Review Article

Beyond Diabetes, Metformin may prove to be a 'Wonder Drug'

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ABSTRACT:

Metformin has been proven to be one of the most safe and effective antihyperglycemic agents. Through more than six decades of metformin use, it became the most studied hypoglycemic agent; through these studies, it showed a marvellous non-glycemic related effect. These effects include modulation of different points of cancer timeline, weight reduction, cardiovascular health, thyroid diseases, polycystic ovaries disease and many other medical conditions like aging. Aging has been targeted by genetic and dietary manipulation and by drugs in order to increase lifespan and health span in numerous models. Metformin, which has demonstrated protective effects against several age-related diseases in humans, will be tested in the TAME (Targeting Aging with Metformin) trial, as the initial step in the development of increasingly effective next-generation drugs. The aim of this review was to assess the effect of metformin on non-diabetes related medical diseases. We have examined the studies published in PubMed and summarized different randomized controlled trials, observational trials and review articles. This review has summarized most of the non-glycemic effects of metformin. Metformin has been solidly shown to be effective in weight control with certain medications, effective in neuroprotection, in endothelial health, in control of anti-HIV agent side effects and many other crucial health jeopardies. The effects in cancer timeline modulation have taken the biggest part, since it was the most studied area outside the diabetes field. Having mentioned all the above privileges, and in addition to the robust evidence in glycemic control, this consolidates the position of metformin as a first line agent in treatment of diabetes and pre-diabetes. Perhaps in the near future, we may see other indications to use metformin in non-diabetes patients.

Keywords: metformin, antitumor effect, antiaging effect, cardiovascular protective, HIV associated diabetes, neuroprotective effect, PCOS.

INTRODUCTION:

Inthe past 2 decades, metformin has become a mainstay of type 2 diabetes management and is now the recommended first line drug for treating the disease in the United States and worldwide**.**

Available in the United States since 1995, metformn is an attractive therapy forclinicians and patients alike. Studies have found the agent to be safe and effectiveand at about $4 for a 1month supply of the generic, that option is affordable at a time when many prescription drugs are being priced out of reach for some patients.

Metformin is most commonly used to treat type 2 diabetes, either alone or combined with other agents, but is also used off label as a treatment for prediabetes, gestational diabetes and PCOS. [1]

Metformin (a biguanide derivative), by controlling blood glucose level decreases these complications. Metformin works by helping to restore the body's response to insulin. It decreases the amount of blood sugar that the liver produces and that the intestines or stomach absorb.[2] Metformin, other than hypoglycaemic activity, has been taken with diet and exercise changes to prevent diabetes in people who are at high risk for becoming diabetic. It is also used in women with polycystic ovarian syndrome. Metformin may make menstrual cycles more regular and increase fertility.[3]

ABOUT PCOD

Metformin has been used for PCOS treatment since 1994,[4] by which most of the metabolic abnormalities of PCOS can be reversed. [5]

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Metformin dose ranged from 850 to 1,700 mg in different studies (Table 1). The mechanism is thought to be mediated through increased insulin sensitivity, increased ovarian secretion of estrogen, decreased ovarian production of androgen and augmentation of the production of sex hormone binding globulin.[5,6] A recent meta-analysis shows that metformin can reduce testosterone and insulin in PCOS women.[7]"Metformin is the first drug of choice, by all standards. It is time tested, proven, has good efficacy, a good safety profile and it's cheap.

MECHANISM OF ACTION OF METFORMIN

The metformin molecule works in the human' bodies at the level of the liver and peripheral tissues, basically, by downsizing the glucose output from the liver, as well as by enhancing the utilization at the peripheral tissues (muscles). This process takes place through the activation of adenosine monophosphate-activated protein kinase (AMPK). The AMPK is the cell regulatory pathway that reduces the energy expenditure at the cellular level. In humans, AMPK is essential for the metabolism of glucose and fatty acids, through reduction of the gluconeogenesis and fatty acids synthesis in the liver, and enhancing glucose uptake, and the fatty acids oxidation by peripheral tissues.[8]

METFORMIN & OBESITY

The efficacy of metformin for the treatment of obesity has been evaluated in few clinical trials and it shows that the patient loseweight in a year, including attempting life style modification.Ultimately, a combination of metformin and lorcaserin worked for the patient, who has since maintained a 50lb weight loss.

