Editorial

Metformin and the promise of geroprotection

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Much has been written about the multifaceted effects of metformin in medical literature.[1] The glycemic and metabolic effects of metformin have been known to us for over half-a-century. In the past decade, however, attention has been focused on the extraglycemic effects of this molecule, including the cardioprotective, hepatoprotective, and anti-malignant effects. The anti-malignant effects of metformin have been discussed in great detail in recent publications.[2]

Cancer is a disease of aging. In general, the factors that initiate and promote tumorigenesis are associated with age-related damage. It stands to reason, therefore, that metformin may hold a potential not only as an anti-tumour drug, but also as a geroprotective agent. This editorial focuses upon this relatively less highlighted aspect of metformin: its anti-aging effect.[3]

Since time immemorial, medical science has searched for an antidote to aging, for a drug to defeat death. References to panaceas for longevity exist in ancient Indian literature, as well as medieval European writings.

Modern medicine has utilized various means of prolonging life. The most promising lead has been that of calorie restriction. Calorie restriction (CR) has been shown to prolong life span in various animal models, from nematodes to rodents to mammals. CR increases resistance to stress and toxicity, while maintaining function and vitality in laboratory mammals. It increases life-span, and reduces or delays age-related disease such as diabetes and cancer.[4]

Calorie restriction works by reducing insulin and the insulin-like growth factor-1, as well as, increasing insulin sensitivity. The genes responsible for the signal transduction from insulin receptor to transcription factors daf-16 are associated with longevity. These genes interact with the daf-2 / age-1 insulin-like signaling pathways, and regulate downstream targets.[5] Even as CR may be an effective means of geroprotection, it may not be accepted by a vast majority of human beings. To create a pharmacological alternative to CR, one needs CR mimetics, that is, drugs that mimic the effects of CR, without the recipient having to limit her or his calorie intake.

These drugs act at various levels of the IGF-1 pathway. They may simulate dwarf mutations, thus reducing the growth hormone production, prevent IGF-1 release from the liver or decrease IGF-1 signalling.[6] One of the most frequently used CR mimetics (CRMs) in endocrine practice is metformin. Metformin acts to reduce hyperglycemia in diabetes by multiple mechanisms, many of which are still being explored. In simple words, it mimics CR by inhibiting processes that consume energy (gluconeogenesis), and stimulating reactions that store or preserve energy (glucose uptake). Metformin achieves these effects by activating AMP kinase (AMPK), which is a cellular energy sensor, and a 'caloristat'. Activation of this kinase is regulated by the tumor suppressor gene *LKB1*, which stimulates threonine 172 phosphorylation; AMPK in turns inhibits a kinase known as the mammalian target of rapamycin (mTOR), thus reducing protein synthesis.[1]

Even as metformin is the only drug of its class in current clinical use, other biguanides such as buformin and phenformin have been used extensively in the past. Senior physicians speak of the safety and tolerability of these drugs when used as anti-diabetic medication.[7] However, the utility of these drugs extends far beyond diabetology. Over 40 years ago, biguanides were suggested

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to be potential geroprotective agents. These drugs were demonstrated to improve the life span in round worms (*C. elegans*), mice, and rats. It was felt that the mechanism of action operated independent of the insulin signaling pathway, but through AMPK and the AMPK activating kinase LKB-1. Metformin, specifically, was found to increase the mean life span in *C. elegans*, when given in a 50 mM dose, but not when given in a 10 mM dose.[8,9]

In mice and rats, multiple workers have seen a reduction in food intake, slowing of age-related decline in metabolic parameters, delay in age-related switch off of estrous function, and prolongation of life span, with metformin supplementation (100 mg/kg in drinking water).[9] However, certain laboratories have reported neutral results as well.[3] However, it must be noted that the metformin concentration utilized in these studies is 10 times greater than the doses used in human beings.[10]

Although the above-mentioned data has not found widespread popularity among the Indian endocrine community, we are certainly aware of the clinical data related to the geroprotective effects of metformin. Metformin has been shown to improve clinical outcomes and reduce all-cause mortality in people with type 2 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), the metformin group had a lower risk of diabetes-related death (42%) and all-cause mortality (36%) than the diet group. All-cause mortality was also lower with metformin as compared to sulfonylurea and insulin.[11] An increase in life expectancy was also seen in overweight patients prescribed metformin.[12] This implies that metformin may have a geroprotective effect in diabetic humans as well.

The geroprotective effects of metformin can be seen in a different field of medicine as well, unrelated to diabetes. The drug has been shown to improve life expectancy in patients with malignancy. This benefit has been noted in pancreatic cancer,[13] breast cancer,[14] and colorectal polyps (a premalignant condition),[15] In a Japanese study done on colorectal polyps, a very low dose of metformin (250 mg / day) was used for the successful prevention of an age-related disease. These findings lend support to the hypothesis that metformin may be used as a geroprotective agent, not only in people with diabetes, but in euglycemic people as well.

Another, and yet again, completely different field of medicine where metformin exerts 'youthful' effects, is female reproduction.

The molecule is accepted as a drug of choice in the polycystic ovarian syndrome.[16] A study using phenformin has shown that it decreases the sensitivity of the hypothalamus to feedback inhibition by estrogen, and thus postpones the age-related decline in productive function.[17] This may be a potential mechanism of action of the geroprotective effects of biguanides. Among the other putative sites of actions for this effect are the brain and immune system.[18,19]

The current clinical evidence supports the use of metformin in conditions where it was hitherto considered contraindicated.[20] In parallel with this, the clinical data has emerged, which shows that metformin has renoprotective, cardioprotective, and hepatoprotective effects.[21-23] Thus, the drug acts upon multiple sites in the human body to prevent organ damage, and may potentially increase the lifespan.

The use of metformin in the elderly is not without certain limitations. Weight loss can be a problem in elderly subjects, who may already have aging-related sarcopenia. Moreover, elderly subjects, who are already at a higher risk of dyspepsia owing to polypharmacy, may not tolerate metformin-related dyspepsia. Finally, the side effects of metformin, like anemia and lactic acidosis, do certainly pose a higher risk to the elderly who may already have multiple comorbidities. Despite all these probable flaws, metformin is a drug that has constantly silenced critics, overcoming the lactic acidosis panic, to emerge as the safest, cheapest, and most popular drug for the management of diabetes, with spin-off effects against polycystic ovaries, fatty liver disease, obesity, and even cancer! This makes it perhaps the best, and most long-lived, example of exaptation in endocrine pharmacology.[24]

The promise of metformin as a geroprotective agent is certainly real, given the likelihood of multiple benefits in this age group. Further studies need to be done to pursue this hypothesis further. For the time being, metformin continues to wait in the wings, awaiting a call from scientists and researchers, who may eventually uncover new bottles to place this old wine. And that is because metformin, a molecule that has constantly reinvented itself over the years, is like the best of wines — aging so gracefully that it might go on to be researched as an antidote to aging itself!

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