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Review

A story of metformin-butyrate synergism to control various pathological conditions as a consequence of gut microbiome modification: Genesis of a wonder drug?

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ABSTRACT

The most widely prescribed oral anti-diabetic agent today in the world today is a member of the biguanide class of drugs called metformin. Apart from its use in diabetes, it is currently being investigated for its potential use in many diseases such as cancer, cardiovascular diseases, Alzheimer's disease, obesity, comorbidities of diabetes such as retinopathy, nephropathy to name a few. Numerous in-vitro and in-vivo studies as well as clinical trials have been and are being conducted with a vast amount of literature being published every day. Numerous mechanisms for this drug have been proposed, but they have been unable to explain all the actions observed clinically. It is of interest that insulin has a stimulatory effect on cellular growth. Metformin sensitizes the insulin action but believed to be beneficial in cancer. Like -wise metformin is shown to have beneficial effects in opposite sets of pathological scenario looking from insulin sensitization point of view. This requires a comprehensive review of the disease conditions which are claimed to be affected by metformin therapy. Such a comprehensive review is presently lacking. In this review, we begin by examining the history of metformin before it became the most popular anti-diabetic medication today followed by a review of its relevant molecular mechanisms and important clinical trials in all areas where metformin has been studied and investigated till today. We also review novel mechanistic insight in metformin action in relation to microbiome and elaborate implications of such aspect in various disease states. Finally, we highlight the quandaries and suggest potential solutions which will help the researchers and physicians to channel their research and put this drug to better use.

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1. Background

Despite being a widely prescribed anti-diabetic drug today [1], metformin's fame eclipses its labored history. Metformin is a dimethyl biguanide, whose natural ancestor is a plant called *Galega officinalis*, which originated in the temperate climes of Southern Europe and Western Asia [2]. *G. Officinalis* (also known as Goat's Rue, French Lilac, and Professor weed) was used in ancient times for patients suffering from polyuria (now known to suffer from diabetes mellitus), to induce perspiration in patients with the plague; worms, snake bites and to induce lactation in cows [3]. The plant is too toxic for agricultural use and is now classified as a noxious weed in many states in U.S.A [4].

G. Officinalis is rich in guanidine and galegine, both of which have demonstrated glucose lowering activity in animals [5]. Due to the toxicity of guanidine in humans, galegine was studied with greater interest in early days. Subsequently, two synthetic diguanide derivatives called as Synthelin A (decamethylene diguanide) and Synthelin B (dodecamethylene diguanide) were used clinically in the 1920s. Much other glucose-lowering biguanides including metformin (dimethyl biguanide) were developed in 1929 and found to be non-toxic in animals [2]. However, no human studies were done at the time which could be attributed to the discovery of insulin during the same period, growing appreciation of limited efficacy and toxicity of diguanide derivatives (synthalins), and world war 2; all of which resulted in metformin along with synthalins being rendered into the history pages. Interest in metformin was rekindled in the 1940s when a French Physician Dr. Jean Sterne observed the glucose lowering effects of 'flumamine,' a formulation containing dimethylguanide used for the treatment of influenza in the Philippines [6]. Simultaneous studies on phenformin and buformin published around the same time, saw the rise of the use of biguanides in clinics, offering an oral anti-hypoglycemic alternative compared to insulin injections [2]. Phenformin and buformin being more potent than metformin were preferred. However, they were also associated with a high incidence of lactic acidosis [7], which led to their and metformin's discontinuation in the U.S.A., Australia, and many other countries despite different pharmacokinetics of metformin compared to phenformin and buformin. Of course, now we know that phenformin and buformin were associated with greater incidence of lactic acidosis due to the inability of certain patients to metabolize the complex alkyl chains present in their chemical structures [8] (see Fig. 1).

Despite its ban in many countries, experienced European endocrinologists continued to prescribe metformin to their patients, and a subsequent meta-analysis by Campbell et al. [9] found that unlike sulfonylureas, metformin could lower blood sugar without causing overt weight gain. Bailey et al. [10] also found that metformin could improve insulin resistance. This led the U.S.A. and other countries to relax their ban on metformin in 1995 [10]. However, it did not gain widespread popularity and acceptance until recently when the United Kingdom Prospective Diabetes Study (UKPDS) showed the independent benefits of metformin on cardiovascular outcomes [11]. This led to metformin being the first line recommendation by U.S.A. and European physicians [12].

Today metformin is the most popular antidiabetic drug. Its cost effectiveness makes it an attractive option for the policy makers, physicians and the patients [13,14]. It is widely believed that metformin is an insulin sensitizer [15]. Insulin is known for cellular growth and anabolic activity [16,17]. So, by sensitizing insulin metformin is expected to enhance carcinogenesis. However, the published observations seem to suggest contrary actions [18–33]. Likewise, insulin stimulates lipogenesis and metformin by sensitizing insulin action, is expected to stimulate lipid synthesis further and thus increase obesity as well as aggravate certain comorbidities such as atherosclerosis, and triglyceride accumulation in the liver. However, metformin is believed by some authorities to be helpful for reduction of body weight [34,35], and is perceived to be beneficial in atherosclerosis [36–43] and non-alcoholic fatty liver disease [44,45]. Therefore, in a contradictory set of pathological situations thinking from an insulin-sensitizing angle, metformin is having to be claimed to possess beneficial role. In fact, with metformin reports of clinical trials are getting published almost every day, and its role beyond an antidiabetic drug is highlighted in several clinical trials (Table 1). There are recent reviews that address the fact that metformin is prescribed in a wide range of clinical conditions [46]. However, a review of the clinical scenario in totality where metformin may have a potentially beneficial role is not yet published. It will be interesting for the clinical researchers to know that in what spectrum the beneficial role of metformin is currently postulated. It is in this context we have done our study to review the metformin action on pathological states where it is believed to be beneficial.

2. Metformin as an antibiotic: a proposed action

Prior research had concluded that insulin has no effect on bacterial growth in the absence of metabolizable sugars [47]. It has been recently observed, supraphysiological concentrations of insulin proliferate bacterial cells independent of glucose [48]. Simply put, insulin may have the capability to enhance bacterial growth independently. Metformin, being an insulin sensitizer is therefore expected to influence this phenomenon. For example, it may be plausible within reason to assume that metformin's insulin sensitizing activity may further enhance the environment favourable for bacterial growth and thus aggravate infections in diabetic patients. However, recent studies seem to suggest that metformin may, in fact, reduce the infections in the diabetic state [49].

Metformin has several actions which make it a very attractive option to consider as an antibiotic. It acts on the bacteria by inhibiting the energy generating processes as well as inhibiting the substrates required for their growth. In humans, it has a dual role of altering the microbiota and modulating the immune system which together should add to its effect as an antibiotic.