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Metformin exerts anti-obesity effect via gut microbiome modulation in prediabetics: A hypothesis

Kunal Maniar [a], Amal Moideen [a], Rajasri Bhattacharyya [b], Dibyajyoti Banerjee [b,*]

[a] Department of Pharmacology, Post Graduate Institute of Medical Education & Research, Chandigarh, India
[b] Department of Experimental Medicine & Biotechnology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

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ABSTRACT

Prediabetic individuals are characterized by high levels of insulin, an anabolic hormone having an important role in the maintenance of glucose homeostasis. However, insulin has also been found to increase the growth of certain bacteria which form the non-butyrate producing part of the gut microbiome. The gut microbiome is recently in focus for its strong association with many chronic diseases such as type 2 diabetes mellitus and obesity. Metformin, a widely popular anti-diabetic medication has been shown to prevent weight gain in many trials. There are many studies postulating the mechanisms of the anti-obesity effect of metformin including improvement in insulin sensitivity (and consequently a reduction in insulin levels). Recently, however, it is becoming evident that metformin's action is likely to be primarily mediated by the gut. Further, metformin has also shown to affect the growth characteristics of certain bacteria which form the part of the human gut microbiome. With this frame of reference in mind, we hypothesize that metformin is likely to exert its anti-obesity effect by altering the composition of the gut microbiome. If proved, this has the potential to contribute to the management of obesity and pave the way for the development of novel anti-obesity drugs.

Introduction

Obesity is currently an epidemic receiving attention due to its rising prevalence and burden on human health [1]. The incidence of morbidity and mortality associated with it is rising [2]. It is also linked to several diseases such as diabetes mellitus, dyslipidemia, hypertension, cardiovascular diseases [3],etc. Although the western populace still shares a significant burden, global trends indicate that obesity is on the rise in several developing nations [4,5]. Its prevalence spans all age groups and is significant enough to be a financial burden on economies [6,7].

Prediabetes, defined non-uniformly by various health organizations is an intermittent state of hyperglycemia and is an important marker for the development of diabetes [8]. Epidemiological data suggests that the incidence and prevalence of prediabetes exceeds that of diabetes mellitus, except for the United States, where the incidence of diabetes mellitus is higher than prediabetes [9]. Prediabetes is a major risk factor for the development of type 2 diabetes mellitus (T2DM). Further, it is also closely related to cardiovascular disease, metabolic diseases and polycystic ovarian disease [8]. Obesity is associated with insulin resistance, which also constitutes prediabetes. Obesity and Prediabetes are frequently found together as a part of spectrum of metabolic syndrome. Such individuals are at a significantly higher risk for development of comorbidities and have higher mortality rates compared to normal populace [10].

Despite the burden, the interventional strategies to control obesity remain limited. Lifestyle intervention, although a good option is not sustainable for most people [11]. Psychological interventions and bariatric surgeries come with their set of unique challenges such as inability to administer on a mass scale and *peri*-operative morbidity/mortality respectively [12,13]. Pharmacological intervention to treat or prevent obesity is an attractive option, but has a chequered past [14]. Currently, there are very few anti-obesity drugs on sale, and most of them are primarily indicated for other diseases, the most prominent example being metformin [14]. Thus, there is considerable interest to develop new alternative strategies to tackle obesity. Recently, the gut microbiome is receiving considerable attention due to its role in obesity and T2DM [15]. Metformin, the recommended first line oral anti-hypoglycemic agent in T2DM, has shown to exert certain beneficial effects in the gut microbiome of T2DM (see below). Metformin intake is also associated with a prevention of weight gain. Although several mechanisms exploring the reasons for this effect

* Corresponding author at: Department of Experimental Medicine and Biotechnology, Research Block B, PGIMER, Sector 12, Chandigarh, India.
E-mail address: dibyajyoti5200@yahoo.co.in (D. Banerjee).

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(i.e. prevention of weight gain) have been reported, recent literature suggests that metformin's action may be predominantly mediated via the gut [16,17]. Keeping this frame of reference in mind, we propose a hypothesis explaining metformin and its role as an anti-obesity drug.

Hypothesis

We hypothesize that metformin exerts its anti-obesity action by enhancing the butyrate-producing taxa in the gut microbiome in the hyper-insulinemic phase of prediabetes. In this article, we propose that metformin exerts such effect by altering the gut microbiome in the presence of hyperinsulinemia. It has the potential to further our understanding of the underlying pathologies of obesity as well as help in the development of new anti-obesity agents.

Validation of the hypothesis

The gut microbiome has been recently associated with obesity and prediabetes [15]. Individuals with obesity and/or prediabetes exhibit a different pattern of gut flora as compared to normal individuals and the gut flora of these individuals (obese and/or prediabetic) is thought to be in a state of dysbiosis [18,19]. The human gut microbiome is predominantly inhabited by bacteria belonging to select phyla such as *Bacteroidetes, Firmicutes, Actinobacteria and Verrucomicrobia*; and the *Bacteroidetes* and *Firmicutes* phyla form the overwhelming majority (>90%) amongst these select group [18]. Although there is considerable inter-individual variation in the gut microbiome, the various taxa are thought to perform the similar functions and hence form the 'functional core' [20]. There are other characteristics of a healthy microbiome such as resistance, resilience, stability and diversity [20]. Obesity and T2DM are states associated with a lack of diversity of microbiome in the gut. Obese individuals were found to harbor lesser short-chain fatty acid (SCFA) producing bacteria compared to controls [15]. Pregnant women with a higher weight gain showed an increase in *Escherichia coli* (*E. coli*) in fecal matter compared to those with normal weight gain [21,22] and a study in Chinese adolescents reported that obesity was associated with a decrease in the stool *Bacteroidetes* to *E coli* ratio [23]. The control of obesity is also associated with a shift in the composition of the gut microbiome [24]. Therefore, as on date, there is a considerable current interest in gut microbiome and obesity.

