COMMENTARY

Metformin: Nature's Gift that Keeps on Giving More!

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Despite many different drugs being available for type 2 diabetes, metformin remains a cornerstone in the management of diabetes. In a consensus statement, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend metformin as the first step in the treatment type 2 diabetes, in the absence of drug contraindications.[1] Thus, worldwide, metformin is now the unanimous first-line glucose-lowering agent. While several recent antidiabetic drugs have been under the cloud, some being withdrawn, others asked to give warnings in labels and a few still under strict Food and Drug Administration (FDA) scrutiny, metformin, a time-tested drug, has surpassed the hurdles and become the most prescribed medicine in diabetes and other conditions of insulin resistance. Why is there now a "metformin wave" everywhere? Here, we will discuss this "metformin paradox" of an old wine in a new bottle.

METFORMIN – THE AFFORDABLE DRUG WITH AN ANCIENT HISTORY

The "metformin wave", which we see now, was not an easy flow for the drug, and it meandered through several ravines and overcame sizeable barriers. This today's affordable drug has an ancient history of its origin in the European folk medicine.[2] Metformin discovery stems from a natural biguanide known as galegine from a flowering plant called *Galega officinalis*.[3] It originated in the Southern Europe and Western Asia, but then spread to other countries, with many names: Goat's Rue, Spanish sanfoin, false indigo, Italian fitch, French lilac, and Professor-weed. It has also been used in Asia to treat various medical conditions. Though the drugs based on the biguanide structure were synthesized in the 1920's, these were quickly overshadowed by the Nobel prize-winning discovery of insulin. With such a long history as a potent herbal remedy, it's actually sad that there was a long wait for a good drug for diabetes! The delay continued during the great depression and World War II until the French developed metformin for clinical use in 1957. The following year it was approved in the United Kingdom and then made its way to Canada as late as in 1972. However, the US FDA did not approve it until 1994. The US population was deprived of a useful drug for 37 years! In India, Metformin was available since 1980. It has now become an evergreen, permanent component of the antidiabetic combination drug regimens. Metformin has been around for so long that it has gone off patent, and as a generic it is easily affordable for the developing world.

METFORMIN: EFFICACY, SAFETY AND OTHER ACTIONS

Metformin has emerged as a major drug not only because it is time-tested, but also the vast evidence that is available. The United Kingdom Prospective Diabetes Study and the Diabetes Prevention Program (DPP) have demonstrated the efficacy of metformin in terms of treatment and prevention of type 2 diabetes.[4] The best evidence for a potential role for metformin in the prevention of type 2 diabetes also came from the Indian DPP (IDPP).[5] It reduces HbA1c to the same degree or more than other drugs. Unlike peroxisome proliferator-activated receptor γ agonists, it does not cause weight gain. Metformin decreases low-density lipoprotein cholesterol and triglycerides. It appears to have a good safety profile. It is one of the very few drugs that have undergone the 7-year postmarketing surveillance required by the FDA. Most side-effects are minimal and easily managed. Its use is restricted due to gastrointestinal intolerance and other challenges like lactic acidosis. However, individual benefit/risk ratio should be critically assessed in order not to deprive patients from this potentially beneficial drug. The patient-centered approach recommended by the ADA-EASD position statement has major clinical value.

Metformin has actions beyond glucose control. These include microvascular and macrovascular benefits, protection against nonalcoholic fatty liver disease, weight loss, neuroprotection, and renoprotection, favorable

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improvements in endothelial dysfunction, thyroid function, hemostasis, inflammation, glycation, oxidative stress, endoplasmic-reticulum stress, autophagy, insulin resistance and fat redistribution. Metformin reduces hyperinsulinemia, and it has been shown to exhibit beneficial effects on metabolism and ovulatory function in patients with polycystic ovary syndrome.[6] Several studies report a lifespan (and even healthspan) extension in animal models after treatment with metformin and it is considered as a prototype antiaging drug.[7]

METFORMIN AND CANCER

There is strong epidemiological evidence that metformin may prevent certain types of cancer. Some *in vitro* and *in vivo* studies have demonstrated a direct antitumor activity by inhibition of cancer cell proliferation and colony formation, induction of cell cycle arrest and apoptosis and suppression of xenograft tumor growth in mouse models. Human observational studies and meta-analyses suggest that metformin, unlike other glucose-lowering therapies, is associated with reduced cancer risk/cancer mortality in diabetic patients.[8] Metformin affects multiple pathways in cancer progression by impacting various cellular processes. Metformin has been shown to exhibit antiproliferative and antineoplastic effects associated with inhibition of mammalian target of rapamycin complex-1. This pluralistic action supports the concept of repositioning metformin in cancer.[9] Hence currently, several trials combining metformin as an adjuvant with established anticancer agents are also underway or planned. We need to wait for the results.

METFORMIN: A CELL BIOLOGIST'S CELEBRITY AND A PHARMACOLOGIST'S PARADOX

Despite several decades of its clinical use, the mechanistic understanding of metformin's actions is still evolving. Diverse glucoregulatory mechanisms are being unraveled. Metformin acts in the liver, reducing its glucose output and secondarily augments glucose uptake in the peripheral tissues (muscle, adipose tissue).[10] At the cellular level, metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK). This is a key mechanism responsible for the wide range of metabolic benefits.[11] Recent evidence also suggests that metformin is capable of inhibiting hepatic gluconeogenesis, a key flux whose increase contributes to elevation of hepatic glucose production and hyperglycemia, through pathway(s) other than AMPK.[12] New biology insights into metformin benefits are continuously evolving including the energy mechanisms in the mitochondria,[13] the glucagon receptor signaling and cyclic AMP production[14] and glucagon-like peptide-1 secretion.[15] Metformin is also an epigenetic modulator.[16] Metformin also appears to work as a meta-genomics modulator, because the paradigm related to multiple modes of action of metformin has been recently extended to reducing glycemia by targeting gut microbiota.[17] All this sounds quite remarkable!

METFORMIN: LESSONS TO BE LEARNT

Metformin is not only a major drug for diabetes, its history and evolving uses also teach us several lessons. It is the globally accepted first option in the treatment of diabetes. Hence, no one now questions "why metformin?" However, the emergent question is: "What is there after metformin?" Ironically, despite the roots of metformin in *G. officinalis*, the other currently known antidiabetic plants are not being pursued with rigor for new drug discovery.[18] Metformin is the best example of how an ancient anecdotal herbal remedy can be transformed into a successful modern drug. Although bio-prospecting and Ayurveda are the thrust areas of research in India, natural products for drugs are pursued more with state-of-the art R&D in countries such as China, Australia, South Korea, and Brazil. The CSIR-NMITLI Program in India was a right step in this direction.

Second, more careful studies are needed to have a consensus on the new indications for metformin, including cancer. Third, studies should also focus on organic cation transporters and other metformin uptake mechanisms that could increase the tissue and cellular bioavailability of metformin. The advantage of multi- and trans-disciplinary teamwork needs to be leveraged to develop new drug delivery systems to maximize the efficacy of metformin and reduce or even nullify its contraindications.

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