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***Corresponding Author**
Zhenyu Zhang
E-mail
zhangzhenyu808@126.com
Phone
+86-025-877266246

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Effects of Metformin on Gut Microbiota and Metabolism

Dosieah Pooja, Luxuan Tan, Zhenyu Zhang*

Department of Gastroenterology, Affiliated Hospital of Nanjing Medical University (Nanjing First Hospital), Nanjing, Jiangsu 210006, China

Abstract

Metformin is considered to be the major line of treatment regarding the metabolic disorders as an example of obesity as well as type 2 diabetes. According to recent studies done, it has been reported that Metformin has a direct influence on the gut microbiota. However, the main aetiology is still unclear about the correlation between metformin and the gut microbiota. In addition, Metformin is also a well-known agent in the biguanide family that plays an important role in the treatment of diabetes because of its ability to decrease the production of glucose in the liver cells, which leads to the enhancement of insulin sensitivity and raising the peripheral glucose intake in both the hepatic as well as the skeletal muscle. Another function of metformin is the rapid induction of the adenosine monophosphate-activated protein kinase (AMPK), which is highly correlated with energy balance and the metabolism of glucose. The cellular ratio of the AMP/ATP could be also maintained via enhancing the consumption of ATP and suppressing the production of ATP, which is highly associated with the AMPK activation. Some studies have demonstrated that metformin has the ability to regulate the hepatic glycogenesis in addition to increasing the hyperglycemia dependent AMPK pathway, thus it is highly revealing that metformin can cause metabolic disorders depending on the energy status of the human body. The main objective of this study was to write a descriptive review of the literature of the past ten years in order to clarify the effects of metformin on the gut microbiota and metabolism.

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Introduction

Metformin is a commonly used drug that is required to be used within a sufficient diet in addition to a proper exercise with a correlation with other medicines for the means of high blood glucose control. It is mainly used for the treatment of type 2 diabetes leading to the control of the high blood sugar that helps to avoid the kidney damage and protects the nervous system in addition to blindness prevention as well as protection of limbs and enhancing the sexual function [1]. In addition, metformin has a very strong effect on the prevention of the disorders related to metabolism and can safely impact on a longer term on the gut microbiota is known to play an important role in harvesting energy from food, metabolic processes, and immune modulation. The main composition of the microbiota is strongly intermittent with obesity as well as type 2 diabetes in addition to some metabolic syndromes [2]. However, it was also reported that dysbiosis of the gut microbiota is highly correlated with other several diseases such as inflammatory bowel diseases, autism and some other cardiovascular diseases [3].

Based on the teamwork, research done by European and Chinese researchers, they illustrated some bacteria in the intestine from a sample taken from Denmark, Sweden and China suffers from type 2 diabetes mellitus in addition to samples taken from healthy individuals, in this study more than seven hundred individuals have been selected and the main goal was to make a separation process in the changes of the gut microbiota that may be highly associated with the usage of some [4]. This applied research shows that the drug used more frequently in patients suffering from relatively high blood sugar in the blood is metformin, which has favorable feedbacks according to the previous studies. However, it has been demonstrated that it causes changes in the gut microbiota. This could enhance the ability of the bacteria to obtain specific short-chain fatty acids, mainly propionic acids and butyric acids that boost the capability of the bacteria to produce certain types of short-chain fatty acids, such as butyric acid and propionic acid. These fatty acids have the ability to reduce the high level of blood glucose in several methods [5]. Metformin has also revealed some side effects in the gastrointestinal tract, as an example excessive flatulence and bloating. The main objective of this study was to write a descriptive review based on studies conducted in the past ten years in order to clarify the effects of metformin on the gut microbiota and metabolism.

Gut microbiota and the correlation with metformin

According to the recent researches done, it has been demonstrated that metformin has an influence on the microbiota in the human intestine, for example, intestine-bacteria suppression in addition to the gut metabolism as the rapid increase in the production of the butyrate [6, 7]. These mentioned observations highly support the relationships between the microbiota composition and obesity in addition to diabetes in one side and metformin and its effects on the other sides [8]. It is highly important to identify whether metformin has a direct impact on the systemic carbohydrate breakdown via the mechanisms of the gastro-enteric, which lacks the direct inclusion of the gut microbiota [9]. It has been also reported a relevant alteration in bile acid and some enteric hormones in addition to the influences on the adenosine monophosphate-activated protein kinase (AMPK) signaling in the duodenum that has a correlation with the decrease of the glycogenesis in the hepatic cells [9,10]. Another study has found an obvious evidence that metformin has the ability to impact the gut microbiota [11]. The baseline of action as the glycogenesis still shows a high evidence to the treatment prognosis of diabetes type 2. Thus, it is highly suggested to conduct more research into the means of the average estimate of the proportion of the positive outcomes from metformin and the changes in the microbiota of the gut [12]. It would not be an illogical result if it differs from an individual to another.

