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Educational Forum

Metformin: A Reflection on My Journey as Antidiabetic Drug

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Editor's Comment: Here is a reflection by Metformin on its metaphoric journey and evolution as an antidiabetic drug and further role it presumes to play in alleviating human sufferings.

What Happened?

I was created out of a chemical compound found in medieval herb Galega officinalis (Goat's rue, French lilac). The immature seed pods of plant were found to be having guanidine chemicals. In Europe, wild G. officinalis was widely recognized as an animal galactagogue from which it gained its name ('Galega' being derived from the Greek for 'milk stimulant'). In 1910, guanidine was reported to lower blood sugar. Then, synthesis of monoguanidines (Galegine-isoamylguanidine) and biguanides (Synthalin A and B) paved the way for my development as antidiabetic drug, though these chemicals were too toxic to be used. Eventually, Werner and Bell, in 1922, became my (metformin is dimethylbiguanide) creator and by 1929, I began to show the glucose lowering effects in animals. Simultaneously, more kins (Buformin and Phenformin) were born but could not match with my effects as I proved to be less toxic. This was the time when insulin began to be available and clinicians were less inclined to experiment with me. This led scientists to explore our potential for other uses. In the 1940s, one of the kins was then groomed (developed) to treat malaria (Proguanil - a biguanide was used as antimalarial in Philippines!). I was rediscovered in the search for antimalarial agents and was repurposed to treat influenza as *flumamine*. The users regularly reported glucose lowering activity. All suspected my role in it![1,2]

The credit for my use to treat diabetes goes to Dr Jeans Sterne, a physician in Paris, France, who in 1956, along with Dr Denise Duval, carefully conducted experimental studies on Biguanides and Dr Elie Azirad conducted clinical studies on me.[3] Most of their patients had T1DM and T2DM and were on insulin. They concluded that I reduced insulin requirement and could replace insulin in some cases. Two significant observations noted were that I did not produce hypoglycemia and second, that little glucose lowering effect was seen in normal individuals. Sterne published his brief account of research in Moroccan Journal in 1957. Thus, Sterne became my foster father for his prodigious research. He actually named me as GLUCOPHAGE (a Glucose Eater!) Thus, M/S Aron Pharma used it as brand name and I became widely used in Europe. As was destiny, I finally found my role in diabetes management by serendipity and prodigy. By 1972, I was available in Canada but not in USA. Thus worldwide, I was used to a limited extent only.[1] This was because:

1. *Simultaneous development of sulphonylurea derivatives and increasing availability of insulin.*

Tolbutamide, the first sulfonylurea, was introduced in Germany in 1956, followed by chlorpropamide, acetohexamide, and tolazamide. In 1984, more than 14 years after their introduction in Europe, glyburide (Glibenclamide) and glipizide, which are more potent second-generation sulfonylureas (SU), became available in the United States. Glimepiride, the most commonly used SU today, became available later in 1995. These SUs were found to be effective and cheap. However, hypoglycemia was noted to be a major adverse drug reaction (ADR). I am proud to say I do not cause hypoglycemia or lower blood glucose in normoglycemics!

2. *Phenformin and buformin are my twin sisters*

Buformin resembles me in pharmacokinetics but phenformin differs as metabolized by CYP2D6 in liver. Both overpowered me (in dose-to-dose potency and mitochondrial binding). Phenformin, little younger to buformin, became popular in USA from 1957 onwards and Buformin was widely used in Germany in early 1960. Obviously, clinicians were less inclined to use me as yet another biguanide and thus, I was sidelined. I suffered the brunt as innocent bystander and remained sparingly used for a considerable period. However, fortune smiled on me ultimately! From 1980 the term maturity onset diabetes was replaced by Noninsulin dependent diabetes, thus; more

stress was given to peripheral extra-pancreatic actions of antidiabetic agents. More and more reports poured in on my prominent extra-pancreatic actions on liver, intestines and skeletal muscles and that enhanced my acceptability as a substitute of twin sisters! Later, large comparative trials (v/s sulphonylureas) were also done in UK. With the withdrawal of phenformin from the University Group Diabetes Program (UGDP) trial in 1971 and its subsequent ban in 1977 in USA due to lactic acidosis, I became a suitable biguanide in use. In 1986, Lipha Pharmaceuticals, that acquired Aron Laboratories, requested US FDA to review and reassess clinical evidence of my efficacy and safety to approve it. I am indebted to Dr. Gerard Daniel and Dr. Anita Goodman, who provided convincing evidence to US FDA. Finally, FDA approval came on 29 December 1994. As prescriber confidence grew, an extended-release formulation was approved in 2000 with reduced gastrointestinal side effects. Subsequently, I was co-formulated with other antidiabetic agents.[2]