Prediabetes is often associated with obesity and hyperinsulinemia. Insulin is a well-recognized factor associated with obesity [25]. It is known to be positively correlated with obesity in vitro and in vivo [26]. Insulin has also been found to enhance the proliferation of two non-butyrate producing bacteria (NBPB) of the gut microbiome, namely *E coli* and *Staphylococcus aureus* (*S aureus*) in the presence of metabolizable sugars [27]. Higher doses of insulin also enhances the proliferation of *E coli*, *mycobacterium spp. and S aureus* independent of such sugars [28]. It is interesting that as on date, growth of any member from butyrate-producing taxa of gut microbiome is not reported in the presence of insulin. Rather members of butyrate-producing taxa of gut microbiome improve insulin sensitivity [29].

The state of pre-diabetes is characterized by high insulin levels, and it is also observed that the concentration of insulin in the portal circulation is greater compared to the peripheral circulation in non-diabetic [30] and diabetic subjects [31]. It is plausible to reason that in hyper-insulinemic phase of prediabetes portal blood insulin will also rise significantly. Such high insulin levels can promote the growth of NBPB in gut microbiome (particularly *E coli* and *S aureus*). This high insulin induced growth of NBPB may consequently result in gut dysbosis, which is often associated with chronic diseases such as obesity [15,32]. A study assessing the changes in the gut microbiome in normal, pre-diabetic and newly diagnosed T2DM individuals found a significant reduction in the butyrate producing taxa between the pre-diabetic and normal individuals [33]. There was significant difference in body mass index (BMI) as well as the insulin levels between these two groups, and similar associations were also found between the T2DM and pre-diabetic groups. This shift of the microbiome towards NBPB may result in a state of gut dysbiosis, typically associated with insulin resistance T2DM and obesity. Increased insulin resistance will further cause a rise in insulin levels and accentuate the growth of NBPB thus resulting in a vicious cycle (see Fig. 1). The gut microbiome of obese animals also demonstrates an increased capacity to harvest energy [34]. Metformin is known to improve the hyperinsulinemic state by reduction of insulin levels [35]. So, metformin by reducing insulin can lessen the growth of at least two non-butyrate producing components of gut microbiome (Fig. 1). Reduced insulin levels are shown to have a positive effect on the control of obesity. It is likely to explain the prevention of weight gain in metformin users observed in many various clinical studies [36–39].

Metformin, which is administered via the oral route is absorbed by the small intestine at varying levels depending on certain factors such as the type of formulation. There is increasing evidence to support that its action may be primarily mediated by the gut [16,17,40]. Observations suggest that its absorption is limited to ~60% of the administered dose, and unabsorbed fraction of the drug is excreted unmodified in the feces [17]. This leads to the contact of a significant amount of metformin, reported to be as high as 50 mM in the small intestine [41], and the microbes inhabiting the gut. Recent studies have indicated that metformin administration is associated with the increase in butyrate producing taxa in type 2 diabetes [42–44]. Metformin is also known to inhibit the growth of *E coli*, a non-butyrate producing component of the gut microbiome [45]. One study has also reported the increase in growth of *Akkermansia muciniphila*, a butyrate producing bacteria in presence of metformin [46]. These changes may be due to the contact of metformin and gut microbiota. Thus, metformin, by decreasing the non-butyrate producing, taxa is likely to increase the butyrate producing component which may shift the composition of microbiome of obese persons to that comparable to healthy individuals and control gut dysbiosis. In a Colombian study comparing the differences in the composition of gut microbiome between obese individuals with and without diabetes, it was found that metformin users had a distinct microbiota compared to diabetic individuals not taking metformin and non-diabetic obese individuals [43]. The metformin users showed a significantly higher composition of butyrate producing taxa in their gut. Another lab has reported the increase in the butyrate producing taxa in vitro and in vivo, along with the upregulation of metabolic pathways involved in fatty acid and sphingolipid metabolism in presence of metformin [46]. This study also reported a significant correlation between the glucose levels and butyrate producing bacteria adding evidence to the theory that metformin's anti-hypoglycemic effect may be primarily mediated by the gut. The increase in the butyrate producing taxa in the gut will likely improve insulin sensitivity [29] associated with the prediabetes and thereby expected to reduce the insulin levels. The reduction of insulin levels will lessen the effect of insulin on the growth of NBPB (at least *E coli* and *S aureus*) and thus break the insulin promoted feedback cycle seen in Fig. 1 and expected to control obesity. The increase in butyrate-producing taxa is expected to increase the butyrate production and improve gut barrier [47]. The increased butyrate present in the gut will then enter the circulation (on account of its lipid solubility), is likely to improve insulin sensitivity [48] (which in turn will reduce insulin levels) and exert its anti-obesity effect in syner-