Biguanides are commonly known for their anti-microbial ability; amongst some of them could have an anti-malarial as well as antiseptic effects. Their anti-malarial activities have been clarified [13], however, the major aims of the anti-bacterial activities reveal an incomplete feedback of knowledge. Thus, it is highly demonstrated that metformin induces impacts on the gut microbiota composition [14]. According to a recent study, it has been reported that there is an additional correlation within the key factors affecting the rate of the concentration of the gut metformin proceeding oral intake [15]. It is well known that the concentration of the metformin in the gut may exceed one hundred-fold, which located in serum, going through their mechanisms, a higher milli-molar rate of concentration is required and it could not be systemically achieved and show an intimate relation

to the effects on the microbiota [16]. The recent studies have been reported a direct correlation between the broad existence of *Akkermansia muciniphila* and obesity in addition to type 2 diabetes. A sufficient change occurred to *A. muciniphila* with the usage of metformin as a medicine of treatment and the mentioned results were confirmed by an experimental study done on rat models [17]. Even though the results of these studies have been just in accordance with the relation between the glucose homeostasis and the gut microbiota for only a short duration of time [18]. In addition to the correlation between the metabolic enhancement and treatment with metformin that is due to the fact that changes in the gut microbiota still not confirmed [19]. The results obtained are significant with the studies done, Additionally, it has been found a high effect of metformin on *A. muciniphila* growth, which positively explains the results illustrated in a mouse model, it has been concluded that metformin may act as a growth factor for *Akkermansia* spp.

Metabolic syndrome

Metabolic syndrome becomes more aggressive within time, the more the intake of the carbohydrates in the daily meals, the more the enhancement of the pancreatic cells to release insulin in order to suppress the blood sugar rate [20]. The epithelium of the intestinal lining, the mucosa of the immune system in addition to the bacterial and non-bacterial materials which show the amorphous-functional entire process [21]. Several pathways regarding metabolism and the functions of the intestine have been illustrated to figure out and identify the effect of the gut microbiota on the metabolic disorder syndrome. One of these was clarified by a study done in the late 90s and it explained the first mechanism as a result of the high amount of energy gained from the diet by breaking down the compound polysaccharides into monosaccharides in addition to short chain fatty acids, thus the carbohydrates that didn't undergo the digestion mechanisms are considered to be a main source of energy for many colonic microbiota members [22]. The microbiota in obesity is highly correlated with the genes indicated in several enzymatic fermentation and transport proteins mainly phosphor-transferase. The high level of concentration of the products of the end fermentation for the short chain fatty acids as butyrate and acetate in addition to propionate considered as not only a highly important source of gaining energy for colonocytes but also as molecules having signals that regulates the energy outgoing with correlation with two G-protein receptors that underwent coupling process (GPR41–GPR43) [20]. It is obviously demonstrated in a recent research that G-protein receptors are located mainly in the endocrine cells of the intestine and act as energy balance regulators. Gut microbiota has really reported as a major factor in the environment that drives metabolic disorders [23]. It goes without saying that the microbiota of the gut is revealed as a separate endocrine part of the body, which is mainly intimated through a molecular interaction with the host cells in keeping the energetic homeostasis and the immunity regulation of the host. Any occasional change or shift in the gut composition of microbes that may be caused by external factors will directly affect the host and the bacteria of the gut relation causing alteration, which leads to the metabolic disorders existence [24]. The microbiota of the gut is considered as a contributor to the disorders of metabolism through low-grade inflammation stimulation. Obesity is a common disease, which is characterized by the extra fat tissue deposition, and it happened when there is a lack of balance between the energy intake and the energy produced [25]. The mechanism of obesity onset is not an easy process which is revealed by the genetic as well as the environmental factors and it is most commonly associated with many chronic complexities establishment, as an example, the high level of blood sugar known as hyper-glycaemia, and also the high level of triglyceride which is known as hypertriglyceridemia in addition to the low level of lipoproteins having a high density which is known as dyslipidemia as well as a rapid rise in the blood pressure which is known as hypertension [26]. Those individuals who are diagnosed with at least three options of these criteria can be tentatively diagnosed for a metabolic syndrome that leads to enhancing the risk of obtaining metabolic disorders as an example some cardiovascular diseases and type 2 diabetes.

Conclusions

Metformin is a mainly used medicine for the treatment of obesity and type 2 diabetes and is highly recommended by all the physicians. According to the research done on this area, a high number of patients revealed better prognosis after its usage, especially for type 2 diabetes, thus it has been concluded that metformin has a an intimate correlation with the microbiota of the gut, leading to the alteration and changes which in accordance leads

to metabolic disorders so, it is highly suggested in the future to pay more attention to the cellular pharmacokinetics and more studies are needed to elaborate the exact mechanisms by where the gut microbiota mediators are capable of obtaining metabolic disorders.

Conflict of Interest

The authors declare that they have no conflict of interest.

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