Meanwhile, my unique features were identified in the UKPDS (1998).[4] I am weight neutral on long term use with low risk of hypoglycemic episodes, and reduce cardiovascular events and improve survival. I delightfully showed that reduced cardiovascular risk was found to be largely independent of my antihyperglycemic action! Substantial literature has accumulated to show my salutary effects on the macro- and microvasculature. A 10-year follow-up of the UKPDS in 2008 showed a continued cardiovascular benefit of early use. Thus, my status was elevated from a neglected child to virtuous stunner, and I became first line drug for management of T2DM, the position which I enjoy even today! I became the most sought (prescribed) glucose-lowering medicine worldwide and was included in the WHO's essential medicines list.[5] Thus, an inexpensive and efficacious drug, me, the metformin, was widely available to mankind.

So What?

I look back and cogitate about my evolution as an antidiabetic agent and ask myself, "Isn't it an example of Reverse Pharmacology?" An inner voice says, "Yes, surely it is."

But, what about serendipity? Yes, "more so", the voice echoed.

"Why should I boast about myself", I ponder over and ask myself, "What is unique about me not found with other antidiabetic medicines?"

Well, an inside of my pharmacokinetics and pharmacodynamics does reveal features that make me unique.

Pharmacokinetics[6,7]

I was formulated as a simple tablet of 500 mg and later reformulated as extended-release preparation to reduce GIT side effects and provide longer sojourn in body.

- I am well absorbed (70%-80%) and remaining goes down colon unabsorbed in feces and food does not affect my bioavailability
- I have no affinity/bondage for plasma proteins and remain free in circulation. I get accumulated in heterogenous manner in various tissues and organs. Thus, I am highly concentrated in jejunum, liver and kidneys. I reach into liver through portal vein and accumulate in hepatic mitochondria (concentration is over 1000 times). I play havoc in mitochondria, inhibiting complex-1 of chain reaction and ATP generation. In addition, I change the NAD^+:NADH ratio, to suppress gluconeogenesis and inhibit the glycerophosphate shuttle. Thus, hepatic glucose output and release is decreased.
- Though, liver is the main site of my action, but I resist metabolism and do not show any metabolic interactions involving hepatic cytochrome system.
- I am a water-soluble molecule so I cannot cross lipid membranes of body cells and require specific protein transporters such as Organic Cation Transporters (OCTs). These reach me to enterocytes, hepatocytes and renal epithelial cells.[8] After oral ingestion, I am picked up (taken up) by enterocytes via the plasma monoamine transporter (PMAT) and the organic cation transporter (OCT-3), both of which are located on the luminal surface of the gut epithelium.[9,10] From here, I am transferred to interstitial fluid from the serosal side by OCT-1.[10] However, my transportation into hepatocytes takes place by OCT-1 and OCT-3.
- Moving around body tissues and organs, I reach kidneys for glomerular filtration. Here, another transporter, OCT-2 takes me up into renal tubular epithelial cells from basolateral membrane. The transporters MATE-1 and MATE-2 (Multidrug And Toxin Extrusion) in the apical membrane of the renal proximal tubule cells contribute to my renal tubular secretion (excretion).

While I have been in use for six decades now, I was intrigued by the fact that some diabetics (ethnic disparity) did not benefit from me. As many as 21% of patients initiating treatment fail to meet glycemic goals in the first 5 years of treatment. The researchers have found the reason. It is in their genes. Among the candidate genes studied, the SLC22A1 gene, encoding OCT-1, is highly polymorphic, with a number of missense SNPs affecting its activity. There are four variants of this gene (alleles) which show reduced function and poor metformin response by impairing intracellular transport in hepatocytes.

Doses and dosing

My usual dose as immediate release tab (500 mg, 850 mg, 1000 mg) is to be taken with meals two times a day (maximum dose 2 grams). But, more frequently used formulation is extended-release Metformin (ER/XR), available as 500, 750 and 1000 mg tablets. My ER form has a dual polymer matrix, which slowly releases the active

drug. It enables slower drug absorption in the upper GI tract, providing an option of once-daily dosing (taken with evening meal), and also decreasing the frequency and severity of GI side effects.[11] The dose adjustment needs to be done in kidney disease as I am excreted by kidney.