When metformin used in a group of 10 patients, about seven of them either lose no weight or lose marginal amounts of weight, "But the three that do respond very dramatically. It may have something to do with central effects of metformin when it is able to get across the blood–brain barrier via the organic cation transporter (OCT2). [9]

HIV-ASSOCIATED DIABETES

Antiretroviral therapies with protease inhibitors inhibit glucose transporter (GLUT)-4 mediated glucose transport. [10] They are likely to be, in part, responsible for the insulin resistance and body composition changes in HIV-infected patients. Metformin has been shown to reduce visceral adiposity and insulin resistance after 8 weeks of drug therapy at dose of 850 mg, 3 times per day. [11]

NEPHROTOXICITY PREVENTION

Recent studies have suggested that metformin may have therapeutic or renoprotective effects against nephrotoxic agents. [10, 11] It has also been shown to have a good efficacy in diabetic nephropathy. Furthermore, it significantly decreases albuminuria in patients with diabetes mellitus. [12, 13, 14, 15, 16] However, the exact mechanism beyond these effects is still unknown. Recent studies have shown that therapeutic effect of metformin is mediated through its action on adenosine monophosphate (AMP)-activated kinase in tissues.[15,16 ,17,18,19,20] Various studies have shown that metformin is capable of decreasing intracellular reactive oxygen species (ROS).[17,18,19,20,21] It protects tubular injury through regulation of oxidative stress and restoring the biochemical alterations on renal tubules. Metformin may also protect the podocytes in diabetic nephropathy.[19, 20, 21, 22, 23]

CARDIOVASCULAR PROTECTIVE EFFECTS OF METFORMIN

Diabetic patients mainly die of cardiovascular complications,[24] including macrovascular complications (such as stroke, coronary artery disease [CAD] and myocardial infarction) and microvascular complications (such as kidney disease, retinal injury and peripheral nerve disease), of which approximately 70% of all diabetic patients die of heart and brain macrovascular diseases. In addition, a 10-year post-interventional follow-up of the UKPDS survivor cohort further examined that metformin treatment had a long-term benefit on cardiovascular risk in overweight patients. Compared with sulfonylurea and insulin treatment, metformin treatment can effectively reduce the risk of myocardial infarction and death.[25]

CANCER RELATED MORTALITY

Epidemiologic studies suggest that metformin use may be associated with both reduced cancer incidence and mortality. Although patients with diabetes had a higher risk for developing colon cancer, patients assigned metformin had a 27% reduced risk, according to researchers. Comparing patients with diabetes for less than 1 year, between 1 and 2 years, and at least 3 years with patientswithout diabetes, adjusted RRs were 1.308 (95% CI, 1.021.679), 1.087 (95%CI, 0.91.313) and 1.185 (95% CI, 1.0551.33), respectively. The duration of metformin use showed an inverse trend, according to researchers, with an RR of 0.643 (95% CI, 0.490.845) in users for at least 3 years vs. nonusers.

"Metformin clearly affects AMP – activated protein kinase, which effect mitochondrial energy generation and may deprive malignant, inefficient cells of energy and therefore reduce their potential growth rate. Although some of the observations [with metformin] imply not just

[preventing] a progression of cancer but an incident of the cancer, which might suggest broader effect than merely energy deprivation. [26]

METFORMIN AND THYROID CANCER

It shows in the studies that metformin act as anti-proliferative effects on differentiated thyroid cancers when they examined 34 patients with differentiated thyroid cancer (DTC) taking metformin versus 21 non-metformin using patients, tumor size was smaller, and progression was slower in the metformin group. One of the theories in DTC response to metformin is the p70S6K/pS6 pathway that induces the cancer cell metabolic stress and the autophagy later. [27] Similar experimental findings shown that medullary thyroid cancer (MTC) cells found slowness of cellular progression in metformin-treated patients. They stated that cyclin D1 (usually overexpressed in cancer cells) was remarkably inhibited, through inhibition of mTOR/p70S6K/pS6 signaling and down-regulation of pERK. Out of this sophisticated process, they concluded metformin could have a potential additional role in treating MTC [28], therefore adding thyroid cancer to the list of cancers showing a decreased cancer-specific mortality with the use of metformin.

METFORMIN AND MELANOMA

An article in 2011 by Tomic et al entertained an additional anti-proliferative effect of metformin in addition to AMPK activation. The activation of the AMPK ends cell proliferation, and subsequently, apoptosis develops within 96 h. Interestingly this article illustrated two findings one is how metformin leads to phagocytosis of cells containing AMPK, which are malignantly mutated, whilst sparing the healthy cells containing AMPK. Secondly, metformin can reduce proliferation of tumor cells effectively in an AMPK-independent manner as well [29].

METFORMIN & THE BLOOD HOMEOSTASIS

It was mentioned earlier that metformin reduces the incidence of cardiovascular events in diabetes patients. This takes place through various cascades (glycemia and non-glycemia related cascades). Metformin, in high doses, was shown to various coagulation factors in humans. Metformin reduces the systemic production of the tissue type plasminogen activator, Von Willibrand factor, and plasminogen activator inhibitor [30]. In addition to that, metformin was found to modulate the fibrin threads formation; this takes place by reducing the factor XIII functions and structural modeling of the fibrin threads [31]. Nonetheless, metformin was found to reduce the levels of plasminogen activator inhibitor-1, and Von Willibrand factor from the unhealthy endothelium in patients with no underlying diabetes mellitus [32].

METFORMIN AS AN ANTI-OXIDANT

This privilege is still to be explained by scientists. The hypotheses include lowering the reactive oxygen species, up-regulation of uncoupled protein 2 in the fat cells, as well as the AMPK system activation [33, 34, 35]. This as mentioned above reduces gluconeogenesis, and increase fatty acids metabolism, as well as B-oxidation in the fat tissues.

