of Tabuk, Saudi Arabia.

Competing interests

The author declares that there are no conflicts of interest.

Availability of data and material

The data included in the study is available upon reasonable request

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