Renal disease

1. GFR > 45 ml/min/1.73m^2: Lower the dose to a maximum of 1000 mg twice daily.

2. GFR > 30 but < 45 ml/min/1.73m^2: A target dose of 1000 mg once a day.

3. GFR is < 30 ml/min/1.73m^2: Do not start

Liver Disease[12]

Potential to cause lactic acidosis, so not preferred

Mild disease: may be used

Moderate disease: Avoid/ may be used at lower dose

Severe disease: Contraindicated

Adverse Drug Effects

I am considered as a well-tolerated drug in diabetics. About 30% recipients may get anorexia, nausea, vomiting or loose stools. These are attributed to my high concentration in enterocytes, release of serotonin from enterochromaffin cells and to altered intestinal microbiome. These GIT effects are lessened with ER or XL tablets.
Other effects are chest discomfort, headache, perspirations, hypoglycemia, weakness, and rhinitis. A cause of concern is B_{12} deficiency occurring in about 6% to 30% of patients on long term therapy and is attributed to B_{12} malabsorption due to changes in the microbiome, altered motility, and/or alterations in the calcium-dependent B_{12} transport via the gastric intrinsic factor glycoprotein. I would advise to monitor B_{12} levels and if required supplemented by exogenous B_{12}. I could significantly alter the relative abundance of several bacterial strains and microbes in gut. I am shown to promote changes in the prevalence of Escherichia and Intestinibacter, and increase lipopolysaccharide biosynthesis and short-chain fatty acid metabolism.[13] Lactic acidosis (Anion Gap acidosis) is uncommonly reported particularly when there is concomitant use of bupropion, acetazolamide, cephalexin, cimetidine, dolutegravir, ethanol, glycopyrrolate, iodinated contrast agents, lamotrigine, ranolazine, and topiramate. Otherwise, I befriend with other antidiabetics.

Male Reproductive Health: A large cohort Canadian study showed that when males used me (Metformin), genital birth defects were noted in male offsprings![14] This needs to be evaluated further. A preconception counselling may be warranted.

Environmental Hazards: Several hundred thousand of diabetics are taking me in a dose of 1000 mg or more. It is estimated that roughly 150,000 kg/day of the drug is voided in the urine and thus in river and other water bodies posing health hazards to fishes and other animals. Additionally, I am also used in animals. This reflects an increasing concern on the health of numerous species including Homo sapiens. Accumulation has been reported in wastewater, drinking water and cosmetics, making it one of the 14 most active pharmacological molecules in the environment.[15]

I reduce TSH levels without altering T3 or T4 levels and that may complicate therapy of hypothyroidism in diabetics and pregnant mothers. The reason is yet to be known but suppression of AMP-Kinase activity in hypothalamus could be the plausible explanation![16]

Pharmacodynamics[17]

The exact cellular mechanism of my antidiabetic action has baffled assiduous researchers and clinicians so far. I am derived from natural source (Galegine) and not an outcome of planned research for a new molecule. I reach minuscules of the target cells changing basic metabolic activities to lower blood glucose. Reduction in glucose output is just one explanation of my pleiotropic effects. I consistently lower both basal and postprandial glucose and HbA1c on long term use. As narrated earlier, I act mainly by suppressing excessive hepatic glucose production by reduction in gluconeogenesis (main action). Other potential contributing effects are: an increase in glucose uptake, an increase in insulin signaling (insulin sensitivity), a decrease in fatty acid and triglyceride synthesis, and an increase in fatty acid β-oxidation. I am found to increase glucose utilization in peripheral tissues, and possibly reduce food intake and intestinal glucose absorption. The beneficial effects on glucose metabolism may be mediated by alterations in gut microbes.[18]

So, what are my unique pharmacodynamics features?

1. I do not act on beta cells of pancreatic islands. It was hypothesized earlier that I need insulin for my actions and I increase insulin sensitivity. Later, it was shown that I act on gut and reduce glucose absorption. I increase anaerobic glucose metabolism in enterocytes resulting in reduced net glucose uptake and increased lactate delivery to the liver. A delayed release formulation is largely retained in the gut, with minimal systemic absorption, and is as effective in lowering blood glucose as the standard immediate-release formulation showing my local intestinal effect to be

important contributor! Still later, it was shown that even without insulin I am active on liver. I reduce hyperglycemia and secondarily reduce hyperinsulinemia. I even act on isolated mitochondria!

2. Unlike insulin therapy, I do not cause weight gain. In fact, weight loss of up to 4 kg after 16–29 weeks (short term) of my use has been reported. This effect may be mediated through carbohydrate malabsorption, enhanced carbohydrate utilization in the GI tract itself, or reduced calorie intake from mild anorexia. In the longer-term UKPDS study, I was found to be weight neutral.