METFORMIN MODULATES THE BIOLOGY OF AGING

Metformin is a drug approved to treat diabetes but appears to target a number of aging-related mechanisms. Some mechanisms are relevant to glucose metabolism, but with respect to aging these may not be the most important ones. Metformin's multiple aging-relevant actions at the cellular and organismal levels are depicted in figure 1.[36]

Specifically for aging, metformin leads to decreased insulin levels, decreased IGF-1 signaling[37],inhibition of mTOR [38], inhibition of mitochondrial complex 1 in the electron transport chain and reduction of endogenous production of reactive oxygen species (ROS) [39], activation of AMP-activated kinase (AMPK)[40], and reduction in DNA damage[41]. Metformin favorably influences metabolic and cellular processes closely associated with the development of age-related conditions, such as inflammation[42],autophagy[43], and cellular senescence[44]. In C. elegans metformin extends lifespan by several possible mechanisms including the alteration of the microbiome, specifically by changing microbial folate and methionine metabolism. [45]

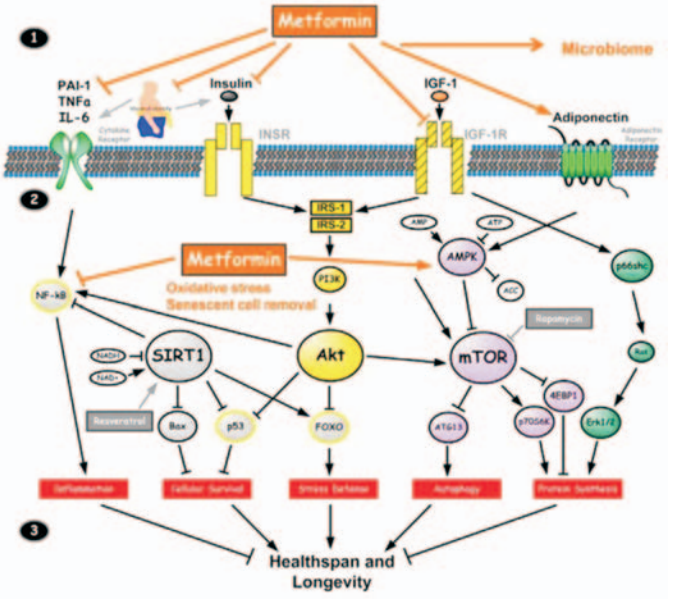

Figure 1 : Metformin Targets Multiple Pathways of Aging

The figure depicts schematically the current consensus within the biology of aging community as to pathways that are important in order to target aging and indicates at which points metformin has been shown to have effects (see text). Key take-away: outside of the cell (1, top), metformin has been shown to affect the receptors for cytokines, insulin, IGF-1, and adiponectin, all pathways that are activated with aging and, when modulated, are associated with longevity. (1) Intracellular (2,middle) metformin inhibits the inflammatory pathway and activates AMPK, increasing inhibition of mtor, which seems to be a major target to modulate aging. Through some of these mechanisms, it also modulates oxidative stress and removes senescent cells (the mitochondrial pathways are not shown, and the mechanisms by which metformin induces senescent cell removal remain unclear). (2) These processes jointly (3, bottom) affect inflammation, cellular survival, stress defense, autophagy, and protein synthesis, which are major biological outcomes associated with aging/longevity. [36

TABLE -1

SUMMARY OF EFFECTIVE DOSE OF METFORMIN IN STUDIES

Antitumor effect of metformin	500mg/day.[46] The greater the metformin exposure, the stronger the risk reduction. [47]
Cardiovascular protective effects of metformin	Starting with one 850 mg tablet per day, then 850 mg twice a day, and then 1,700 mg in the morning and 850 mg with the evening meal (maximum dose =2,550 mg)[48] 1.4±0.2 g10
Polycystic ovary syndrome	Range from 850 to 1,700 mg
Neuroprotective effect of metformin	Starting with 0.5 g tablet, two tablets a day with meals. If the blood glucose level is not controlled for 7 days after taking metformin, it should be increased to 1.5 g/day over 2 weeks (maximum dose <2.0 g/day) [49] 1,000 mg twice a day. [50]
An Obesity	Range from 850 to 1,700 mg

SUMMARY

Metformin is the most commonly prescribed therapy for patients with T2DM. It has a good safety profile and is associated with low cost. With further exploration of the clinical effect and possible mechanism of metformin, its indications have been extended to antitumor effect, HIV-associated diabetes, cardiovascular protective effects, neuroprotective effects, anti-oxidant, cancer and an optional treatment for PCOS.Beyond its impact on glycaemic control and diabetes-related outcomes, metformin has pleotropic effects targeting multiple age-related mechanismsalso. Furthermore, many questions such as whether these potential indications of metformin can be observed in non-diabetics and whether genetic factors have an influence on the effect of metformin need to be clarified by substantial basic experiments and clinical trials.

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