3. I offer cardiovascular benefit. When compared to conventional therapy (diet alone), my use was associated with a reduction in heart attacks and all-cause mortality in overweight, newly diagnosed type 2 DM subjects. The improvement in outcome was greater than predicted from my glucose-lowering effect, implying my pleiotropic actions on the cardiovascular system.[19]

The cardiovascular protective effects have been shown in healthy individuals also. The likelihood of CVD was reduced by 6% among otherwise healthy individuals, by 18% among those at risk of frailty and by 48% among those at high cardiovascular risk. Metformin improves endothelial function & angiogenesis, reduces inflammation and helps in achieving ideal body weight. In addition, it reduces depressive manifestations and enhances cognitive function (dementia risk was lower in those taking metformin compared with other glucose lowering medications).

Cardiovascular effects of Metformin

Vascular Effects	Anti-thrombotic	Anti-inflammatory
↓ Cholesterol deposition	↓ Platelet activation	↓ C-Reactive protein
↓ Lipid peroxidation	↑ Blood flow	
↓ Oxidative stress	↓ PAI-1	
↑ Endothelial function	↑ Fibrin breakdown	

4. My antidiabetic mechanism is contributed by my effects on gut microbiota. I am present in high concentration (100 times) in gut and due to my antibacterial activity, particularly on Intestinibacter spp, increase butyrate production and promote the growth of short chain fatty acid-producing bacteria. Gut microbiome is known to alter GLP-1 secretion and a reduction of Lactobacilli is associated with GLP-1 resistance related to alterations in enteric neuron nitric oxide production.[20]

5. I possess anti-inflammatory and immunomodulatory actions! I induce AMPK activation which is known to influence T cell proliferation and function. For example, increase in the number of CD8-positive tumor-infiltrating lymphocytes occurs experimentally by me and enhancement of anti-tumor immunity by phenformin. Anti-inflammatory activity (Reduced NF-κB activation and reduction in secretion of inflammatory cytokines) is already demonstrated in senescence. Experimentally, I am shown to reduce inflammation in SLE, pulmonary tuberculosis and lessen CNS inflammation in multiple sclerosis.[14]

My Role in Gestational Diabetes[21-24]

Perhaps, I am the only oral medicine so extensively evaluated in pregnancy. I am considered among Pregnancy Category-B drugs. I easily cross placenta achieving similar concentrations in fetal and maternal blood. So, it was feared that fetal anoxic conditions could favor occurrence of feto-maternal lactic acidosis with my use. Animal studies did not show embryopathic effects. Observational studies found that my use was safer during early pregnancy. Small human studies also showed similar safety. Finally, MiG trial and meta-analysis of clinical studies provided convincing evidence on my safety. The initial dose for immediate release formulation is 500 mg once or twice a day that may be increased up to 2000 mg - 2500 mg in two to three divided doses to achieve the glycemic targets. The insulin may be co-administered therapy.

My Role in prevention of Diabetes[25]

I have been shown to possess potential to delay occurrence or prevent diabetes in prediabetics. It is so satisfying that I am contributing significantly in reducing the economic burden of diabetes in this manner. The Diabetes Prevention Program (DPP) and its follow-on Outcomes Study (DPPOS) with over 20 years of follow-up, revealing significant benefits of both intensive lifestyle intervention (ILI) and my use in preventing overt type 2 DM. The initial dose is 850 mg once a day for a month for immediate release oral formulation. The dose may be increased up to 850 mg twice a day.

My use in Type-1 DM[26,27]

I am a recommended therapy for adolescents (> 10 years) with Type-2 DM. A number of small studies performed since 1980 onwards in France showed promising results in Type-1 DM but clinicians were not yet convinced. So, I remained quiet for over a decade. Now, I have dared to intervene type-I diabetes (T1DM) also. Insulin is the main drug for T1DM, but causes weight gain. The resulting insulin resistance increases its requirement consequently. Furthermore, insulin may increase blood pressure and LDL-cholesterol levels in T1DM. Here comes my role as an adjunct therapy to reduce insulin dose requirement by 25%, lower HbA1c, reduce weight (10%), and have direct effects to reduce the risk of cardiovascular disease and improve life expectancy. In 2010, the UK National Institute for Health and Care Excellence (NICE), and later ADA, recommended my use for obese adults with type 1 diabetes (BMI ≥ 25 kg/m^2).

My Role in Polycystic Ovarian Disease (PCOD)

I am shown to improve fertility outcomes in females with insulin resistance associated with PCOD. I improve ovarian cyclicity, oocyte maturation and reduce androgen levels. I am combined with clomiphene for inducing ovulation. Clinically, there is lower incidence of cesareans and number of premature births with my use. Interestingly, I am shown to improve fertility of adult men with metabolic syndrome associated with increased testosterone production as well![28]
A word of caution: recently, a study demonstrated that in-utero exposure to me (Metformin) resulted in children with a higher body mass index (BMI) and increased prevalence of overweight/obesity at 4 years of age compared to children of the placebo group (Hanem et al). Therefore, I must be used judiciously in PCOD.

Role in Obesity

Antipsychotic (Olanzapine and clozapine) induced weight gain is reduced by me. I have been shown to reduce weight and appetite in nondiabetic obese or overweight adults.[29]

Role in Non-alcoholic fatty liver Disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

I reduce insulin resistance, improve abnormal liver enzymes but may not reliably improve liver histology.[30]

Role in Dermatology

I am increasingly being used in dermatology for conditions like acne, pigmentary disorders, acanthosis nigricans, hydradinitis suppurativa, eruptive xanthoma, psoriasis and squamous cell carcinoma.[31]

What Next?

I am over sixty-five years old now serving mankind with diabetes and feel young and energetic to alleviate human sufferings further. I introspect and foresee my new roles and most exciting future in front. Studies are already underway to explore such potential in seemingly unrelated disorders such as Human immunodeficiency virus (HIV)-associated lipodystrophy, acanthosis nigricans and, possibly, dementia-type neurodegenerative disorders, hirsutism and cancer prevention.[14]
In hirsute females, I enhance the anti-hirsutism effect of spironolactone. Days are not far when individuals would wear a 'megachip' at an affordable cost and the information would become part of that person's electronic medical record. Statistical algorithms will inform clinician about the responder/non-responder status and tailor my therapeutics as personalized medicine.[8,9]

Prevention of Cancer

In patients with diabetes, my continued use is demonstrated to reduce the risk of pancreatic cancer and cholangiocarcinoma slightly as compared to insulin and glucagon like peptide-1 based therapy (sitagliptin) which may increase the risk.[8,9,10,30] My use has been associated with a decreased risk of breast, colon, liver, pancreas, prostate, endometrium and lung cancer as revealed by many metanalyses.[32] The benefit is related to activation of AMPK and blocking invasion of tumor cells by inhibiting matrix metalloproteinase-9 activation, activating growth suppressors through phosphorylation of retinoblastoma protein (pRb) resulting in G0/G1 arrest in prostate cancer cells, and inhibiting cancer stem-cell activity. In addition, I indirectly lower insulin levels thus reducing cell proliferation. The expression of my transporters is downregulated in breast tumor cells. A phase-III study in prostate cancer prevention is going on and time shall come soon for my use as adjuvant for cancer prevention.[33]

Antiaging Effects[33-37]

An exciting field in which I have been explored is antiaging actions which if proved may prolong the life span of an individual! Studies in nonhuman primates and systemic reviews of several studies have already paved the way to show "gero-protective" actions independent from antidiabetic efficacy. It is hypothesized that I might delay the ageing process and increase health span and lifespan by reducing inflammation and ameliorating DNA and cellular damage. I am shown to exhibit neuroprotective effects in Alzheimer's disease.

Two large, randomized clinical trials (The Veterans Affairs' Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes: VA-IMPACT-in 2017 and The Targeting Ageing with Metformin: TAME in 2018) have begun with aims to evaluate my additional benefits for individuals without diabetes. The primary outcomes of first trial include the time to death from any cause, myocardial infarction, stroke, hospitalization for unstable angina, or symptom-driven coronary revascularization. The TAME trial is also evaluating my potential ability to slow down the development of age-dependent and age-related diseases, including cancer, CVD and dementia.[37]

CONCLUSIONS

Metformin is a small molecule drug in clinical use for over 70 years now. It has withstood test of time and proven itself as foundation drug for initiation of treatment of Type-2 DM alone and along with other medications. Despite its efficacy and safety its underlying mechanism of action has

continuously baffled researchers and is still being explored. Meanwhile, it has shown multiple salutary actions which contribute to its widespread utility in seemingly unrelated disorders. It has indeed emerged as proverbial "phoenix from the ashes", as stated by Dr Campbell in his personal commentary on metformin on its 75 years of existence. Triggle et al summarizes metformin actions as "a drug for all reasons and diseases." It still holds surprises in its bosom which time shall unveil!

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